Drug-induced Long QT Syndrome

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*** The initiated reader to drug-induced Long QT Syndrome concepts is invited to concentrate reading on Section 6 and 7.**

1. Executive Summary

While medications are a critical intervention for the prevention and treatment of disease, disability and death, they also can cause problems on a broad scale. One particular side-effect that could be associated with certain drugs is a perturbation of the heart's capability to regain its resting membrane potential after a heartbeat. Such a condition is associated with a prolongation of the QT interval on the surface electrocardiogram (ECG) and is generally described as the drug-induced Long QT Syndrome (LQTS). Prolongation of the QT interval may predispose patients to syncopal events and a particular polymorphic ventricular tachycardia described as Torsade de Pointes (TdP), which may lead to sudden death. Herein we will review basic electrophysiological mechanisms behind drug-induced LQTS as well as proposed mechanisms for mitigating this risk.

There is an unmet need to develop measures of drug risk for prolonged QT interval and TdP. Three research groups have created limited quantitative and qualitative ways to measure drug-associated risk, evaluating various combinations of preclinical electrophysiological data, potassium channel effects, other ion currents, and retrospective clinical data. Each of these groups took into account only selected factors and neglected to use a comprehensive approach. Our group has created an inclusive model to account for additional factors that may influence a medication's likelihood of causing drug-induced LQTS or TdP, called the Long QT-JT index.

While the aforementioned medication-specific risk index will be helpful when scrutinizing a single medication, the reality is that patients take many medications and have individual risk factors that may predispose or protect them from QT prolongation and TdP. Up to this point, there have been two groups that have created risk scores that take into account various factors that may cause QT prolongation and increase risk of TdP. Our group developed a more advanced and comprehensive patient-specific tool, called the Long QT-JT Score, which is dynamic based on the patient's current conditions and concomitant medications.

2. Introduction

2.1. History

Back in the 1950's, Jervell and Lange-Nielsen reported a family where 4 children out of 6 were affected by deaf-mutism and experienced "fainting attacks" between the ages of 3 to 5 years. Three of the affected children passed away suddenly at the ages of 4, 5, and 9 years old. In their publications, Jervell and Lange-Neilsen described a potential association between this "peculiar" heart disease – which they discovered had a corresponding long QT interval on surface electrocardiogram (ECG) – and deaf-mutism.[2] Shortly after, Ward observed syncope due to ventricular fibrillation in a brother and sister whose resting electrocardiogram showed abnormal prolongation of the QT interval.[3] Their mother, although asymptomatic, presented with a prolonged QT interval as well. One of the daughters had attacks of syncope and died during one such attack at the age of 30 years. Deafness was not a feature, making this disorder distinct from the recessively inherited syndrome described by Jervell and Lange-Nielsen. Similar families with involvement of multiple generations were reported by Romano and his colleague,[4,5] and Garza *et al*.[6] Gamstorp *et al.* also reported a family with prolonged QT interval and cardiac arrhythmias without the characteristic deafness. They found that patients benefitted from potassium administration to correct hypokalemia.[7] It was these observations and particular conditions that became the fundamentals for the description of the ***inherited*** LQTS.[8] Several mutations in potassium (K^+), sodium (Na^+) and calcium (Ca^{2+}) voltage-gated ion channels have been associated with various familial forms of inherited LQTS[9]. (Table 1). Our description of this condition will be limited to these comments in the context of the current document.

As early as the 1920's, syncopal events were noted upon initiation of quinidine administration to patients. In 1964, Selzer and Wray provided further insight into this condition, which they described as ''quinidine syncope''.[10] Two years later, Dessertenne coined the term "*torsade de pointes"* (French; meaning, twisting of the points) while describing the visual appearance on the surface ECG of the associated particular polymorphic ventricular tachycardia (*tachycardie ventriculaire à deux foyers opposes variables; Figure 1*).[11] Since that time, many more medications have been implicated in

Table 1. Major genetic defects associated with the inherited forms of LQTS[9]

LQT subtype	Gene Name	Configurations with 2 variant gene copies	Encoded protein	Ion current affected	Effect of mutation	Common triggers
LQT1	KvLQT1, KCNQ2	Homozygous mutations cause Jervell and Lange-Nielsen syndrome (JLNS); compound heterozygous mutations described	Alpha subunits forming a tetramer	IK_s	Loss-of-function; rare gain-of-function with short QT syndrome has been observed	Exercise, esp. swimming; emotional stress
LQT2	HERG, KCNH2	Homozygous and compound heterozygous mutations described; homozygous may present with congenital AV block	Alpha subunits forming a tetramer	IK_r	Loss-of-function; rare gain-of-function with short QT syndrome has been observed	Rest/sleep, auditory stimuli, emotional stress; postpartum state
LQT3	SCN5A	Homozygous and compound heterozygous mtuations described	Four-domain alpha subunit	I_{Na}	Gain-of-function; loss-of-function mutations lead to varied presentations (Brugada syndrome, conduction system disease)	Rest/sleep
LQT4	ANKB, ANK2		Membrane anchoring protein	Affects Na+, K+, Ca2+ exchange	Loss-of-function	Exercise, emotional stress (based on limited data)
LQT5	minK, IsK, KCNE1	Homozygous mutations can cause JLNS; compound heterozygous mutations described	Beta subunit to KCNQ1	IK_s	Loss-of-function	(Insufficient data)

LQT6	MiRP1, KCNE2		Beta subunit to HERG	IK_r	Loss-of-function	(Insufficient data)
LQT7	Kir2.1, KCNJ2		Kir2.1 subunits forming a tetramer	IK_1	Loss-of-function; rare gain-of-function with short QT syndrome has been observed	Accompanied by alterations in serum K+ level in some cases
LQT8	CACNA1C		Alpha subunits forming a tetramer	$I_{Ca,\ L}$	Gain-of-function	Hypoglycemia, sepsis (2 cases)

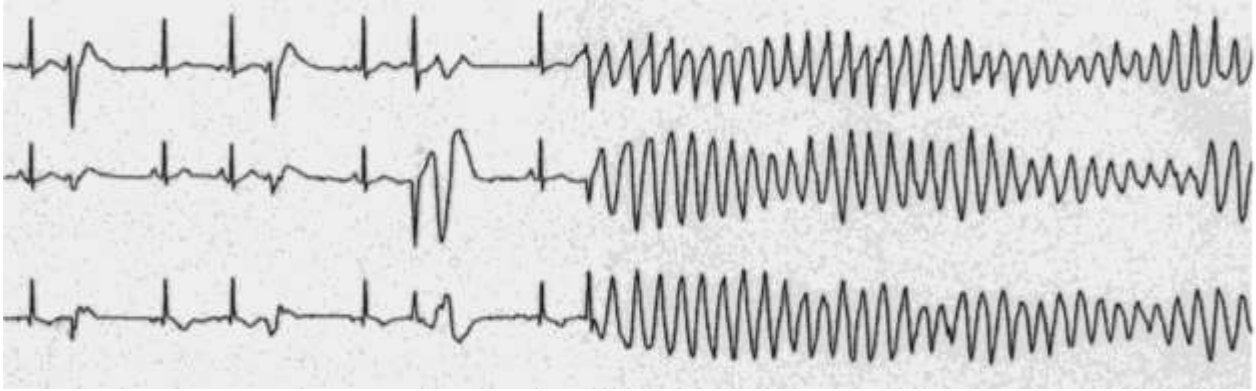


Figure 1. A typical example of a polymorphic ventricular tachycardia characteristic of a torsade de pointes. A twisting of the QRS complexes gives the typical sinusoidal pattern. From Fanoe *et al.* 2014 (http://dx.doi.org/10.1093/eurheartj/ehu100).

the induction of such events which constitute the fundamentals of the ***drug-induced*** LQTS. In the past 20 years, QT prolongation, and the corresponding risk of *torsade de pointes*, has led to withdrawal from the market of at least six medications and publication of several black box warnings in the United States, starting with one of the most publicized cases, terfenadine, in 1997.[12] Our document will concentrate on the description of drug-induced LQTS.

2.2. Basic Electrophysiology

A complete heart beat is generated by a single electrical signal initiated by a very small number (100) of very specialized cells that are localized at the upper part of the right atrium; the sinus node. It is this single event that will drive, over the next 250-500 msec, the entire cascade of channel opening, depolarization, contraction, repolarization and active ion transport associated with a simple heart beat. Hence, the electrical signal will

be conducted from the sinus (SA) node to the ventricles by different cell types in different structures of the heart through the sequential depolarization of one cell to the other (Figure 2).

The surface ECG reflects the local cardiac electrical activity. It is the voltage derivative (*d*V/*d*t) – reflecting the change in voltage *vs* time – of ionic charges flowing during cardiac systole and diastole. The signal associated with the firing of sinusoidal cells is too small to be recorded, but resides at the very first inflexion point of the P wave (Figure 3). The P wave *per se* represents depolarization and contraction of atrial cardiomyocytes. The PR segment

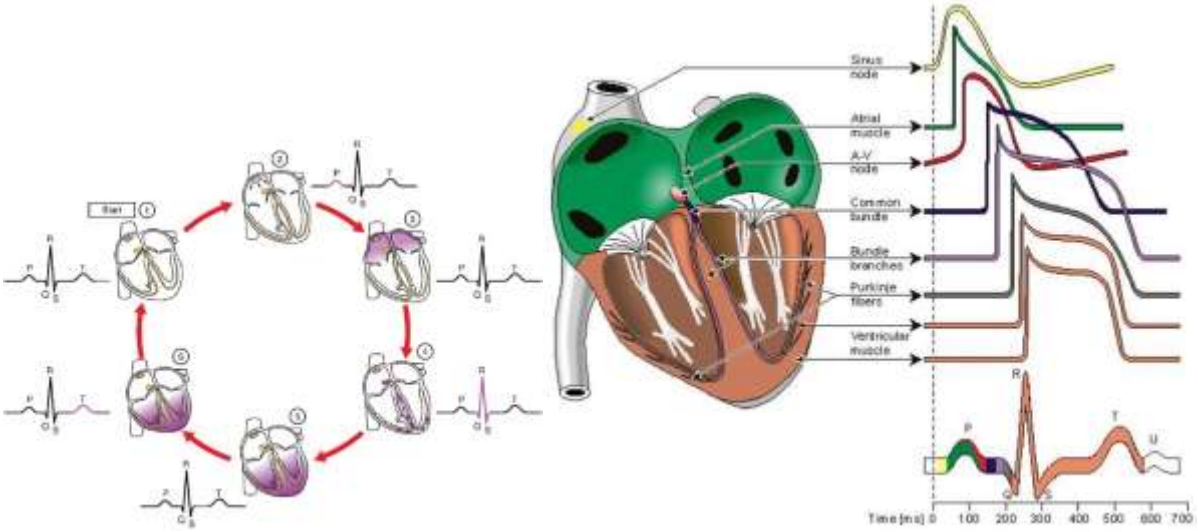


Figure 2. A single electrical signal originating from the sinus node will provoke a cascade of sequential depolarizations in various specialized heart tissues (left panel). Note that action potentials differ from areas of the heart to other areas and that repolarization in some areas occurs at the same time other areas will depolarize (right panel). Reproduced with permission from X and X

corresponds to the time it takes for the electrical influx initiated by the sinus node to reach the atrio-ventricular (AV) node. There is very little change in voltage (dV/dt) during the transmission of the electrical signal through the AV node, as depicted by a flat line on the surface ECG. AV nodal cells are slowly conducting, allowing efficient filling of the ventricles secondary to atrium contraction. The influx then fires down the His-Purkinje system, very rapidly, to depolarize the ventricles. This corresponds to the QRS complex on the ECG. This excitation occurs first through the septum in a downward manner, then back up the ventricular walls. The ST segment depicts the plateau phase of depolarization in the ventricular action potential. Calcium influx through the cardiomyocyte plasma membrane triggers Ca^{2+} release from the sarcoplasmic reticulum (Ca^{2+}-induced Ca^{2+}-release), which fuels actin-myosin interactions and contraction: it is the ventricular systole. The ST segment is a flat line and does not depict any change in current (dV/dt) as the entry of positive charges (Ca^{2+}) equals the efflux of positive charges (K^+). The T wave represents the major phase of ventricular repolarization. During this phase, a large quantity of K^+ ions flows out of the cardiomyocytes to restore the negative resting membrane potential of the cell. The QT interval represents the entire duration of ventricular depolarization and repolarization. The JT interval represents only ventricular repolarization time after complete depolarization (Figure 3). This may be a more accurate representation of risk of TdP, as it considers only the ventricular repolarization period. During diastole (at the end of the T-wave), Na^+/H^+, Na^+/K^+ and Na^+/Ca^{2+} pumps recreate the initial ionic equilibrium as Na^+ and Ca^{2+} concentrations increase in the extracellular cleft, while K^+ increases intracellularly. Excess positive charge through additional entry of positive charges (especially Na^+) or a decrease in K^+ efflux is associated with a prolongation of the QT interval.

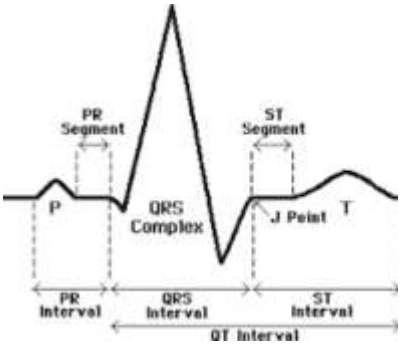
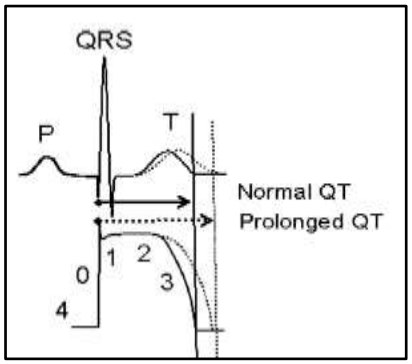
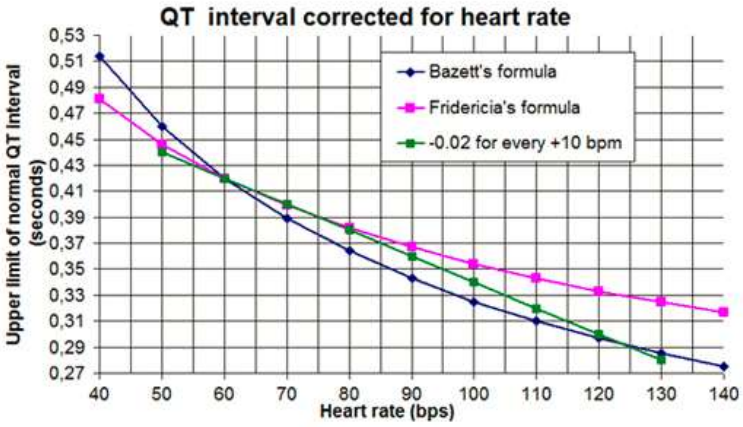


Figure 3. The surface ECG.

2.3. Correcting QT Interval for Heart Rate

Physiologically, as heart rate increases, repolarization of the ventricles must shorten as the time between each heart beat shorten. The opposite is also true that as the heart rate slows down, repolarization occurs more slowly in proportion to the lengthening of the entire cardiac cycle. The QT interval, which reflects ventricular action potential duration, will lengthen as heart rate decreases, and shorten as heart rate increases (Figure 4). Hence, the QT interval must be corrected for this variability in order to have a consistent quantitative measure of actual repolarization capability. Heart rate correction typically





incorporates a function of the RR inter
heartbeat, as it is the peak of one R w
next R wave (the next ventricular
Fredericia's ($QTc = QT/\sqrt[3]{RR}$) formula

Figure 4. The QT interval reflects mostly duration of ventricular repolarization as depolarization (Phase 0) is a very rapid phenomenon (<80 msec) for both ventricles (left panel). As heart rate increases, the QTc tends to decrease by about 20 msec for every 10 beat increase (right panel). Reproduced with permission from …

2.4. Molecular Basis of Cardiac Electrophysiology of a Ventricular Cardiomyocyte

The cardiomyocyte plasma membrane is, in principle, impermeable to ion flow. Thus, influx and efflux of ions can occur only following the opening of voltage-gated or agonist-gated ion channels or through the action of ion transporters (pumps). With respect to these channels and transporters underlying the ventricular action potential and as such, the corresponding surface ECG waves, Phase 4 of the action potential corresponds to ventricular diastole when ventricular myocytes are at their resting potential (Figure 4 (left panel), and Figure 5). During this phase, the concentration of K^+ is higher inside the cell

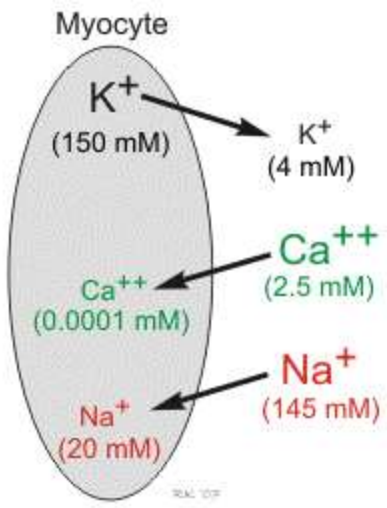


Figure 5. Intracellular and extracellular distribution of major ions around a cardiac myocyte.

than outside and the concentrations of Na^+ and Ca^{2+} are higher outside the cell than inside. Only specific K^+ channels (I_{K1}, I_{Kach}, I_{KATP}) will open during this phase, creating an inward electrical gradient (as positives charges like K^+ prefer to stay inside the cell which has a negative potential) and an outward chemical gradient (as K^+ prefers to exit the intracellular milieu where there is a large concentration of this ion compared to the extracellular cleft). In ventricular myocytes, when the extracellular K^+ concentration is 3.5 mM and intracellular K^+ is 150 mM, electrical and chemical ionic forces come into equilibrium at a voltage of -80 mV (Figure 5). Phase 0 of the action potential is characterized by the opening of voltage-gated Na^+ channels when the plasma membrane reaches -70 mV (the small electrical impulse coming from the SA node causes this membrane potential to go from -80 mV to -70 mV). Hence, a rapid influx of Na^+ occurs due to both an inward chemical gradient and an inward electrical gradient. As the transmembrane potential reaches -50 mV, voltage-gated Ca^{2+} channels open allowing the influx of Ca^{2+}. The increase in intracellular Na^+ depolarizes the nearby cells (as Na^+ flows through gap junctions between cardiac myocytes) and assures propagation of the influx. Simultaneously, the increase in intracellular Ca^{2+} will trigger calcium release (calcium-induced calcium release) from the sarcoplasmic reticulum and contraction will occur. The depolarization of ventricular cardiac myocytes and the conduction of the influx throughout the ventricles is depicted on the surface ECG by the QRS wave. This is followed by Phase 1, corresponding to an early repolarization phase, where there is some outward transient K^+ current (I_{to}) and a decreased inward flow of Na^+. There is heterogeneity between various regions of the ventricles as for the density of I_{to}. This explains various action potential shapes and durations between endocardium, M cells and epicardium (Figure 6) Epicardial cells, the cells on the outermost layer of the heart, are made mostly of simple squamous cells, and have the shortest action potential duration. Endocardial cells make up the inner endothelial lining of the heart, and they have an intermediate action potential duration. Myocardial cells (M cells), the cells in the

largest middle layer, have the longest action potential duration. These differences create heterogeneity in cardiac ventricular repolarization, which may underlie some proarrhythmic events.

Phase 2 is considered the plateau phase. During this phase there is a roughly equivalent influx of Ca^{2+} via L-type channels in proportion to the efflux of K^+: this is the systole of the ventricles during which actin and myosin interact. Phase 3, the recovery phase, involves a decrease in Ca^{2+} influx, a recovery of intracellular Ca^{2+} by the sarcoplasmic reticulum, and a significant increase in the efflux of K^+. There are two main channels to consider with regard to K+ efflux during Phase 3. The channel I_{Kr}, synonymous with *hERG-KCNH2* + *Mirp1-KCNE2*, is responsible for rapid repolarization; whereas, delayed (slow) repolarization is attributed to I_{Ks} (*KvLQT1-KCNQ1* + *mink-KCNE1*).[15] Finally, Phase 4 represents the cell's return to its resting membrane potential of -80 mV. Figure 7

3. Mechanisms of QT Prolongation

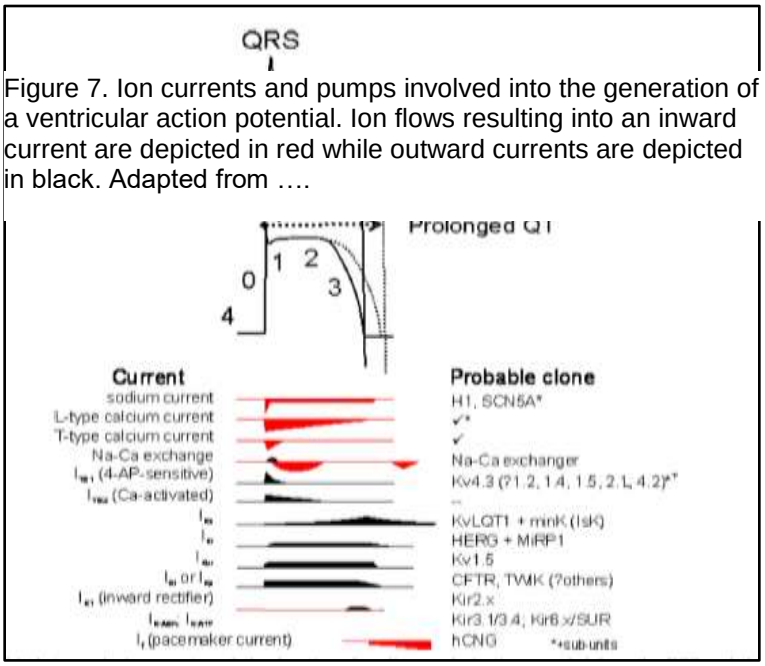


Figure 7. Ion currents and pumps involved into the generation of a ventricular action potential. Ion flows resulting into an inward current are depicted in red while outward currents are depicted in black. Adapted from ….

There are many factors that can impact a ventricular cardiomyocyte's capacity to repolarize. As discussed above, repolarization of ventricular cardiac myocytes primarily occurs in Phase 3 via the efflux of K^+ through I_{Kr} and I_{Ks} channels. By far, blocking of I_{Kr} is associated with significant prolongation of the QTc interval, as it is the major outward current at physiological heart rate. On the other hand, the slow component (I_{Ks}) is a reserve current, which contributes to repolarization when the action potential duration (APD) is prolonged due to dysfunctional I_{Kr}, or when heart rate accelerates. Indeed, it is the accumulation of I_{Ks} (which is slow to

open but also slow to close) that explains shortening of the APD at a faster heart rate. Blocking I_{Ks} by itself has little effect on the APD at physiological heart rates but it does change the adaptation curve of QT shorthening due to an increase in heart rate (QTc curve). Inappropriate inactivation of the late Na^+ current (SNC5A: window current) can also prolong the ventricular action potential duration as more Na^+ (positive charge) will enter the cardiomyocyte for a longer period of time. Mutations in I_{Kr}, I_{Ks}, and I_{Na} have all been associated with the inherited and drug-induced forms of LQTS.

Practitioners must assess patients for their overall risk based on these multiple mechanisms in combination – viewing only one medication or mechanism at a time may significantly underestimate a patient's risk

4. Development of Torsade de Pointes (TdP) Following Long QT Interval

4.1. Long QT as a Risk Factor for TdP

There are varying degrees to which medications can affect the QT interval based on various properties. Several studies have attempted to analyze the effect of medications on the QT interval length, as well as the relationship between QT interval length and adverse outcomes, the most significant being sudden cardiac death. A study performed in 2015 looked at patients who had previously taken medications in each of the categories listed at www.crediblemeds.org: known TdP risk, conditional TdP risk, and possible TdP risk. Results showed that the QTc interval was prolonged by 15 milliseconds when patients were given a drug categorized as "known" TdP risk; whereas, for drugs with "possible" TdP risk, the QTc lengthened by 3msec. The addition of a 2nd or 3rd QTc prolonging drug to the patient's regimen produced no substantial increase in QTc. It could be hypothesized that if the 2nd and/or 3rd medication prolongs the QTc interval by the same mechanism as

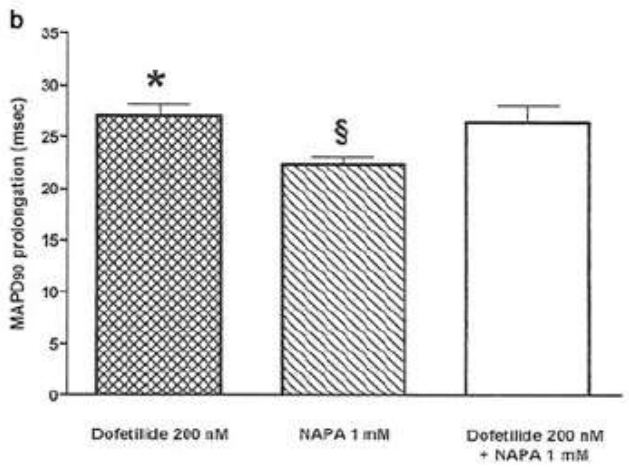


Figure 8. The combined block of I_{Kr} by two I_{Kr} blockers does not provide much additional prolongation of APD as the two drugs may competitive for the same effective site (Hreiche *et al*).

the first medication, then there is little room for QTc prolongation beyond that caused by the first medication[16,17] (Figure 8).

The clinical significance of QTc prolongation lies with the risk that TdP can degenerate into ventricular fibrillation, causing sudden cardiac death. This progression is more common with long episodes of TdP, but it has also been related to QTc interval length.[18] It has been estimated that each 10 msec increase in QTc corresponds to a 5-7% exponential increase in risk for TdP.[19] Another study showed that 89.5% of drug-induced TdP occurred when QTc was greater than 500 msec.[20] In general, TdP is rare when QTc is <500ms, accounting for less than 10% of all cases.[20]

Several studies have shown a positive correlation between increased QTc length and mortality, reinforcing the need to take action when a prolonged QTc is identified.[21,22] In a study by Haugaa *et al*, mortality from any cause for patients with QTc of 500ms or greater was 19% (87 out of 470) compared to 5% for those with QTc less than 500ms (total 51,434 patients) ($p<0.001$).[21] Specifically, results showed that the QTc interval length was a significant predictor of mortality with a hazard ratio of 1.13 (1.12-1.14, $p<0.001$), meaning patients with a prolonged QTc interval are 13% more likely to experience death than those with a normal QTc interval length.[21]

4.2. Initiation of TdP: Mechanism of Early After Depolarizations

There is a characteristic short-long-short cycle seen on the ECG preceding episodes of TdP (Figure 8). The first short cycle is the pre-initiating cycle due to one or several premature ventricular or atrial extrasystoles. The following cycle is long as a normal sinus rhythm recovers from overdrive suppression (one SA node influx could not conduct to the ventricle); the QT interval associated with this cycle is very long. Due to the prolonged QT associated with this cycle (and prolonged plateau phase of the ventricular myocytes' APD), an early after depolarization (EAD) may occur, displaying as a second short cycle on the ECG[1,18] (Figure 9). This EAD will initiate the ventricular tachycardia.

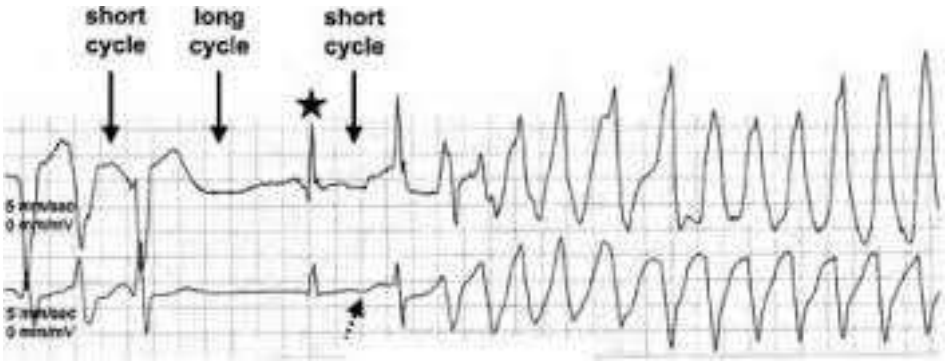


Figure 9. Characteristic short-long-short cycles associated with the initiation of Torsade de pointes.

It was first shown by Roden in the 1980's that as the action potential prolongs, specifically during the plateau phase, there is risk for an EAD: a second, premature ventricular depolarization. There are currently three proposed mechanisms by which an additional inward current causes triggered upstrokes (EADS) in the ventricular myocyte's action potential (Figure 10). First, and by far the most widely accepted, is the hypothesis that EADs are due to influx of Ca^{2+} through L-type calcium channels.[23] Two other proposed mechanisms suggest the involvement of the Na^{+}-Ca^{2+} pump and the late Na^{+} channel.[24] These mechanisms are important to consider when trying to prevent TdP. For example, if a medication prolongs the QTc interval but also prevents Ca^{2+} entry through the L-type Ca^{2+} channels, such as amiodarone, it may be less likely to produce EADs and TdP. It is important to consider medications' effects on late Na^{+} currents, for similar reasons.

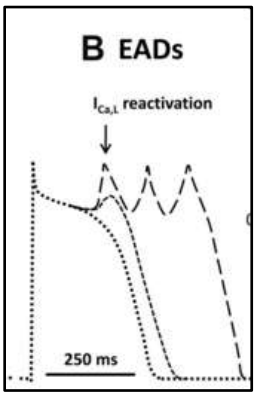


Figure 10. Induction of EADs when APD is prolonged. EADs are due to a reopening of Ca^{2+} channels leading to Ca^{2+} influx.

There is very little predictability regarding the time at which EADs or TdP will develop when starting a new medication. A study was conducted along these lines, and there was wide variation found in the timing of onset of arrhythmia after starting oral therapy that may have contributed to TdP. In the study, 18% of patients had an arrhythmia develop within 72 hours of starting oral therapy, 42% developed within 3-30 days, and 40% occurred >1 month after starting oral therapy[25]. Thus, it is important to consider the risk of TdP, regardless of when patients began therapy with a potentially torsadogenic medication.

4.3. Estimating Risk of TdP

Age – Rijnbeek *et al.* showed that women over their entire lifetime have a QT that is 5-10 msec longer than seen in men, although the difference may get smaller with age.[26] As men age, their QT interval lengthens, with an overall difference of 10-15 msec from younger males[26]. This was confirmed by a study done by Keller *et al*. which found that there was no difference in QTc values in a sub-group analysis in either gender over the age of 50 (i.e. women only have comparatively longer QTc at younger ages).[27] Thus, both genders should be assessed for lengthened QTc intervals at ages above 50 years.

4.3.1. Female gender - Women accounted for 67.2% of all TdP cases in a study done by Bednar, *et al*[20]. Liu *et al* showed that administering dihydrotestosterone to orchiectomized male rabbits shortened the QTc with no effect on QRS.[28] This is consistent with the theory that the sex difference in QTc interval is due to QT shortening in males as they produce increasing levels of testosterone during puberty, rather than a lengthening of QTc in females during their reproductive years.[29] Kaab estimated that around age 50, men and women have similar QTc intervals again.[30] While there is a difference in baseline QTc interval, both sexes were found to respond similarly when given QTc-prolonging medications. Vicente *et al.* found no difference in the degree of QTc prolongation between sexes after administration of dofetilide, quinidine, ranolazine or verapamil, all of which have high risk of prolonging the QT interval.

4.3.2. Bradycardia - May be person-specific, or may be induced by medications. For example, use of beta-blockers may lead to underestimating the QTc interval, and thus underestimating a patient's risk of TdP.[31] Additionally, I_{Kr} blockers prolong the repolarization time more at slower heart rates, thus compounding the risk of prolonged QTc.[31] At slower heart rates, there is increased heterogeneity of repolarization, which in turn increases risk of proarrhythmias.[32] Bradycardia, pause and the short-long sequence seen frequently before initiation of TdP also increase the heterogeneity of repolarization times, increasing the likelihood of reentrant excitation.[1]

Physiologically, at slower heart rates, there is a longer interval between beats, hence a longer QT. In general, the risk of Torsade de Pointes increases with heart rates < 50-60 bpm.[1] Practitioners must be aware that medications that can diminish heart rate, such as beta-blockers and acetylcholinesterase inhibitors, may contribute to increased risk.

4.3.3. Hypokalemia – Low extracellular potassium (clinical hypokalemia) paradoxically prevents sufficient potassium current to flow out of the cell through I_{Kr} or I_{Ks}, which prolongs the action potential, increasing risk for TdP. Two proposed mechanisms are via enhanced channel inactivation or exaggerated competitive blockage by Na^+.[33] In other words, Na^+'s typical inhibitory effect on K^+ channels may become more apparent when there is less competition from K^+. The second mechanism relates to the fact that inactivation of K^+ channels increases inversely with extracellular K^+ levels. This means hypokalemia will cause more K^+ channels to be in the inactivated state and as such, fewer will be available to transfer K^+ out of the cell during the action potential. Hypokalemia may also increase drug-binding to the channel, resulting in prolonged repolarization.[34,35]

4.3.4. Hypomagnesemia – Magnesium is a cofactor for appropriate functioning of the voltage-gated K^+ channels. With low Mg^{2+} levels, mechanistically there may be overall less functional I_{Kr} and/or I_{Ks}, which could prolong the action potential. Kannankeril *et al.* hypothesize that Mg^{2+}'s role in increasing risk of TdP is due to its modulatory effects on L-type Ca^{2+} channels.[1] Generally, higher Mg^{2+} levels decrease the inward Ca^{2+} current, shortening phase 2 (plateau) of the action potential.[37] With less Mg^{2+}, there may be less inhibition of L-type Ca^{2+} channels (more functional Ca^{2+} channels), which would prolong the action potential.. Notwithstanding the exact mechanism, intravenous Mg^{2+} are often successful in practice to treat TdP.

4.3.5. Diuretics – As discussed above, electrolyte disturbances, including hypokalemia, can predispose a patient to TdP. The most commonly implicated are thiazide-type and loop diuretics, due to their propensity to induce hypokalemia. Indapamide has been reported to inhibit I_{Ks} in addition to causing hypokalemia, and it has been associated with cases of TdP.[38,39] This blockage of K^+ current through I_{Ks} can be most detrimental when coadministered with an agent that blocks I_{Kr}, thus rendering both K^+ efflux mechanisms

inadequate. While triamterene can prevent hypokalemia, it has been associated with significant block of I_{Kr} and I_{Ks}.[40] Thus, it must be considered in the overall risk picture.

4.3.6. Medications that Affect Cardiac Repolarization - Class IA and Class III antiarrhythmics are used therapeutically to prevent reentrant arrhythmias. This can be accomplished through extending the action potential's duration, causing a lengthening of the refractory period, as depicted by the QT interval on a surface ECG. However, extending the QT interval too long may add risk of early afterdepolarizations (EADs). For example, quinidine (Class IA), dofetilide (Class III) and sotalol (Class III) cause TdP in 1-5% of patients.[41] Amiodarone routinely prolongs QT, but rarely causes TdP, as it also blocks L-type Ca^{2+} currents, decreasing the likelihood of EAD formation.[42] A prospective clinical trial designed to investigate other mechanisms of TdP risk, demonstrated that blocking the late Na^{+} current (decreasing the overall entry of positive charges and shortening the APD) can offset some of the QTc prolongation effects of medications.[43]

Many medications that are associated with QT prolongation are implicated due to block of $I_{Kr.}$ It has been shown that most drugs that block I_{Kr} do so by binding to the intracellular domain.[24] Some of the medications removed from the market due to these concerns include fenfluramine/dexfenfluramine (Sept 1997), terfenadine (Feb 1998), sertindole (Dec 1998), astemizole (Jun 1999), grepafloxacin (Nov 1999), and cisapride (July 2000). Since this time, the FDA has required thorough QT studies as part of the approval process, generally comparing the novel agent to an agent with known QT-prolonging properties, moxifloxacin, as discussed below.

Assessing a medication's impact on the movement of potassium ions through I_{Kr} is critical for gaining a true understanding of the risk of Torsade de Pointes. While it is the functional mechanism of action for Class IA and Class III antiarrhythmics, many other non-cardiovascular medications can block this current, prolonging ventricular repolarization, and increasing risk for Torsade de Pointes.

List of IKr blockers.

Astemizole	Terfenadine	Dofetilide
Cisapride	Ibutilide	Sertindole
Pimozide	Droperidol	Haloperidol

Domperidone	Iloperidone	Risperidone
Dronedarone	Ziprasidone	
Clomipramine	Rosuvastatin	

A specific example where a medication blocks I_{Kr} but does not increase risk of TdP is with ranolazine. Ranolazine blocks I_{Kr}, but it prevents experimental TdP potentially due to its inhibitory effect on Na^+ influx during the plateau (Phase 2) of the action potential. QTc prolongation due to I_{Kr} effects may also be due to impaired I_{Kr} component trafficking (moving protein components to the cell membrane where they can have activity), where there is less functioning I_{Kr} channels to transfer the K+ channels out of the cell.[32]

Medications that prolong the QT interval less than 10msec are generally not cause for concern regarding QT-related safety.[32] Interestingly, moxifloxacin is generally considered a positive control for producing QT prolongation even though it prolongs QTc by only 7-10msec. This highlights that FDA-approved medications administered alone may not show significant QT prolongation. Yet under conditions of drug-drug interactions, where metabolism is impaired, a medication may exhibit significant levels of QT prolongation, such as with terfenadine. Thus, we believe that even small increases in QTc upon administration of a given medication should be regarded with much caution.

4.3.7. Pharmacokinetic and Pharmacodynamic Interactions - When metabolism is inhibited, medications will have higher concentrations throughout the body, including the heart. Zeltser *et al* found that roughly 35% of 249 patients experiencing TdP from non-cardiac drugs had a potential metabolic interaction.[25] It is also important to take into consideration the patient's renal function, since medications like sotalol and dofetilide, which are primarily eliminated by the kidneys, will have increasing concentrations in proportion to loss of kidney function.[46] It is imperative to also evaluate over-the-counter medications (OTCs) and non-prescription products, including those like cimetidine and grapefruit juice, to get an accurate picture of a patient's metabolizing enzyme functionality.[47]

Van der Sijs *et al* looked at drug-drug interaction alerts for potential risk of QTc prolongation and found that, compared to baseline, 31% of patients had QTc prolongation

to the extent that they were considered at risk for TdP. The average increase in QTc duration was 31msec. They also found that giving the prescriber the ability to override a QT-prolongation alert unfortunately did not result in subsequent recording of ECGs.[48]

It is also important to note that many compounds that are CYP3A substrates have similar capabilities of blocking $I_{Kr,}$ indicating the potential for structural similarities between the two proteins (CYP3A and I_{Kr}). Morisette *et al*, identified erythromycin, cisapride, droperidol, pimozide, sildenafil, thioridazine, and domperidone, as having these coexisting properties.[31]

4.3.8. Co-administration of K^+ Channel Blockers - General administration of more than one medication that can prolong the QT interval has been described frequently as a risk factor for TdP,[49] and many authors and regulatory agencies suggest that co-administration of medications that have potential to prolong the QT interval is contraindicated. However, there may be a maximum level of I_{Kr} blockade achieved by a single mechanism, whereby adding another agent with a similar mechanism will not add to the level of risk. For example, it has been demonstrated that when two I_{Kr} blockers are used concomitantly, there is no significant difference in QT interval length compared to using one I_{Kr} blocker individually (see Figure 8).[17] The story may get more complex as we co-administer medications with different QT-prolonging mechanisms, such as an I_{Kr} and an I_{Ks} blocker like indapamide,[50] triamterene,[40] or propofol (methanesulfonamide).[51] Since these medications are blocking two separate K+ channels, there can be an additive negative effect on the QTc interval.

INSERT NEW FIGURE FROM Fiset et al. as Figure 11

Looking at a single medication's properties alone is not sufficient; practitioners must review patients' entire medication regimens to assess for drug-drug interactions that may increase risk for Torsade de Pointes

4.3.9. Non-modifiable Risk Factors

Genetic risk factors have been studied by numerous groups and in a few large studies, but they lack specific and substantial evidence to demonstrate the role of genetics in drug-induced LQTS.[24,52-54]. The genetic variant with the most evidence for affecting drug-

induced LQTS is the KCNE1 mutation D85N, which impacts I_{Ks} function. The odds ratio of having this unfavorable mutation is between 9-12.[55] Kaab *et al.* found that the *KCNE1 D85N* mutation predicted drug-induced LQTS with an odds ratio of 9.0 (95% confidence interval 3.5-22.9). This study looked at drug-induced LQTS cases in European countries, where population controls were all from Germany.[56]

4.3.10. Effect of co-morbidities on QTc interval

Patients with heart failure and left ventricular hypertrophy have an up-regulation of Ca^{2+} channels[57] and down-regulation of K^+ channels,[58] which may contribute to prolonged action potential duration, thus a prolonged QT interval. In heart failure, the I_{to} current is reduced, so adverse effects on other mechanisms of repolarization, such as I_{Kr} and I_{Ks} may be more pronounced.[59]

Keller *et al.* in 2016 reported that QTc prolongation was associated with a variety of clinical conditions including: congestive heart failure, ischemic cardiopathy, diabetes, renal failure, arrhythmias, hypothyroidism and bradycardia.[27] Patients with diabetes are at risk of TdP due to cardiovascular complications, nephropathy, acidosis that affects electrolyte balance, and polypharmacy. It was also shown that PI3K signaling is decreased in mouse models of diabetes, which may alter I_{Kr} trafficking to the membrane.[60]

Situations that may precipitate electrolyte disturbances may be a preliminary indicator of risk, such as severe dieting or eating disorders, depressed/mentally ill patients, acidosis (i.e. in patients with diabetes), and renal insufficiency.[47]

5. Prevention of LQTS and TdP

The primary management strategy of drug-induced LQTS should be prevention. It has been estimated that one death may be prevented by screening 3000 patients with an ECG at admission to a Psychiatric Hospital of Geneva.[61] Overall, TdP has a mortality rate of 15% in the inpatient psychiatric population.[62] If QTc was 500ms+ and there were at least 4 QT-prolonging medications or QT-prolonging electrolyte abnormalities present, mortality was 40%.[21]

6. Drug-specific Long QT-JT Index

There have been multiple groups attempting to identify distinct drug risk of TdP as well as risk scores for individual patients. As was referenced earlier, Credible Meds gives individual medications a qualitative assignment based on available clinical evidence. (www.crediblemeds.org) Through the use of Adverse Drug Event Causality Analysis (ADECA™), the CredibleMeds® Team works to classify drugs as "known risk", "possible risk", or "conditional risk" with approval from their Advisory Board, as seen below.[63]

> ***Risk of TdP:*** *Substantial evidence supports the conclusion that these drugs prolong QT intervals and have a risk of TdP when used as directed in labeling.*
>
> ***Possible risk of TdP:*** *Substantial evidence supports the conclusion that these drugs can cause QT prolongation but there is insufficient evidence that the drugs, when used as directed in labeling, have a risk of causing TdP.*
>
> ***Conditional risk of TdP:*** *Substantial evidence supports the conclusion that these drugs prolong QT and have a risk of developing TdP but only under certain known conditions (e.g. excessive dose or overdose, or being the index or interacting agent in a drug-drug interaction).*

This process assesses available laboratory and clinical evidence, including Adverse Event Reporting System (AERS) hosted by the FDA, laboratory research reports, and thorough QT trials or clinical trial data. One of the major drawbacks of this method is it cannot predict a novel drug's risk of TdP; it is dependent on clinical trial reports and historical cases of such significant adverse effects.

Two groups have created a more quantitative measure of risk. Redfern *et al.* created a model using preclinical electrophysiological data to predict risk of QT prolongation. They took into account the following factors: hERG (or I_{Kr}), cardiac action potential duration (at 90% repolarization), QT prolongation in dogs compared against QT effects and reports of TdP in humans for 100 drugs, and free plasma concentrations during clinical use ($ETPC_{unbound}$). The results from analyzing fifty-two drugs from five classes reinforced the notion that most drugs associated with TdP in humans are also associated with hERG block at concentrations at or near clinically relevant levels, based on approved dosage guidelines. In order to avoid overlap between the clinically relevant C_{max} and the hERG

IC_{50}, the researchers recommend a separating the two by a 30-fold margin during the drug-development phase. A second group from Texas developed the MICE (Multiple Ion Channel Effects) model and analyzed other ion currents beyond just I_{Kr}/hERG. They found that including a drug's effects on Ca^{2+} current (Cav1.2) together with I_{Kr} provided a more sensitive and specific model that could be used to predict torsadogenic potential independent of effective therapeutic plasma concentrations. They evaluated models that incorporated Na^{+} current as well, but these models were not as successful.

Our work has taken a more comprehensive approach to include additional factors that may influence a medication's likelihood of causing drug-induced Long QT Syndrome or TdP. The Long QT-JT Index takes into account the scenario where a medication has the greatest chance of causing TdP – when a medication is the most "risky". The following factors are considered in our model and are specific to each medication:

1. IC_{50} for block of I_{Kr} or I_{Ks}
2. Nav1.5 (sodium) current
3. Cav1.2 (calcium) current
4. C_{max} at a test Dose
5. Maximum daily dose
6. Extent of protein binding
7. Drug-drug interaction coefficient (DDIC)

As explained in the "Risk Factors" section, each of the ion currents may increase or decrease a drug's propensity to cause TdP. The Drug-Drug Interaction Coefficient takes into account the pharmacokinetics of the medication: whether it has a high extraction ratio (low bioavailability) or low extraction ratio (high bioavailability). This is important since changes in concentration will occur with varying magnitudes, with the percent change in concentration calculated per the equations below:

- High extraction drugs = 1/F
- Low extraction drugs = [100/(100-MP)], where MP is the relative contribution of major metabolic pathways to drug clearance (CL) as:

$$CL = CL_{ren} + CL_{1A2} + CL_{2B6} + CL_{2C9} + CL_{2C19} + CL_{2D6} + CL3_{A4} + CL_{3A5} + CL_{transporters} + CL\ldots$$

For example, mexiletine has F=95% (low extraction ratio, high bioavailability) and 75% is cleared by CYP2D6. If the CYP2D6 enzyme is inhibited, its concentration could increase by 100/(100-MP), or 100/(100-75), roughly equivalent to a 4-fold increase in mexiletine concentration over the course of multiple doses.

On the other hand, simvastatin has F=5% (high extraction ratio, low bioavailability). If mechanisms underlying this low bioavailability are inhibited (CYP3A4 enzyme, transporters such as SLCO1B1, favored absorption), its concentration could increase by 1/F, or 1/0.05, roughly equivalent to a 20-fold increase in simvastatin concentration almost immediately.

In validating the Long QT-JT Index, we compared the quantitative value calculated for each medication with its propensity to cause TdP in the literature, according to the classification by CredibleMeds. We would hope to show that the lowest Long QT-JT Index values (X-axis) correspond to the medications with known TdP risk according to CredibleMeds (colored red). This is depicted below in Figure 12.

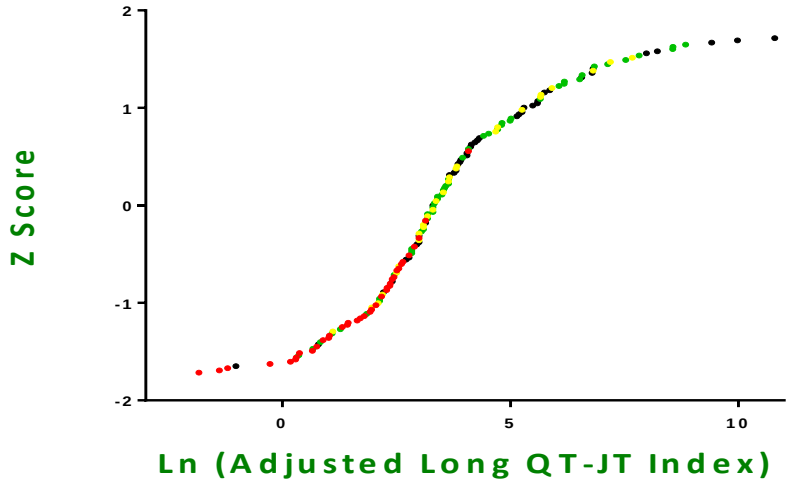


Figure 12. Colors correspond to classification by CredibleMeds, where red = Known TdP Risk, yellow = Possible TdP Risk, green = Conditional TdP Risk, and black = Unclassified at the time of publication.

The sensitivity of the Long QT-JT Index is 86.8%, meaning it captures roughly 87% of all medications that have been clinically shown to have effects on the QT interval and/or

TdP. The specificity of the Long QT-JT Index is 68.1%, meaning it captures more medications as high risk (low score) than CredibleMeds classifies as being Known TdP. There may be a few reasons for this. First of all, the Long QT-JT Index captures the maximum risk scenario, where a drug is administered at a maximal dose and under conditions of a drug interaction. CredibleMeds may not be taking this into account (or these medications may mostly fall under their "conditional TdP risk" category). Another possible explanation is that there is limited evidence published at this time to guide CredibleMeds' classification strategy, and their strategy is dependent on cases occurring and being published in order to classify medications with high risk. Our tool allows for the prediction of risk based on medication-specific properties and may be superior to other methods.

Overall, it will be beneficial to pharmacists, prescribers, and regulatory agencies to have a pre-emptive, quantitative view of what could occur under maximal risk conditions.

7. Patient-specific LQTS Score

While our medication-specific risk index will be helpful when scrutinizing a single medication, the reality is that our patients take many medications and have individual risk factors that may predispose or protect them from QT prolongation and TdP.

It has been demonstrated that risk alerts may be beneficial if they are specific to the given patient's scenario.[64] Woosley *et al.* have provided example alerts to be embedded in clinical decision support systems with risk factors, potential adverse outcomes, and alternative treatments or prerequisites to safe treatment, but they have not yet demonstrated its clinical utility.[65]

Only two groups to date have created risk scores that take into account various factors that may cause QT prolongation and increase risk of TdP.

Tisdale *et al.* created a risk score based on odds ratios for several factors, including: female gender, diagnosis of myocardial infarction, sepsis, left ventricular dysfunction, administration of a QT-prolonging drug, 2 QT-prolonging drugs, loop diuretic, age >68 years, K^+<3.5mEq/L, and admitting QTc>450msec.[66] Based on the relative contributions

of each risk factor and point allocation, low, moderate and high risk ranges were created. This study showed equal risk of QT prolongation between taking one QT-prolonging medication and two or more QT-prolonging medications. They did not take into account potential drug-drug interactions. Their study population was limited to patients in the cardiac intensive care unit, thus it may be difficult to generalize the results to another population.[66]

Haugaa *et al* created a risk score weighing each of the following categories equally: female sex, clinical diagnoses and conditions that may influence the QT itnerval, QT-prolonging electrolyte disturbances (hypokalemia, hypomagnesemia), and QT-prolonging medications according to CredibleMeds.org. The range of risk scores (Pro-QTc scores) they created was 0-9, with a mean of 3.1. Their results showed that a Pro-QTc score of 4 or greater predicted mortality with a HR of 1.72 (1.11-2.66, p<0.001).[21] This means that their pro-QTc score could be used as an independent predictor of mortality, and it would be helpful in identifying high-risk patients in a hospital setting.

Our group has developed a patient-specific LQTS score that is dynamic, based on the patient's current conditions and concomitant medications. The risk factors are included based on the evidence above, and are assigned points as follows:

Risk Factor	Description	Points Range
1	Male or female gender, also includes age for males	0-0.5
2	Heart Rhythm: sinus rhythm, AFib, Sick Sinus Syndrome, Pause, Heart Rate, Beta-blocker usage	0-1
3	Hypokalemia (K<3.5 mEq/L); use of triamterene	0-1
4	Hypomagnesemia (Mg <1.5 mEq/L)	0-1
5	Diuretics	0-1
6	Antiarrhythmics: Class IA, Class IC, Class III; amiodarone	0-9
7	QT-prolonging drugs and drug interactions	0-12
8	QTc interval (Cut-offs: <450, <475, <500, <550, 550+msec)	0-10

We have validated this scoring mechanism against literature cases of known TdP. We identified more than 50 cases of documented TdP due to medication use and/or medication interactions and calculated the patient's risk score based on the above algorithm. We found that in these cases, the risk scores are generally above 10, whereas in a sample group of the patients we service (n=7500), the risk scores are generally less than 10 (Figure 13).

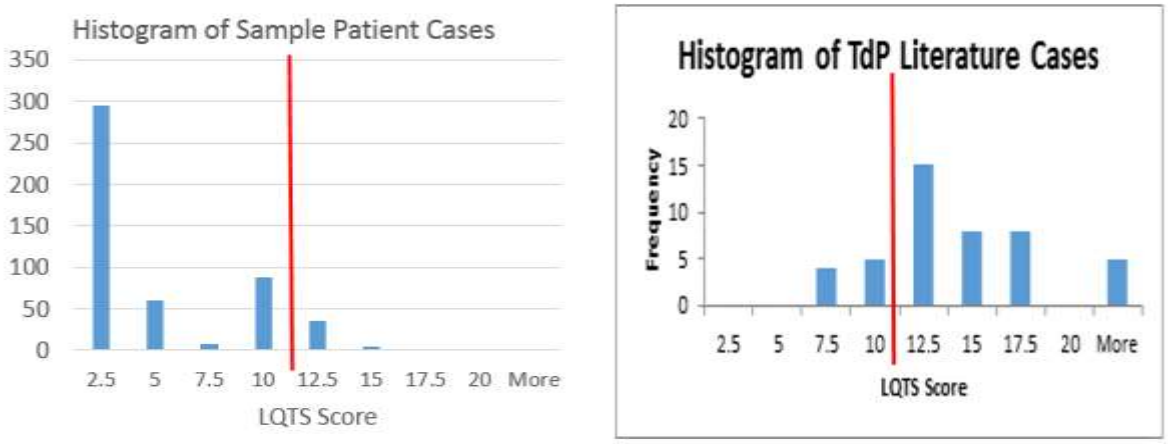


Figure 13. Distribution of Patient-specific LQTS Score for control patients (n=7500, left) and literature cases of known TdP (right). Bins are up to and including the number on the X axis (i.e. the bin 2.5 represents all scores 0-2.5; the bin 5 represents all scores 2.6-5).

8. Management of LQTS and TdP

Once QTc prolongation has been identified, the primary treatment is identification and discontinuation of any precipitating drug.[67] Magnesium sulfate infusion may be administered as a 2 gram IV bolus, followed by IV infusion of Mg^{2+} at rate of 2-4mg per minute.[18] This protocol was effective even when Mg^{2+} levels were within normal limits at the time of the arrhythmia.[68]

Another strategy consists of increasing heart rate and indirectly shortening APD. This can be rapidly achieved by inserting a pacing catheter in the right ventricular chamber attached to an external pacemaker. Finally, an Implantable Cardioverter Defibrillator (ICD) may be used to pace the heart rhythm and prevent bradycardia leading to an increased QTc interval. It has the added benefit of delivering an electric shock if an arrhythmia is detected.

Conclusion

QT prolongation is clinically relevant due to the risk of deterioration into TdP, ventricular fibrillation, and sudden death. It is crucial to recognize the risk factors of QTc prolongation early on in the patients we are treating so we can prevent this potentially fatal outcome. We must not analyze these risk factors in a silo; rather, we must take into account drug-drug interactions as well as drug-disease interactions that may affect drug metabolism and disposition in a negative way. In the future, a quantitative way to predict the risk of individual medications and medications in individual patients would be critically beneficial to empower prescribers and pharmacists to make informed decisions.

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