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Proarrhythmic and Torsadogenic Effects of Potassium Channel Blockers in Patients

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Summary

The most common arrhythmia requiring drug therapy is atrial fibrillation, which affects 2–5 million Americans and continues to be a major cause of morbidity and increased mortality. Despite recent advances in catheter-based and surgical therapies, antiarrhythmic drugs continue to be the mainstay of therapy for most patients with symptomatic AF. However, many antiarrhythmics block the rapid component of the cardiac delayed rectifier potassium current (I_{Kr}) as a major mechanism of action, and marked QT prolongation and pause-dependent polymorphic ventricular tachycardia (torsades de pointes) are major class toxicities. Although this arrhythmia is usually seen in patients with one of the congenital long QT syndromes, torsades de pointes has also been observed with certain antibiotics, antipsychotics, antihistamines and chemotherapeutic agents and is a leading cause of post-market drug withdrawal and relabeling. Clinical risk factors associated with drug-induced long QT syndrome include female gender, bradycardia, electrolyte disturbances, recent conversion from atrial fibrillation to sinus rhythm, variations in drug distribution and sub-clinical long QT syndrome. A unifying concept of reduced repolarization reserve has been proposed to explain the variable risk of torsades de pointes. In this monograph, we provide a historical perspective on drug-induced long QT syndrome, briefly discuss the underlying mechanisms, and detail recent advances in torsadogenic risk factors and the complex interplay between individual patient-related clinical risk characteristics and the development of torsades de pointes with potassium-channel blocking drugs.

Keywords

arrhythmia; potassium channel blocker; torsades de pointes

Introduction

Vaughn Williams Class III antiarrhythmic drugs, of which blockers of the rapid component of the delayed rectifier potassium current, I_{Kr} are most prevalent, are known to cause QT interval prolongation on the electrocardiogram (ECG) and have been well-described to

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predispose patients to ventricular arrhythmias (^{1–3}). Drug-induced long QT syndrome (diLQTS) is now a well-characterized mechanism whereby patients develop torsades de pointes (TdP) and risk for arrhythmic death (⁴). Mechanistic details of the underlying genetic and pharmacologic risk factors for ventricular arrhythmias are discussed elsewhere in this series. However, many patient-related risk factors for the development of TdP have been identified including female gender, bradycardia, electrolyte disturbances, recent conversion from atrial fibrillation (AF) to sinus rhythm, variations in drug distribution and sub-clinical forms of the congenital LQTS, all of which are important for modifying ventricular arrhythmia risk (Table 1). In this review, we discuss the history and mechanisms of risk factors for diLQTS and TdP, and then detail recent advances in patient clinical characteristics and the complex interplay of how these patient-related clinical risk factors predispose patients with inherited potassium channelopathies to life-threatening ventricular arrhythmias and sudden arrhythmic death.

A History of Pro-Arrhythmogenic Potential of Potassium Channel Blockers

The first description of the LQTS was reported as far back as the 1800s (⁵). By contrast, diLQTS was described by Levy in 1922 when he explained clinical outcomes of abrupt syncope and sudden death in patients undergoing treatment for AF with quinidine (⁶). Selzer and Wray, who considered ECG tracings to represent “paroxysmal ventricular fibrillation,” described arrhythmia-associated syncope several decades later (⁷). This pattern was observed and subsequently coined “torsades de pointes” (TdP) by Dessertenne, consisting of polymorphic ventricular tachycardia (Figure 1) (⁸). The oscillating waveform of TdP runs the risk of progressing to ventricular fibrillation if not stabilized, and predisposes the patient to arrhythmic sudden death. Although several mechanisms have been proposed, the underlying pathophysiology of LQTS-triggered polymorphic ventricular tachycardia remains poorly understood. Current efforts at uncovering the mechanisms underlying TdP include *in silico* modeling of cellular repolarization reserve, evaluation of hormonal effects on potassium channel function, induced pluripotent stem cell (iPSC) modeling of TdP, and mathematical modeling of T-wave properties associated with risk of the arrhythmia (Table 1).

Relating Risk Factors to Pharmacologic Mechanisms

Initial case reports of diLQTS were associated with hypokalemia and atrio-ventricular block (AVB) as primary risk factors for the development of TdP (⁸). However, as this phenomenon became a more clinically appreciated entity in the 1970s and 1980s underlying clinical risk factors, for example hypokalemia and female gender, became increasingly recognized as key contributors in determining TdP susceptibility (⁴). The observation that TdP may have both a clinical/environmental trigger and also genetic susceptibility led to the hypothesis that normal cardiac rhythm is supported by multiple, redundant mechanisms for the repolarization of ventricular myocardium (³). The term “repolarization reserve” was first coined by Dan Roden to describe the inherent variability of arrhythmic response to QT interval prolongation with the relationship between perturbations of one ion channel (such as I_{Kr}) in relation to the sum total repolarizing currents (⁹). In other words, clinical and genetic risk factors affect cellular repolarization reserve, which modulates susceptibility to TdP.

Of the plasma membrane ion channels that contribute to myocardial repolarization reserve, the rapidly rectifying inward potassium current, I_{Kr} , has been most widely recognized to be responsible for TdP risk (10–17). In contrast, the slow delayed rectifier potassium current (I_{Ks}) contribution to TdP formation has been more controversial (18), as the effects of selective I_{Ks} -blocking drugs on action potential duration (APD) have been variable (19–22). However, recent genetic evidence from whole exome sequencing of 65 diLQTS patients suggests that the *KCNE1* gene is responsible for risk of life-threatening TdP, thus implicating an I_{Ks} -mediated risk (23). Other ion channel currents implicated in repolarization reserve include I_{NaP} , $I_{Ca,L}$, I_{to} , $I_{Na/K}$, and I_{NCX} , and is detailed by Varró *et al*, in an excellent review of the ionic contributors to cellular repolarization reserve (3).

Measurement of repolarization reserve in whole animal models has provided additional insights into clinical risk factors for TdP. These models highlight the importance of Triangulation, Reverse use-dependence, Instability (of repolarization current), and Dispersion of Refractoriness, together known as the TRIaD model (2). Haraguchi *et al* who modeled transmural dispersion of repolarization (TDR) during ventricular tachycardia provide a good example of applying this approach to TdP (24–16). They found that arrhythmia risk in TdP is related to scroll wave stability, and is not directly associated with QT interval width. In a rabbit heart model of TdP, Wu *et al* found that reverse use-dependence of I_{Kr} -blocking drugs, such as sotalol, is directly associated with endogenous late sodium current (I_{Na-L}) (25). This contributes to increases in APD and beat-to-beat variability of repolarization, both independent risk factors for TdP.

Attempts to use the TRIaD model to screen and predict torsadogenic risk associated with pharmaceutical agents have been met with variable success. Yang *et al* found that some but not all I_{Kr} -blocking drugs (such as dofetilide) augment I_{Na-L} through the phosphoinositide 3-kinase pathway, and thus directly contribute to proarrhythmia through a novel mechanism that is distinct from I_{Kr} -related APD prolongation that is used by regulatory agencies to stratify TdP risk (26). Likewise iPSC models for screening TdP risk have been described which can model patient-specific genetic variants and link this variation to diLQTS risk (27,28) directly aligning with the Precision Medicine Initiative of the National Institutes of Health (29). With improved understanding of the underlying mechanisms of both genetic and acquired forms of TdP, the opportunity to personalize selection of AAD therapy based on individual risk factors may become a reality (Table 1).

Female Gender

Female gender has long-been recognized as an independent risk factor for prolongation of the QT interval, congenital LQTS, diLQTS, and TdP (30). Females have a higher resting heart rate than males with QT intervals on average that are 20 msec longer (31,32). Adult females are 2–3 times more likely than men to experience episodes of TdP. However, the underlying mechanism(s) for this differential effect in females remains poorly understood (33). Yang *et al* used the O'Hara-Rudy model, an established *in silico* model of ventricular repolarization, to create simulated “male” and “female” cells and tissues to explore reduced repolarization reserve in females (32). The model incorporated reduced repolarizing potassium currents and connexin-43 expression, both observed in human females, and

showed that such differences were sufficient to predict prolongation of APD in epicardial and endocardial cells in females. In addition, Gonzalez *et al* used a related Luo-Rudy *in silico* model to show that adult female myocytes have reduced ventricular repolarization reserve, and that simulated exposure to dofetilide is associated with decreased I_{Ks} , steeper APD to basic cycle length relationship, and increased susceptibility to early afterdepolarizations (EAD) when compared to adult male cells under the same conditions (³⁴). Interestingly, these investigators found that this difference was age-dependent; there were essentially no differences between *in silico* models of young male and young female ventricular myocytes. One significant difference in TdP risk between young and adult females may be due to the effects of hormone-related changes in ventricular repolarization. Ando *et al* showed that the contribution of I_{Kr} encoded by *KCNH2*, is significantly affected by β -estradiol when stably expressed in human embryonic kidney (HEK)-239 cells *in vitro* (³⁵). *KCNH2* currents were inhibited to 62% of control at baseline; when combined with erythromycin, a known I_{Kr} -blocking antibiotic, there was additional *KCNH2*-mediated current inhibition to 42%, suggesting that in some cases, females may be more susceptible to dILQTS. However, these findings need to be confirmed with additional *in vitro* experiments.

Sex hormone experiments in rabbit hearts, which unlike mice or rats express I_{Kr} , have yielded several informative observations regarding risk of TdP. In Langendorff-perfused rabbit hearts, estradiol prolongs monophasic APD in a concentration-dependent manner (³⁶). In contrast, progesterone prolongs it at lower concentrations (1–3 μ M), but shortens the monophasic APD at higher, more physiologic conditions (10–30 μ M), suggesting a biphasic pattern (³⁷). Additionally, progesterone protected against sotalol-induced pro-arrhythmic events, suggesting that hormone-based APD prolongation may mediate risk of TdP. In a related study, Cheng *et al*, showed in a chronic model of female hormone modulation (ovariectomy followed by hormone replacement therapy with either estrogen, progesterone, or both) that estradiol may potentiate the QTc prolonging effects of d,l-sotalol, whereas progesterone protects against QT prolongation and related arrhythmias by accelerating the process of repolarization (³⁷). Tisdale *et al* showed a similar protective effect of progesterone (versus estrogen) in female rabbits ovariectomized and implanted with estrogen, progesterone, and testosterone (³⁸). Thus, there is strong evidence to support sex hormones as a significant contributor to APD, QT prolongation, and risk of ventricular arrhythmias including TdP.

Bradycardia

Bradycardia and bradyarrhythmias are risk factors for the development of life threatening arrhythmias, including TdP. However, it is not possible to fully predict TdP risk from QT interval duration and/or AVB alone (³⁹). In a study of 20 patients (15 females, age 65.9 ± 15.6 years), Cho *et al* characterized specific 12-lead ECG patterns in patients diagnosed with atrioventricular (AV) block and displaying TdP waves, and compared these ECGs with 80 age- and sex- matched controls without TdP. The development of TdP was typically induced by premature ventricular complexes and all TdP ECGs displayed significant differences in phase 4 repolarization parameters including increased mean QT interval (716.4 ± 98.9 ms vs 523.2 ± 91.3 ms, $P = .001$), mean T peak to end interval (334.2 ± 59.1 ms vs 144.0 ± 73.7 ms, $P = .001$), and a higher T peak to end interval/QT ratio

(0.49 ± 0.09 ms vs 0.27 ± 0.11 ms, $P = .001$) (³⁹). The following additional T-wave parameters also proved to be more prevalent in TdP-displaying AV block patients compared to non-TdP controls: notched T waves (i.e., $T_2 > T_1$); triphasic T waves; reversed asymmetry; and T wave alternans; ($P = .001$). A combination of these wave parameters allowed delineation of TdP cases from non-TdP cases with high sensitivity (85%) and specificity (98%).

Rosso *et al* realized comparable results when examining arrhythmogenic effects of cardiac memory in patients with LQTS complicating AV block (⁴⁰). The concept of cardiac memory purports that T waves that were once abnormal secondary to irregular QRS waves (e.g., AV block), possess a memory of the vectors of the altered QRS waves and continue to behave under those abnormal conditions. During AV block, the magnitude of the QT prolongation in response to the bradycardia is a determining risk factor for TdP. Rosso *et al* assessed patients with similar bradycardic profiles and sought to answer why some patients experience more QT prolongation than others, and if this variation in magnitude predisposes to TdP. They examined 91 patients with either 2:1 or high-degree/complete AV block (mean age of 77 ± 12 years, 53% males). On average, patients with complete AV block presented with longer R-R interval and QT interval duration than those with 2:1 block. Specifically, the analysis focused on alterations in three parameters: change in QRS (QRS) morphology, QRS axis, and both QRS morphology and axis together, in the setting of AV block and effect on QT prolongation. Despite similar age, sex and ECG parameters, including R-R intervals during AV block, subjects with positive QRS morphology showed significantly longer QT and corrected-QT interval (QTc), using Bazett's Formula to assess risk for TdP, compared to cases without QRS morphology (229 ± 84 ms vs. 51 ± 86 ms, $P < 0.001$; and 46 ± 80 ms vs. -6 ± 74 ms, $P = 0.001$). Eight cases of AV block-related TdP were recorded for patients with QRS morphology versus four in those without, ($P = 0.026$). Spearman correlation showed a significant correlation between QRS axis and QT ($r = 0.218$; $P = 0.025$), as well as QTc ($r = 0.308$; $P = 0.001$). A similar number of cases were recorded for TdP in QRS axis versus no changes (eight vs. four; $P = 0.023$, respectively). AV block presented the greatest QT prolongation (250 ± 100 ms; $P < 0.001$) when changes in both QRS morphology and axis were present. Rosso *et al* showed that a change in QRS morphology during AV block independently predicted LQTS and was strongly associated with TdP (⁴¹). They believe this analysis supports cardiac memory playing a vital role in enhancing QT prolongation; which can further predict TdP during bradycardic events. Moreover, the longer the period of irregular ventricular QRS complexes, the more likely it is that T waves will display a longer period of abnormal behavior. Interestingly, Obreztkhikova *et al* claimed that the morphology of abnormally transcribed I_{Kr} leads to reduction of myocyte potassium channels, which can further potentiate QT prolongation (⁴²). In addition, in a canine model, the heterogeneity of transmural repolarization gradients were attributed to the induction of cardiac memory T wave morphology, increasing epicardial left ventricular repolarization gradients (⁴³).

Hypokalemia and Hypomagnesemia

Approximately 28% of TdP reports in the literature are associated with either hypokalemia or hypomagnesemia (⁴⁴). Hypokalemia is strongly associated with TdP and has been shown to play a significant role in diLQTS (⁴⁵). Drug-induced hypokalemia occurs primarily through three recognized mechanisms: 1) transcellular potassium shift (β_2 -agonists, insulin,

caffeine); 2) increased renal potassium loss (diuretics, mineralocorticoids, penicillins, glucocorticoids); and 3) excess potassium loss in stool (phenolphthalein, sodium polystyrene sulfonate) (46). Recent reports of the effects of hypokalemia on myocardial repolarization currents have implicated I_{Kr} and I_{Ks} in the pathogenesis of TdP. Heterogeneity of potassium channel concentration may partially explain reduction in repolarization reserve in hypokalemia. Guo *et al* showed in HEK-293 cells that extracellular (serum) $[K^+]_o$ is directly associated with expression of the *KCNH2* gene and I_{Kr} (47). Reduction of $[K^+]_o$ was associated with accelerated internalization and degradation of *KCNH2*-channels within hours through ubiquitination. Later work from this group showed that in HEK-293 cells co-expression of I_{Kr} and I_{Ks} may delay hypokalemia-induced *KCNH2* degradation through a direct protein-protein interaction; this was not seen by single channel expression of either channel alone (48). Heterogeneity in TDR may also partially explain TdP susceptibility in hypokalemia. Killeen *et al* showed, in isolated mouse hearts, that hypokalemia reduces

APD₉₀ between epicardium and endocardium resulting in EADs and non-sustained ventricular tachycardia and sustained ventricular tachycardia upon programmed electrical stimulation (49). Likewise, Melgari *et al* performed whole-cell patch-clamp measurements of HEK-293 cells stably expressing *KCNH2*-channels, and showed that under conditions of hypokalemia (4 to 1 mmol/L potassium) that there is a significant reduction in the I_{Kr} contribution to ventricular repolarization, resulting in pathological premature extrastimuli (50). Thus, there is a direct link between extracellular potassium concentration $[K^+]_o$, and the function and expression of I_{Kr} and I_{Ks} .

In addition to the direct effects on $[K^+]_o$, hypokalemia is known to worsen repolarization reserve in patients who have drug-related or genetic alterations in ventricular repolarization. Common drugs known to induce QT interval prolongation and resultant TdP include: citalopram, escitaloprim, methadone, ondansetron, and azithromycin. For a more complete list and accompanying discussion, Trinkley *et al* offer an excellent overview (Table 2) (51). Each one of these drug categories may have increased TdP risk by the presence of hypokalemia due to partial inhibition of I_{Kr} . Of interest, licorice is a known cause of hypokalemia due to inhibition of the 11 β -hydroxysteroid dehydrogenase (type II), which leads to excess cortisol excretion and “pseudohyperaldosteronism,” and in extreme cases may result in TdP (52). Genetic mutations in *KCNH2* (T473P) and *KCNE1* (G38S) increase susceptibility to hypokalemia-induced TdP by reducing repolarization reserve and QT interval prolongation, demonstrating a drug-independent, genetic predisposition to hypokalemia-related TdP risk (14,53). These findings underscore the importance of pharmacogenetic mechanism in the determination of TdP risk (discussed further in Chapter 10 Pharmacogenetics of Potassium Channel Blockers).

Although hypomagnesemia has been implicated in risk for TdP, the underlying mechanism has been less well described. Hypomagnesemia primarily occurs through chronic use of loop diuretics, thiazide diuretics, or alcohol; other causes include intestinal malabsorption and reduced dietary intake (54). Although Mg^{2+} flux is not a direct contributor to repolarization current, extracellular $[Mg^{2+}]$ has a membrane-stabilizing effect by facilitating normal function of the Na/K pump; without sufficient Mg^{2+} available to this membrane channel, there is depletion of intracellular $[K^+]$, reducing transmembrane K^+ gradient and leading to membrane depolarization and TdP (54). Hypomagnesemia has been linked to increased

inpatient mortality (⁵⁵) and arrhythmia risk; though the link between hypomagnesemia and TdP related mortality is yet unproven (⁵⁶⁻⁵⁸). Recently, there has been some controversy regarding the arrhythmic risk of proton-pump inhibitor (PPI)-related hypomagnesemia. It is currently unknown whether PPIs contribute to TdP risk in patients with gastrointestinal disease and electrolyte disturbances (⁵⁹⁻⁶¹). As the mechanism of this observation is currently unknown, further translational studies and controlled prospective trials will be necessary to determine the contribution of PPIs towards TdP risk.

Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its incidence is steadily on the rise (⁶²). Currently, the lifetime risk of AF is 1:4 for men and women, and by the year 2050, over 12 million Americans will be affected (^{62,63}). AF remains an independent risk factor for the development of stroke, thromboembolism, heart failure, and impaired quality of life. Likewise, conversion of AF to sinus rhythm is associated with modest long-term improvements in cardiac function, stroke risk, and quality of life (⁶⁴). Dispersion of refractoriness of atrial tissue contributes to the mechanism of AF, and thus I_{Kr} -blocking AADs are prominent anti-arrhythmic therapies to treat patients with AF. However, many AADs used to treat AF block I_{Kr} and may result in toxicity that includes QT prolongation and TdP (⁶⁵).

Conversely, there is evidence to support the idea that AF in and of itself, protects against TdP risk, and that after conversion from AF to sinus rhythm, risk of TdP actually increases (⁴). For example, TdP has been noted to occur immediately after conversion of AF to sinus rhythm (^{6,66,67}). While this may reflect a reduction in the heart rate that often accompanies restoration of sinus rhythm, recent studies suggest that the underlying mechanisms are likely to be more complicated. In an elegant study, Choy *et al* examined the extent of QT prolongation by intravenous dofetilide during AF and immediately after restoration of sinus rhythm (⁶⁸). Surprisingly, there was minimal change in the QT interval during AF after intravenous dofetilide. However, shortly after return of sinus rhythm, the QT interval prolonged markedly despite dofetilide not changing the heart rate (Figure 2). This group has subsequently gone to show that QT-RR slopes are very flat during AF even after long pauses, and steepen markedly after restoration of sinus rhythm supporting the hypothesis that AF itself modulates the QT interval both during AF and shortly after conversion to normal rhythm (^{69,70}).

The mechanism whereby AF may reduce TdP risk is currently unknown. However, AF-related cellular remodeling may be related to preservation of TDR, which in turn, may lead to reduced susceptibility of TdP in patients with diLQTS (⁴). In addition, our group has postulated that AF generates mechanisms rendering the QT interval resistant to marked prolongation, despite variable R-R intervals and short-long-short cycles. In ongoing studies, detailed phenotyping of a large cohort of patients undergoing elective direct current (DC)-cardioversion for AF is being performed, and the extent of QT interval change is being related to measures of candidate QT modulators, such as inflammation, oxidant stress, catecholamines and atrial natriuretic factor (ANF) (Figure 3) (⁷¹). Furthermore, with the development of reliable methods of measuring the QT interval during AF allows us to assess

QT during AF and compare it to QT in sinus rhythm, taking into account changes in rate (69). The QT intervals during and following atrial pacing will also be assessed and related to pacing rate, duration and measures of candidate QT modulators. Other groups are also relating atrial rate to molecular changes underlying ventricular function and rhythm maintenance in order to further dissect this mechanism (72).

The Role of Variable Drug Concentrations in Torsades de Pointes Risk

Initial reports with quinidine noted that the adverse effect often occurred within 24 hours of starting the drug, at a time when excessive accumulation of drug (or potentially active metabolites) would not be expected. Indeed, with routine plasma concentration monitoring came the frequent observations of “sub-therapeutic” quinidine concentrations in patients developing TdP (6,73,74). Studies as early as the 1940s (75,76) identified multiple quinidine metabolites, raising the possibility that variability in response to the drug might reflect variable activity or accumulation of metabolite(s). However, subsequent studies established that the multiple metabolites demonstrate less *in vitro* electrophysiologic activity than the parent drug (77) and that plasma concentrations at the time of TdP were generally lower for the metabolite compared to the parent drug (78). The lack of a relationship between plasma quinidine concentrations and TdP risk likely reflects the drug’s inhibition of multiple ion currents with a range of potencies: block of I_{Kr} at low concentrations (79) to prolong action potentials; and at higher concentrations block of other potassium currents to prolong action potentials (80,81) and block of sodium current (in a frequency-dependent fashion) to shorten action potentials (82,83).

By contrast, TdP developing during therapy with most other AADs (sotalol, dofetilide) and non-cardiovascular therapies (thioridazine, methadone) appears to be dose- or concentration-related (84,85). Thus, conditions leading to accumulation of QT-prolonging agents in plasma are in general risk factors for TdP. Sotalol and dofetilide undergo renal excretion and therefore require dose reductions in patients with reduced renal function to avoid TdP (84,86). This concept extends to drug metabolism: thioridazine is a CYP2D6 substrate and some data suggest that the drug accumulates in plasma in poor metabolizers with more marked QT prolongation (87). Similarly, the QT prolonging S-enantiomer of methadone is eliminated by CYP2B6-mediated metabolism and individuals with reduction-of-function alleles in this gene may therefore be at increased risk for methadone-induced TdP (88).

Effects of Drug Concentration on QT Interval and Arrhythmia Risk

The treatment of arrhythmias with traditional antiarrhythmics has long been known to be beneficial, but also to carry proarrhythmic and pro-torsadogenic side effects. Blockade of the KCNH2 channel, specifically I_{Kr} , and subsequent QT prolongation as observed on surface ECG can predict torsade de pointes (52). However, QTc prolongation alone could not be attributed to either pure I_{Kr} -blockade from multichannel blockade. In order to differentiate the effects, in a prospective, randomized controlled trial with 22 patients (mean age of 26.9 ± 5.5 years, 11 females) Johannesen *et al* administered dofetilide (pure I_{Kr} -blocker) along with three other antiarrhythmics - quinidine (Na^+ channel blockade), ranolazine (Na^+ channel blockade; commonly used as an anti-anginal), and verapamil

(cardiac specific L-type Ca^{2+} channel blockade), each exhibiting varying degree of I_{K_r} channel blockade as well. Direct blockade of the K^+ channel by class III antiarrhythmic dofetilide prolonged both early (J-T_{peak}) and late ($\text{T}_{\text{peak}} - \text{T}_{\text{end}}$) repolarization currents, while multichannel blockade from the other antiarrhythmic classes primarily resulted in shortening of early repolarization (J-T_{peak}) segment. This observation allowed differentiation of the effects of antiarrhythmics during repolarization. This has clinical significance of course; the ability to track changes in J-T_{peak} and $\text{T}_{\text{peak}} - \text{T}_{\text{end}}$ offers more precise observations in cardiac drug safety evaluation. Specifically, in understanding the triggers for arrhythmias and TdP, it has been shown that blockade of I_{K_r} can potentiate TdP due to increased Na^+ and Ca^{2+} inward current, EAD. Thus, inhibition of this inward ion flux through multichannel blockade may minimize EADs and reduce the risk of arrhythmogenesis and subsequent TdP. While the direct I_{K_r} blockade by the class III antiarrhythmic dofetilide has been shown to prolong both early and late repolarization currents, the effect of drugs from other classes on I_{K_r} channels (in addition to their respective target channel) appear to alter either the Ca^{2+} and/or Na^+ inward currents, resulting in prolongation of early repolarization.

Sugrue *et al* (⁵³) examined 13 cases of drug-induced TdP secondary to administration of either dofetilide (5 cases, 80% female) or sotalolol (8 cases, 75% female), both known to affect cardiac K^+ channels with pro-arrhythmogenic and pro-torsadogenic properties (⁵⁹, ⁶⁰). Compared to 26 age and sex-matched controls, the accuracy in predicting TdP risk improved by 9% in cases receiving class III antiarrhythmic drugs when QTc and T wave right slope measurements during phase 4-repolarization were combined (QTc, 79%; QTc and T wave right slope, 88%) (⁵³). QTc in lead V6 and the T wave right wave slope in aVR were most prominent T wave parameters contributing to a strong correlation with TdP (QTc in V6, mean case vs. control: 500 ± 44 vs. 410 ± 38 msec, $p < 0.001$, $r = 0.77$; T wave right wave slope in aVR, mean case vs. control: -682.88 ± 38 vs. -1509.53 ± 44 mV/s, $p < 0.001$, $r = 0.56$). ECG analysis showed comparable correlations with QTc in lead V3 and T wave right slope in lead I. Of the parameters, this analysis showed that T wave right slope in Lead I possessed high correlation to risk of arrhythmias and allowed delineation of TdP risk from the control groups. Specifically, the characteristics of the slope of the T wave in Lead I were of focus, amplitude and duration of the terminal portion of the wave. The results suggest that the TdP cases (13/39) presented with shallower right slopes, possibly implicating substantial dispersion of the refractoriness in both the transmural and apicobasal gradients. Sugrue *et al* further investigated alterations in index center of gravity (COG), comprising of mean x and y -coordinates during T wave progression. They suggest COG x accounted for subtle differences in T waves in TdP cases compared to the control cases. This indicates that in cases with T wave abnormalities, particularly the amplitude and duration, COG x interpretations have the potential to predict those most likely at risk for arrhythmogenesis and TdP.

Conclusions/Summary

Torsadogenic and ventricular arrhythmic risk from ion channelopathies do not occur in isolation, and involve underlying clinical risk factors that represent stressors to the homeostasis of potassium repolarization currents. Risk factors such as female gender,

bradycardia, hypokalemia, hypomagnesemia, restoration of sinus rhythm from AF, drugs and genetic variants encoding *KCNH2*-mediated currents that affect QT interval all figure prominently in the assessment of a patient's overall risk for developing a malignant ventricular arrhythmia. Through the evaluation of clinical risk factors and relating this data to knowledge of drug-induced or genetically determined alterations in potassium channel current (such as I_{Kr}), it is possible to more accurately stratify and then ameliorate their torsadogenic risk. Further research into improved understanding of the underlying mechanisms by which I_{Kr} -blocking drugs mediate QT interval prolongation and TdP are necessary to bridge the clinical and basic factors of arrhythmia risk and prediction scores. Furthermore, incorporating data from both realms will help to prevent these lethal arrhythmias before they happen, thus fulfilling the promise of predictive and precision medicine.

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Key Points

- The most common arrhythmia requiring antiarrhythmic drugs is atrial fibrillation
- Many antiarrhythmic drugs used to treat atrial fibrillation block the rapid delayed rectifier K^+ current (I_{Kr}), and marked QT prolongation and torsades de pointes are major class toxicities
- Risk factors associated with drug-induced QT prolongation and risk of torsades de pointes including female gender, bradycardia, electrolyte disturbances, recent conversion from atrial fibrillation to sinus rhythm, variations in drug distribution and sub-clinical congenital long QT syndrome
- Incorporating data from the clinical and basic realms will improve our understanding of the underlying mechanisms by which potassium-channel blocking drugs mediate QT prolongation and increased susceptibility to torsades de pointes
- Bridging this gap will not only help prevent drug-induced torsades de pointes but also fulfill the promise of predictive and precision medicine.

Figure 1. A 12-lead ECG demonstrating induction of torsades de pointes

The 12-lead ECG was taken from a 79 year-old patient with advanced heart failure, who recently began taking dofetilide. The long QT interval is followed by a long pause (as indicated by a star), followed by 4 beats of torsades de pointes (TdP), and then sustained TdP. [Reprinted from Kannankeril P, Roden DM, Darbar D. Drug Induced Long QT Syndrome ⁽⁴⁾. Courtesy of American Society for Pharmacology and Experimental Therapeutics, Bethesda, MD; with permission.

Figure 2. Evidence for abnormal QT control revealed by infusion of dofetilide prior to and following conversion of atrial fibrillation (AF)

This study compared the effect of dofetilide on QT Interval when the drug was administered as a bolus and maintenance infusions over 100 minutes during AF, and again within 24 hours of conversion to sinus. There was no major effect of dofetilide on QT when the underlying rhythm was AF (top panel). When the same infusion, reaching the same concentrations (bottom panel) was administered during sinus rhythm (SR), two groups of responses were delineated: group I had marked QT interval prolongation (requiring premature cessation of the infusion), while group II responded as in AF, with no major

change in QT, and received the whole infusion. Note that dofetilide produced no change in heart rate from pre-drug baseline in any group, and that baseline heart rates differed by <10 beats per minute (bpm) in groups I and II during SR. Thus, heart rate slowing by cardioversion cannot be the sole explanation for the marked drug sensitivity seen here.

Figure 3. Potential mechanisms by which the QT interval is modulated prior to and following cardioversion in patients with AF

As described in the text, challenge with an I_{Kr} -blocking drug when the underlying rhythm is AF generates little change in QT interval whereas the same challenge shortly after SR is restored can produce marked QT prolongation and torsades de pointes (Figure 2). The rhythm strips show such a result with dofetilide; note the heart rates during AF and SR are similar, and that the drug did not change heart rate. These and other data described in the text suggest that AF generates mechanisms rendering the QT resistant to marked prolongation, despite variable RR intervals and short-long-short cycles. In ongoing studies, detailed phenotyping of a large cohort of patients undergoing elective DC-cardioversion for AF is being conducted and changes in QT will be related to measures of candidate QT modulators, such as inflammation, oxidant stress, catecholamines and atrial natriuretic factor (ANF). The development of reliable methods to assess QT interval during AF will permit the evaluation of QT intervals during AF and in SR taking into account changes in heart rate. In addition, comparison of QT intervals during and following atrial pacing, and relating the pacing rate, duration and measures of candidate QT modulators will be performed.

Table 1

Clinical risk factors, mechanisms, the magnitude of risk and novel models used to define the underlying mechanisms relating patient characteristics with the development of QT interval prolongation and torsades de pointes.

Clinical Risk Factor	Mechanism	Magnitude of Risk	New Models of TdP
Female gender	Estrogen-induced reduction in repolarization reserve	Females at increased risk: 2:1 to 3:1 versus males	Yang <i>et al</i> , 2012 Gonzalez <i>et al</i> , 2010 Ando <i>et al</i> , 2011 Cheng <i>et al</i> , 2012
Bradycardia	Pause-dependent QT prolongation. Short-long-short sequence	Typically with heart rates < 60 bpm	Cho <i>et al</i> , 2015 Rosso <i>et al</i> , 2014
Hypokalemia	Decreased I_{Kr}	Serum K^+ < 3.5 mg/dL	–
Hypomagnesemia	Modulation of I_{CaL}	Serum Mg^{2+} < 1.5 mg/dL	–
Conversion from AF to sinus	Increased QT interval variation	1–3% incidence of TdP associated with diLQTS	Choy <i>et al</i> ., 1999 Darbar <i>et al</i> ., 2007 Kannankeril <i>et al</i> , 2010
Pharmacotherapy	Prolongation of QT interval by direct modification of ion channel function	QT-prolonging drugs may increase QT interval by up to 50 msec in clinically-prescribed doses	Johannesen <i>et al</i> , 2014 Sugrue <i>et al</i> , 2015

AF, atrial fibrillation; bpm, beats per minute; diLQTS, drug-induced long QT syndrome; TdP, torsades de pointes

Table 2

Potassium channel blocking antiarrhythmics and common drugs that block I_{K_r} and lead to QT prolongation and increased susceptibility to torsades de pointes.

Antiarrhythmic drugs

Disopyramide

Dofetilide

Sotalol

Procainamide

Ibutilide

Bepridil

Amiodarone

Common drugs

Arsenic trioxide

Cisapride

Calcium-channel blockers: lidoflazine

Antiinfective agents: Clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxacin

Antiemetics: domperidone, droperidol

Antipsychotic agents: chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide

Methadone