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Persistent Atrial Fibrillation Is Associated With Reduced Risk of Torsades de Pointes in Patients With Drug-Induced Long QT Syndrome

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Objectives The goal of this study was to identify markers of torsades de pointes (TdP) in patients with drug-associated long QT syndrome (LQTS).

Background Drug-induced LQTS includes individuals developing marked prolongation of ventricular repolarization on exposure to an offending drug. Under these conditions, TdP develops in some but not all patients.

Methods This was a case-control study of 123 adults with drug-associated LQTS. Patients were divided into LQTS only (LQTS; n = 40, QT >500 ms on drug) and LQTS + TdP (TdP; n = 83).

Results Baseline QT intervals were similar in the 2 groups (381 ± 38 ms [LQTS] vs. 388 ± 43 ms [TdP]). Clinical variables associated with risk of TdP included hypokalemia and female gender; by contrast, persistent atrial fibrillation (AF) at the time of drug discontinuation for QT prolongation was protective despite similar heart rates in AF and sinus rhythm (n = 20, 71 ± 13 beats/min vs. 69 ± 13 beats/min). Electrocardiographic variables that significantly increased the risk for TdP included absolute and rate-corrected QT intervals (QTc) on drug therapy, the magnitude of QT and QTc interval prolongation, and the change in T_{peak} to T_{end} (ΔT_p–T_e), a relatively new index of transmural dispersion of repolarization and potential arrhythmogenicity. Multivariable logistic regression analysis revealed that only gender was predictive for TdP, whereas persistent AF at the time of drug discontinuation for QT prolongation (odds ratio 0.14, 95% confidence interval 0.03 to 0.63, p = 0.01) was negatively associated with the arrhythmia.

Conclusions This study strongly suggests that despite ongoing rate irregularity, AF reduces the likelihood of developing TdP after the administration of drugs that prolong cardiac repolarization. (J Am Coll Cardiol 2008;51:836–42)

Marked prolongation of ventricular action potential duration, shown on the surface electrocardiogram (ECG) as QT prolongation, can cause the life-threatening arrhythmia torsades de pointes (TdP) (1,2). Administration of QT-prolonging antiarrhythmic drugs is the most common cause of the drug-associated (acquired) long QT syndrome (LQTS), although other drugs, notably antihistamines, antipsychotics, and gastrointestinal prokinetic agents, have been implicated (3–5). In the past decade, the single most common cause of the withdrawal or restriction of the use of drugs that have already been marketed has been the prolongation of the QT interval associated with TdP. Although guidelines aimed at predicting whether a new drug carries this risk have been developed, current predictors of this serious side effect are imperfect, both for individuals and for populations of patients exposed to a given drug (6,7).

Risk factors for acquired LQTS have been identified and include high drug doses, bradycardia, and hypokalemia (8). However, predicting development of TdP, particularly in the absence of high doses or plasma concentrations, can be problematic (9,10). Although it may be possible to predict that a given drug may carry some risk, neither accurate assessment nor quantification of the risk has so far been possible. In fact some drugs that significantly prolong the QT interval are only rarely associated with TdP; this may be because of their limited effect on transmural dispersion of

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repolarization (TDR) (11). One reason that predicting TdP remains challenging relates to the impracticality of performing large-scale, prospective, placebo-controlled studies that may delineate individual characteristics predisposing to drug-induced TdP. The goals of this study, therefore, were to evaluate clinical and electrocardiographic characteristics predictive of development of TdP in a cohort of patients with drug-associated LQTS.

Abbreviations and Acronyms

AF = atrial fibrillation
ECG = electrocardiogram
LQTS = long QT syndrome
SR = sinus rhythm
TdP = torsades de pointes
TDR = transmural dispersion of repolarization
T_p–T_e = T_{peak} to T_{end}

Methods

Patient ascertainment. This was a retrospective case-control study of patients enrolled in the Vanderbilt Acquired LQTS Registry. Inclusion criteria included age >18 years, documented QT prolongation (≥500 ms), and/or TdP after exposure to a known QT-prolonging drug or drug combination with a baseline QT interval that was normal (QT ≤440 ms). Torsades de points was defined in terms of typical ECG features, including QT prolongation or deformity, pause-dependent onset, and sustained polymorphic ventricular tachycardia (faster than 150 beats/min and lasting ≥10 beats) with QRS complexes of changing amplitude that twist around the isoelectric line. Often however, this twisting morphology may not be apparent when only short bursts occur; consequently, episodes of ventricular tachycardia that were <10 beats were not considered diagnostic for TdP. Over a 15-year period, 146 patients were enrolled in the registry. Of these, 93 patients developed TdP and 50 had QT prolongation alone. However, for these analyses patients (n = 8) without baseline ECGs before initiation of the drug therapy or those in whom an ECG was not obtained within 24 h of either discontinuing drug therapy because of QT interval prolongation or an episode of TdP were excluded. In addition, in 15 patients telemetry strips were of insufficient quality to measure the QT intervals and the data from these patients were also excluded from the analyses. For Vanderbilt patients, informed consent approved by the institutional review board was obtained. For non-Vanderbilt patients, local Human Subjects approval was obtained.

Atrial fibrillation (AF) was defined as the replacement of sinus P waves by rapid oscillations or fibrillatory waves that varied in size, shape, and timing and were associated with an irregular ventricular response when the atrioventricular conduction was intact. Documentation of AF on an ECG, rhythm strip, event monitor, or Holter monitor was required.

Arterial hypertension was defined by a history of hypertension and patients taking an antihypertensive agent. Criteria for coronary artery disease (CAD) included a history of myocardial infarction or typical angina, previous bypass surgery, or angioplasty or drug treatment. Congestive heart failure (CHF) was defined by a history of CHF or drug treatment for heart failure. Left ventricular hypertrophy was electrocardiographically defined by either the Cornell voltage (SV_3 + RaVL) >2.8 mV for men and >2.0 mV for women or Sokolow-Lyon voltage amplitude (SV_1 + RV_5 or RV_6) >3.5 mV.

QT analysis. The ECGs were analyzed using a semiautomated digitizing program by an experienced observer blinded to all clinical details. The QT interval was measured from the onset of the QRS interval to the end of the T-wave in all of the leads where the end of the T-wave could be clearly defined. The longest QT interval in any of these leads was used as the measured QT interval. The mean of 3 consecutive QT intervals were measured not only in sinus rhythm (SR), but also when the patient was in AF. The mean QT was then corrected for the heart rate (QTc) with the preceding time duration between 6 consecutive R waves of the ECG (RR interval) and the Bazett formula ($QTc = QT/RR^{1/2}$) (12). However, formulas that normalize QT-interval measurements to heart rate may be problematic in acquired LQTS; additionally, formulas designed for SR may be inappropriate for irregular rhythms such as AF, therefore changes in absolute QT durations are also reported (13). A new measure of arrhythmogenicity that has been proposed is the T_{peak}–T_{end} (T_p–T_e) interval, which is the interval from the summit of the T wave to the end of the QT interval (14–16). Whenever double T waves (also known as notched, humped, or pathological U waves) were present, the first and second components of the T-wave were defined as T1 and T2. The QT interval was then measured from the onset of the QRS interval to the end of T2, whereas Tp–Te was measured from the summit of T1 to the end of T2 (17). Physiological U waves, defined as U waves that are smaller than the T-wave and are completely separated from it by an isoelectric segment, were not counted as part of any of the QT interval. Although baseline 12-lead ECGs were available in all patients, 25 (20%) patients only had single-lead telemetry strips at the time of drug discontinuation because of QT prolongation or TdP. In these patients, the same lead was used for QT interval measurement at baseline and after initiation of drug therapy.

Intraobserver variability was examined by randomly selecting 50 ECGs to be reanalyzed by the same observer; the coefficient of variation (standard deviation/mean × 100) for QT and T_p–T_e measurements were 3% to 7% and 2% to 4%, respectively. To examine for interobserver variability, independent duplicate determination were made by a second blinded observer; the coefficient of variation between patients was 7% to 9% and 6% to 8% for QT and Tp–Te evaluations, respectively.

Statistical analysis. Continuous variables are expressed as mean ± standard deviation, and their distributions were analyzed using the Shapiro-Wilks test of normality. A comparison between the groups was performed with Stu-

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Table 1 Patient Characteristics

	TdP Group (n = 83)	LQTS Group (n = 40)
Age (yrs)	59 ± 13	59 ± 15
Female (%)	56 (67)	14 (42)*
Hypertension (%)	54 (65)	22 (55)
CHF (%)	34 (41)	10 (25)
Coronary artery disease (%)	30 (36)	16 (40)
Left ventricular hypertrophy (%)	15 (18)	8 (20)
Cardiomyopathy (%)	12 (14)	4 (10)
Diuretics	21 (25)	8 (20)
Serum potassium (mEq/l)	3.9 ± 0.6 (n = 79)	4.1 ± 0.5 (n = 38)
Serum magnesium (mEq/l)	1.9 ± 0.5 (n = 45)	1.9 ± 0.2 (n = 20)
Hypokalemia, <3.5 mEq/l (%)	53 (64)	3 (8)†

*$p < 0.01$ versus TdP group. †$p < 0.001$.
CHF = congestive heart failure; LQTS = long QT syndrome; TdP = torsades de pointes.

dent *t* test or the nonparametric Wilcoxon rank-sum test, as appropriate. Categorical variables, expressed as numbers and percentages, were compared with the Fisher exact test. The relationship between clinical and ECG variables and development of TdP was further assessed with univariate and multivariable logistic regression analyses, and results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). All tests of significance were 2-tailed, and a p value of <0.05 was considered to indicate statistical significance.

Results

One hundred twenty-three unrelated patients whose ECG showed QT prolongation ≥500 ms and/or TdP during drug challenge, and whose ECG recovered to normal after the offending drug was stopped, constituted the study cohort. These 123 patients included 83 patients (TdP group) who were diagnosed with drug-associated TdP. The remaining 40 patients (LQTS group) who developed QT interval prolongation without TdP constituted the control group. There were no episodes of polymorphic ventricular tachycardia <10 beats in the study cohort. Cases are included here both from Vanderbilt University Medical Center (n = 104) and elsewhere (n = 19). The clinical history was obtained by review of patient medical records.

Clinical characteristics. The clinical characteristics of the 2 groups of patients are shown in Table 1. The 2 groups were matched for age, the prevalence of CAD, hypertension, and ECG-defined left ventricular hypertrophy. However, the proportion of women was significantly higher in the TdP group.

Table 2 shows the drugs that patients were taking at the time of QT interval prolongation or development of TdP. Nine of the drugs were conventional antiarrhythmic drugs, and 11 were noncardiovascular agents. A 12-lead ECG showing QT interval prolongation (700 ms) from a 36-year-old man treated with quinidine for AF is shown in Figure 1.

In contrast, Figure 2 (top panel) shows an ECG from a patient started on sotalol during AF, showing minimal change in QT intervals despite frequent short-long-short cycles. After direct current cardioversion, the QT interval has increased dramatically to over 640 ms (middle panel) and an episode of TdP is triggered (bottom panel).

AF in cohort. Baseline heart rate in AF was comparable in the TdP group (80 ± 16 beats/min) and LQTS group (78 ± 14 beats/min, $p > 0.05$), as was the heart rate in the non-AF groups (TdP 62 ± 12 beats/min vs. LQTS 66 ± 10 beats/min, $p > 0.05$). The QT and QTc in the AF group were similar to those patients who were in SR before initiation of a QT-prolonging drug (QT: AF 384 ± 40 ms vs. SR 390 ± 34 ms; QTc: AF 410 ± 38 ms vs. SR 420 ± 36 ms, $p > 0.05$). At baseline, 29 (35%) patients in the TdP group were in AF compared with 17 (42%) patients in the LQTS group. The AF was of the persistent type in the majority of these patients (Table 3). However, AF was present at the time of TdP in only 5 of 83 (6%) patients versus 15 of 40 (38%) in the LQTS group. In the remaining 78 patients in whom TdP occurred during SR, it developed in 17 (22%) patients after termination of AF by antiarrhythmic drugs. Eight patients were treated with intravenous antiarrhythmic drugs, and TdP occurred after restoration of SR in 7 patients. In patients who were initiated on oral antiarrhythmic drugs for restoration or maintenance of SR, TdP developed an average of 2.8 ± 1.2 days after initiation of the therapy. Furthermore, there seemed to be no difference in the culprit drugs between the TdP and LQTS groups. Fifty patients were initiated on class I antiarrhythmic drugs, and TdP developed in 27 (54%) compared with 23 (44%) patients, in whom LQTS only developed. There was a similar finding with class III antiarrhythmic drugs

Table 2 Culprit Drugs

Drug Type	No. of Patients
Antiarrhythmic drugs	
Quinidine	35
Sotalol	28
Dofetilide	9
Procainamide	8
Disopyramide	7
Amiodarone	3
Others/combined AADs	11
Nonantiarrhythmic drugs	
Trimethoprim-sulfamethoxazole	4
Phenothiazines	3
Haloperidol	3
Fluconazole/itraconazole	3
Cisapride	2
Pentamidine	2
Lithium	1
Terfenadine	1
Clarithromycin	1
Others/combined drugs	2

AADs = antiarrhythmic drugs.

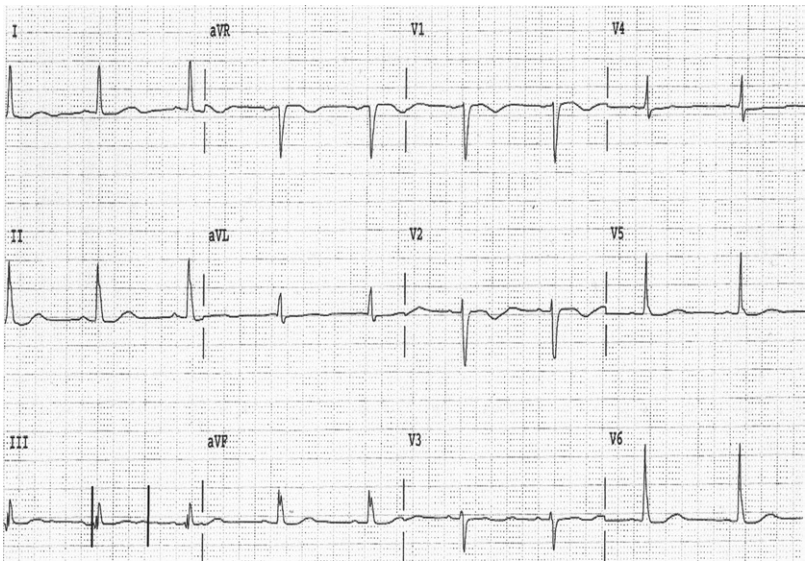

Figure 1 **A 12-Lead ECG Taken in a Patient 2 Days After Commencing Quinidine for AF**

The longest QT interval was measured at 700 ms in lead III. AF = atrial fibrillation; ECG = electrocardiogram.

(TdP 49% vs. LQTS 51%, $p > 0.05$). It is not possible to evaluate whether there were differences in nonantiarrhythmic culprit drugs because there were only a limited number of patients in the 2 groups.

QT interval analyses. A comparison between the TdP and LQTS groups was performed with the Student *t* test for the majority of the ECG variables except when comparing the change in QT (ΔQT), ΔQTc, on drug Tp–Te, and Δ Tp–Te when it was more appropriate to utilize the Wilcoxon rank sum test. Heart rates at baseline and on drug therapy were similar, as were QT intervals in the 2 groups (Table 4). However, absolute, Bazett-corrected and ΔQT were significantly longer in the TdP group compared with control patients. In addition, TDR measured as the absolute and ΔTp–Te was also significantly longer in patients who experienced TdP.

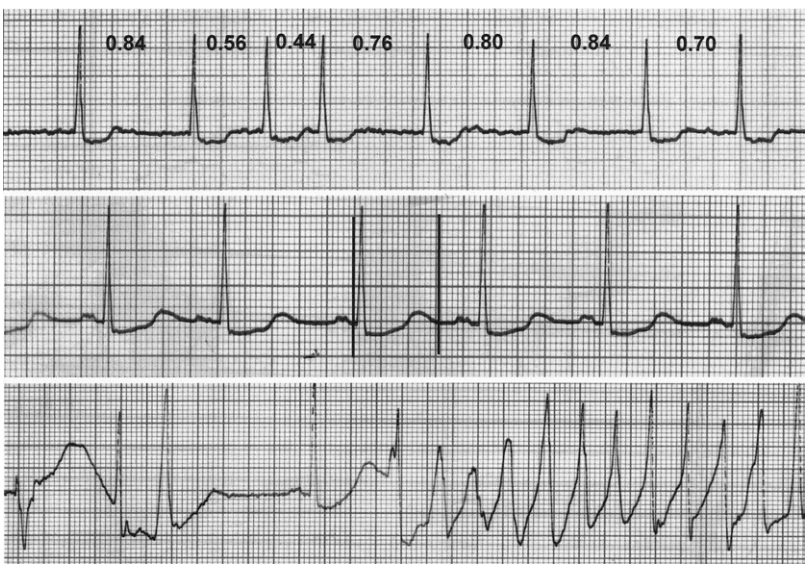

Figure 2 **ECG From a Patient Started on Sotalol**

(Top) During AF, there is irregularity of ventricular response creating frequent short-long-short cycles, but there is minimal change in QT intervals. **(Middle)** After direct current cardioversion, the QT interval has increased dramatically to 640 ms and **(bottom)** an episode of torsades de pointes is triggered. Abbreviations as in Figure 1.

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Table 3 Characteristics of Patients With AF in the Study Cohort

	TdP Group (n = 83)	LQTS Group (n = 40)
AF at baseline (%)	29 (35%)	17 (42%)
Type of AF (paroxysmal/persistent)	11/18	7/10
Oral AADs (%)	58 (70%)	30 (75%)
Intravenous AADs (%)	8 (10%)	6 (15%)
Persistent AF at time of TdP or drug discontinuation (%)	5 (6%)	15 (37%)*
DC cardioversion (%)	18 (22%)	10 (25%)

*$p < 0.0001$ versus TdP group.
AF = atrial fibrillation; other abbreviations as in Tables 1 and 2.

The relationship between clinical and ECG variables and development of TdP was further assessed with univariable and multivariable logistic regression analyses. On univariate analysis, the following variables were found to be associated with the development of TdP: gender (OR 3.40, 95% CI 1.23 to 5.19, $p < 0.0001$); on drug QT (OR 1.01, 95% CI 1.01 to 1.02, $p < 0.001$); on drug QTc (OR 1.01, 95% CI 1.00 to 1.01, $p = 0.02$); ΔQT (OR 1.01, 95% CI 1.01 to 1.02, $p < 0.001$); ΔQTc (OR 1.01, 95% CI 1.00 to 1.01, $p = 0.01$); ΔTp–Te (OR 1.02, 95% CI 1.00 to 1.04, $p = 0.02$); hypokalemia (OR 4.98, 95% CI 1.38 to 17.93, $p = 0.01$) and AF at time of TdP (OR 0.08, 95% CI 0.02 to 0.26, $p < 0.0001$). On multivariable logistic regression analysis (Table 5), lack of persistent AF was the strongest predictor of development of TdP. However, female gender was also associated with increased risk of TdP, and there was a trend toward significance for hypokalemia.

Discussion

In this study, we showed for the first time that patients exposed to QT prolonging drugs are less likely to develop TdP when the underlying rhythm is persistent AF as compared with SR. However, female gender was identified as a significant risk factor for development of TdP.

Table 4 Electrocardiographic Variables in Patients With TdP and LQTS

	TdP Group (n = 83)	LQTS Group (n = 40)
Baseline HR (beats/min)	66 ± 14	68 ± 12
On drug HR (beats/min)	71 ± 13	69 ± 13
Baseline QT (ms)	381 ± 38	388 ± 43
Baseline QTc (ms)	408 ± 31	416 ± 36
On drug QT (ms)	598 ± 76	547 ± 57†
On drug QTc (ms)	615 ± 70	584 ± 48*
ΔQT (ms)	217 ± 79	159 ± 61†
ΔQTc (ms)	207 ± 81	168 ± 61*
Baseline Tp–Te (ms)	94 ± 21	94 ± 16
On drug Tp–Te (ms)	152 ± 39	133 ± 30*
ΔTp–Te (ms)	58 ± 34	39 ± 30†

*$p < 0.05$. †$p < 0.001$ compared with TdP group.
HR = heart rate; Tp–Te = T-wave peak to T-wave end; Δ = change; other abbreviations as in Table 1.

Table 5 Multivariate Logistic Regression Analysis

	Multivariate Logistic Regression Analysis		
	OR	95% CI	p Value
Hypokalemia (K^+ <3.5 mEq/l)	4.88	0.95–24.97	0.06
Gender (female)	2.40	1.11–5.19	0.03
Persistent AF at time of event (TdP or drug discontinuation)	0.14	0.03–0.63	0.01

CI = confidence interval; OR = odds ratio; TdP = torsades de pointes; other abbreviations as in Table 3.

Although TdP can occur in many settings (such as heart block, as originally described), it is usually seen in patients with one of the congenital LQTS or in association with drug therapy. In recent years, a growing list of cardiac and noncardiac drugs (many of which are listed in Table 2) with action potential prolonging properties, and a discernible prolongation of the QT interval on the surface ECG has been reported (8). This effect is frequently seen in clinical practice (e.g., in approximately 2% of patients receiving quinidine) and results from a drug-mediated action on specific cardiac ion channel (I_{Kr}), which leads to a net imbalance between inward and outward ion currents during repolarization.

Multiple risk factors for drug-induced TdP have been delineated. However, estimating an individual patient's risk is difficult. Often, a combination of individual disease factors (e.g., hypokalemia, underlying heart disease), environmental factors, and specific triggers are present, which in association reduce repolarization reserve and thus markedly prolong the QT interval to a critical threshold level (18). Although hypokalemia and female gender have previously been identified as independent predictors of TdP (19), AF at the time of QT interval prolongation has not previously been shown to reduce the risk of developing TdP.

Measurement of QT intervals during AF. Rate correction of the QT interval using standard Bazett (12) and Fridericia (20) formulae can introduce significant errors in assessment of drug effects on the QT interval (13). In a variable rhythm such as AF with constantly changing RR intervals, this is even more pronounced, because the QT interval adapts to changes in heart rate and simply averaging multiple QT intervals will not provide adequate assessment of QT during AF. The most reliable method for rate correction is one that is based on the QT–RR relationship (21). Recently, a method of measuring the QT interval that is rate independent has been proposed, and one study showed that cardioversion of AF acutely increases the QT interval and the steepness of the QT/RR slope (22). Thus, in the LQTS group, in which AF is more prevalent, the correction formulae would predict ΔQTc to be greater than ΔQT. In contrast, in the TdP group, in which SR is more prevalent, the Bazett formula would predict the opposite. Consequently, the application of correction formulae that normalize QT interval measurements to heart rate and were designed for SR may be inappropriate for irregular rhythms

such as AF. Our data presented in Table 4 clearly show that changes in absolute QT durations may be more valid under these circumstances (13).

AF and TdP. In this study we show that persistent AF reduced the likelihood of patients developing TdP when administered QT-prolonging drugs. This is surprising given the frequent short-long-short cycles in AF, but is in accord with previous reports indicating heightened risk after conversion of AF (23). There are a number of lines of evidence that suggest dysregulation of the QT interval in AF. One piece of evidence comes from studies of QT prolonging antiarrhythmic drugs, whose major contemporary indication is prevention and conversion of AF. Virtually all of these drugs block the rapid component of the cardiac-delayed rectifier (I_{Kr}) as a major mechanism of action, and marked QT prolongation and pause-dependent TdP are the major class toxicities. Clinical anecdotes have long suggested that TdP, when it occurs in this setting, develops after conversion of rhythm to SR and rarely when the underlying rhythm remains AF (23,24). To test these anecdotes, we have previously infused the potent I_{Kr} blocker dofetilide in 9 patients before and immediately after cardioversion of AF, and showed that although there was little QT prolongation during AF, some patients displayed striking QT prolongation (and 1 had TdP) in the post-cardioversion challenge (25). Additionally, a recent study not only confirmed that QT intervals are longer for any given RR interval after restoration of SR, but also that the slope of the QT–RR relationship was found to be unexpectedly flat in AF when compared with SR (22). Steepening of the QT–RR relationship after cardioversion of AF is consistent with the hypothesis that susceptibility to TdP is low during AF (despite frequent short-long-short cycles) and elevated after cardioversion.

Tp–Te and TdP. Recent experimental studies involving the canine arterially perfused wedge preparation have supported the idea that the substrate for TdP develops as a consequence of the amplification of electrical heterogeneities intrinsic to the ventricular myocardium (26–28). These heterogeneities exist because of differences in the time course of repolarization of the 3 predominant cell types that make up the ventricular myocardium, giving rise to transmural voltage gradients and a TDR responsible for the electrocardiographic T-wave. In these studies, the duration of the second part (T2) of the T-wave is thought to represent a measure of TDR (i.e., a long Tp–Te interval is thought to indicate augmented TDR). The arrhythmogenic role of increased TDR under long QT conditions as well as in the Brugada syndrome has been reported (14–16). In this study, we found that prolongation of Tp–Te and ΔTp–Te correlated with development of TdP and that this may be useful for predicting TdP in patients with drug-induced LQTS.

Potential mechanism. Atrial fibrillation is associated with significant remodeling that includes alterations in L-type calcium current, inward rectifier current, transient outward current, and ultrarapid delayed rectifier current (among other changes) (29). The magnitude of these changes is sufficient to alter responses to antiarrhythmic drugs. However, molecular changes in the left ventricle secondary to AF are less well established. Nonetheless, there are echocardiographic data that link AF, atrial remodeling, reverse remodeling, and changes in left ventricular systolic function (30). Although the precise mechanism by which AF reduces susceptibility to TdP is unknown, AF-associated electrophysiological and cellular remodeling may perhaps be associated with preservation of TDR that correlates with reduced susceptibility to the development of TdP among patients with acquired LQTS. Additionally, a recent study that modeled LQTS by infusing veratridine into Langendorff preparations of rabbit hearts was able to show that the risk of developing TdP could be significantly decreased through preventing prolongation in TDR by verapamil administration (31). Their finding is in agreement with our current study in which TDR (ΔTp–Te) was significantly shorter in acquired LQTS patients who did not develop TdP.

Study limitations. Although this was a retrospective analysis, the data for this study were obtained from one of the largest single-center acquired LQTS registries. However, to fully evaluate the role of AF and risk of TdP requires a much larger multicenter clinical study. Another limitation relates to the fewer number of subjects in the LQTS group. This was probably related to discontinuation of QT prolonging drugs, and it is possible that continued administration of QT prolonging drugs in this group could have resulted in further prolongation of myocardial repolarization and TdP. The time course of QT interval changes may be an important determinant of development of TdP, and in our study an accurate assessment of this variable in patients exposed to nonantiarrhythmic drugs was not available, nor were there comprehensive data on how QT intervals changed if conversion from AF to SR occurred. The availability of only telemetry strips, albeit performed around the time of drug discontinuation or an episode of TdP, is another potential limitation of the study. Although potassium levels and diuretic regimes in patients with heart failure were known for many patients in this cohort, magnesium levels were not, and hence reliable determination of this factor as a predictor of TdP was limited.

There are no established methods for evaluating QT intervals in patients with AF. We and others have used QT averaging over multiple heart rates and then rate-corrected QT (25,32). Although averaging at least 10 beats for QT measurement would have provided more representative mean QT values, we were limited to averaging 3 consecutive beats because prolonged ECG recordings were not available for most patients in this study.

In conclusion, this study has shown that patients in persistent AF are at reduced risk of developing TdP after exposure to QT-prolonging drugs. Reduced risk of developing TdP was also strongly associated with preserved TDR. Additionally, female gender was also an independent predictor of developing TdP.

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