

## THE PRESENT AND FUTURE

### REVIEW TOPIC OF THE WEEK

# Predicting the Unpredictable

## Drug-Induced QT Prolongation and Torsades de Pointes



Peter J. Schwartz, MD,<sup>a</sup> Raymond L. Woosley, MD, PhD<sup>b,c</sup>

#### ABSTRACT

Drug-induced long QT syndrome (diLQTS) and congenital LQTS (cLQTS) share many features, and both syndromes can result in life-threatening torsades de pointes (TdP). Our understanding of their mechanistic and genetic similarities has led to their improved clinical management. However, our inability to prevent diLQTS has resulted in removal of many medicines from the market and from development. Genetic and clinical risk factors for diLQTS and TdP are well known and raise the possibility of TdP prevention. Clinical decision support systems (CDSS) can scan the patient's electronic health records for clinical risk factors predictive of diLQTS and warn when a drug that can cause TdP is prescribed. CDSS have reduced prescriptions of QT-prolonging drugs, but these relatively small changes lack the power to reduce TdP. The growing genetic evidence linking diLQTS to cLQTS suggests that prevention of TdP in the future may require inclusion of both genetic and clinical predictors into CDSS. (J Am Coll Cardiol 2016;67:1639-50) © 2016 by the American College of Cardiology Foundation.

There are few instances in medical history of a single clinical entity that has been as disruptive for so many diverse groups and individual patients as drug-induced long QT syndrome (diLQTS) (1,2). diLQTS is associated with a special form of ventricular tachycardia (VT) called torsades de pointes (TdP), which can be transient and cause a reversible syncope, or it can deteriorate into ventricular fibrillation (VF) and cause cardiac arrest and sudden death. The realization that the unsuspected link between drugs commonly used for a wide range of clinical conditions and unexpected sudden deaths caused by this arrhythmia with a fancy French name was, in fact, prolongation of the QT interval opened one of the most intriguing chapters in medicine and cardiology.

What initially looked like tragic but rare anecdotes turned out to be a common entity with far-reaching ramifications. After extremely expensive investments in development, drug companies were forced to

withdraw established products from the market and halt promising new molecules in development. Regulatory agencies were baffled. Otherwise healthy patients encountered cardiac arrest or sudden death while being treated for disorders as benign as hay fever. Eventually, physicians realized that a large number of drugs could precipitate this special type of arrhythmia.

This study reviews how knowledge about diLQTS developed, the significance and mechanisms underlying TdP, and its clinical and genetic risk factors, which raise the possibility of facilitating prevention. We also review what has been achieved by the creation of an independent organization aimed at evaluating the evidence and identifying drugs that have the potential of favoring or causing TdP and its success in impacting on therapeutic choices for patients potentially at risk. We conclude with our views on future directions and approaches to prevention.

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From the <sup>a</sup>Center for Cardiac Arrhythmias of Genetic Origin and Laboratory of Cardiovascular Genetics, IRCCS Istituto Auxologico Italiano, Milan, Italy; <sup>b</sup>Department of Biomedical Informatics, University of Arizona College of Medicine, Phoenix, Arizona; and <sup>c</sup>AZCERT, Inc., Oro Valley, Arizona. This study was supported by U.S. Food and Drug Administration grant HHSF223201400189C. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## ABBREVIATIONS AND ACRONYMS

**CDSS** = clinical decision support systems

**cLQTS** = congenital long QT syndrome

**dLQTS** = drug-induced long QT syndrome

**ECG** = electrocardiogram

**MC** = mutation carrier

**NMC** = nonmutation carrier

**SCD** = sudden cardiac death

**TdP** = torsades de pointes

**VF** = ventricular fibrillation

**VT** = ventricular tachycardia

## HISTORICAL BACKGROUND

It all started with quinidine syncope. To the best of our knowledge, the first such report goes back almost 100 years (3) and was eventually followed by several others almost 40 years later (4,5). Cardiologists were initially focused on quinidine because it was the only drug effective for the management of atrial fibrillation (6), and this prompted the realization that these dramatic episodes of syncope had 2 key features: prolongation of the QT interval and occurrence of TdP VT. It was only in 1982, in the pre-genetic era, that Schwartz and Moss (7) advanced the hypothesis that these events could represent a “forme fruste” of the congenital long QT syndrome (cLQTS) (8,9), thus suggesting that patients with a borderline QT prolongation might have been predisposed to develop TdP when treated with drugs sharing some pharmacological actions with quinidine. We will return to this point when discussing the genetic basis for dLQTS.

In 1966, the French cardiologist Dessertenne (10) described the electrocardiographic pattern of VT, which he named *torsades de pointes* (“twisting of the points”), and noted its association with a markedly prolonged QT interval (Figure 1). As most of the initial cases of TdP reported in the 1970s and 1980s were observed in patients treated for cardiac arrhythmia, it was generally assumed to be a relatively rare form of proarrhythmic event, mainly confined to antiarrhythmic drugs, such as quinidine, disopyramide, and procainamide, that prolong the QT interval. However, in 1990, the medical community’s attitude toward TdP changed dramatically when it became known that noncardiac drugs taken by millions of patients, such as the nonsedating antihistamine terfenadine, could also cause QT prolongation and TdP (11). Shortly thereafter, reports emerged of TdP with another antihistamine, astemizole, followed by the gastrointestinal drug cisapride, the antibiotic erythromycin (12), the opiates levomethadyl and methadone (13), a drug for hypercholesterolemia, probucol, and many other nonantiarrhythmic drugs, including antifungal agents and anticancer drugs. It became clear that TdP could occur with drugs in any therapeutic class, and, despite its uncommon occurrence, the incidence for many drugs became intolerable, prompting removal of several from the market (14). Since 1989, 14 clinically important drugs have been removed from the market due to TdP (14), and development of an unknown number has been

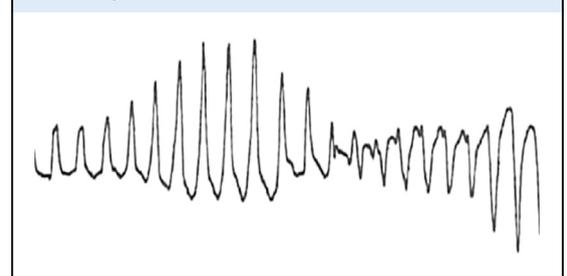
stopped due to concern that they might pose a risk of causing QT prolongation and TdP. In the 1990s, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) began requiring routine preclinical and clinical testing to determine whether drugs had the potential to cause QT prolongation (15). Today, according to the CredibleMeds website, which has become the standard reference for drug-induced TdP, 38 marketed drugs are now recognized for their potential to cause TdP and another 72 to cause QT prolongation (16).

## CELLULAR MECHANISM OF TdP

TdP is one of the most extensively studied and best understood adverse drug reactions and, for that reason, should be potentially preventable. A rich scientific basis exists for understanding the mechanisms underlying TdP and many of the clinical risk factors for TdP are known (17-19). As discussed previously, much of our understanding comes from similarities between the characteristics of cLQTS (8,9) and the actions of the medications that cause TdP, especially their shared ability to block  $I_{Kr}$ , a major cardiac potassium current contributing to the repolarization phase of the cardiac action potential. Other causes of acquired QT prolongation include electrolyte abnormalities (hypokalemia, hypomagnesemia, and hypocalcemia), hypothyroidism, hypothermia, and extreme bradycardia, any of which can cause TdP or contribute to the risk of drug-induced TdP (17).

Although QT prolongation is an essential first step in TdP, it is usually not considered sufficient to induce TdP. Nonetheless, there is an increased risk for TdP whenever QTc exceeds 500 ms and whenever a drug increases QTc by >60 ms to 70 ms, especially when the increase occurs rapidly (17). QT interval prolongation is particularly proarrhythmic when associated with increased dispersion in the recovery of excitability (20). Additional steps appear to be

**FIGURE 1** Example of Drug-Induced Torsades de Pointes Following Quinidine Treatment



required for TdP to occur; for example, the development of early afterdepolarizations that are calcium-mediated and were identified as a cause of reentrant arrhythmias in vitro models (19). The ability to block or disrupt the *hERG* potassium channel, thereby reducing  $I_{Kr}$  and prolonging the QT interval, is a common feature of drugs that induce TdP (17). Yang et al. (21) recently reported that some drugs that block  $I_{Kr}$  and are known to cause TdP (dofetilide, E-4031, d-sotalol, thioridazine, and erythromycin) also increase the late sodium current, which may contribute to their proarrhythmic effect.

In 1978, Schwartz and Wolf (22), following a cohort of patients with acute myocardial infarction for 7 years with an electrocardiogram (ECG) recorded every 2 months, provided the first nonanecdotal evidence that QT interval prolongation is associated with an increased risk for sudden death, independently of cLQTS. This finding has been confirmed in numerous studies that show conclusively that a prolonged QT interval is an independent risk factor for sudden cardiac death (SCD) (23,24). Also, numerous drugs with the ability to cause QT prolongation have been associated with a higher than expected incidence of sudden death (25-29). However, the fact that only a subset of patients who develop drug-induced QT prolongation experience TdP or death suggests that QT prolongation alone is not a perfect biomarker for predicting TdP (29) and must be combined with other known risk factors for TdP to have clinical utility (30). Be that as it may, QT prolongation remains the single most useful warning signal to alert for the risk of TdP.

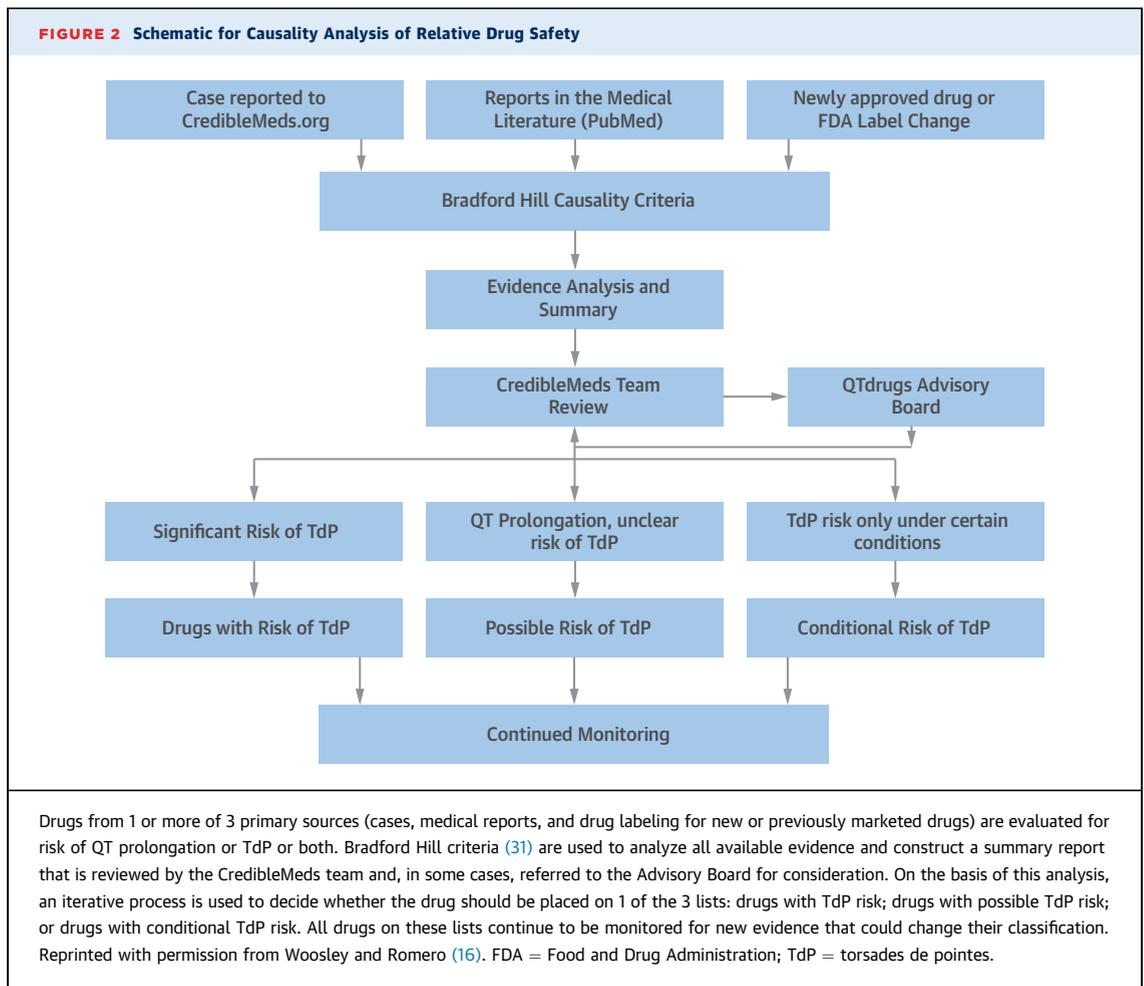
### CredibleMeds RISK CATEGORIZATION OF DRUGS

In 1999, because of increased concern for the potential scope of drug-induced TdP, the Georgetown University Center for Education and Research on Therapeutics (GUCERT) was awarded a federal grant to evaluate the available evidence to assess drugs for their relative risk to cause TdP and make their findings freely available to the medical community and the public. The Center subsequently moved to the University of Arizona and, in 2012, became a freestanding nonprofit organization incorporated as Arizona Center for Education and Research (AZCERT), also known as Arizona CERT. Under a contract with the FDA's Safe Use Initiative, AZCERT now maintains the Web-based lists of drugs that have a risk of QT prolongation and/or TdP. The lists were initially known as the QTdrugs lists (31) and are now also available on the CredibleMeds Website (32) and are provided free to over 55,000 registered visitors from

193 countries. AZCERT has recently developed an application program interface that enables health information technology systems to have online open-source access to the lists. To prevent real or perceived conflicts of interest and to assure independence in the decision making process for TdP causality, AZCERT has been entirely supported by peer-reviewed federal awards and charitable public contributions.

The methods that AZCERT uses to analyze evidence and assess TdP causality are described on the CredibleMeds Website (33) and in peer-reviewed publications (16,34). Because the available evidence frequently has limitations and gaps and is often of variable quality, AZCERT uses a systematic, in-depth analysis of all available data to assess causality (see later summary). Since the lists began in 1999, over 130 new drugs have been added, and many have been moved among categories or removed. Beginning in 2012, many drugs marketed outside the United States, especially in Europe and Canada, have been reviewed, and some have been included on the lists and designated as non-United States.

The risk categorization process begins when suspect drugs are brought to the attention of AZCERT scientists, usually in 1 of the 3 ways shown at the top of Figure 2. The professional staff assesses the ability of each drug to cause TdP by analyzing the available laboratory and clinical evidence and applying Bradford Hill criteria for causality (i.e., conditions necessary to provide adequate evidence of a causal relationship between incidence and consequence) (35). The analysis includes a thorough review of published studies (PubMed search using standardized search terms) and all adverse events reported to the FDA's Adverse Event Reporting System (AERS) and uses the empirical Bayesian data-mining statistical software developed for the FDA (Empirica Signal Software, Oracle Health Sciences, Redwood Shores, California) (16). CredibleMeds places drugs in 4 categories of TdP risk. Drugs with "known risk of TdP" are those found to have convincing evidence that they can cause TdP, even when administered as recommended on the drug's FDA label. Drugs that prolong the QT interval during routine clinical use, but do not at this time have convincing evidence of TdP causality, are classified as having a "possible risk of TdP." Beginning in 2006, the "conditional risk" category was added and includes drugs for which there is a risk of TdP but only under certain specific conditions, such as overdose, hypokalemia, hypomagnesemia, bradycardia, or when there is an interaction with another drug(s). This category also includes drugs that are associated with TdP because

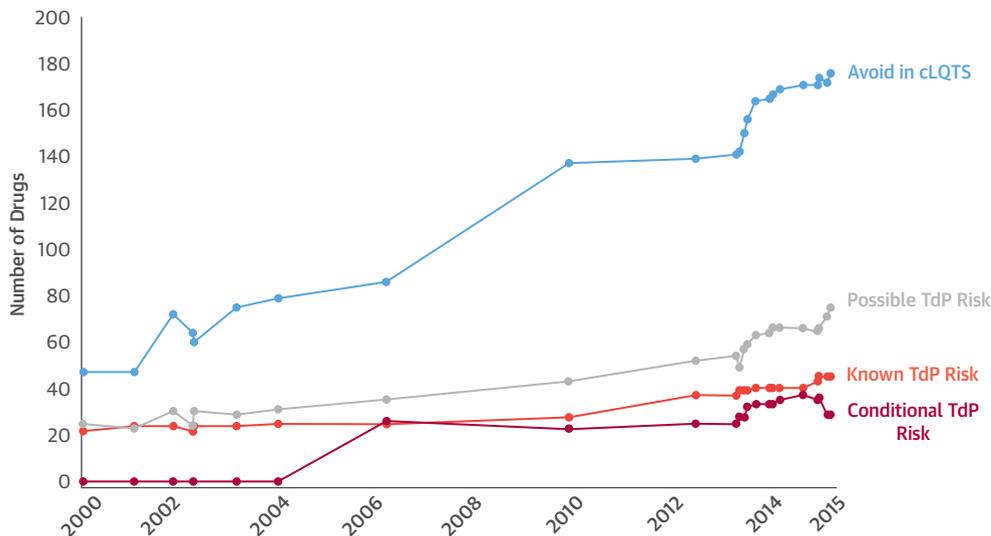


they have the ability to create the conditions that enable another drug to cause TdP (e.g., loop diuretic agents or metabolic inhibitors of a QT-prolonging drug). The website also posts a fourth list of drugs that should be avoided by patients with congenital LQTS, if clinically feasible. This list is generated by combining all of the drugs in the 3 risk categories listed previously and adding the adrenergic drugs that are considered to place some LQTS patients at high risk of sudden death (16). The process for evaluating drugs and decisions regarding their inclusion on lists are overseen by an international advisory board of clinical and pharmacological experts. The board's advice is also sought whenever conflicting evidence must be resolved or when any board member has a concern. Medications in all 4 lists are continuously monitored for new evidence and, in recent years, the lists have been revised every 4 to 8 weeks. Figure 3 shows how the number of drugs in each list has changed since they were first posted in

1999. Currently, 48 medications are on the list of drugs known to cause TdP (including 10 removed from the U.S. market but which may still be available in some countries). Another 72 are on the list for possible risk of TdP, and 32 are on the list for conditional TdP risk. Figure 4 shows the broad range of therapeutic areas for the drugs on the QTdrugs lists and demonstrates the breadth of medical impact.

CredibleMeds has become an invaluable tool for the clinical management of patients affected by cLQTS (9). Any experienced center dealing with these patients refers them to the public portal of CredibleMeds and provides patients and their families with an updated list of drugs to avoid or to take only under specific circumstances (9). As most general practitioners and many cardiologists are unaware of the QT-prolonging potential of many cardiac and noncardiac drugs, this practice has probably saved many lives and has become an essential part of the proper management of patients with channelopathies.

**FIGURE 3** Number of Drugs in Each of 4 Categories of TdP Risk: CredibleMeds Website, 1999-2015



The figure shows the changing number of drugs in each of the 4 categories of TdP risk from the initial postings at the CredibleMeds website in 1999 through January 2015. The number of drugs on the list of drugs with known risk of TdP at any point in time are shown as red dots and are connected by a red line. The number of drugs with possible risk of TdP are shown in gray. The number of drugs with conditional risk of TdP (i.e., associated with TdP under certain conditions) are shown in maroon. The number of drugs on the list of Drugs to Avoid in patients with congenital long QT Syndrome are shown in blue. This last list includes all drugs listed in the other 3 risk categories plus other drugs that do not prolong QT per se (e.g., adrenergic drugs) but have actions known to place some patients with cLQTS at risk. cLQTS = congenital long QT syndrome; TdP = torsades de pointes.

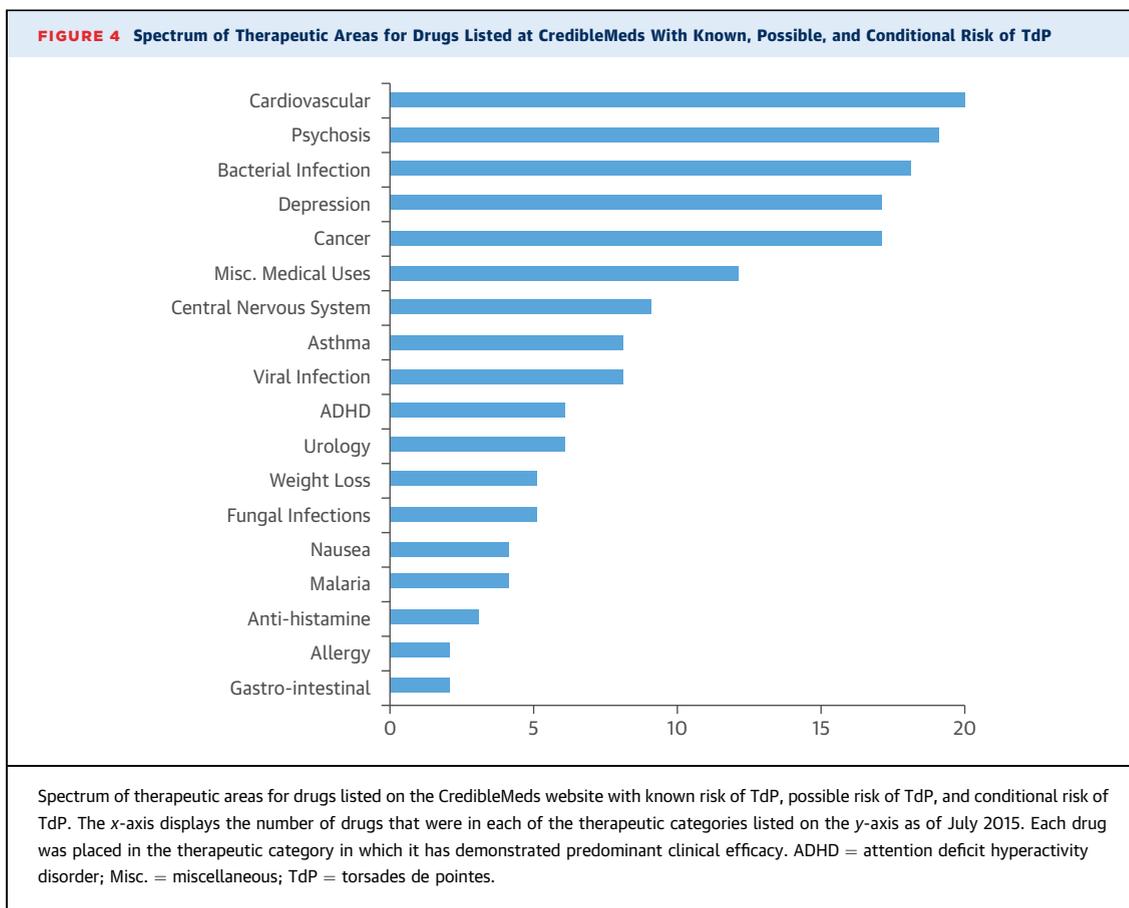
### EPIDEMIOLOGY OF TdP AND DEATH ASSOCIATED WITH QT-PROLONGING DRUGS

For specific drugs, the incidence of TdP is difficult to quantify. It varies greatly and ranges from extremely low for many of the macrolide antibiotics (36,37) to 1.5% to 9% for quinidine (38,39) and from 0.5% to 1% for drugs such as sotalol (17) and azimilide (40). Because of these differences, the overall incidence of TdP in a given population will depend on the relative risk of the drugs prescribed and the frequency of their use. For example, a cardiac care unit (CCU) population is frequently prescribed antiarrhythmic drugs and will likely have a much higher frequency of TdP than would be seen in a routine outpatient population.

The overall incidence of drug-induced TdP in a given population is difficult to estimate, partly because the arrhythmia is often transient and because an accurate diagnosis requires that an ECG be taken during an arrhythmic episode to document the presence of QT prolongation and the characteristic twisting ECG pattern of VT. Furthermore, the International Classification of Diseases (10th revision) used in medical records has no specific code for

drug-induced TdP or excessive QT prolongation. diLQTS and TdP tend to be reported under codes for VT, VF, or SCD. One study estimated that between 5% and 7% of reports of VT, VF, or SCD were, in fact, diLQTS or TdP (41). Despite these caveats regarding under-reporting, European pharmacovigilance centers in Sweden, Germany, and Italy have found an annual reporting rate for diLQTS or TdP of approximately 0.8 to 1.2 per million person-years (41). In an epidemiological study, Sarganas et al. (36) reviewed patient records, looking for episodes of TdP or cases of symptomatic QT prolongation (defined as QTc >450 ms for men and >470 ms for women, associated with ECG evidence of TdP, successful cardiac resuscitation, syncope, or severe dizziness) in Berlin and found the reporting rate for symptomatic diLQTS to be 2.5 per million person-years for men and 4.0 per million for women, with 60% attributed to drugs.

The frequency of death due to TdP is also difficult to estimate because if a patient dies before an ECG is obtained, TdP may not be recognized as the cause of sudden death. Perhaps this is why reports of death are not a dominant feature in most case series of TdP (39,42,43). Despite these potential confounding



factors, numerous studies have found that many of the drugs that prolong the QT interval are associated with a significantly higher risk of SCD (25-29,44-46). Straus et al. (45) compiled a list of noncardiac drugs that prolong the QT interval, taken from the lists on the CredibleMeds Website, to examine the associated all-cause mortality in a population-based, case-control study in the Netherlands and found an approximately 3-fold greater risk of death (95% confidence interval [CI]: 1.6 to 4.7) among patients who had been treated with these drugs. On this basis, they estimated that the use of these noncardiac drugs causes >15,000 deaths annually in the United States and Europe. Because many of these drugs, especially antibiotics, have therapeutic alternatives that lack QT-prolonging activity, it is possible that many of these deaths could have been prevented. Levofloxacin, erythromycin, clarithromycin, and azithromycin are among the most commonly prescribed antibiotics in the world, and all have been associated with QT prolongation, a risk of TdP, and an increased risk of sudden death and/or ventricular arrhythmias (25-27,37,46-48). TdP and related deaths

due to these antibiotics are a special concern, made more serious because of their widespread and sometimes unnecessary use. In 2013, the FDA issued warnings and expressed concern regarding the nation's overuse of antibiotics, especially citing the excess numbers of deaths with levofloxacin, azithromycin, and other macrolides (25,27,46,47). It was noted that in 2011, 40 million people took azithromycin and, on the basis of the study by Ray et al. (25), which found 1 excess death for every 21,000 prescriptions compared with amoxicillin, this would result in an estimated 1,900 excess deaths with this drug in the United States alone. In 2014, another study from the U.S. Veterans Health System estimated that 4,560 people die each year due to azithromycin when amoxicillin would have been a safe alternative (46). A recent meta-analysis of 33 studies involving 20,779,963 patients taking macrolides compared outcomes with those of patients who took no macrolides and found an increased risk of developing SCD or ventricular tachyarrhythmias (relative risk [RR]: 2.42; 95% CI: 1.61 to 3.63), SCD (RR: 2.52; 95% CI: 1.91 to 3.31), and cardiovascular

death (RR: 1.31; 95% CI: 1.06 to 1.62) (37). The authors concluded that treatment with macrolides is associated with an absolute risk increase of 118.1 additional SCDs or VT and 38.2 additional cardiovascular deaths per 1 million treatment courses. Because of the magnitude of TdP associated with these antibiotics, the FDA's Safe Use Initiative has focused on the safe use of antibiotics and ways to reduce their risk of TdP.

### FACTORS CONTRIBUTING TO RISK OF TdP

In 2010, Drew et al. (17) published a thorough and thoughtful consensus paper on the prevention of drug-induced TdP in the hospital setting and described an approach for monitoring the QT interval as part of a prevention strategy. For most drugs that have demonstrated the potential for causing QT prolongation, the cost and inconvenience of routine, untargeted screening for QT prolongation cannot be justified because of the relatively low number of patients expected to develop clinically significant QT prolongation, usually defined as >500 ms or >60 to 70 ms change from baseline (17). Furthermore, the number of patients who develop TdP is usually only a small subset of these patients. However, for some drugs, such as dofetilide, the frequency of TdP is much higher and the FDA recommends inpatient monitoring of the QT interval as part of a specific risk evaluation and mitigation strategy. However, no strategy has presently been shown to prevent or reduce the incidence of TdP.

Importantly, it has become apparent that the QT interval, despite its obvious importance, is but 1 of several risk factors that must be considered in order to assess a patient's risk profile for TdP. Numerous studies suggest that in order for a strategy to have an acceptable level of predictive accuracy and be cost effective, it must include consideration of those risk factors that are patient-specific, drug-specific, and clinical scenario-specific (17).

**PATIENT-SPECIFIC RISK FACTORS.** Patient-specific risk factors for drug-induced TdP are the same factors that are known to be associated with an increase in the QT interval, that is, female sex, bradycardia, hypokalemia, hypomagnesemia, hypocalcemia, diuretic agent use, hypothermia, and history of heart disease (30). Haugaa et al. (49) have extracted patient-specific information from electronic medical records to identify which of these risk factors are most closely associated with QT prolongation in order to calculate a "pro-QTc" risk score. They found that the score could identify hospitalized patients that have a 4-fold higher mortality in the Mayo Clinic Hospital

(Rochester, Minnesota). This risk score has been incorporated into alerts that are part of a clinical decision support system (CDSS) that has been implemented across the institution (49,50). Using this CDSS and the lists of QT-prolonging drugs on the CredibleMeds Website, Sorita et al. (5) were able to reduce the prescribing of many of the QT-prolonging medications. Similarly, in a CCU population, Tisdale et al. (51) developed a CDSS and QT risk score that they found could identify patients with excessive QT interval prolongation. Tisdale et al. (51) also used the CredibleMeds drug lists and found that their CDSS was able to reduce the overall incidence of diLQTS, the prescribing of QT-prolonging drugs and the prescribing of these drugs to patients who had baseline QT prolongation (52). In addition to the risk factors in the pro-QT score of Haugaa et al. (49), the Tisdale score for CCU patients identified sepsis and heart failure, and assigned greater weight to the patients' use of multiple QT-prolonging drugs. The different risk factors and their assigned weights in these 2 scores most likely reflect the fact that they were developed using different patient populations. This suggests that institutions may have to determine the risk score that is most appropriate for their clinical environment.

**DRUG-SPECIFIC RISK FACTORS.** As discussed earlier, the common feature of drugs that cause TdP is their ability to block *hERG* channels and to prolong the QT interval (53). In theory, a system to prevent TdP could use a ranking of drugs by their in vitro toxicity or QT prolongation in humans. However, attempts to find correlations between the TdP risk of drugs and their potency to produce *hERG* block (54) or QT prolongation (29) have not been found to be of predictive value. Most likely, the interindividual variability in drug sensitivity and the variable influence of factors that affect each patient's drug exposure (e.g., dose, drug metabolism, route of administration, and so forth) reduce the predictive accuracy of such ranking to levels that lack clinical utility. For example, terfenadine and astemizole have very high *hERG* blocking potency but are usually extensively metabolized so that it is unusual for them to reach blood levels that can cause TdP (i.e., only when their metabolism had been inhibited or impaired).

Prevention strategies must consider not only the drug's toxic potential but also its route and rate of administration and the dose and actions of any concomitant medicines. The roles of these factors are not always well defined for a given drug. For some drugs, like sotalol, extensive testing during its

clinical development characterized the relationship between dose and QT prolongation and investigators found a positive dose response relationship for sotalol-induced TdP (55). In contrast, the risk of TdP with quinidine appears to have little, if any, relationship to dose and may be affected more by clinical factors, such as the presence of atrial fibrillation, which can cause long pauses that facilitate TdP (38). For many drugs, like haloperidol, the available data suggest that the risk of TdP is influenced by the route of administration, with a larger proportion of cases occurring after intravenous injection (56).

Although ranking drugs for TdP potential on the basis of their inherent toxicity in laboratory models has not proven useful, it is possible to categorize drugs according to the strength of the available evidence for QT or TdP potential under general conditions of use. This is the approach taken by CredibleMeds, as described previously.

**SCENARIO-SPECIFIC RISK.** Analyses of case series of TdP due to a specific drug reveal that the great majority of cases fall into certain categories of drug use that are influenced by the patients' medical condition (39,42,43,57). Many of the patients in these reports had been successfully treated with the offending drug for extended periods of time, but developed TdP after a change had occurred in their clinical condition or in the way it was managed. Many of these changes could have further reduced the patient's repolarization reserve (1) and caused excessive QT prolongation. For example, patients with heart failure may tolerate QT-prolonging drugs until their clinical condition deteriorates and a loop diuretic agent is prescribed. Antibiotics that prolong the QT interval can also eradicate normal bowel flora, causing diarrhea and electrolyte disturbances that can potentiate a patient's risk of TdP. A partial

list of scenarios that, like these, can accentuate the TdP risk of a medication appears in **Table 1**.

## DRUG-INDUCED LQTS VERSUS CONGENITAL LQTS

The fact that the life-threatening arrhythmia of diLQTS and of cLQTS are the same (TdP) and that both conditions are associated with major prolongation of the QT interval, often with bizarre morphology of the T-wave, should have immediately raised the issue of a relationship between the 2 conditions. However, as briefly alluded to in the introduction, it was only in 1982 that Schwartz and Moss (7) first made such a suggestion, when they proposed that diLQTS could be a "forme fruste" of cLQTS.

It took several years for their hypothesis to be confirmed and accepted. Indeed, this novel concept remained dormant until the first major genes for cLQTS were identified in 1995 to 1996 (58), a step certainly not foreseen in 1982. A key component here was the realization that the second most frequent type of cLQTS, LQT2, is due to mutations in the *hERG* gene, which encodes the protein that mediates the  $I_{Kr}$  current. When it became clear that a key mechanism for the development of TdP is the block, even partial, of  $I_{Kr}$ , the connection with cLQTS became obvious. In this regard, another critical step was the development of the concept of repolarization reserve by Roden (1). This concept maintains that every person has a physiological cardiac repolarization reserve, which is genetically determined and compensates for any factor (e.g., drugs) that might either decrease repolarizing or increase depolarizing currents during the action potential. Subjects with reduced repolarization reserve are more likely to develop QT prolongation and TdP when exposed to  $I_{Kr}$ -blocking drugs. It follows that patients with cLQTS who, by definition, have a reduced repolarization reserve will be more likely than normal subjects to develop TdP. In theory, depending on the magnitude of genetically-induced loss of repolarizing currents, smaller or higher doses of  $I_{Kr}$ -blocking drugs will trigger TdP.

This was the theory, but, as always, facts and evidence were needed. An elderly female patient with documented cardiac arrest related to the  $I_{Kr}$ -blocking drug cisapride was found to carry a *KCNQ1* mutation causing a loss in the  $I_{Ks}$  repolarizing current (59). While this patient was taking cisapride, her QTc was markedly prolonged, but after cisapride withdrawal, the QTc normalized. She had 2 sons with normal QT intervals but who were also carriers of the mutation. This was the first evidence that, as proposed by

**TABLE 1 Clinical Scenarios for TdP Risk**

|   |
|---|
| Concomitant therapy with another QT-prolonging drug   |
| Concomitant therapy with a potassium-wasting diuretic agent   |
| Concomitant drug therapy that blocks the metabolism of a QT-prolonging drug   |
| Development of renal failure in a patient treated with a QT-prolonging drug that requires renal elimination (e.g., sotalol)   |
| Development of liver failure in a patient treated with a QT-prolonging drug that requires hepatic metabolism for clearance (e.g., methadone)                          |
| Development of vomiting or diarrhea resulting in electrolyte disturbances that potentiate the QT-prolonging effects of drugs such as antiemetic agents or antibiotics |
| Extended therapy with a proton pump inhibitor that leads to hypomagnesemia and/or hypokalemia   |
| Therapy with a beta-blocker or ivabradine that slows heart rate and thereby prolongs the QT interval.   |
| Excessive titration to high dosage for a QT-prolonging drug due to lack of desired clinical response (e.g., methadone)  |
| Depression causing attempted suicide with toxic doses of QT-prolonging drugs (e.g., antipsychotics and antidepressants, among others)                                 |

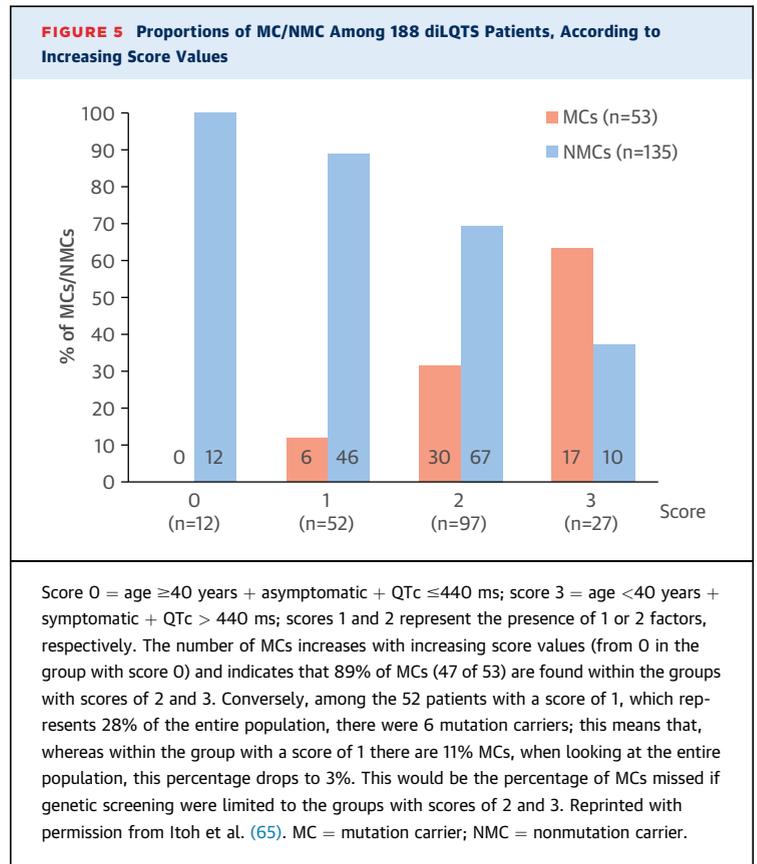
Schwartz and Moss (7), some cases of diLQTS with life-threatening arrhythmias may be a “forme fruste” of cLQTS with an apparently normal baseline QTc. That single case had wide-ranging implications and indicated that not all cases of diLQTS occur in a totally unpredictable way, but that some of those at risk might be identified by the presence of genetic mutations causing a loss in repolarizing currents. This report paved the way to a number of studies attempting to quantify the relationship between diLQTS and cLQTS.

In 2002, the report by Yang et al. (60) of 90 diLQTS patients suggested that cLQTS mutations could be found in 10% to 15% of diLQTS cases. Several studies have since followed, with mixed results (2,61-64). For example, whereas the *KCNE1* D85N polymorphism was found to be associated with an increased risk for diLQTS (61), 3 other studies suggested that rare variants play a prominent role (2,62-64).

The most recent data, from a comparison of 188 diLQTS patients with more than 1,000 cLQTS patients (65), provide a different and more positive set of findings. The first finding was that disease-causing mutations were found in 28% of these patients; the second was that under baseline conditions, the QTc of diLQTS patients ( $453 \pm 39$  ms), although shorter than that of cLQTS patients ( $478 \pm 46$  ms), is significantly longer than that of control subjects ( $406 \pm 26$  ms); the third is that *KCNH2* mutations are more common than *KCNQ1* mutations, at variance with cLQTS; and the fourth is that a score on the basis of simple clinical features allows the identification of the diLQTS patients more likely to be carriers of cLQTS mutations (Figure 5).

It is likely that some of the minor cLQTS genes (58), usually not tested, may be involved in some cases of diLQTS, thus further increasing the contribution of 1 syndrome to the other. One can hope that a combination of rapid genetic screening, risk profiling and monitoring of the QT interval during the first days of treatment with  $I_{Kr}$ -blockers may result in a decrease of the number of patients manifesting TdP in response to a drug treatment.

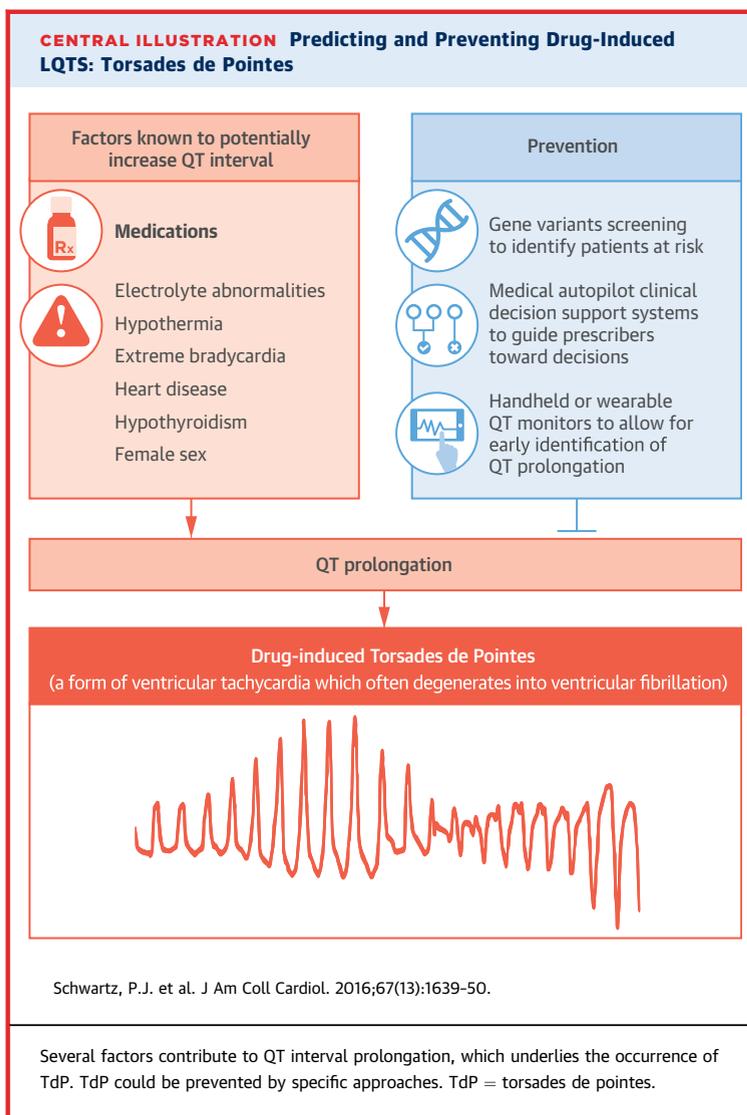
Just as genes that control expression of ion channels can directly increase risk of TdP, as described previously, genes that control the rate of a drug’s metabolism can also affect its ability to cause TdP by limiting or increasing the amount of drug that reaches the heart tissue (66). Genetic defects in drug metabolism have been shown to accentuate the ability of some drugs to cause diLQTS in affected patients (66). Because some drugs that cause TdP, such as thioridazine or methadone (66), are strongly influenced by genetic variability in drug metabolism and



others, such as the renally cleared sotalol (55), are not, genetic associations may have limited predictive ability when analyzing data for TdP cases caused by multiple drugs that have varied routes of elimination.

**FUTURE OPPORTUNITIES FOR TdP PREVENTION: POTENTIAL ROLE OF GENOMICS AND CDSS**

The massive amount of information that must be considered for the safe use of medicines has prompted the development of CDSS to help physicians and other members of the health care team to reach optimal medical and therapeutic decisions. To support better prescribing of medicines, most CDSS developed to date have issued alerts that warn of potential harm from a prescribing decision (52,67,68). As discussed earlier, investigators at the Mayo Clinic (49) and the University of Indiana (52) have developed CDSSs that can reduce the risk of QT prolongation in hospitalized patients. Unfortunately, the beneficial impact of these CDSS has been limited because in 75% to 95% of cases, physicians and pharmacists override or ignore the alerts (50,52,69), and no CDSS has yet been found to have sufficient impact on prescribing to reduce the



signals to guide prescribers toward decisions that result in maximum benefit and minimal risk of TdP. Hopefully, in the near future, a CDSS with these characteristics will be able to prevent TdP by incorporating all of the clinical and genomic risk factors that we know can contribute to a person’s risk of TdP.

**CONCLUSIONS**

The **Central Illustration** displays the counteracting forces on the left that increase the QT interval versus the newest approaches on the right designed to prevent QT prolongation and therefore reduce the risk of diLQTS and TdP. Most of the causative factors involved in diLQTS have been identified, as well as the major clinical risk factors for TdP. This is true also for the type of drugs most likely to prolong the QT interval and to trigger TdP. Nonetheless, there is a considerable gap between the increased level of understanding and our currently limited ability to effectively prevent diLQTS.

The advances in genetics, including not only the clear evidence that genetic variants causing or favoring cLQTS play a major role in diLQTS, but also the faster turnaround time due to faster methods, could open new options. For example, they may allow the possibility of screening the patients destined to receive drugs that are clinically necessary, but also have TdP risk, to rule out at least the presence of the most common variants associated with this life-threatening arrhythmia.

Finally, the use of simple handheld or wearable devices capable of monitoring QTc changes and transmitting the results may allow the early identification of those subjects more prone to development of a significant and worrisome QT prolongation, thus leading to the immediate withdrawal of the offending drug.

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**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Peter J. Schwartz, IRCCS Istituto Auxologico Italiano, Center for Cardiac Arrhythmias of Genetic Origin, c/o Centro Diagnostico e di Ricerca S. Carlo, Via Pier Lombardo, 22, 20135 Milan, Italy. E-mail: [peter.schwartz@unipv.it](mailto:peter.schwartz@unipv.it).

incidence of TdP. To improve the acceptance of alerts and the effectiveness of CDSS overall, an expert panel has recommended that CDSS should only provide clinically relevant and essential information at the time when a decision is being made, without overwhelming the decision makers with more information than they need (70). Moving away from the use of alerts to signal prescribing errors, the concept of “medical autopilots” has been suggested as a preferred approach for CDSS (71). These programs will monitor the electronic medical record and send

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