The QT Interval in Clinical Practice

SECTION 4: When and how to measure the QT interval

The objective of Section 4 of The QT Interval in Clinical Practice is to discuss when and why to measure the QTc interval, the role of QTc risk assessment in Clinical Decision Support and QTc measurement in clinical research.

When & Why to Measure the QTc:

The QTc interval can be measured to detect patients at high risk of sudden cardiac death. These patients fall in two general categories, those with inherited channelopathies such as congenital Long QT syndrome or those with acquired prolonged QTc which serves an independent predictor of sudden cardiac death. Acquired prolonged QTc has many potential causes, for example, drug-induced QT prolongation, electrolyte disorders or cardiac disease such as a previous myocardial infarction.

Diagnosis of Congenital Long QT Syndrome:

Accurate measurement of the QTc is an essential element in the diagnosis of the congenital Long QT Syndrome, a condition that is associated with the development of torsades de pointes and sudden death. However, accurate diagnosis requires more than just an accurate measurement of QTc.

This chart shows the Schwartz-Ackerman Score that has been developed to provide proportional weighting to the other diagnostic features of this illness.

			Points
Electrocardiographic findings[a]			
A	QTc[b]	≥480 ms	3
		460–479 ms	2
		450–459 (male) ms	1
B	QTc[b] 4th minute of recovery from exercise stress test ≥480 ms		1
C	Torsade de pointes[c]		2
D	T-wave alternans		1
E	Notched T-wave in three leads		1
F	Low heart rate for age[d]		0.5
Clinical history			
A	Syncope[c]	With stress	2
		Without stress	1
B	Congenital deafness		0.5
Family history			
A	Family members with definite LQTS[e]		1
B	Unexplained sudden cardiac death below age 30 among immediate family members[e]		0.5

Acquired prolonged QTc and Sudden Death Risk – 1978:

Acquired QTc prolongation is also associated with sudden death as shown by the early data from Schwartz and Wolf in 1978. These authors found that the presence of an abnormally prolonged QTc interval in patients with a prior myocardial infarction was an independent predictor of sudden death.

This is but one of many studies that have found an association between QTc prolongation and adverse clinical outcomes (sudden death, cardiac arrhythmias and all-cause mortality). The following segments reference these studies.

QTc and Mortality: Healthy Persons – 1991:

In 1991, Schouten et al. reported that a prolonged QTc significantly predicted cardiovascular death and all-cause mortality in a population of apparently healthy Dutch men.

QTc and Mortality: Healthy Men – 1994:

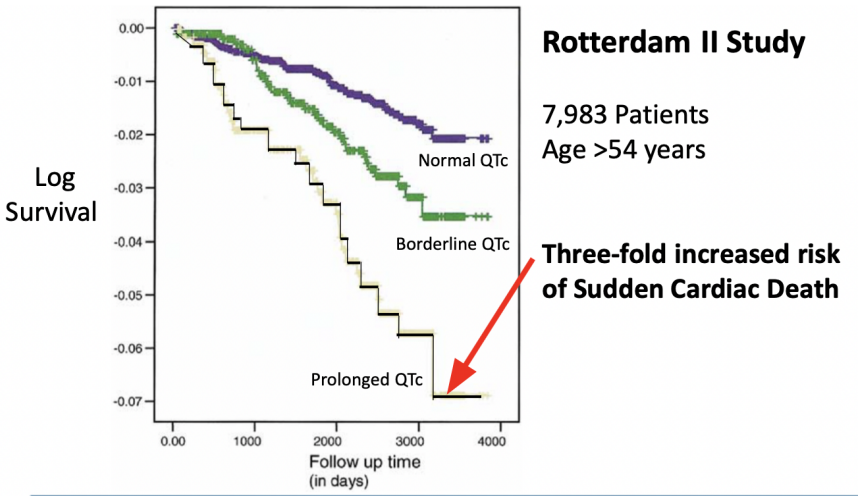
In 1994, Dekker and investigators in the Netherlands found that higher QTc values were associated with a higher risk of cardiovascular, ischemic and all-cause mortality in what has become known as the Zutphen study.

QTc and Mortality: Elderly – 1999:

The Rotterdam study, published in 1999, confirmed the earlier results from the Zutphen Study. This study included over 5,000 men and women age 55 and older. Patients in the highest quartile of QTc intervals had a 70% higher all-cause mortality and 95% higher cardiac mortality compared to those in the lowest quartile. The increased risk associated with prolonged QT for cardiac death was more pronounced in women than in men.

Prolonged QTc: Sudden Cardiac Death – 2006:

In the Rotterdam II study published in 2006, almost 8,000 patients aged 55 or older were followed for an average of 6.7 years and stratified by baseline QTc. A borderline increased QT was defined as 431-450 in men or 451-470 in women and prolonged QTc was defined as ≥ 451 in men and ≥471 in women.



As shown in the Kaplan-Meier log survival plot, compared to those with a normal QTc, the incidence of sudden cardiac death was higher in patients with borderline increased QTc and three-fold higher in those with a prolonged QTc. The results of an analysis of covariates led the authors to conclude that QTc prolongation is an independent predictor of sudden death in an elderly population.

Prolonged QTc: Sudden Cardiac Death in CHF – 2013:

Similar findings have been reported by Vrtovec et al. in patients with congestive heart failure. Patients who had a >10% increase in QTc at 3 months after diagnosis of heart failure were at 2.9-fold greater risk of sudden cardiac death. Again, an increased QTc was found to be an independent predictor of sudden cardiac death.

When & Why to Measure the QTc:

Next, we will discuss the role of QTc measurement in the diagnosis of the clinical syndrome: Torsades de Pointes.

Torsades de Pointes (TdP):

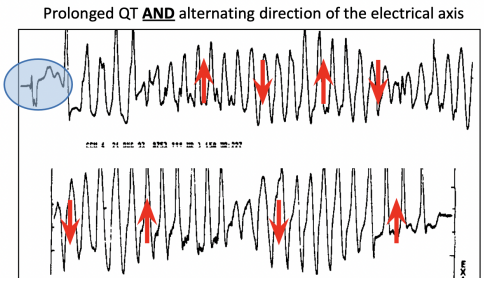
First, what is Torsades de Pointes?

QTc prolongation, whether inherited or acquired (induced by drugs, electrolyte disorder, hypothermia, etc.), has been associated with this ventricular arrhythmia which was first described by the French cardiologist, Francois Dessertenne in 1966. He named the arrhythmia torsades de pointes, or “twisting of the points,” because of its characteristic pattern in which the direction of the R waves appear to rotate around the isoelectric line.

In 1964 Selzer and Wray were among the first to recognize this arrhythmia as a cause of syncope in patients who developed marked QTc prolongation during therapy with quinidine.

Torsades de Pointes Syndrome:

Today torsades de pointes is considered a clinical syndrome in which QTc prolongation (shown in the tracing with blue shading) is observed prior to the development of a rapid, polymorphic (continually changing shape) ventricular tachycardia that has the pattern described by Dessertenne.

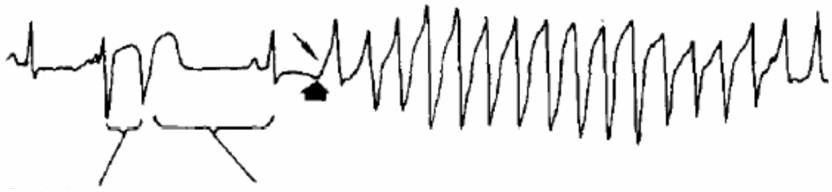


The R waves of the ventricular depolarizations (or “pointes” as Dessertenne called them) alternate, pointing upward, coming to a node and then pointing downward as the signal rotates (twists) about the heart’s electrical axis.

Pause-dependent Initiation:

In the 1980s, Roden et al. observed a characteristic of quinidine-induced torsades that has become recognized as a feature of torsades induced by other drugs and in many patients with congenital long QT syndrome (Viskin, Heart 83(6): 2000).

Roden noticed that the initiation of Torsades often has a pattern of short-long-short cycles.



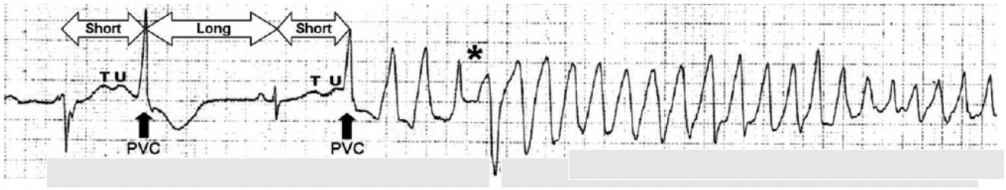
This slide shows a typical pattern in which a short cycle, he termed a “pre-initiating cycle, is followed by a longer initiating cycle. This has become known as pause-dependent initiation and is considered a characteristic but not required feature of the syndrome.

Characteristic Features of TdP:

In recent years, several consensus papers such as the one by Drew et al. from the American Heart Association and the American College of Cardiology in 2010 have brought clarity to our understanding of torsades de pointes and the characteristic features that help in its diagnosis.

This ECG tracing of an episode of methadone-induced TdP shows these features:

- First is the pathognomonic twisting of R waves around the isoelectric line.
- Second, the often-seen, short-long-short pattern of initiation
- Third, the “warm up” phenomenon in which the rate of the ventricular tachycardia accelerates
- Fourth, spontaneous termination (not seen in the tracing)
- And the essential feature, a pre-existing QTc greater than 500 msec



TdP Clinical Presentation:

The clinical presentation of TdP is highly variable and is influenced by the length of the bursts of polymorphic ventricular tachycardia. Brief bursts of TdP may only cause the patient to experience lightheadedness, dizziness, vertigo or palpitations. If the arrhythmia is longer in duration, hypo-perfusion of the brain can lead to loss of consciousness, syncope and/or seizures.

In many cases, the arrhythmia self-terminates, perhaps because the arrhythmia has caused hypotension that stimulates release of epinephrine, an endogenous, potentially therapeutic agent. Prolonged arrhythmia can degenerate into a sustained, potential lethal, ventricular fibrillation. If the patient is not being monitored by ECG during an episode of torsades, the most apparent clinical diagnoses may be epilepsy or simply sudden death.

Death – Result of drug-induced TdP?:

As discussed above, death is a potential outcome when a patient develops Torsades but it is not recognized as a frequent outcome. Torsades seems to be most often transient and self-limited.

Case series:		Percent
Amiodarone (i.v.)	0 / 4	0
Quinidine	1 / 28	4
Methadone	5 / 43	12
Sotalol	0 / 24	0
Azimilide	4 / 56	7
Dofetilide	7 / 89	8
Ibutilide	0 / 58	0
Terfenadine	2 / 25	8
		Average 6%

Death is not a frequent outcome.

This slide summarizes reports of torsades and shows the number of cases that were recognized to result in death. On average, only 6% of the reports of TdP with these drugs resulted in death.

1. Amiodarone: Shenthar J, et al Indian Heart J 2017;69:707-13.
2. Quinidine: Roden DM, et al. Am Heart J 1986;111:1088-93.
3. Methadone: Pearson EC, et al. Pharmacoepidemiol Drug Saf 2005;14:747-53.
4. Sotalol: Soyka LF, et al. Am J Cardiol 1990;65:74A-81A.
5. Azimilide: Pratt CM, et al. J Am Coll Cardiol 2006;48:471-7.
6. Dofetilide: Jaiswal A, et al. Indian Heart J 2014;66:640-8.
7. Ibutilide: Gowda RM, et al. Int J Cardiol 2004;95:219-22.
8. Terfenadine: Woosley RL, et al. JAMA 1993;269:1532-6.

Excess Deaths due to drug-induced TdP?:

There are very little data available that address the question of how many deaths occur due to TdP each year. Straus conducted a population-based case control study in the Netherlands and concluded that patients taking “non-cardiac” QT prolonging drugs had a three-fold greater risk of sudden cardiac death, which would translate to 320 excess deaths per year. The authors assumed many of these deaths were the result of TdP but acknowledged the lack of proof.

Higher TdP Incidence in Women:

One of the earliest recognized features of torsades was the higher-than-expected frequency of occurrences in women. This slide lists many of the drugs that have demonstrated a higher number of cases of torsades in women.

Cisapride	Pimozide
Disopyramide	Probucol
Erythromycin	Quinidine
Halofantrine	Sotalol
Ibutilide	Terfenadine
Pentamidine	Amiodarone
Bepridil	Astemizole

These data are limited by the lack of accurate information on relative exposure, that is, the relative numbers of men and women being treated with the drugs.

1. Pedersen HS, Elming H, Seibaek M, et al. Risk factors and predictors of torsade de pointes ventricular tachycardia in patients with left ventricular systolic dysfunction receiving Dofetilide. Am J Cardiol 2007;100:876-80.
2. Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA: The Journal of the American Medical Association 1993;270:2590-7.
3. Ebert SN, Liu XK, Woosley RL. Female gender as a risk factor for drug-induced cardiac arrhythmias: evaluation of clinical and experimental evidence. J Womens Health 1998;7:547-57.

Excess Deaths due to TdP?

If there are increased deaths due to TdP one would expect that the patients taking drugs known to be associated with TdP should have a greater death rate compared to those not taking drugs that can cause TdP.

Although the data are limited, the drugs shown here, Azithromycin, Clarithromycin, erythromycin, antipsychotics, levofloxacin, methadone and trimethoprim/sulfa are all drugs known to cause TdP and which have been found to be associated with an excess number of

deaths in large case-controlled population studies. All of these studies are limited by their inability to confirm whether any of the deaths were in fact due to torsades de pointes.

- Trimethoprim/sulfamethoxazole, CMAJ 2015;187:E138-E143.
- Clarithromycin, BMJ 2014;349:g4930.
- Levofloxacin, Ann Fam Med 2014;12:121-7.
- Erythromycin, NEJM, 2004;351:1089-96.
- Antipsychotics, Arch Intern Med 2004; 164:1293-7.
- Methadone, JAMA Intern Med 2015;175:420-7.
- Azithromycin, NEJM 2012;366:1881-90.

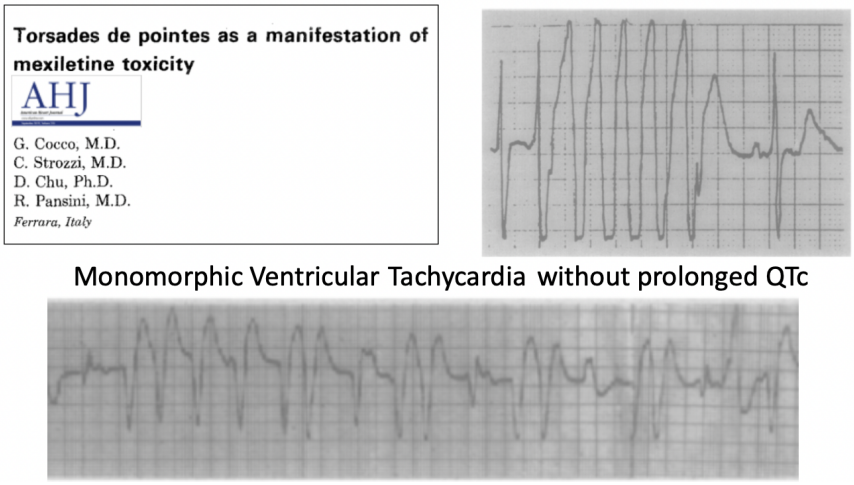
Higher TdP Incidence in Women:

A review of the literature by Othong et al. found that 69% of 292 cases of torsades were women. As will be discussed, numerous studies have reported that women have a greater sensitivity to the QT prolonging effects of drugs and that female sex is a consistent risk factor associated with excessive QT prolongation and TdP.

TdP - Often Misdiagnosed:

Another factor complicating estimates of the frequency of TdP is the possibility that it might be misdiagnosed.

This report is an example of a case reported as “torsades de pointes” that had none of the clinical features of TdP. The QT is not prolonged and the arrhythmia lacks the classic alternating pattern of polymorphic VT.



Monomorphic Ventricular Tachycardia without prolonged QTc

Because mexiletine is a sodium channel blocker that is actually known to shorten the QT interval, the correct diagnosis should be mexiletine-induced monomorphic Ventricular Tachycardia, not TdP.

Torsades de Pointes Epidemiology:

Although the pathogenesis of torsades is well understood, the epidemiology is not well characterized. There are several possible reasons. It is a relatively rare clinical event, and like any rare event, it takes a lot of time, informed surveillance, recognition and data capture to inform estimates of its frequency of occurrence.

Also, a correct diagnosis requires access to an ECG prior to and during an arrhythmic event to verify the presence of a prolonged QT and the characteristic pattern of twisting of the pointes. An ECG is often not available, especially for outpatients.

Even when the correct clinical diagnosis is made, there is no standard ICD-10 diagnosis code for recording TdP in the medical record.

Torsades de Pointes Frequency:

Nevertheless, there are some reports in the medical literature that provide some estimates for how often TdP is likely to be seen clinically.

Molokhia reviewed reports of Ventricular Tachycardia or sudden cardiac death in medical records in France and concluded that 5% were in fact drug-induced torsades. The authors estimated the incidence in France was approximately 10.9 per million per year and acknowledged that this is likely to be an underestimate. Sarganas reported a similar incidence, 1.5-2.4 cases per million per year in Germany. Vandeal estimated a frequency of TdP in hospitalized patients in Belgium to be 0.16 per thousand per year and Pickham reported that 6% of cardiac arrests in the ICUs at Stanford University Hospital were due to TdP. These data, obtained by retrospective analyses, have many limitations but provide rough estimates of the magnitude of the problem.

In summary, torsades is clearly a rare event in most clinical environments which suggests that efforts to prevent it will require greater understanding of the risk factors and which patients are at greatest risk.

1. Molokhia, Br. J. Clin. Pharmac. 2008; 66:386

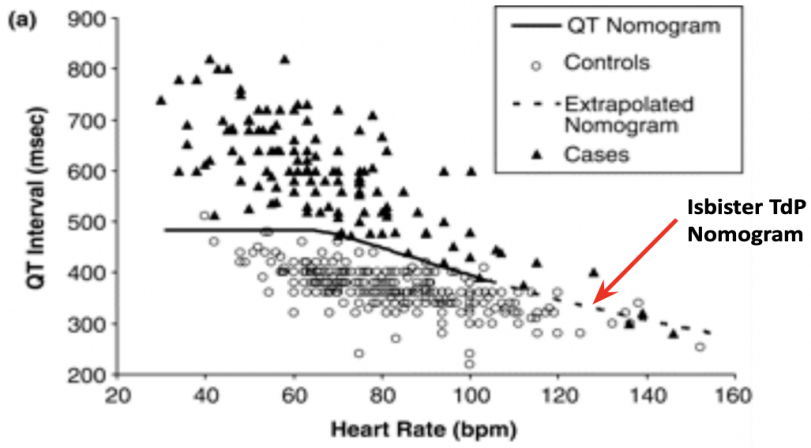
2. Sarganas, Europace 2014; 16;101
3. Vandael, Int. J. Cardiol. 2017; 243:511
4. Pickham, Crit. Care Med. 2012; 40:394

Prolonged QTc in Drug-Induced TdP:

QTc prolongation is a *sine qua non* for TdP but the question often arises, "How much prolongation is required for the presumptive diagnosis of TdP versus polymorphic VT?"

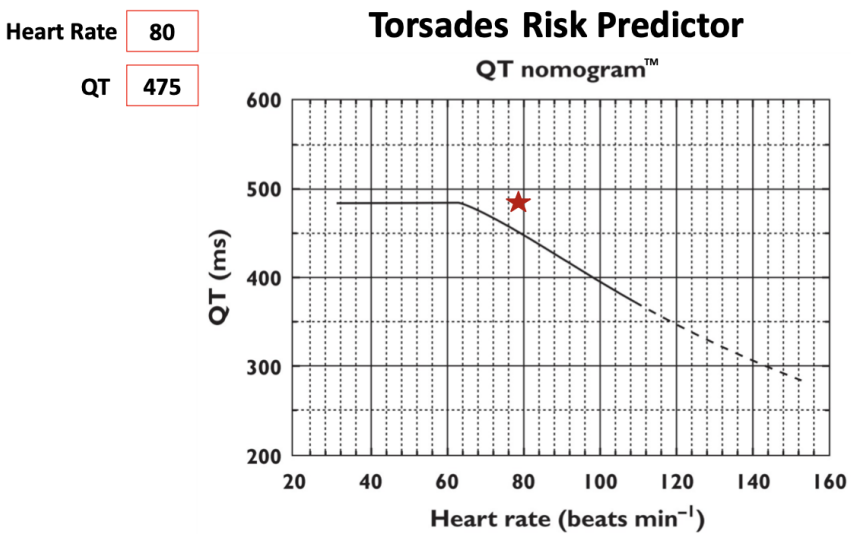
Isbister TdP Nomogram:

Although QTc prolongation is a required element of the TdP syndrome, many patients develop some QTc prolongation without developing TdP. When assessing a patient's risk of TdP or assessing the likelihood that a patient such as one with syncope may have had TdP as the cause, knowing the degree of QT prolongation could be helpful. Chan, et al. have examined reports of TdP and created a nomogram (the Isbister TdP Nomogram) to assess the predictive value of a prolonged QT.

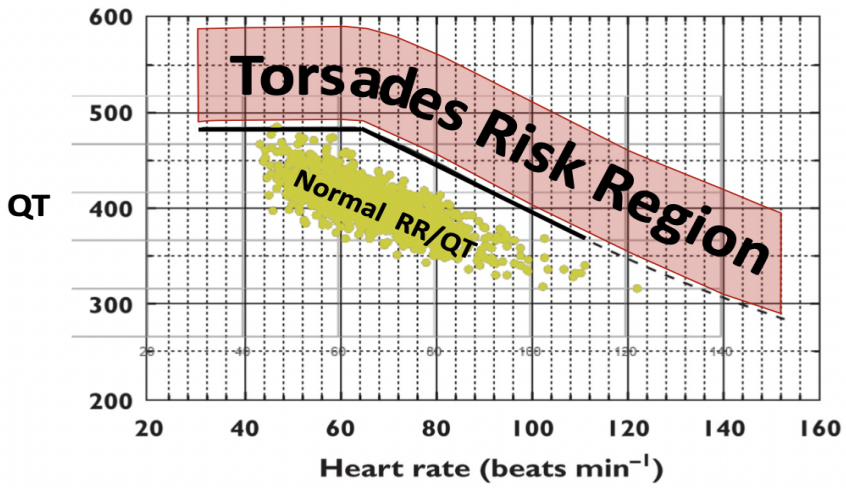


97% sensitivity and 99% specificity

This chart shows the QT and heart rate for 130 cases of drug-induced TdP (open circles) and compares them to the QT and heart rate for a control population of 318 patients who had overdosed with a non-cardiac drug (solid triangles). The nomogram (marked as the solid and dotted black line) distinguished cases of TdP from non-TdP cases with 97% sensitivity and 99% specificity. As can be seen, almost all of the open circles for TdP patients are above the nomogram (solid line). For heart rates higher than 100, the line is dashed because, in that region, there were fewer cases and the data points overlapped.



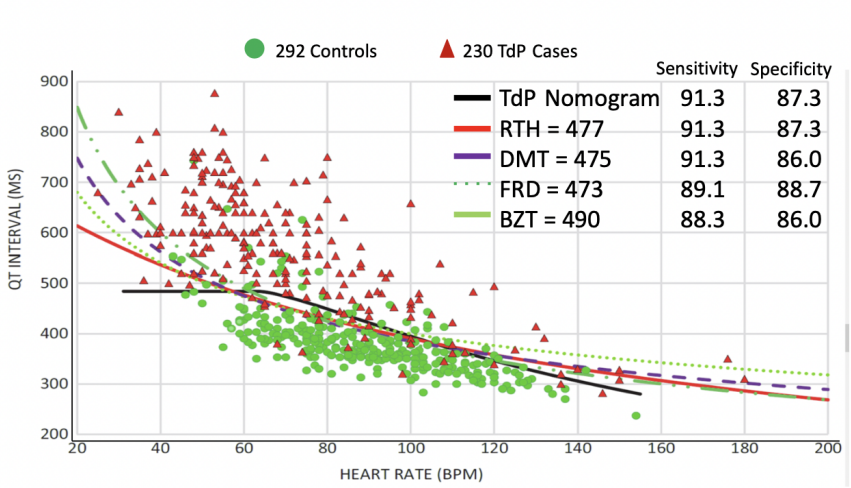
This chart demonstrates how the authors recommend that the Isbister Nomogram could be used as a risk assessment tool for drug-induced QT prolongation and/or TdP. For example, if a patient's QT value is 475 at a heart rate of 80 bpm, the data point (red star) would be above the nomogram line and thereby predict that the patient has a risk of TdP.



To assess the nomogram for its potential to have false positives, we tested data for QT-RR pairs of data collected from 1,330 healthy adults. All but two data points fell below the nomogram line indicating that the nomogram correctly identified most patients to be free of a risk of drug-induced TdP.

Isbister TdP Nomogram vs. QTc:

This chart shows data from another study that compared the sensitivity and specificity of the Isbister Nomogram to data using four different heart rate correction formulae. The investigators utilized QT-RR data for 230 cases of drug-induced TdP and compared them to a control population who had overdosed on QT prolonging medications but who did not develop TdP.



As can be seen in the upper right, the sensitivity and specificity for the various methods to predict TdP at its most accurate cut-off were very similar with the possible exception of the Bazett method which had a slightly lower sensitivity and required a slightly higher cutoff for QTc, i.e., 490 msec. The need to use this higher cut-off for Bazett corrected QTc values may be due to the over-correction associated with the method that yields higher values for QTc at heart rates below 60.

A general conclusion from these data might be that the nomogram is a rapid method to visualize a patient's relative risk of TdP, but it may be only slightly better statistically than using the usual clinical cut-off of 500 msec for QTc corrected by Bazett.

Beware the "½ RR rule":

Berling and Isbister have compared the Isbister Nomogram and the use of a 500 msec cut-off for Bazett or Fridericia rate-corrected data to a commonly used and popular method called the "½ RR rule." This rule states that the QT is abnormally prolonged if the QT is greater than half of the RR interval.

These investigators found that the rule had very low specificity which could lead to numerous false positive diagnoses and the potential for unnecessary treatment of many patients. They concluded that the ½ RR rule should not be used, especially when simple methods like the Isbister Nomogram or a cut-off of QTc >500 have such proven accuracy and similar ease of use.

When & Why to Measure the QTc:

Another reason to measure the QT interval is to detect high risk patients before they develop torsades.

Estimates of TdP Frequency by Drug:

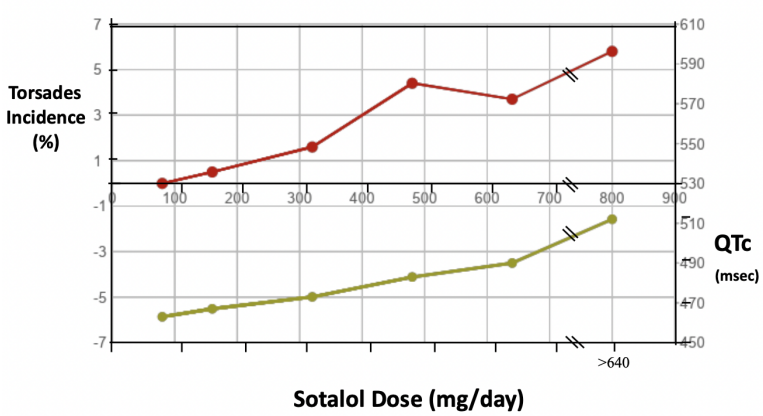
The estimates of risk for torsades with specific drugs are limited in their accuracy due to factors previously discussed. The most reliable data come from clinical trials where there is a control group for comparison. As shown in this list of drugs and their estimates from clinical trials, the incidence is highly variable from drug to drug.

Macrolide Antibiotics	< 0.0001%
Azimilide	1%
Amiodarone (i.v.)	1.5%
Dofetilide	2.4%
Ibutilide	3.9%
Sotalol	4.3%
Quinidine	~ 9%

1. Macrolides: Viskin, S., et al. JACC 2015;66(20):2185=88
2. Azimilide: Pratt CM, et al. J Am Coll Cardiol 2006;48:471-7.
3. Amiodarone: Shenthar J, et al. Indian Heart J 2017;69:707-13.
4. Dofetilide: Jaiswal A, et al. Indian Heart J 2014;66:640-8.
5. Ibutilide: Gowda RM, et al. Int J Cardiol 2004;95:219-22.
6. Sotalol: Soyka LF, et al. Am J Cardiol 1990;65:74A-81A.
7. Quinidine: Roden DM, et al. Am Heart J 1986;111:1088-93.

QTc and TdP Incidence: Sotalol:

Most of the estimates of the frequency of TdP induced by specific drugs are crude because most lack a randomized group for comparison. The estimates for Sotalol are much better than that for most drugs because during the drug's development, the FDA required careful surveillance and documentation of cases of torsades.



This chart is adapted from data in Sotalol's label and shows the almost linear dose-relationship for Sotalol's effect on QTc and the incidence of torsades during clinical development.

Drug Label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019865s019lbl.pdf

When & Why to Measure the QTc:

Another reason to measure the QTc interval is to be compliant with drug labels that contain recommendations from the Food and Drug Administration and drug manufacturers. Currently, 30 drug labels recommend that the prescriber check the QTc prior to initiating therapy and another 15 recommend that the QTc be monitored during therapy. 65 drug labels recommend monitoring the QTc under certain conditions such as in patients with heart failure or drug overdose.

The measurement of QTc is a rapid way to monitor exposure and response for some drugs, specifically anti-arrhythmic drug efficacy (e.g., Sotalol's antiarrhythmic efficacy is related to its effects on QTc). It can also be used to prevent toxicity from QT prolonging meds, e.g., preventing QTc prolongation that exceeds 500 msec or a 60 msec increase, preventing torsades de pointes or preventing sudden arrhythmic death.

QTc can also be used to detect electrolyte disorders in high-risk patients or to monitor the clinical response to electrolyte replacement.

In patients who develop a ventricular arrhythmia or syncope, the QTc can help detect inherited channelopathies such as those that cause the Short QT Syndrome in which the patient's QTc is less than or equal to 390msec. The inherited Short QT Syndrome is very rare and will not be covered in this presentation but has been associated with sudden death and ventricular arrhythmias. The congenital Long QT Syndrome is more common and is estimated to affect approximately 2,000-5,000 people in the US.

Acquired QT prolongation is the most commonly encountered form of LQTS and in clinical medicine is usually due to the effects of medications. Other causes of acquired QT prolongation are shown in the slide, i.e., hypokalemia, hypomagnesemia or hypocalcemia. Miscellaneous causes should also be considered, such as acute hemorrhagic stroke and hypothermia which have been documented to result in QT prolongation. Fever, liver failure, obesity and inflammation are among the many clinical conditions that have been associated with small increases in QTc interval.

A list of these clinical factors is maintained on the CredibleMeds website at: https://crediblemeds.org/ndfa-list/

The Role of QTc Risk Assessment in Clinical Decision Support:

We will now discuss the use of QTc Risk Scores in Clinical Decision Support systems designed to detect patients at high risk of torsades de pointes.

QTc Risk Scores:

Torsades is a rare clinical syndrome preceded by QTc prolongation. A person's risk of torsades can be influenced by many factors that contribute to risk by different degrees. QTc Risk Scores are designed to quantify an individual patient's relative risk of TdP.

Applications for QTc Risk Scores:

Most QTc Risk Scores are programmed in the electronic medical record as part of a Clinical Decision Support (CDS) System. Clinical Decision Support systems vary widely. Minimal CDS systems generate only "Alerts" that are interruptive and not patient-specific. Moderately complex CDS systems generate "Alerts" and provide general risk information. Complex CDS

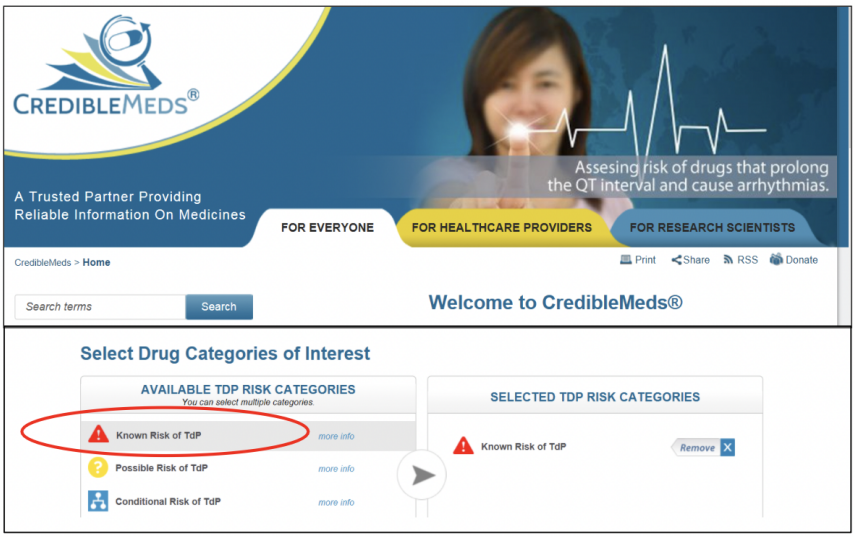
systems generate “Advisories” that include risk information and patient-specific management options for clinicians to consider.

Complex TdP CDS - QTc Risk Scores:

Most Risk Scores utilize a “Trigger” which usually initiates calculation of the score (e.g., Rx of drug with Known Risk of TdP). The Risk Score depends on risk due to drugs prescribed with the following criteria: the known risk of TdP drugs, the possible risk of TdP drugs, the drug metabolism inhibition and the dose (where data are available, e.g., citalopram, methadone). The Risk Score also depends on risk due to clinical risk factors (e.g., sepsis, electrolytes).

QTdrugs.org Lists:

All of the QT Risk Scores that have been developed for CDS and reported at this time have utilized the QTdrugs List that is maintained by AZCERT and made available on the CredibleMeds website as shown here.



All but one have used as a trigger to calculate a risk score, the prescription of a drug with Known Risk of TdP. The only exception was a study that used either a Known Risk or Possible Risk of TdP drug.

Clinical Risk Factors for Drug-induced TdP:

Underpinning the prediction of torsades risk is the multiple hit hypothesis which states that a person can have several risk factors that coincide to induce torsades.

It most often begins with exposure to a QT prolonging drug and requires secondary factors such as bradycardia, hypokalemia (or other electrolyte disorder), female sex, a drug that blocks metabolism of a QT prolonging drug, the exposure to additional QT prolonging drugs, underlying heart disease (such as heart failure, left ventricular hypertrophy or atrial fibrillation) and in some cases silent or overt genetic polymorphisms that result in channelopathies.

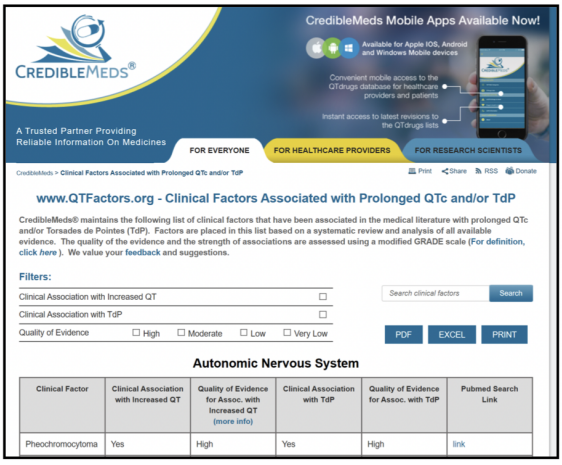
Repolarization Reserve Hypothesis:

Roden has refined the multiple-hit concept in what he has termed the "Repolarization Reserve hypothesis." This states, "Normal cardiac repolarization depends critically on the interplay of multiple ion currents and these provide some redundancy, or 'reserve,' to protect against excessive QT prolongation by drugs. Lesions, possibly genetic or clinical risk factors, in these repolarizing mechanisms can remain subclinical (i.e., normal QTc) but can increase TdP risk upon exposure to QT prolonging drugs."

Clinical Factors Associated with Increased QTc (n = 92):

To develop a QT Risk Score for a specific population, one must first conduct the necessary research to screen for and quantify the relative contribution of the many clinical risk factors for QT prolongation.

To assist clinicians and scientists in identifying those clinical factors, AZCERT maintains this list of factors for which there is any evidence of an association with QT prolongation or TdP. The list currently includes 92 factors, some of which have extensive evidence for their contribution to torsades, e.g., hypokalemia, and many are at the other end of the spectrum where the evidence may simply be a weak statistical association, for example obesity or renal failure.



The web page, www.QTfactors.org, also includes an assessment of the strength of the evidence and its scientific quality for each potential risk factor.

QT Risk Score & Decision Support:

Increasingly, clinical informatics scientists are conducting research to identify Risk Factors and validate Risk Scores that identify patients at risk of QT prolongation. One might ask, why focus on QT prolongation and not torsades de pointes?

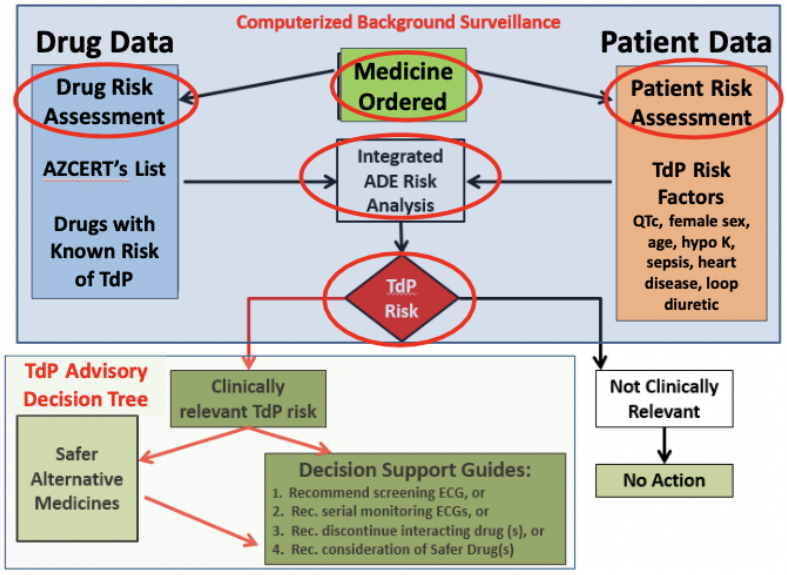
The main reason is that TdP is a rare event and validation of risk factors would require enormous clinical databases, prolonged periods of observation and may have ethical challenges due to the need to intervene and attempt to reduce risk. Therefore, most studies seek to identify factors that predict which patients are likely to develop a QTc greater than 500 msec or a change from baseline > 60 msec.

One of the earliest QT risk scores was reported by Ackerman from the Mayo Clinic and identified a population with a four-fold higher mortality than others in the health system. Dr. Jim Tisdale of Purdue developed a score that was able to identify patients at high risk of excess QT prolongation in an ICU population at the University of Indiana. Researchers in Belgium and the Netherlands have developed QT risk scores for their national networks of tertiary care hospitals.

The patient populations of each of these studies have extensive differences and the frequency and impact of each risk factor can - and does - vary by site. This means that any QT risk score should be limited to use in clinical populations similar to the one in which it was developed and validated. The article by Tomaselli and Tisdale is a detailed review of these risk scores.

AZCERT's Decision Support System for Hospitals:

In 2015, the Arizona CERT was awarded an FDA contract to develop a decision support system for hospitalized patients to improve the safe use of medicines that are known to cause QT prolongation. The system was developed in collaboration with scientists in the Department of Medicine at the University of Arizona and in Banner Health, a large health system with 29 hospitals in 7 western states.



This is a schematic of the clinical decision support system and its underpinning logic. Operating in the background, the computer system that manages the electronic medical record (EMR) for 29 hospitals and clinics has been programmed so that, whenever a drug that has a known risk of torsades de pointes (i.e., in the QTdrugs List of drugs with known risk of TdP) is ordered the system initiates a risk assessment and calculates a QT risk score for that patient.

The program first performs a "Drug Risk Assessment" by screening all of the patient's medicines to identify those with known risk of torsades. This is done by searching the ERM's list of drugs for the patient and identifying those drugs that are on the QTdrugs List (www.QTdrugs.org).

It also performs a "Patient Risk Assessment" by extracting clinical data from the patient's EMR to identify clinical factors that are known to increase the risk of torsades. In this program these factors include, female sex, the patient's age, hypokalemia, a diagnosis of sepsis or heart disease and the use of loop diuretics. These are the risk factors identified by Tisdale (Circ. Cardiovasc. Qual. Outcomes 7(3): 381, 2014) and subsequent slides will describe why these factors were chosen.

The results of these two assessments are integrated by the computer and it then calculates the patient's overall QTc risk score. If the number exceeds a preset threshold that has been shown to identify the highest risk population, a torsades advisory is created and sent immediately to the prescriber.

The wording and content of the Torsades Advisory are determined by a decision tree that we will discuss later, and which contains patient-specific recommendations for the physicians to consider similar to those shown in the list of Decision Support Guides at the bottom.

The use of this Torsades Advisory was initially confined to Banner hospital's ICU patients, but the program is now operating system wide for all patients prescribed a drug in AZCERT's Known Risk of TdP category and is being evaluated for effects on clinical practice and outcomes.

Tisdale CCU QT Risk Score:

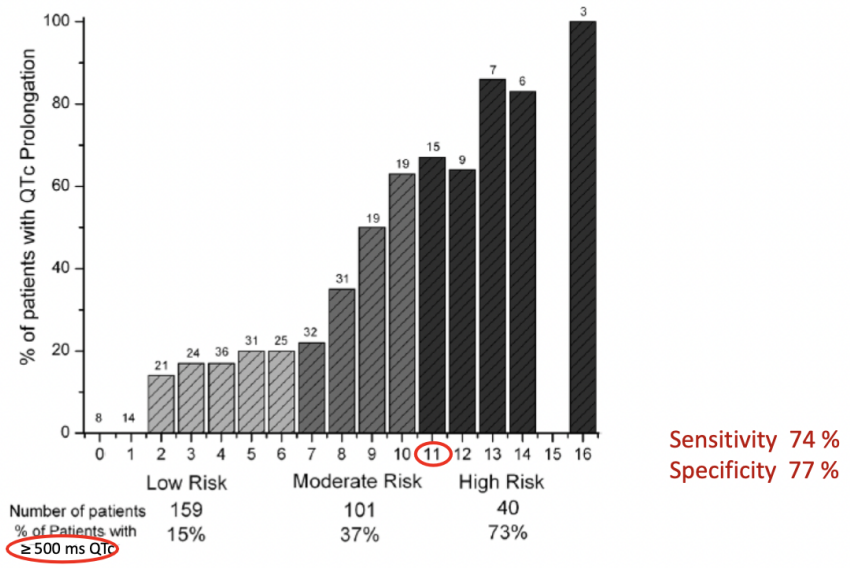
First let's look at the QT risk score that is being used in Banner Health system's Torsades Advisory.

Risk Factor	Points
Age ≥ 65y	1
Female Sex	1
Loop diuretic	1
Serum $K^+ \leq 3.5$ mEq/L	2
Admission QTc ≥ 450 ms	2
Acute MI diagnosis	2
1 QT_c prolonging drug	3
≥2 QT_c prolonging drugs	3
Sepsis diagnosis	3
Heart failure diagnosis	3
	Max = 21

This is a list of the risk factors and the number of points that our collaborator, Dr. James Tisdale, and his team at Purdue found can identify CCU patients who have excessive QT prolongation. The maximum score is 21 and a score greater than or equal to 11 was found to be a reliable predictor identifying 73% of the patients that had a QTc > 500 msec.

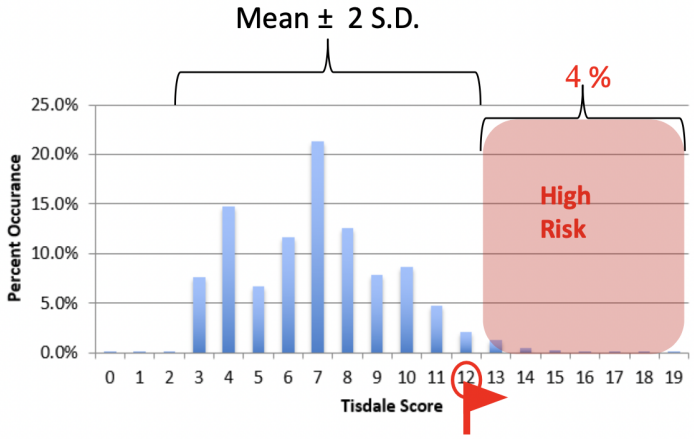
QT Risk Score Validation:

This chart, taken from Dr. Tisdale's validation study, shows the distribution of scores for the patients and the percent of patients in the low-, moderate- and high-risk groups. Dr. Tisdale found that a score cutoff of 11 identified most of the patients with a QTc greater than or equal to 500 msec with a sensitivity of 74% and a specificity of 77%.



QT Risk Score - 201,939 Inpatients:

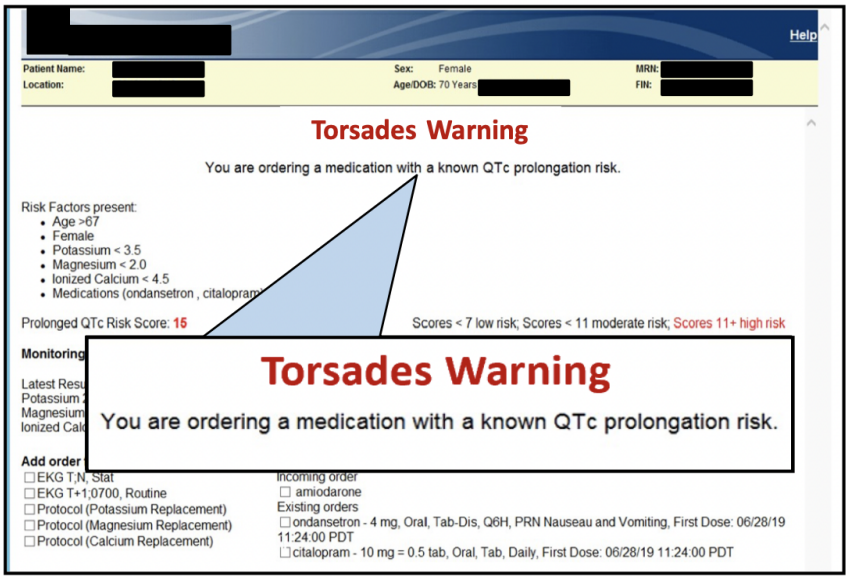
This chart shows the distribution of the Tisdale score in data collected from the Banner Health system for more than 200,000 inpatients who had been prescribed a drug with Known Risk of TdP. You can see that the distribution is generally normal in shape but it has a rightward skewness because some patients have extremely high values.



You can also see that about 4% of these patients had a score greater than 12. We chose 12 as our threshold for triggering our Torsades Advisory in order to have greater specificity and limit the risk of "alert fatigue."

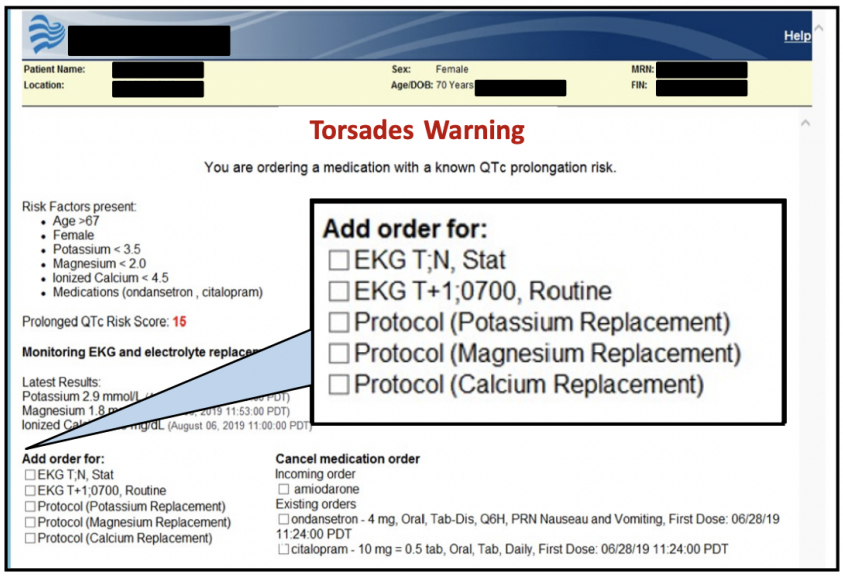
QT Risk Score & Decision Support:

This chart shows the Torsades Warning that appears when a patient that is prescribed a drug with Known Risk of TdP has a QT risk score of 12 or greater. The prescriber is informed that they "are ordering a medication with known QTc prolongation risk." The warning includes a list of the risk factors that contributed to the score, and it includes the score and how the score identifies patients with low, moderate or high risk. In this case, the score of 15 is highlighted in red font and shows that it is in a range with high risk.



Extensive research has shown that clinicians favor decision support systems that suggest options for management of risk (Payne. T, J. Am. Med. Inform. Assoc. 22(6): 1243, 2015). In this case, the CDS recommends monitoring the EKG and replacing electrolytes - which are abnormally low for this patient and are contributing to the patient's risk of prolonged QTc.

The CDS also offers the clinician "one click" options to order EKGs or to activate protocols for electrolyte replacement. The Torsades Advisory also suggests which medications could be canceled to reduce the risk of QTc prolongation. This helps the clinician identify which of the several medications have the potential to prolong QT and again offers "one-click" options for cancellation.



Experience with Torsades Advisories:

This chart summarizes the initial experience with the Torsades Advisory. In 29 ICUs with approximately 500 total beds, 526 Advisories were sent - an average of about 3 per month for each unit.

Actions taken in first hour after first Advisory issued
(n = 526 in 6 months)

- Discontinue Known Risk Med: 32.3%
- ECG ordered: 17.1%
- Electrolytes ordered: 4.2%
- Any of the above: 45.1%

By tracking medical orders that were placed shortly after the Advisory was issued, it was found that, in the first hour, a drug in the Known Risk of TdP category was discontinued in approximately 32% of cases, an ECG was ordered in 17% and serum electrolytes were ordered in 4%. Overall, some action that is considered to be a positive response occurred in the first hour after 45% of the Torsades Advisories had been sent. This is 2-4 times greater than any system previously described. Further analysis is now being conducted to determine if these changes in clinical practice result in improved clinical outcomes.

Survey of 38 Advisory Recipients:

Recipients of the Torsades Advisory were surveyed and the results from the first 38 respondents is summarized here. The response was generally positive for the first four questions. The negative response to the last two was caused by a problem that has since been corrected, in which multiple warnings were issued for multiple versions of the same medicine.

The Advisory…	Agree or Strongly Agree
Helped provide better care	79%
Info provided was correct	89%
Actions to consider clear	87%
Appeared in good place in workflow	82%
Appeared too frequently	46%
Did not apply to my patients	37%

Comprehensive Decision Support for Prescribers:

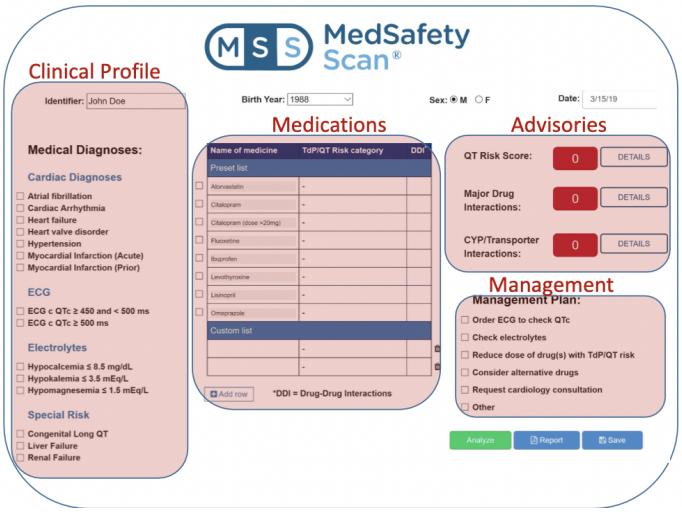
This slide shows the MedSafety Scan website which provides access to a free Comprehensive Decision Support program for prescribers. Healthcare providers can click at the top to review the Terms of Use and register for access to the program. Registration to use MedSafety Scan is free for clinical purposes. Once registered, visitors can log in, create their personal site within the system and begin entering patient data. Users are instructed to only enter clinical data that has been de-identified and free of any protected health information.

To demonstrate how to use MedSafety Scan, two training videos are available for viewing by clicking the links at the bottom for either an introductory video or for a real clinical case presentation that demonstrates the type of guidance MedSafety Scan can provide clinicians.[PP1]

MedSafety Scan® - Mobile:

MedSafety Scan is a decision support tool developed by AZCERT that can operate on multiple platforms. This photo shows the mobile version that operates on a tablet, but it can also function on a desktop or be imbedded in an EMR that accesses the MedSafety Scan Application Programming Interface, or API.

To enter data, there are three primary work areas, arranged in left to right sequence:



The operator first completes the data fields for the patient's unique identifier, their age, relevant diagnoses and data such as QTc or electrolytes. The list of these parameters can be tailored for the population of interest, for example, patients treated in oncology, mental health and many others, even student health.

Next, the operator inputs the patient's drug list. The page has a list of the most commonly used medicines that can be selected with a click. Drugs not on the preset list can be entered manually, and that process is enhanced by spell check and autocomplete functionality.

As the operator enters data and clicks "analyze," decision support Advisories are displayed in order of their clinical importance. If the operator wants to see more details, they can click on any of the buttons labeled "details."

Next, the operator can select their management plan and click save to create a pdf report that can be emailed or securely stored for later review.

The operator will then enter data for a real patient who was admitted to the ICU for treatment of Q Fever. This case is described in detail in a separate introductory training video on the homepage for MedSafety Scan.

Let's see what MedSafety Scan, when configured for ICU patients, would recommend to those caring for this clinical case:

He was 31 years of age.

Among the cardiac diagnoses, he had heart failure.

His QTc on admission was markedly prolonged and exceeded 500 msec.

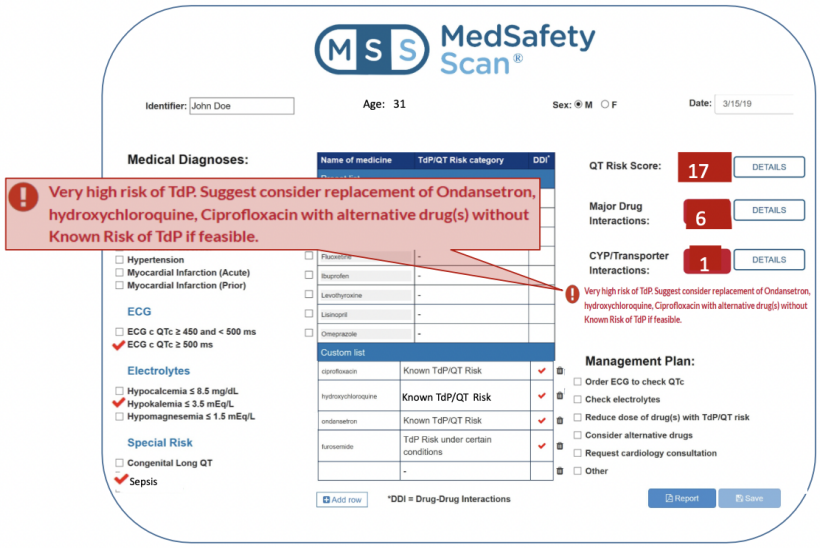
The operator will next enter the list of drugs:

Ciprofloxacin
Hydroxychloroquine
Ondansetron
and Furosemide

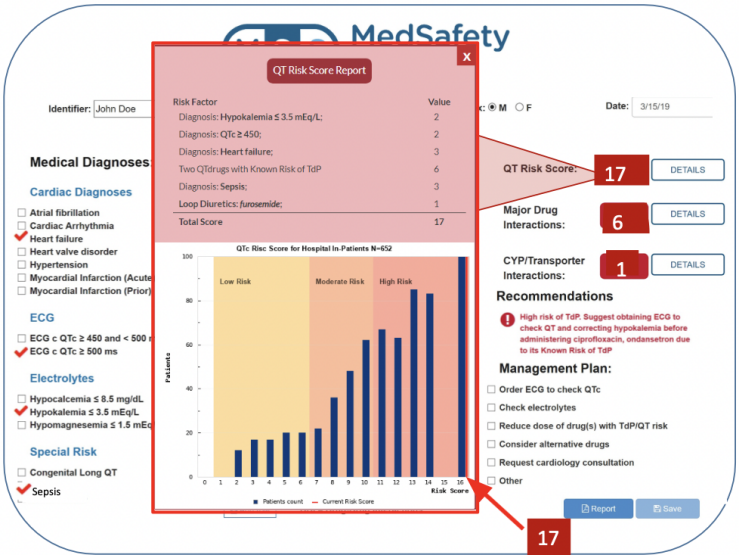
and the system informs the operator that three of the drugs are in the Known Risk of Torsades category, and one is a loop diuretic in the Conditional Risk of TdP category - and all four have a check mark indicating that they have potential drug-drug interactions that should be considered.

The system analyzes the data and the fields in red are populated. You see that the patient's QT Risk Score is 17, there are six major drug-drug interactions and at least one CYP/Transporter interactions.

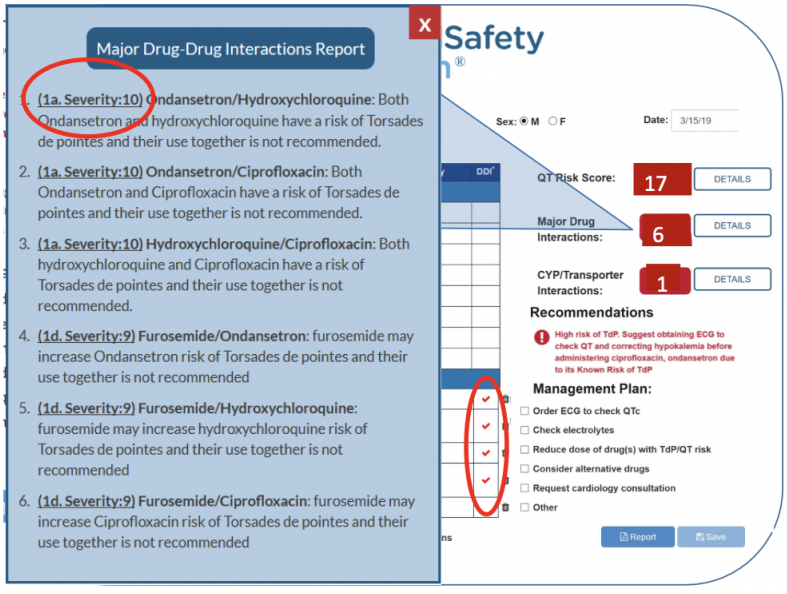
Notice that there is a prominent warning that is enlarged here. "Very high risk of TdP. Suggest consider replacement of Ondansetron, hydroxychloroquine, Ciprofloxacin with alternative drug(s) without Known Risk of TdP, if feasible."



If the operator wishes to see the factors that contributed to the patient's QT risk score of 17, she would click on the "Details" box next to the score to see a risk value of 2 for hypokalemia, etc.



Also, the operator will see that there are 6 potential drug-drug interactions to be considered, and by clicking on the "Details" box a list appears with the highest severity interactions shown first.



In this case, the first three interactions are reported because there are three drugs ordered which are each known to cause torsades. The next three interactions are reported because the

loop diuretic, furosemide, can cause hypokalemia which would increase the torsades risk for either ondansetron, ciprofloxacin or hydroxychloroquine.

Summary of Features:

So, to conclude, here is a summary of the features of MedSafety Scan. It can be customized to Identify high risk patients in any clinical environment.

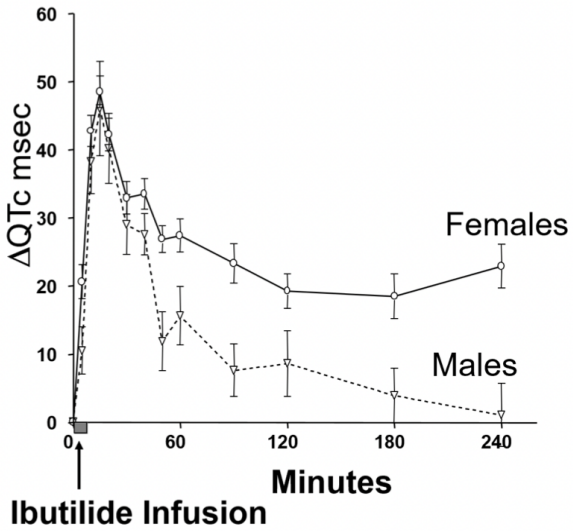
- It has facilitated data entry with preset drug lists to choose from and Autocomplete and Spell Check.
- Drug-Drug interactions detected are those likely to be clinically relevant and are based only on CMS and FDA label recommendations.
- The interactions can be tiered by severity, a feature designed to prevent alert fatigue.
- It informs the user when drug combinations are contraindicated.
- And it presents a range of options for decision making, such as Check ECG or Correct Electrolytes.

The QT Interval in Clinical Practice:

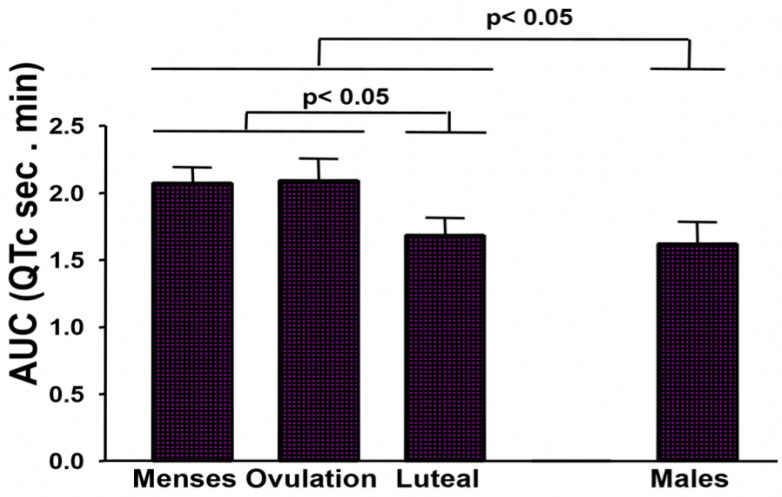
We will now discuss the role of QTc measurement in clinical research.

Ibutilide QTc Response:

This is an example of how measurement of the QTc interval can be used as a biomarker to identify biologic differences in clinical response.



In this study, a significant difference in the sensitivity of men and women to the QT-prolonging effect of the antiarrhythmic drug Ibutilide was seen and provides a potential explanation for the higher incidence of TdP in women than men observed in clinical practice.



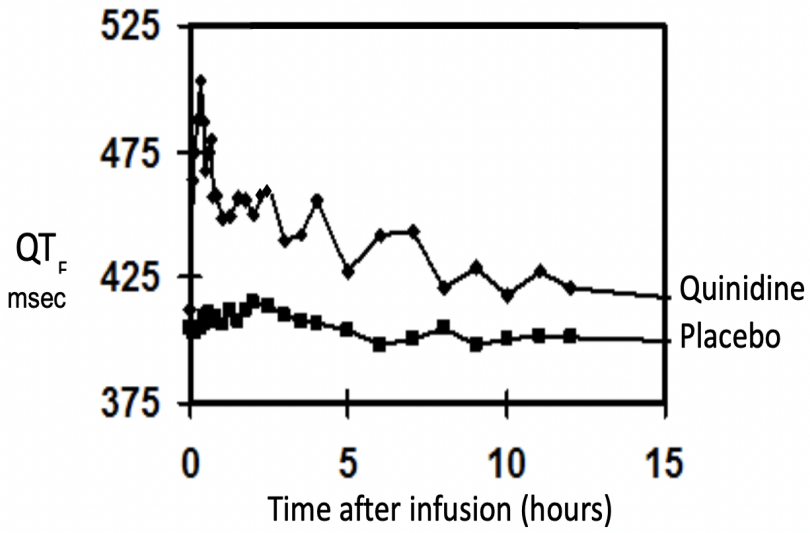
The QTc response to Ibutilide was used in this study to examine the differences during the menstrual cycle and explore the effects of sex hormones on cardiac repolarization.

QTc as a Biomarker in Research:

If QTc is to serve as a reliable biomarker in clinical research, it must be shown to be stable over time and the results reproducible.

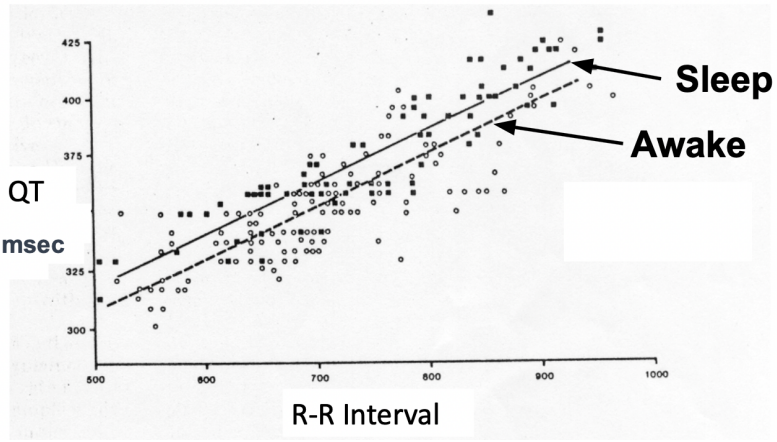
QT_c "Stable" During Day:

These data are recorded from one individual and demonstrate the hour-to-hour stability of the QTc (Fridericia) interval on a day that placebo was given and can be compared to a day when quinidine was administered and marked QTc prolongation was observed.



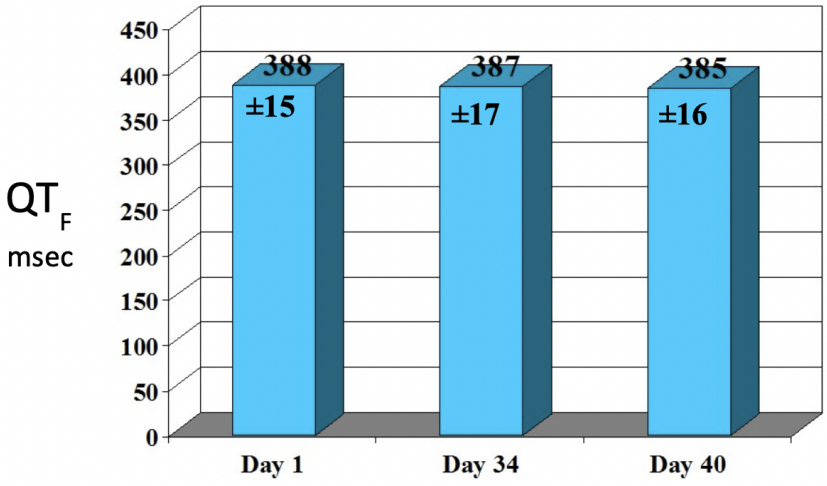
Effect of Sleep on QT Interval:

This graph shows the QT – R-R relationship for a group of subjects when the ECG was recorded during awake and sleep states. While the difference was statistically significant, it was only approximately 10 msec and such a small difference is unlikely to be clinically relevant for most patients. However, in a research study, such a difference should be considered when analyzing the data.



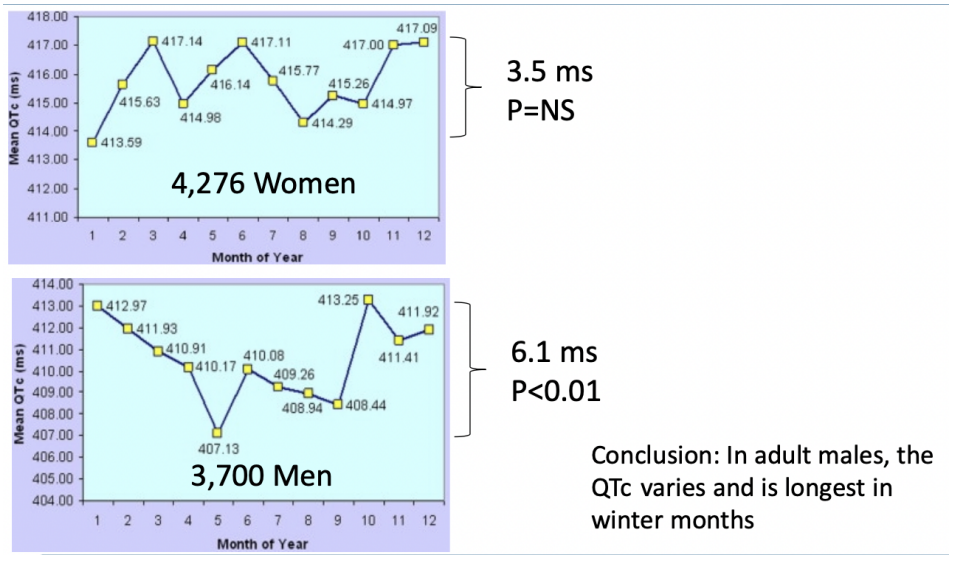
QT_c Stable Over Weeks:

These data for a group of 12 patients administered placebo over a 40-day period show that QT (Fridericia-corrected) is stable over this time and has a narrow standard deviation that ranged from 15-17 msec.



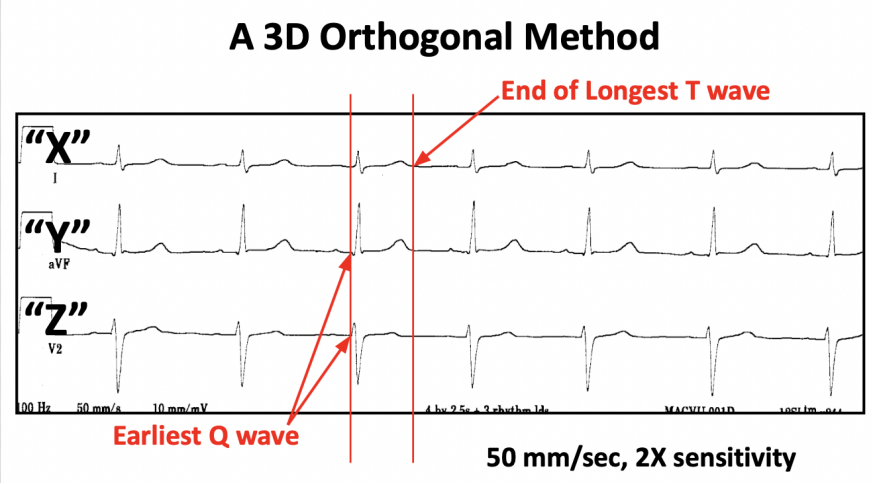
Seasonal Variation in QTc:

However, Beyerbach et al. found that QTc can vary significantly in men (6.1 msec) and suggest that seasonal variation should be considered in long term studies.



3-Dimensional QT Measurement:

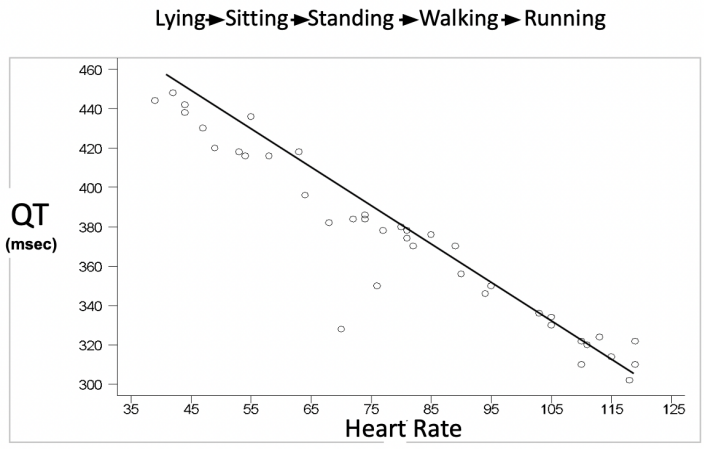
In cardiac research, a three-dimensional approach is often used to more accurately measure QT intervals.



This high-speed tracing (50mm/sec) shows the three leads (I, aVF and V_2) that most closely approximate the orthogonal leads (X, Y and Z). The earliest Q is seen in aVF and V_2 but the longest T wave is in Lead I. Therefore, when making multiple comparisons of QT over time, it is preferable to use multiple simultaneous leads or, if not feasible, use the same lead.

R-R / QT Exercise Protocol:

As discussed earlier, it is preferable to rate-correct QT data based on the QT/RR relationship for each individual. In clinical research projects, it is often possible to obtain multiple ECGs over a range of heart rates for each subject.



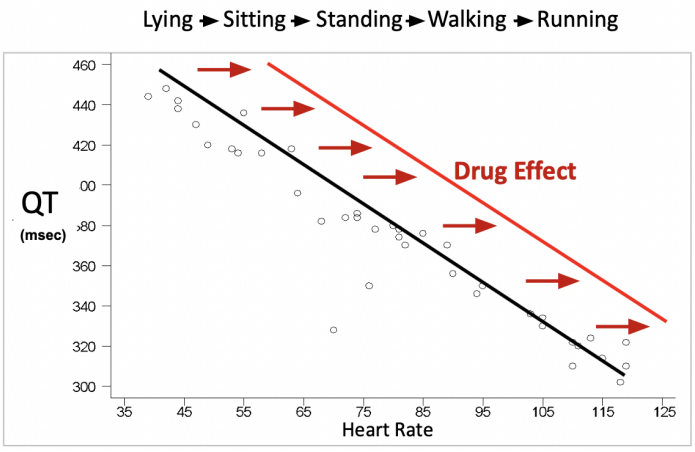
This chart shows the QT and heart rate data from one subject during a standardized protocol in which the ECGs were obtained. After the subject rested for 20 minutes, a baseline 12 lead ECG was recorded. Each subject was then asked to sit upright and after 30 seconds another ECG was recorded and then the subject was asked to stand quietly for 2 minutes. Another ECG was recorded and the subject was then asked to walk on a standard exercise treadmill through seven stages and individualized in order to result in a steadily increasing heart rate to a maximum of 120 bpm. The speeds ranged from 1 to 3.5 mph, with concurrent increases of incline from 0% to 20%.

The stages were timed for 2 minutes each to allow the participant to maintain a fairly consistent heart rate at each stage while steadily reaching a heart rate of approximately 120 bpm. As the heart rate increased, ECG tracings were obtained when the signal was stable and at times when the heart rate had increased in 10-bpm increments and/or at the end of each stage. ECGs were also obtained during the post-exercise phase at 10-bpm decrements as the heart rate returned toward resting baseline.

These data can be used to determine a QT rate correction formula for each subject. In this study, this approach was used to ask the question, “Is the effect of Ibutilide on QTc dependent on the heart rate?”

Drug Effect on R-R / QT:

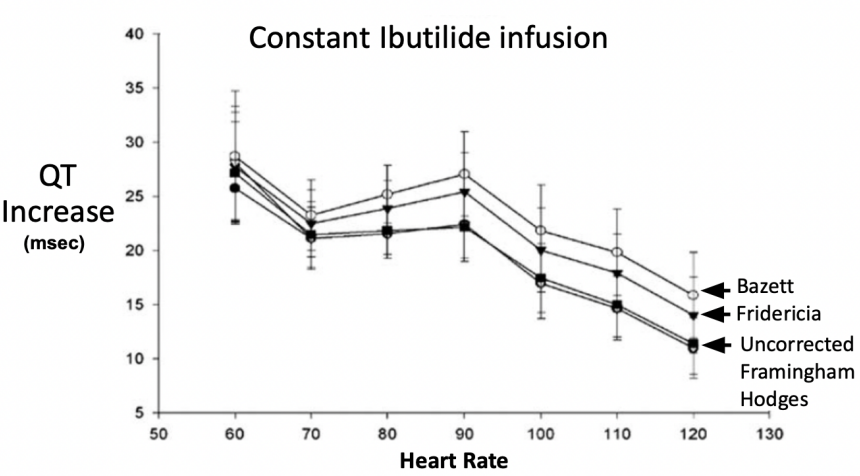
On a second day of the study, the subjects were given an infusion of the antiarrhythmic drug Ibutilide at a dosage expected to produce a 10-20 msec mean increase in the QT interval.



This chart shows the control RR/QT data and the red arrows show the hypothetical change that would be expected if the drug’s actions are not rate-dependent.

Rate Correction & Drug Effect on QT:

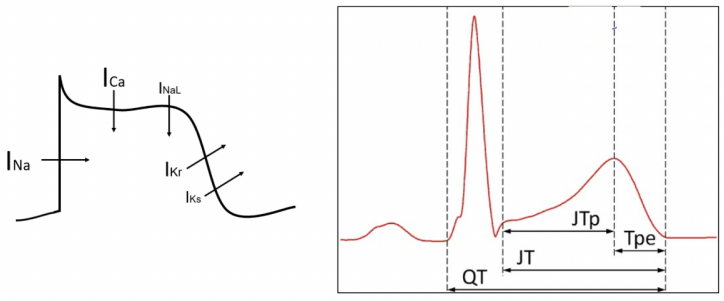
This chart demonstrates that the magnitude of the QT change caused by the antiarrhythmic medication Ibutilide is dependent on heart rate and it can be artificially exaggerated by using either the Bazett or Fridericia rate correction formula. The magnitude of the QT change was not altered by correcting the QT for heart rate using either the Framingham or Hodges formula.



For most research applications, it would be preferable to obtain RR/QT data for each person in the study and use those data for any comparisons to be made. If that is not feasible, we would recommend using the Framingham linear correction formula.

QT Segmentation:

Recent clinical research has examined the possibility that analysis of portions of the QT interval could be more informative than the entire interval.



QRS – Depolarization – Early Sodium Current

JTp (JTpeak) – Early Repolarization – Calcium and Late Sodium Current

Tpe (Tpeak-end) – Late Repolarization – Potassium Currents (I_{kr}, I_{ks})

Based on the contribution of specific currents (I_{Na}, I_{Ca}, I_{NAL}, I_{kr} and I_{ks}) during the cardiac action potential shown on the left, the initial portion of the QT interval (the QRS, on the right) is assumed to be mainly due to the rapid sodium current, I_{Na}.

The next segment of the QT, the time from the J point to the peak of the T wave (JTp) represents a mix of the inward calcium currents (I_{Ca})and the late sodium current (I_{NaL}).

The final segment, from Tpeak to Tend (Tpe), is thought to represent the rapid and slow components of the delayed rectifier potassium current, I_{kr} and I_{ks}.

These proposed associations are supported by studies that have examined the changes in these QT segments produced by drugs with relatively specific actions on the currents but further study is needed to determine whether drug-induced changes in these segments have value in clinical medicine.

This is the end of Section 4 and the end of our presentation. Thank you for visiting CredibleMeds.

Our Resource Sites and Programs:

In closing, we encourage you to visit the CredibleMeds website to access the extensive information about QT prolonging drugs and their relative risk for causing Torsades de Pointes and sudden cardiac death. Also, the MedSafety Scan website is available for QT risk assessment for individual clinical cases.

Thank you for your interest in AZCERT.

AZCERT

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