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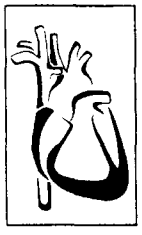

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The QT Interval

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The effects of disease states and therapeutic drugs on the QT interval have been extensively studied in an attempt to understand the relationship between QT and the risk of torsade de pointes and sudden cardiac death. Differences in heart rate correction methods, electrocardiogram lead placement, and other internal (eg, genetic, physiologic) and external (eg, food, time of day) factors have confounded the interpretation of this relationship. A comprehensive review of the epidemiologic literature suggests that the corrected QT interval (QTc) is an important but imprecise marker of cardiovascular disease. The association between QTc prolongation and mortality has been identified in patients with cardiac disease but is unclear in patients without cardiac disease. Drug-related prolongation of QTc can clearly increase the risk of torsade de pointes, but this arrhythmia is rarely associated with a QTc of less than 500 ms. It also appears that noncardiac drugs that are associated with QTc prolongation are not identical in their proarrhythmic capacities and that increased exposure via clinically significant drug interactions is a major contributor to the liability of noncardiac drug-induced arrhythmia. Recognition of the aforementioned variables in conjunction with careful QTc measurements assists in establishing a more precise benefit-risk ratio for a specific drug therapy or for arrhythmia risk associated with various pathophysiologic or genetic states.

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Since Matteucci's observations on the electrical current in pigeon hearts in the mid-19th century,[1] the electrical activity of the heart has been the object of scientific inquiry and experimentation. As anatomists and pathologists were elucidating the structure of cardiac conduction tissue, parallel progress in the development and interpretation of the surface electrocardiogram (ECG) was pioneered by Waller, Einthoven, and their successors, leading to widespread clinical application of electrocardiography in the early 20th century. Despite the accompanying accumulation of knowledge and experience, uncertainties persist in ECG interpretation. A thorough understanding of the importance of the duration of the QT interval remains elusive, with knowledge necessarily acquired in the context of pathological states and, more recently, drug-induced prolongation. Among the most instructive case histories is that of terfenadine, a widely and safely used antihistamine observed to cause a slight prolongation of the corrected QT interval (QTc).[2] However, this effect was dramatically magnified[3,4] when the drug was administered to individuals with impaired metabolism of the parent compound, leading to a significantly

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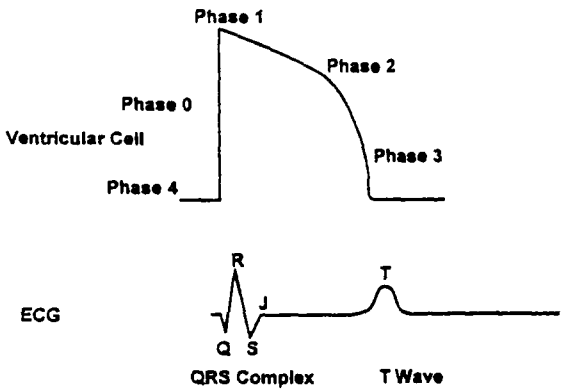

Fig 1. Action potential ECG.

increased risk for fatal ventricular arrhythmias. The importance of understanding this sequence of events underscores the purpose of this article, which is to describe the QT interval as a measurement of cardiac repolarization and summarize the existing literature on the clinical significance of QT interval prolongation.

Physiologic Basis of the QT Interval

The QT interval is an indirect measure of the duration of the ventricular action potential (depolarization) and ventricular repolarization, which is the ventricular refractory period. Measured by the surface ECG, the QT interval consists of 2 components: the QRS complex, which reflects depolarization within the His-Purkinje system and ventricles, and the JT interval, a measure of the duration of ventricular repolarization (Fig 1). The T wave is generated by repolarization of the different layers of the myocardium (epicardium, endocardium, or midmyocardium). This repolarization process spreads from the apex to the base of the ventricles, driven primarily by the outward movement of potassium.

The wave of depolarization (phase 0, Fig 2) in ventricular tissue is caused by the rapid movement of sodium ions from extracellular to intracellular spaces, a process also known as the fast sodium current. A transient egress of cations (I_{TO} [transient outward channels] and other currents) is responsible for a slight repolarization (phase 1). This is followed by a plateau phase (phase 2), which is the major determinant of the action potential duration. The duration of the plateau phase is determined by the balance of inward and outward currents through competing ion channels. These include slow inactivating sodium channels, L-type calcium channels, and potassium channels. Repolarization (phase 3) results from inactivation of calcium currents coupled with increasing net outward potassium current, carried by rapid (I_{Kr}) and slow (I_{Ks}) components of the delayed rectifier potassium channel. Inward-rectifier potassium channels are then responsible for maintaining the resting membrane potential (phase 4).

Measurement of the QT Interval

The QT interval on the surface ECG is measured from the beginning of the Q wave (or R wave if there is no Q wave) to the end of the T wave. It is sometimes difficult to discern the return of the T

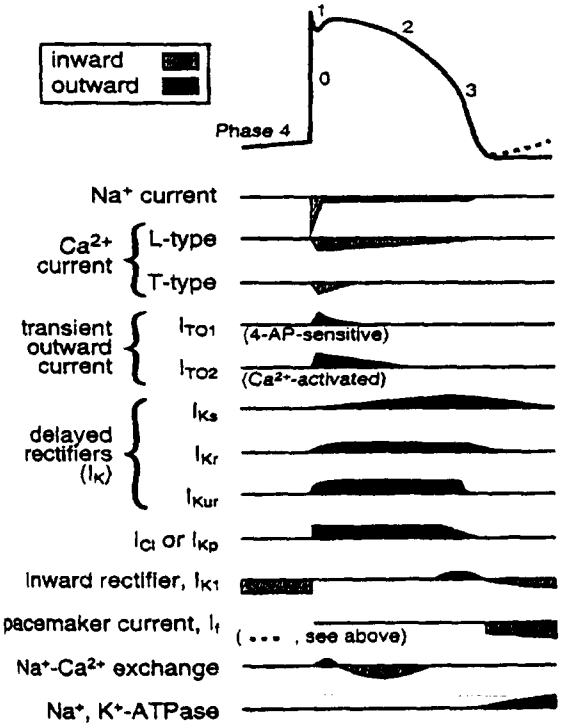

Fig 2. ECG-ionic current relationship. Abbreviations: I_{TO1}, transient outward current 1; 4-AP, 4-aminopyridine; I_{TO2}, transient outward current 2; I_{Kur}, ultra rapidly transient outward delayed rectifier potassium current; I_{Cl}, voltage-activated time independent chloride current; I_{K1}, inward rectifier potassium current 1; I_f, pacemaker current. (Reprinted with permission from Goodman LS, Gilman AG (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics (ed 9). New York, NY, McGraw-Hill, 1996)

wave to baseline, and a U wave may further interfere with this determination. The U wave is sometimes mistaken for a delayed T wave or it may overlie the T wave, which may lead to an inaccurate measurement of the QT interval. Because U waves are typically less prominent in lead II,[5,6] it has been suggested that lead II be used to measure QT. However, it is also well recognized that the QT interval can vary considerably between leads within the same ECG, a phenomenon known as QT dispersion (see Assessment of QTc). This has led many investigators and clinicians to adopt the practice of measuring the QT interval from the lead with the longest interval.[7]

The method by which the QT interval is measured has also been studied. Comparisons between automated and manual measurements of the QT interval have been undertaken. It was suggested that automated readings yield the least accurate data, in part related to the inability of automated systems to define precisely the end of the T wave or to distinguish T from U waves.[7] However, others[8] have provided evidence that both automatic and manual QT measurements produce similar values, with the possible advantage of greater reproducibility with the former. In either approach, consistency is maximized by having all ECGs read and overread by 1 central reader so that uniform procedures may be practiced.

The use of Holter monitoring has also been examined.[5,9-11] Although Holter monitoring has the advantage of measuring QT interval over a long period and wide range of heart rates (HRs), Holter-based QT measures may range from 100 ms shorter to 55 ms longer than QT measures of the same complexes recorded on a simultaneous 12-lead ECG tracing. Thus, the use and interpretation of data obtained from Holter monitoring should be limited to comparisons with similarly derived Holter data and not be compared with standard 12-lead ECGs.[5,12]

The Corrected QT Interval

Interpretation of the QT measurement is hampered because the QT interval is not constant, but varies inversely with HR, first described by Lombard and Cope[13] in 1919. Accordingly, when there is a need to determine whether the intrinsic duration of the QT interval has been altered by a pathologic process or a drug, comparison must include a correction for the intrinsic effect of HR on the QT interval. This is precisely what QT correction formulas attempt; to substitute for each measured QT interval a corrected QT (QTc) value that corresponds to one that would have been measured had each ECG tracing been recorded at the same HR.

If the relationship between HR (or its reciprocal, the RR interval) and QT interval were known for each individual, it would be possible to express this relationship in a model that would allow the correction to be made by a simple calculation. This approach is impractical if multiple measurements at a range of HRs are not available for an individual. Instead, the set of QT:RR pairs observed in a population is used for a similar purpose, ie, to derive a mathematical model that will correct the observed QT for the RR at which it is measured. The unfounded assumption and possible limitation of this approach is that the QT:RR relationship is the same for all subjects within the population.

Derivation of an appropriate QT correction formula begins with assessment of the QT:RR relationship in the population under study (Fig 3). Within a physiologic range of HRs, a linear model reasonably describes the variable QT:RR data (or a transformation of that data, eg, log). A linear $\{QT = [a(RR) + b]\}$ or log linear $\{QT = [aRR^b]\}$ model is then used to calculate a reference QTc, typically for a reference HR of 60 beats/min (RR = 1 second). An observed QT can then be corrected by calculating a predicted QT, using the equation for QT previously derived. The difference between observed and predicted QT [QT obs–QT pred] is then added to the reference QTc to produce the derived QTc. As noted in Fig 3, a plot of derived QTc versus RR values should yield a horizontal linear regression line (zero slope) so that QTc is independent of RR (HR). A number of statistical models have been used to describe (fit) observed QT:RR relationships in various studies (Table 1). Although the formula of Bazett[14] is most widely used, the variability of the QT:RR relationship among different populations (particularly at extremes of HR) prohibits the use of a single correction formula for all patient groups. This suggests caution when interpreting studies of the effects of drugs and other interventions on the QTc interval. The large number of methods devel-

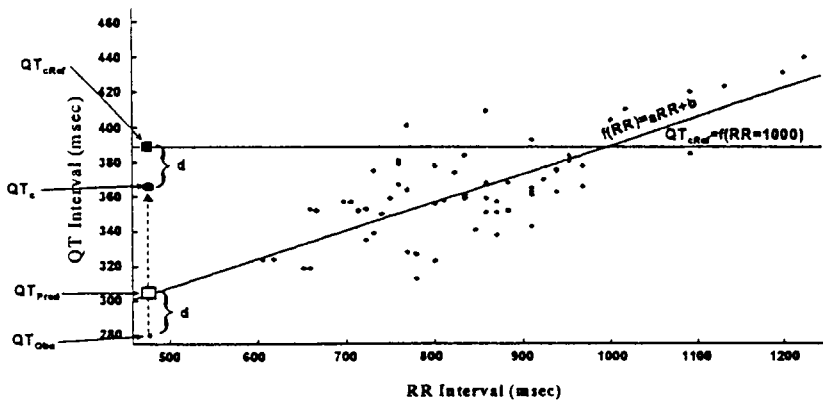

Fig 3. Baseline (preintervention) QT versus RR and derivation of QTc. A number of observed QT:RR pairs, ie, ECG measurements of QT intervals [QT obs] at various HRs. Application of the mathematical function that best fits these values to a straight line (a least-squares regression line [f(RR) = 0.163 (RR) + 226]) will produce a predicted QT [QT pred] for each observed QT. The difference between these 2 values [QT obs–QT pred] is equal to the difference between the derived QTc [QTc] and the reference QTc [QTc Ref = QT pred at reference RR interval, here illustrated at 1,000 ms]. Therefore, QTc = QTc Ref + (QT obs–QT pred). For instance, a QT of 280 ms is observed at an RR of 476 ms (HR, 126 beats/min). The linear regression model predicts a QT of 304 ms [0.163(476) + 226]. The difference of −24 ms [280–304] is added to the reference QTc, 389 ms [0.163(1,000) + 226], yielding a QTc of 365 ms.

oped for correction of the QT interval measurement indicates how difficult this has proved to be.

Two other caveats are worthy of note.[28] First, although the QTc measurement typically reflects a correction for the simultaneous HR, the effect on the QT interval of a change in HR is not instantaneous.[28] It is unclear to what extent this phenomenon should be considered when measuring QT interval. Therefore, correction of the QT for HR may conceal important information, such as the kinetics of the QT interval adaptation to a change in HR.

Second, the assessment of drug effects is generally based on QTc measurements made in the absence and presence of the drug. However, compounds that affect both QT (ventricular repolarization) and RR (HR) intervals pose additional difficulties, not only because off-drug and on-drug measurements are made at a different range of HRs, but also because the drug itself may alter the QT:RR relationship. A possible but generally impractical approach to this problem is to avoid QT correction and measure QT intervals at similar HRs before and after drug administration.[29,30]

Assessment of QTc

Normal Range

Despite long-standing recognition that QTc shows considerable interindividual and intraindividual differences, attempts have been made to define an upper limit of normal. In assessing the risk for proarrhythmia, it was proposed that maximum QTc may be most predictive. A QTc (Bazett correction) value of 440 ms has been identified by some as an upper limit of normal.[5,10] The European regulatory body, the Committee for Proprietary Medicinal Products, suggested upper limits of normal (Bazett QT correction) of 450 ms for adult men and 470 ms for adult women and that values greater than 500 ms should cause concern.[12] However, both QT and QTc are dynamic parameters, and individual QTc values in excess of 500 ms have been observed in healthy individuals.[11,31] The difficulty defining a normal range of values for QTc results from both the inherent intraindividual variability of the parameter and the limited frequency and timing of the observations. The use of Holter monitor recordings have allowed investigators to assess more systematically the variability of QTc over time. In two 24-hour Holter studies, mean intraindividual ranges of 95 ms[10] and 76 ms[11] were measured, confirming the highly variable nature of this parameter. Although a complete understanding of the sources of QT interval variability within an individual are not completely understood, some[10,32-34] but not all[11] studies suggest that at least part of the QT interval variability is predictable in that it is diurnal in nature.

Table 1. QT Correction Formulas

Formula	Relationship Between QT and RR/HR	Mathematical Expression for QTc	Original Cohort: No.	Original Cohort: Mean Age and Range (yr)	Comments
Log-linear					
Bazett[14]	0.368$\sqrt{}$ RR (male) 0.399$\sqrt{}$ RR (female)	QT/$\sqrt{}$ (RR interval in seconds)	Total 39 (20 male, 19 female)	26 (<14-53)	First formula; most universally applied
Fridericia[15]	8.22$^3\sqrt{}$ RR (RR in hundredths of seconds)	QT/$^3\sqrt{}$ (RR interval in seconds)	50	26 (2-81)	Included children to examine a wider range of HR
Mayeda[16]	$[0.2574\ (100 \times RR)]^{0.604}$	$QT/RR^{0.604}$	200	18-64	Adult cohort without heart disease
Ashman[17]	0.375 log (10[RR + 0.07]) (male & children) 0.385 log (10[RR + 0.07]) (female)	QT/log (10RR + 0.07)	1,083	Unknown	Included 226 children (0-14 yr); this correction uses a reference RR of 930 ms
Linear*					
Adams[18]	0.1464RR + 0.2572 (all subjects) 0.1536RR + 0.2462 (male) 0.1259RR + 0.2789 (female)	QT + 0.1464(1-RR) (all subjects) QT + 0.1536(1-RR) (male) QT + 0.1259(1-RR) (female)	Total 104 (50 male, 54 female)	28	Gender-based formula
Ljung[19]	0.2RR + 0.18 ± 0.04	QT + 0.2(1-RR)	22	17-54	Adults with hypocalcemia (<7.5 mg/dL)
Schlamowitz[20]	0.205RR + 0.167	QT + 0.205(1-RR)	495	25 (18-44)	Cohort of healthy soldiers at rest and after exercise
Simonson et al[21]	0.2423 + 0.14RR + (0.0003) age	QT + 0.14(1-RR)	Total 960 (649 male, 311 female)	20-59	Healthy subjects
Akhras and Rickards[22]	522 − 1.87(HR)	QT + 1.87(HR-60)	49	Unknown	25 Patients underwent treadmill exercise to evaluate QT-RR relationship (15 patients, β-blocking drugs), 15 patients with atrial pacing/stress testing, 9 patients with complete heart block exercised at a fixed ventricular rate of 70 beats/min
Boudoulas et al[23]	521 − 2.0HR (male) 511 − 1.8HR (female)	QT + 2(HR-60) (male) QT + 1.8(HR-60) (female)	100 Male, 100 female	40 (19-77)	200 Patients undergoing minimally stressful diagnostic tests
Karjalainen et al[24]	0.156RR + 0.236	QT + .156(1-RR)	324	21 (18-28)	Men only; formula intended for HR from 60-100 beats/min
Rautaharju et al[25]	$1/(1.64 \times 10^{-3} + 1.41 \times 10^{-5}$ HR) (male) $1/(1.50 \times 10^{-3} + 1.54 \times 10^{-5}$ HR) (female)	$QT/(1 + 1.41 \times 10^{-5}$ QT(60-HR) (male) $QT/(1 + 1.54 \times 10^{-5}$ QT(60HR) (female)	14,379	Birth-75	Populations derived from NHANES 2 and HHANES; gender-based formula
Framingham[26]	0.154RR + .222 (male) 0.154RR + .234 (female)	QT + 0.154 (1-RR in seconds)	5,018	44 (28-62)	Large population-based (noncardiac) study
Hodges et al[27]	496 − 1.75(HR)	QT + 1.75 (HR-60)	607	(20s-80s)	Healthy subjects; equal allocation of males and females

Abbreviations: NHANES 2, National Health and Nutrition Examination Survey 2; HHANES, Hispanic Health and Nutrition Examination Survey.
*Formulas presented are linear for either HR or for RR, as specified.

The effect of a drug or intervention on QT interval or QTc can be assessed in several different ways: maximum change from baseline, mean change from baseline, JT interval effect, or QTc dispersion.

Maximum Change From Baseline

The difficulty associated with defining an upper limit of normal for QTc has led investigators to examine the change in QTc from a baseline (reference) value. One disadvantage with this approach is that unless multiple measurements are obtained throughout the course of a 24-hour period, it is difficult to determine whether the value obtained is related to the intervention being studied or simply caused by the inherent variability in QTc over time. Because some of this variability may be nonrandom (eg, postprandial prolongation), appropriate sampling frequency should be accompanied by careful control of experimental conditions.

Thus, QT interval comparisons should be made between ECGs recorded under the same conditions (eg, posture, activity, time of day). Moreover, as reviewed by Bonate and Russell,[35] regression toward the mean further complicates interpretation of serial measurements: a QTc that is relatively long for a given individual is more likely to be followed by a shorter rather than a longer interval in a random sampling of that individual. Thus, the designation of a normal range should consider the number of observations and method of measurement. It has been suggested that "a clinically significant change in the QTc, as measured by 24 hour Holter, occurs when an individual subject has a range of QTc values > 75 ms;"[11] The Committee for Proprietary Medicinal Products identified an individual change greater than 60 ms as a cause for concern and a change greater than 30 ms of "potential" concern.[12]

Mean Change From Baseline

Assessment of the mean change from a baseline (reference) value permits bias introduced by sampling frequency to be expressed in terms of the precision of the estimate (eg, SD, SEM, confidence intervals) of the mean. This may facilitate comparisons of different interventions or drug therapies, given appropriate cautions concerning the similarity of the populations studied and a vigilance for systematic bias.

JT Interval

Because QTc reflects the duration of both QRS complex (depolarization) and JT interval (repolarization), it may be prolonged by drugs that increase the duration of depolarization (eg, a sodium channel blocker, flecainide) or repolarization (eg, a potassium channel blocker, sotalol). Although JT interval is another helpful measure of ventricular repolarization and should be considered wherever a drug increases the duration of the QRS complex,[36] this parameter is not widely used in clinical practice.

QT/QTc Dispersion

The degree of QT/QTc variability between simultaneously recorded ECG leads is believed to reflect the dispersion of repolarization within an individual subject.[6,37,38] This parameter is determined by measuring the difference between the longest and shortest QT intervals or QTc in a standard 12-lead ECG recording. A dispersion of 40 to 60 ms is considered normal,[12,39-41] with dispersion greater than 100 milliseconds or a change greater than 100% from baseline has been associated by some investigators with increased risk.[12,39,41,42] However, other investigators[43,44] have recently found that QT/QTc dispersion is not a reliable prognostic marker, and the utility of this surface ECG measurement remains to be established.

Nonetheless, it is clear that repolarization of ventricular myocardial cells is not completely synchronous. Drouin et al[45] described a subpopulation of midmyocardial cells (M cells) with electrophysiologic properties intermediate between cardiac muscle and conduction tissue. Differential sensitivity of M cells to interventions or drug exposure may increase the heterogeneity of repolarization and result in dispersion of action potential duration within the ventricular wall. This increase in M cell action potential duration relative to cells in epicardium and endocardium may thus provide an anatomic and electrophysiologic substrate for the potentially fatal arrhythmia, torsade de pointes (TdP), as a form of transmural reentry[46-49] (see QTc Prolongation).

Table 2. Factors Prolonging QTc

Congenital[57,58]
Increasing age[55]
Female sex[10,26,50-54]
Meals[59,60]
Sleep[5,10,34,61,62]
Drugs[63]
Obesity/weight gain[64-68]
Liquid protein diet[69]
Alcoholism[70,71]
Electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia)[72,73]
Hypoglycemia[74]/diabetes mellitus[75-80]
Myocardial ischemia and infarction[81,82]
Cardiomyopathy[83,84]
Hypertension[85]
Hypothyroidism,[86] pituitary insufficiency[84]
Central nervous system insult: stroke, subarachnoid hemorrhage, trauma, infection, tumor[72,73,84]
Cirrhosis[71]

Adapted from Funck-Brentano et al[29]: Rate-corrected QT interval: Techniques and limitations, Am J Cardiol 72:17B-22B, Copyright (1993) with permission from Excerpta Medica Inc and Zehender et al[56]: QT-interval prolonging drugs: Mechanisms and clinical relevance of their arrhythmogenic hazards, Cardiovasc Drugs Ther 5:515-530, 1991 with permission from Kluwer Academic.

Variables Affecting QTc

QTc is affected by a broad set of influences, both internal (genetic, physiologic, and pathophysiologic) and external (food, drugs) for a given individual. A partial list is included in Table 2. In general, women have a longer (~10 to 20 ms) QTc than men[10,26,50-54] and there is a positive correlation between QTc and age.[53,55] Additionally, QTc changes markedly during the course of the day. A mean lengthening of QTc by 13 ms has been observed during sleep, believed to be related to either increased vagal or reduced sympathetic tone.[34] Increased variability of QTc during sleep has also been described, with the longest values recorded during the hour after awakening.[10]

QTc Prolongation

Overview

Prolongation of ventricular repolarization results in an increase in the absolute refractory period. Although this is the mechanism by which some antiarrhythmic drugs (eg, class III agents) prevent or terminate ventricular tachyarrhythmias, prolonging repolarization can also cause arrhythmias.

The most common type of drug-induced ventricular arrhythmia is a form of polymorphic ventricular tachycardia known as TdP (twisting of the points), so named because there is a progressive rotation of the QRS axis.[87] This is frequently a self-limiting tachyarrhythmia that typically causes intermittent dizziness or syncope, but it can degenerate into ventricular fibrillation and sudden death.

Although QTc is widely viewed as a surrogate marker of the arrhythmogenic potential of a drug, the precise relationship between the extent of QTc prolongation and the risk for sudden death is unknown. In an attempt to examine comprehensively clinical experience in this area, a complete literature search was performed for all approved noncardiac medications listed as prolonging the QT interval,[88,89] using MEDLINE and other databases (Drug Datafile, EMBASE, Cancer Lit, Biosis, Commonwealth Agricultural Bureau, Sci Search) for 1966 to 1999. QT and QTc values reported in association with the identified cases of TdP are listed in Table 3. It is recognized that an absolute threshold of risk for TdP cannot be proven, but it is apparent that almost all reported cases of TdP occurred in individuals with a measured QTc value exceeding 500 ms (92.2%; 107 of 116 cases). The reported literature therefore suggests that TdP rarely occurs unless the QTc exceeds 500 ms.

Population-Based Studies

Several epidemiologic databases have described QTc (corrected by Bazett formula, except the nomogram-corrected QT interval of Karjalainen et al)[55] in populations of healthy volunteers

Table 3. Relationship Between QT Interval or QTc and TdP

QT Interval (ms)	TdP Cases	QTc (ms)	TdP Cases
<500	17	<500	9
500-549	9	500-549	13
550-599	16	550-599	24
600-649	33	600-649	36
650-699	6	650-699	21
≥700	5	≥700	13
Total cases	86	Total cases	116
Cases <500 ms (%)	19.8	Cases <500 ms (%)	7.8

Data from.[90-191]

Table 4. QTc Prolongation in Population-Based Studies: General and Noncardiac

Study	Size of Population (no.)	Age* (yr)	Follow-Up (yr)	Risk Parameter	Reference QTc (ms)	Risk Relative to Reference QTc Population	
						QTc Range (ms)	Relative Risk
Framingham[192]	5,125	30-62	30	All-cause death	<360	360-380	0.80
						390-400	0.93
						410-430	0.93
						>440	1.02
				Sudden death	<360	360-380	0.95
						390-400	1.15
						410-430	1.05
						>440	1.31
				Coronary artery disease–related death	<360	360-380	0.96
						390-400	0.97
						410-430	0.97
						>440	0.85
Amsterdam[193] (general population)	3,060	40-65	15	All-cause death	<420	420-440	1.5 men,† 1.7 women†
						>440	1.7 men,† 1.6 women†
			15	Cardiovascular death	<420	420-440	1.6 men,† 1.5 women
						>440	1.8 men,† 1.4 women
			28	All-cause death	<420	420-440	1.1 men, 1.3 women
						>440	1.3 men,† 1.1 women
			28	Cardiovascular death	<420	420-440	1.2 men, 1.3 women
						>440	1.4 men, 1.2 women
Amsterdam[193] (healthy subset: no report of angina or ECG evidence of ischemia, left ventricular hypertrophy or intraventricular conduction disturbance or a cardiac infarct injury score > 20)	2,741	40-65	15	All-cause death	<420	420-440	1.7 men,† 1.6 women
						<440	1.5 men, 1.6 women
			15	Cardiovascular death	<420	420-440	1.9 men,† 1.3 women
						>440	1.2 men, 1.7 women
			28	All-cause death	<420	420-440	1.2 men,† 1.3 women
						>440	1.4 men,† 1.1 women
			28	Cardiovascular death	<420	420-440	1.3 men, 1.3 women
						>440	1.4 men, 1.2 women
Danish[37] (general population)	3,455	30-60 (44 ± 11)	13	All-cause death	310-380	380-440	1.60
						>440	1.89†
			11	Cardiovascular death	310-380	380-440	1.79
						>440	3.31†
			11	Cardiac fatal + nonfatal events	310-380	380-440	1.24
						>440	1.87
			11	Nonfatal cardiac events	310-380	380-440	1.25
						>440	1.91
Danish[37] (normal subgroup: no cardiac disease, diabetes, hypertension)	2,269	30-60 (43 ± 11)	13	All-cause death	310-380	380-440	1.30
						>440	1.17
			11	Cardiac fatal + nonfatal events	310-380	380-440	1.60
						>440	1.10
			11	Nonfatal cardiac events	310-380	380-440	2.30
						>440	2.09

Table 4. (Continued)

Study	Size of Population (no.)	Age* (yr)	Follow-Up (yr)	Risk Parameter	Reference QTc (ms)	Risk Relative to Reference QTc Population	
						QTc Range (ms)	Relative Risk
Zutphen[194] (middle-aged men)	877	40-60	25	Coronary heart disease–related death	<385	385-420	3.3†
						>420	4.3†
Zutphen[194] (elderly men)	835	65-85	5	Coronary heart disease–related death	<385	385-420	1.3
						>420	3.1†
Rotterdam[53]	5,241	>55 (68.2 ± 8.7)	3-6	All-cause death	<406 men, <418 women	>437 men, >446 women	1.5 men, 1.9 women†
				Cardiovascular death	<406 men, <418 women	>437 men, >446 women	1.3 men, 2.4 women†
				All-cause death	<420	>420	1.6 men,† 1.6 women†
						>440	1.8 men,† 1.7 women†
						>460	2.4 men,† 2.1 women†
				Cardiovascular death	<420	>420	1.3 men, 1.5 women
						>440	1.6 men, 1.9 women
						>460	2.2 men, 2.3 women†
Finnish[55] (general population)	10,717	30-59	23	All-cause death	372-410 men, 378-417 women	Men / Women	
						<353 / <358	1.06 men, 1.19 women
						353-371 / 358-377	0.99 men, 0.99 women
						411-430 / 418-437	0.99 men, 1.04 women
						>430 / >437	1.33 men,† 0.98 women
				Cardiovascular death	372-410 men, 378-417 women	Men / Women	
						<353 / <358	1.04 men, 0.92 women
						353-371 / 358-377	1.03 men, 1.04 women
						411-430 / 418-437	1.07 men, 1.10 women
						>430 / >437	1.42 men,† 1.32 women
				Coronary artery disease–related death	372-410 men, 378-417 women	Men / Women	
						<353 / <358	0.93 men, 0.86 women
						353-371 / 358-377	1.07 men, 0.87 women
						411-430 / 418-437	1.04 men, 1.21 women
						>430 / >437	1.44 men,† 1.38 women
				Sudden death	372-410 men, 378-417 women	Men / Women	
						<353 / <358	0.73 men
						353-371 / 358-377	0.86 men
						411-430 / 418-437	1.21 men
						>430 / >437	1.50 men
Finnish[55] ("no cardiac disease," no known heart disease, effort angina, ECG evidence of MI, or use of digitalis, nitroglycerin or antiarrhythmic drugs)	9,888 (5,103 men, 4,785 women)	30-59	23	All-cause death	372-410 men, 378-417 women	Men / Women	
						<353 / <358	1.02 men, 1.09 women
						353-371 / 358-377	0.99 men, 1.01 women
						411-430 / 418-437	0.93 men, 1.07 women
						>430 / >437	1.21 men, 0.91 women

Table 4. (Continued)

Study	Size of Population (no.)	Age* (yr)	Follow-Up (yr)	Risk Parameter	Reference QTc (ms)	Risk Relative to Reference QTc Population		
						QTc Range (ms)		Relative Risk
				Cardiovascular death	372-410 men, 378-417 women	Men	Women	
						<353	<358	0.95 men, 0.72 women
						353-371	358-377	1.05 men, 1.08 women
						411-430	418-437	0.97 men, 1.18 women
						>430	>437	1.25 men, 1.28 women
				Coronary artery disease–related death	372-410 men, 378-417 women	Men	Women	
						<353	<358	0.89 men, 0.78 women
						353-371	358-377	1.11 men, 0.94 women
						411-430	418-437	0.93 men, 1.21 women
						>430	>437	1.29 men, 1.32 women
				Sudden death	372-410 men, 378-417 women	Men	Women	
						<353	<358	0.49 men
						353-371	358-377	0.80 men
						411-430	418-437	1.09 men
						>430	>437	1.48 men
Rotterdam QT Project[195]	6,693	Not available	2	Sudden death	400-440	<400		2.4†
						>400		2.3†

* Values expressed as range (mean ± SE).
† Confidence interval does not include 1.00.

(Table 4) and reported on the usefulness of QTc as a predictor of clinical outcome (variously defined). In those studies reporting QTc measurements for the general population,[37,192,194] a range of means from 394 to 405 ms were reported. QTc prolongation was defined as an interval greater than 440 ms in most of these reports.

However, the QTc of the reference group (to which a risk value of 1.00 was assigned) was not consistent among studies, ranging from 360 to 440 ms. It is also important to note that most available epidemiologic data are cross-sectional, relating the characteristics of a population based on 1 ECG at 1 time point to the clinical outcome observed during succeeding years of follow-up.

The Framingham study[192] reported a 30-year follow-up of a cohort of 5,125 subjects aged 30 to 62 years at the time of entry. This group did not include patients with known coronary artery disease at baseline or those administered medications known to prolong QTc (total, 84 subjects excluded). Baseline QTc values from a single ECG for men and women were 385 ± 29 and 401 ± 27 ms, respectively (mean ± SD). Subjects were distributed into groups as a function of QTc values based on baseline measurements of less than 360, 360 to 380, 390 to 400, 410 to 430, and greater than 440 ms. Mortality in each group was compared with the group of subjects with a QTc less than 360 ms. There were no statistically significant differences between each group and the reference group, leading the investigators to conclude there was no association between baseline QTc and mortality.

In the Amsterdam[193] study, similar follow-up (28 years), age at entry (40 to 65 years), and population size (3,091 subjects) to the Framingham design were used. The investigators examined the data for both 15- and 28-year follow-ups. Men and women were analyzed separately, although data and conclusions were very similar. Of interest, the investigators noted that for both men and women, the association between baseline QTc greater than 440 ms and cardiac death was greater at the 15-year than 28-year follow-up, although even at the earlier time point, risk ratios were modest. However, separate analysis of those subjects without cardiac disease failed to show a relationship between QTc prolongation (QTc > 440 ms) and cardiac mortality.

The Danish study[37] examined 3,455 subjects (aged 30 to 60 years) with a follow-up of 11 years. This study also conducted a separate analysis of healthy (no reported cardiac disease, hypertension, or diabetes) and cardiac disease groups. The baseline QTc value (mean ± SD) for the entire population (405 ± 25 ms) was intermediate between the healthy cohort (400 ± 23 ms; n = 2,269) and cardiac group (413 ± 26 ms; n = 821). Mortality was greatest in the group with a baseline QTc greater than 440 ms, intermediate in the group with a QTc of 380 to 440 ms, and lowest in those with a QTc less than 380 ms (the reference group). In the subset analysis of subjects with and without cardiovascular disease at baseline, the mortality risk attributable to the baseline QTc was contained within the cardiovascular disease subset. In subjects without cardiovascular disease at baseline, no association was found between baseline QTc and mortality.

The Zutphen study[194] followed up 877 middle-aged men (age, 40 to 60 years) for 25 years, extending the study at that time to include an elderly cohort (n = 835; 65 to 85 years) evaluated after a 5-year follow-up. A statistically significantly greater risk for cardiac death was noted for men with a baseline QTc greater than 420 ms compared with a reference QTc less than 385 ms in both the middle-aged and elderly cohorts. Interestingly, QTc (mean ± SD) increased in the original cohort from a baseline value of 395 ± 23 ms (n = 851) to 410 ± 26 ms (n = 720) over the 25-year follow-up period. Moreover, those subjects with heart disease at the 25-year follow-up were noted to have a significantly greater mean QTc (425 ± 39 ms) compared with the cohort without cardiac disease (402 ± 30 ms).

The Rotterdam study[53] followed up a cohort of 5,241 elderly subjects (age > 55 years) for 3 to 6 years. Median baseline QTc values for men and women were 421 and 432 ms respectively. Risk ratios were assigned for all-cause and cardiac mortality by using the values for QTc in the lowest quartile as the reference group (< 406 ms for men and < 418 ms for women). A statistically significant 2-fold increase in all-cause and cardiac mortality was noted only for women with QTc prolongation within the highest quartile (> 446 ms). Interestingly, application of different correction formulas (Bazett, Fridericia, linear regression) did not affect the results. Moreover, the uncorrected QT interval had minimal prognostic value for car-

diac mortality, suggesting that HR is a confounder that has an important role in prediction of mortality by QTc. This was shown by the finding that both QTc (using a correction formula) and adjusted QT (using a multivariate model of age, sex, history of myocardial infarction [MI], and HR) had similar predictive values.

The Finnish study[55] followed up a cohort of 10,717 middle-aged subjects (age, 30 to 59 years) for 23 years. The reference QTc range was defined for men (372 to 410 ms) and women (378 to 417 ms). Analysis of the entire population noted a significant correlation between the highest QTc category for men (> 430 ms) and death (all-cause, cardiovascular, and coronary artery disease–related), but not women. However, after excluding subjects with cardiovascular disease (n = 829) and adjusting for cardiac risk factors (blood pressure, smoking, diabetes, age, cholesterol level, body mass index [BMI]), no significant association was noted between QTc and mortality for either men or women.

The Rotterdam QT Project[195] studied 6,693 consecutive patients who had undergone 24-hour ambulatory ECGs. An overall 2-fold increase in the risk for sudden death was noted for subjects with either a shortened (< 400 ms) or prolonged (> 440 ms) QTc compared with intermediate (400 to 440 ms) mean QTc values.

In summary, most[37,53,55,194] but not all[192,193] studies suggest that in the general population, a prolonged QTc is associated with increased risk for cardiac death. The lack of uniformity in these results could be caused by a number of factors, including imprecision in the measurement of QT intervals, differences in the prevalence of heart disease at baseline, and duration of follow-up, as well as insufficient power to detect a difference between groups in the incidence of sudden death. The consistent observation that patients with a QTc greater than 440 ms have a greater risk for cardiovascular mortality than patients with a QTc less than 440 ms may reflect the role of QTc as a marker of underlying cardiac disease. In support of this conclusion, all general population studies that performed additional analyses on a healthy (noncardiac) subset failed to show a relationship between QTc and cardiac-related mortality. Moreover, recently published data[196] showed a correlation between QTc and carotid artery atherosclerosis in patients with no clinical history of diabetes or coronary artery disease, suggesting that QTc is a marker of subclinical atherosclerotic disease. The use of epidemiologic data to estimate the risk for fatal ventricular arrhythmia associated with a drug-induced prolongation of QTc must therefore carefully distinguish between delayed repolarization as a cause of death (by ventricular arrhythmia) and prolonged QTc as a marker of clinical, subclinical atherosclerotic, or other structural cardiac diseases.[197]

Cardiac Disease

Congenital. Congenital long QT syndrome (LQTS) was first described by Jervell and Lange-Nielsen[198] in 1957, in which the prolonged QT interval was associated with congenital deafness and an autosomal recessive pattern of inheritance in 4 siblings. This report was followed by the description of a second form of LQTS described in 2 separate families by Romano et al[199] in 1963 and Ward[200] in 1964. Deafness was not a feature in these patients, and an autosomal dominant pattern of inheritance was suggested. Subjects with congenital LQTS are recognized by their pattern of multiple syncopal episodes, many of which appear to be precipitated by adrenergic excess, such as might be seen with anxiety, fright, or physical exertion. Sudden death is not infrequent in this population. It has become apparent that the Romano-Ward LQTS syndrome comprises a heterogeneous population with at least 6 different genetic defects characterized to date, all associated with abnormalities of the potassium and/or sodium channels (Table 5).[201] Accumulating evidence shows that some of these syndromes may be characterized by distinctive clinical and morphologic (ECG) criteria,[57,202] although a single sodium channel mutation, SCN5A, has been reported to result in the cardiac abnormalities associated with both LQT_3 and Brugada syndrome.[203] The established notion that congenital LQTS is associated with a very high penetrance (~90%) has recently been challenged by studies that noted these genetic defects in unaffected family members of patients with congenital LQTS, with penetrance rates as low as 25%.[204] Finally, families have been identified with documented LQTS that show unique point mutations.[205] Thus, it is becoming increasingly evident that multiple other point mutations exist that may be responsi-

Table 5. The Molecular and Ionic Basis for QT Prolongation

LQTS	Gene	Chromosome Locus	Ion Current	Additional Clinical Features
1	KvLQT1*	11p15.5	I_{Ks}	Cardiac events triggered by exercise. Marked sensitivity to catecholamines. Generally Romano-Ward syndrome is associated with heterozygous mutations in KvLQT1, whereas Jervell and Lange-Nielsen syndrome (LQT and deafness) is associated with homozygous mutations in KvLQT1. ECG: T wave broad-based.
2	HERG†	7q35-q36	I_{Kr}	Cardiac events triggered by emotion and alarm. Treatment with potassium shortens QTc. ECG: T wave notched/ bifurcated, low amplitude.
3	SCN5A	3p21-p23	I_{Na}	Cardiac events triggered by sleep and by rest without arousal. Less protection with β blockers and potassium channel openers than other LTQS. Significant QTc shortening with mexiletine not sensitive to catecholamines. ECG: ST segment long and T wave peaked; late appearance
4	Not identified	4q25-q27	Not identified	
5	KCNE1* (MinK)	21q22.1-p22	I_{Ks}	Generally heterozygous mutations cause Romano-Ward whereas homozygous mutations result in Jervell and Lange-Nielsen syndromes.
6	KCNE2† (MiRP1)	21q22.1	I_{Kr}	

Abbreviations: I_{Na}, inward sodium channel.
* Coassemble to form the I_{Ks} channel.
† Coassemble to form the I_{Kr} channel.
Data from.[201,202,206]

ble for ion channel defects in the cardiac conduction system.

An estimate of cardiovascular risk caused by a prolonged QTc has been described in patients with congenitally long QTc syndrome.[54] It has been proposed that the hazard ratio for cardiac events (arrhythmic syncope or probable long QTc syndrome–related death) was $1{,}052^{x}$, where x equals 1 for every 10 ms increase in QTc.

Post-MI. A number of studies have reported a direct correlation between ventricular tachyarrhythmia and QTc prolongation during the acute post-MI recovery period.[207,208] QTc thresholds for increased risk for ventricular tachycardia and/or arrhythmias were variously reported to be 430 to 437,[55] 440,[37,209] 460,[208] 475,[210] and 520 ms.[207] All studies used a QTc interval by the Bazett correction, except the nomogram QT-corrected interval of Karjalainen et al.

The association between QTc prolongation and mortality is much stronger for the post-MI population (Table 6) than for the general population. Mean QTc values of 460 to 490 ms have been reported acutely, whereas patients dying within 1 year appear to have longer QTc intervals (425 to 443 ms) than survivors (413 to 438 ms). These QT prolongations are associated with a 2- to 13-fold increase in the risk for cardiac death. Those studies reporting the greatest mortality risk specifically examined cardiac mortality and/or sudden death (compared with all-cause mortality) and typically involved a short follow-up of 1 year. Thus, QTc prolongation may identify patients at greater risk for mortality because of its association with more severe underlying ischemic heart disease.

Diabetes Mellitus

The prevalence of QT prolongation is greater in patients with insulin-dependent diabetes mellitus (IDDM).[80] In the EURODIAB IDDM Cohort (n = 3,250), mean QTcs (Bazett correction) were 412 and 422 ms for men and women, respectively. Moreover, QTc duration positively correlated with ischemic heart disease. In a separate study of 182 subjects without IDDM, the relationship between QTc and cardiac death was examined.[78] With follow-up of 6 years, this study showed a highly significant ($P < .001$) relationship between cardiac death and maximum QTc, although the methods of QTc measurement and analysis were

Table 6. QTc Prolongation: Analysis of Cardiovascular and Post-MI Patients

Study/Author	Size of Population (no.)	Age* (yr)	Follow-Up (yr)	Risk Parameter	Reference QTc (ms)	Risk Relative to Reference QTc Population		
						QTc Range (ms)		Relative Risk
Danish[37] (cardiovascular subgroup)	821	(48 ± 11)	11	All-cause death	310-380	380-440		2.84
						>440		3.83†
				Cardiac death	310-380	380-440		4.08
						>440		8.09†
Finnish[55] (known cardiac disease)	829	30-59	23 average, 20-26	All-cause death	372-410 men, 378-417 women	Men	Women	
						<353	<358	1.26 men, 1.95 women
						353-371	358-377	0.99 men, 0.87 women
						411-430	418-437	1.22 men, 0.91 women
						>430	>437	1.92 men,† 1.22 women
				Cardiovascular death	372-410 men, 378-417 women	Men	Women	
						<353	<358	1.30 men, 1.80 women
						353-371	358-377	0.90 men, 0.83 women
						411-430	418-437	1.41 men, 0.77 women
						>430	>437	2.12 men,† 1.50 women
				Coronary artery disease–related death	372-410 men, 378-417 women	Men	Women	
						<353	<358	0.94 men, 1.20 women
						353-371	358-377	0.93 men, 0.50 women
						411-430	418-437	1.38 men, 1.18 women
						>430	>437	2.11 men,† 1.62 women
				Sudden death	372-410 men, 378-417 women	Men	Women	
						<353	<358	1.25 men, NA women
						353-371	358-377	1.15 men, NA women
						411-430	418-437	1.61 men, NA women
						>430	>437	2.17 men, NA women
Schwartz and Wolf[211] (post-MI cohort)	26	41-60	10	Sudden death	<440	>440		2.2†
Boudoulas et al[212] (post-MI cohort)	100	(53 ± 8)	3.6	Cardiac death	≤430 men, ≤455 women	>430 men, >455 women		1.7
Ahnve et al[213] (post-MI cohort)	865	18-95 (61.8 ± 12.5)	1	Cardiac death	<440	>440		13.3†
Peters et al[214]	1,849		2.1	Sudden death	<450	>450		1.8
Juul-Möller[215] (post-MI cohort)	99	33-65 (mean 55)	1	Cardiac death	<480	>480		5.6†
Pohjola-Sintonen et al[216] (post-MI cohort)	457	<66	4	All-cause death	<440	>440		1.4
Puddu and Bourassa[217] (coronary artery disease)	251	NA	3.8, 4.1 (survivors), 2.5 (nonsurvivors)	Sudden death	<440	>440		1.7
Fioretti et al[218] (post-MI cohort)	474	(57 ± 11)	1	All-cause death	<440	>440		1.8
Peters et al[214]	1,849	NA	2.1	All-cause death	≤440	≥450		1.7
Puddu and Bourassa[217]	251	NA	3.8, 4.1 (survivors), 2.5 (nonsurvivors)	All-cause death	<440	>440		1.3

Abbreviation: NA, not available.

* Values expressed as range (mean ± SD).

† Confidence interval does not include 1.00.

Adapted and reprinted with permission from Algra et al: QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. Circulation 83:1888-1894, 1991.[82]

not described. This finding is consistent with a number of other uncontrolled observational studies of patients with diabetes mellitus.[219-221]

Obesity

Obesity is an independent risk factor for cardiovascular morbidity and mortality in the general population.[68,222-224] In the Framingham study (n = 5,209), baseline weight correlated with an increased risk for sudden death (2- to 7-fold), coronary disease, and congestive heart failure. These findings were independent of other risk factors, including those comorbidities that could result from obesity (eg, hypertension, glucose intolerance, cholesterol).

Although the mechanism responsible for the association between obesity and mortality is unclear, some investigators have implicated autonomic disturbances leading to QTc prolongation.[225,226] Obesity also has been associated with increased ventricular ectopy[227] and eccentric left ventricular hypertrophy.[228] The latter feature appears to be anatomically distinct from the concentric ventricular hypertrophy seen as a sequela of hypertension.

An association between BMI and QTc was found in the Framingham population, in which significant differences in QTc were observed in groups with a BMI less than 23 to 27 and/or greater than 27 kg/m^2 compared with a BMI less than 23 kg/m^2 (Fig 4A and B). QTc prolongation was recently examined in a study of 139 adults referred for obesity evaluation.[64] Increasing relative body mass was associated with significant lengthening of QTc regardless of the QT correction formula applied. Approximately 26% of morbidly obese subjects (BMI > 40 kg/m^2) were found to have a QTc greater than 440 ms (Bazett correction) compared with a mean of 4.6% (men, 3.2%; women, 5.4%) of individuals without heart disease in population-based studies.[37,55,192,193] Carella et al[67] found that in 343 obese patients without associated cardiac disease, hypertension, or diabetes, a QTc greater than 420 or greater than 440 ms was present in 53% and 23% of the patients, respectively. Moreover, a direct relationship was observed between QTc and fat mass. These studies are supported by other analyses that also suggest QTc prolongation is directly related

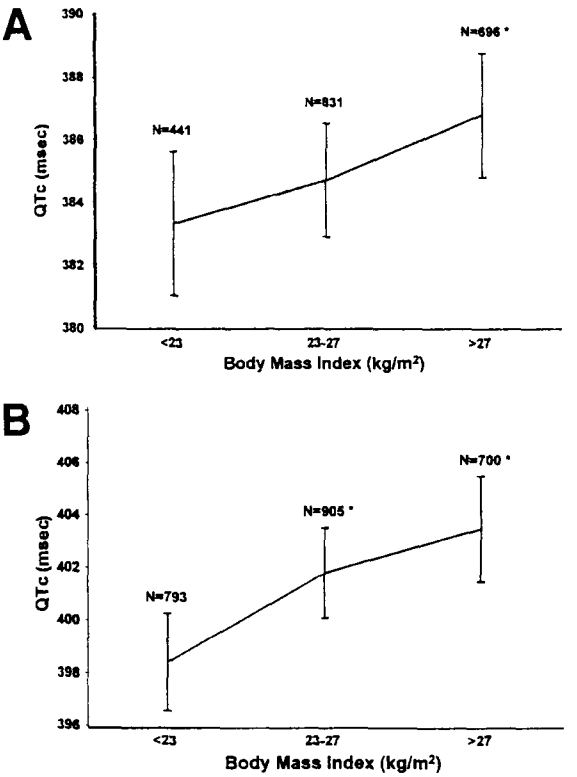

Fig 4. Mean QTc with 95% confidence intervals versus BMI category for (A) males and (B) females. * $P < .05$ *v* BMI < 23 kg/m^2. (Data from Sagie et al[26])

to the degree of excess weight[66] or regional fat distribution[65] in otherwise healthy adults (Fig 5).

Interestingly, the prolongation of QTc seen with obesity may be at least partially reversible. Carella et al[67] observed an average QTc shortening of 10 ms in 522 patients who experienced an average 6-month weight loss of 50 pounds. Weight loss over shorter periods was also associated with QTc shortening.[229-231] These findings led Carella et al[67] to hypothesize that weight loss in an obese population may improve the cardiovascular mortality rate, in part by shortening QTc. Drenick and Fisler[225] estimated that morbid obesity (>100 pounds or 100% over desired weight) is associated with a 40-fold increase in risk for sudden death compared with age-matched nonobese populations.

Drug-Induced QTc Prolongation

Prolongation of cardiac repolarization has been reported for a number of drugs with different therapeutic uses. The Georgetown Department of

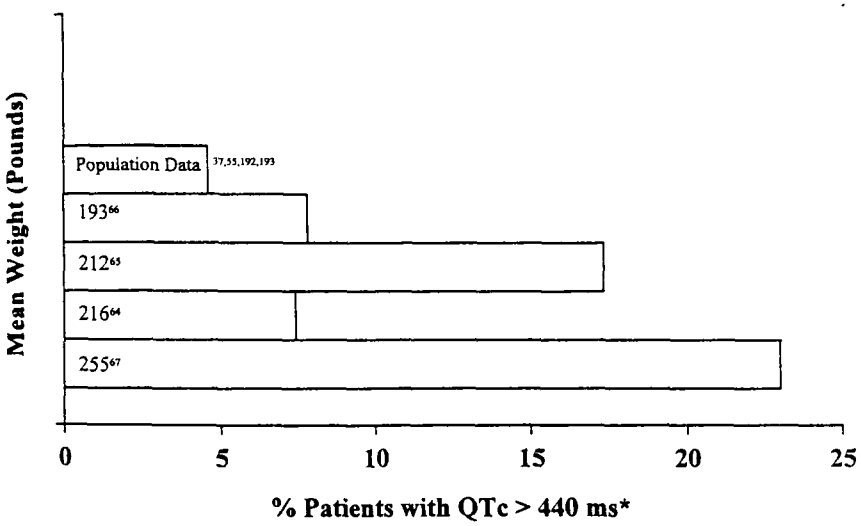

Fig 5. Body weight and QTc. Data from Karjalainen et al[55] used the highest category for both males (>430 ms) and females (>437 ms); all other data were greater than 440 ms. (The superscripted numbers indicate the corresponding references for the data.)

Pharmacology Web site[88] and the Canadian Adverse Drug Reaction Newsletter[89] identified 50 drugs associated with QT interval prolongation (Table 7). Although this list identifies many drugs associated with QT interval prolongation, it should be considered illustrative, not comprehensive. More recently, moxifloxacin and dofetilide were approved in the United States, whereas sertindole, grepafloxacin, terodiline, and cisapride were withdrawn, suspended, or their use greatly restricted because of cardiac issues. Of those drugs currently in use, only cisapride, ibutilide, and dofetilide have "black box" warnings in their US package inserts.

To better understand the evidence underlying the inclusion of QT prolongation in the labeling for these products, a review of all available sources of such information was performed (Tables 8 and 9).

It is notable that a number of chronically administered drugs have been associated with QTc prolongation in excess of 10 ms, with a possibly acceptable cardiac safety profile (eg, tricyclic antidepressants at recommended doses). Also noteworthy is the paucity of carefully controlled trials designed to measure peak drug effect on cardiac repolarization. A discussion of key issues surrounding a number of these agents is instructive.

Terfenadine. Terfenadine is a histamine$_1$-receptor antagonist structurally related to haloperidol[310] that has recently been found to block the I_{Kr} current, as well as the plateau (phase 2) portion of the fast sodium current and the L-type calcium channel.[49,311] In an examination of the effect of terfenadine on QTc in both the presence and absence of cardiac disease, it was suggested that a 5- to 15-ms prolongation did not have an obvious impact on clinical end points.[2] In an examination of the effect of terfenadine (60 mg twice daily) on QTc, a mean prolongation of 6 ms[4] and a peak prolongation of 18 ms[312] were measured in the absence of metabolic inhibition. Subsequently, concerns arose after reports of adverse cardiac events in association with terfenadine administration. Further investigation showed that all or nearly all these events occurred in association with a notable increase in plasma drug concentrations. This increase was the result of a decrease in drug elimination by inhibition of the cytochrome P-450 3A4 (CYP3A4) isoenzyme system through drug-drug interactions[3] or an impairment in hepatic function in association with liver disease.[2,3,313] The consequent increase in the parent terfenadine levels resulted in a significant prolongation of QTc (82 ms; Bazett correction)[3] and increased the risk for ventricular arrhythmia.

Cisapride. Cisapride is a gastric prokinetic agent that increases acetylcholine release and inhibits the I_{Kr} channel (HERG). It is primarily metabolized by CYP3A4. In a study of healthy adult volunteers, cisapride administration was associated with mean and peak QTc prolongations of 6 ms[260] and 18 ms,[262] respectively.

However, the administration of cisapride with either a metabolic (CYP450) inhibitor or in those with limited CYP450 function (eg, neonates) rep-

Table 7. Drugs That Prolong the QT Interval

Category	Drugs
Antihistamines and combinations	Astemizole, terfenadine
Anti-infectives	Amantadine (Symmetrel), clarithromycin (Biaxin), chloroquine, ery-tab/erythromycin/erythrocin, grepafloxacin (Raxar), halofantrine, mefloquine HCl, moxifloxacin (Avelox), pentamidine (Pentacarinat), sparfloxacin (Zagam), trimethoprim-sulfamethoxazole
Antineoplastics	Tamoxifen (Nolvadex)
Antispasmodics	Terodiline
Cardiovascular agents	
Antiarrhythmics	Amiodarone (Cordarone), bretylium, disopyramide (Norpace), flecainide (Tambocor), ibutilide (Corvert), moricizine (Ethmozine), procainamide (Procanbid), quinidine (Cardioquin), sotalol (Betapace), tocainide (Tonocard), dofetilide (Tikosyn)
Antilipemic agents	Probucol
Calcium channel blockers	Bepridil (Vascor)
Diuretics	Indapamide (Lozol)
Gastrointestinal agents	Cisapride (Prepulsid), ipecac
Hormones	Fludrocortisone, vasopressin
Immunosuppressives	Tacrolimus (Prograf)
Psychotherapeutic agents	
Antidepressants	Amitriptyline (Elavil), amoxapine, clomipramine (Anafranil), desipramine (Norpramin), imipramine (Tofranil), maprotiline, nortriptyline (Pamelor), protriptyline (Vivactil)
Antipsychotic agents	Chlorpromazine (Thorazine), fluphenazine, haloperidol (Haldol), perphenazine, pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), sertindole (Serlect), thioridazine (Mellaril), thiothixene (Navane), trifluoperazine (Stelazine)
Antianxiety agents	Doxepin (Sinequan)
Antimanic agents	Lithium
Sedatives and hypnotics	Chloral hydrate

NOTE. Endo Labs of Chadds Ford, PA, manufactures Symmetrel. Abbott of Chicago, IL, manufactures Biaxin. GlaxoWellcome of Research Triangle Park, NC, manufactures Raxar. Bayer of West Haven, CT, manufactures Avelox. JHC Healthcare Ltd of Dublin, Ireland, manufactures Pentacarinat. Bertek of Morgantown, WV, manufactures Zagam. AstraZeneca of Wilmington, DE, manufactures Nolvadex, Tonocard, Elavil, and Seroquel. Wyeth Ayerst of Philadelphia, PA, manufactures Cordarone. Searle of Chicago, IL, manufactures Norpace. 3M of St Paul, MN, manufactures Tambocor. Pharmacia and Upjohn of Peapack, NJ, manufactures Corvert. Roberts of Eatontown, NJ, manufactures Ethmozine. Monarch of Bristol, TN, manufactures Procanibid. Purdue Frederick of Norwalk, CT, manufactures Caridoquin. Berlex of Wayne, NJ, manufactures Betapace. Pfizer Inc of New York, NY, manufactures Tikosyn, Navane, and Doxepin. Ortho-McNeil of Raritan, NJ, manufactures Vascor and Haldol. Rhone-Poulenc-Rorer of Collegeville, PA, manufactures Lozol. Janssen of Titusville, NJ, manufactures Prepulsid and Risperdal. Fujisawa of Deerfield, IL, manufactures Progaf. Novartis of East Hanover, NJ, manufactures Anafranil, Tofranil, and Pamelor. Hoechst Marion Roussel of Kansas City, MO, manufactures Norpramin. Merck of West Point, PA, manufactures Vivactil. SmithKline Beecham of Pittsburgh, PA, manufactures Thorazine and Stelazine. Gate of Sellersville, PA, manufactures Orap. Lundbeck of Copenhagen, Denmark, manufactures Serlect. Novartis of Basel, Switzerland, manufactures Mellaril.
Data from.[88,89]

resent circumstances associated with further QTc prolongation. Specifically, the coadministration of cisapride with clarithromycin, a CYP3A4 inhibitor, resulted in a 3-fold increase in cisapride concentrations and an average QTc increase of 25 ms.[260] An 8-fold increase in cisapride concentrations was reported in association with ketoconazole coadministration, but ECG data were not reported.[314] In a cohort of neonates aged younger than 3 months, a mean QTc prolongation of 31 ms was noted after cisapride therapy (n = 73).[267] The combination of sparfloxacin (an antibiotic associated with QTc prolongation) with cisapride was associated with a 29-ms prolongation of the QTc.[291]

Since its launch in 1993, more than 30 million prescriptions have been written, primarily for gastroesophageal reflux disease and gastrointestinal motility–related disorders.[315] A recent prescription database review showed no association between cisapride use and serious rhythm disorders.[316] Nonetheless, from July 1993 to May 1999, 270 adverse events involving serious cardiac arrhythmias such as TdP and/or QT prolongation, including 70 deaths, were spontaneously reported to the US Food and Drug Administration.[316]

Table 8. Drugs Known to Prolong QTc and Ventricular Arrhythmic Indication: Controlled Studies

Drug	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms)			Comments	Reference
								B/L	Change Preinh/Con Med	Change Postinh/ Con Med		
Amiodarone	7 M, 1 F with recurrent VT/VF	1,600 mg/d × 7-14 d	Amiodarone, 1,600 mg/d × 7-14 d, then single IV dose PA EPS. EPS also done after PA alone	Bazett	Procainamide	15 Min after end of PA infusion	15 min after PA infusion end	427	50	89		232
Disopyramide	10 Cardiac patients (6 M, 4 F)	Disopyramide, 200 mg	Not specified	Bazett	None	B/L and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 h after drug administration	QTc max	440	30			233
Disopyramide	5 Healthy volunteers	(+) and (−) disopyramide, 100 mg IV	Randomized crossover with 2 periods separated by 1 wk	Linear regression	None	B/L and 10, 20, 25, 40, 50, 80, 140 and 260 min after drug infusion	QTc max	R(+) 511 R(−) 506	50 24			234
Disopyramide	6 M healthy volunteers	1.5 mg/kg IV of either d-, l-, or dl-disopyramide	Open label with each subject receiving all 3 isomers.	Not specified	None	−30, −20 and −10, B/L and 5, 15, 30, 45, 60, 120 and 180 min postdrug	15 min postdrug	d 385 dL 395	56 26		No significant QTc prolongation noted with L isomer	235
Disopyramide	12	1.5 mg/kg/5 min bolus, 0.4 mg/kg/h × 6 h, switched to 250 mg po twice daily	Open	Not calculated, only QT value given	None	Hourly during IV infusion, twice daily during po	QT max (uncorrected) at 18 h	430	10			236
Flecainide	280 With chronic PVCs	Flecainide 200 mg every 12-h; quinidine, 300 mg every 6 h as low dose; flecainide, 300 mg every 12 h; quinidine 400 mg every 6 h as high dose	Double-blind parallel study with 2 weeks of active drug (first week as low dose, second week dependent on < or > 80% suppression of PVCs in first week by Holter) and a 1-week placebo period before and after therapy.	Not specified	None	Continuous Holter monitoring	Not specified	382	24-28		3 Active patients on quinidine died within 3 d of starting drug; 1 placebo patient died in week 4	237
Flecainide	8 M healthy volunteers	Flecainide, 200 mg; verapamil, 120 mg, each as a single dose	Double-blind randomized placebo controlled design using 4 treatment arms separated by 7-10 d each	Not specified	Verapamil	B/L, 1, 2, 3, 4, 8, 12, 24 h after drug	Peak differences	404	22	14		238
Flecainide	30 With ventricular arrhythmias (21 M, 9 F)	11 patients, low dose (median daily dose, 240 mg po); 19 patients, high dose (median daily dose, 480 mg po)	Open	Bazett	None	Holter ECG recorded at baseline and on each of 3 treatment days	Not specified	NA	13 (low dose); 29 (high dose)			239
Flecainide	31 (17 M, 14 F)	All patients received all 3 treatments: (sotalol, 160 mg every d; flecainide, 200 mg every d; propafenone, 405 mg every d	Open; time between therapies not noted	Bazett	None	ECG in free-drug state and at steady state	Steady state	429	20			240
Flecainide	10 M healthy volunteers	Flecainide, 200 mg 2 times daily; propranolol, 80 mg 3-times daily	Flecainide d 8-11 and 19-23; propranolol d 1-11 and 23		Propranolol	D 1, 5, 8, 11, 19, 22, 23	Propranolol d 5; flecainide d 22; propranolol and flecainide d 11	NA	33			241

Table 8. (Continued)

Drug	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms) B/L	QTc (ms) Change Preinh/Con Med	QTc (ms) Change Postinh/ Con Med	Comments	Reference
Moricizine	Target population 10 (9 M, 1 F)	15 mg/kg/d	7 d antiarrhythmic washout; 3 d single blind placebo therapy; followed by 10 d moricizine therapy (single blind); completed with 3 d single blind placebo washout.	Bazett	None	12-lead ECGs d 1-16, then d 30, 46 and 106 and every 3 mon thereafter	Steady state (d 10 drug)	419	16			242
Moricizine	42 M	16 males: single oral 100, 200, 300, 400 mg PO moracizine; the rest, repeated oral doses (300 mg po 3 times daily) for 1 and 7 d	Phase I pk/pd (multiple designs: open, single blind, crossover for effects on meals)	Not specified	None	B/L, d 1, 4, 7 at h 1, 7, and 13 postdose	QTc reported for 7-d test with 300 mg 3 × daily	410	−10 to −20			243
Procainamide	10 M healthy volunteers	Trimethoprim, 200 mg; procainamide, 1,000 mg	Open, randomized, placebo controlled 2 period crossover evaluation comparing procainamide with and without trimethoprim each as single dose; 1 wk washout between arms	Not specified	Trimethoprim sulfa	2 h after drug	2 h after drug	NA	NA	30	No baseline ECG	244
Procainamide	8 M healthy volunteers	Procainamide 500 mg every 6 h; trimethoprim, 200 mg every d	7 d washout; procainamide × 7 d; trimethoprim d 4 through d 7; 3 d washout; followed by 3 d trimethoprim.	Bazett	Trimethoprim sulfa	d 1: B/L; 1, 3 h after drug; d 2; random ECG; d 3, 4, 7, 14 (last d): every h × 6 h after drug; d 5, 6 single ECG after drug	At steady state; value is the mean of 4 ECGs taken over a 6-h period	NA	NA	10	Average QTc with procainamide alone was 410 *v* 390 ms with trimethoprim alone	245
Procainamide	4 M healthy volunteers	Procainamide, 500 mg IV	Procainamide 1 dose, repeated weekly × 4	Linear regression	None	B/L and at "frequent intervals" postdrug	C_{MAX}	NA	20			246
Procainamide	8 with recurrent ventricular arrhythmias (7 M, 1 F)	Procainamide, 6-15 mg/kg IV; amiodarone, 1,600 mg/d	Open label; procainamide alone or after amiodarone therapy of 7-14 d	Bazett	Amiodarone	B/L and with each drug addition	Not specified	427	43	89		232
Propafenone	31 (17M, 14F)	All patients received all 3 treatments (sotalol, 160 mg every d; flecainide, 200 mg every d; propafenone, 405 mg every d)	Open; time between therapies not noted	Bazett	None	ECG in free-drug state and at steady state	Steady state	429	4			240
Quinidine	12 M healthy volunteers	Quinidine, 400 mg; GFJ, 240 mL.	Open, randomized, crossover design; 2 doses of quinidine given separated by 1 wk with GFJ or water.	Bazett	GFJ	B/L and continuously for 12 h after drug	Peak effect in first 12 h after drug	NA	69	61		247
Quinidine	280 with chronic PVCs	Flecainide, 200 mg q 12 h; quinidine, 300 mg q 6 h as low dose; flecainide, 300 mg q 12 h; quinidine, 400 mg q 6 h as high dose	Double-blind parallel study with 2 wk of active drug (wk 1 as low dose, wk 2 dependent on < or >80% suppression of PVCs in first week by Holter) and a 1-wk placebo period before and after therapy.	Not specified	None	12-lead tracings at unspecified time	Not specified	387	27			237

Table 8. (Continued)

Drug	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms) B/L	QTc (ms) Change Preinh/Con Med	QTc (ms) Change Postinh/ Con Med	Comments	Reference
Quinidine	24 (8 M, 16 F)	Not specified	Retrospective cohort analyses	Not specified	None	Not specified	Not specified	423	218			248
Quinidine	10 healthy volunteers	Quinidine, 3.74 mg/kg IV × 25′	Randomized, double-blind placebo controlled at intervals of 1 wk	Not specified	None	B/L and at multiple time points from 0-1,440 min after drug	At QTc max (~25 min)	NA	63			249
Quinidine	10	Quinidine, 3.74 mg/kg PO × 1	Randomized, double-blind placebo controlled at intervals of 1 wk	Not specified	None	B/L and at multiple time points from 0-1,440 min after drug	At QTc max (~100 min)	NA	34			249
Quinidine	12 M healthy volunteers	Diltiazem, 60 mg, or quinidine, 200 mg × 1	4-way counter-balanced crossover design, each separated by 1 wk	Bazett	Diltiazem	B/L, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 26 h after drug	QTc max (~C_{MAX}, 2 h postdrug)	421	42	55		250
Quinidine	9 (4 M, 5 F)	Itraconazole, 200 mg every d × 4 d; quinidine, 100 mg × 1 on d 4	Randomized, double-blind 2-phase crossover at intervals of 4 wk	Bazett	Itraconazole	0.5, 1, 1.5, 3, 5, 12, 24 h after quinidine therapy	3 h after quinidine (C_{MAX})	410 418	38	37		251
Quinidine	4 (2 M, 2 F)	Quinidine, 300 mg; cimetidine, 300 mg q h	Open; quinidine 300 mg IV/PO on 4 occasions, separated by 1 to 2 wk (before cimetidine and after at least 5 days of pretreatment with cimetidine, 300 mg every 6 h	Boudoulas linear correction factor	Cimetidine	B/L, 0.5, 1, 2, 3, 4, 5 h after quinidine	QTc max	510	41	52		252
Sotalol	Multiple groups of 6	Sotalol, 50, 100, 200 or 300 mg	Single dose escalation followed by multiple dose study of 200 mg twice daily × 13 doses	Not specified	None	B/L, 1, 2, 4, 8, 12 and 24 h after single dose therapy	4 h after drug (QTc max) 300 mg (200 mg)	360 (378)	56 (27)		Figure indicates QT, text states rate-corrected	253
Sotalol	31 (17 M, 14 F)	All patients received all 3 treatments: (sotalol: 160 mg QD; flecainide, 200 mg QD; propafenone, 405 mg QD	Open; time between therapies not noted	Bazett	None	ECG in free-drug state and at steady state	Steady state	429	2			240

Note. Some data were extrapolated from available figures.

Abbreviations: F, female; GFJ, grapefruit juice; M, male; NA, not available; B/L, baseline; Con Med, concomitant medication; Inh, inhibitor; VT, ventricular tachycardia; VF, ventricular fibrillation; PVC, premature ventricular contraction; IV, intravenously; PO, orally; PA, procainamide; EPS, electrophysiologic study; C_{max}, maximum drug concentration; pk/pd, pharmacokinetic/pharmacodynamic.

Table 9. Drugs Known to Prolong QTc and Nonantiarrhythmic Indications: Controlled Studies

Drug	Reference	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms)			QTc (ms; %)						QTc Change (ms; % with increased QTc value)						Comments
												>450		>480		>500		>30		>60		>75		
									B/L	Change Preinh Con Med	Change Postinh Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	
Amitriptyline	254	Depressed population, 20 (13 M, 7 F)	Wk 1: 100 mg nightly Wk 2: 150 mg nightly Wk 3: 200 mg nightly	Randomized and blinded to either desipramine or amitriptyline	Not specified	None	B/L and weekly	Not specified; performed at wk 3	407	17														One amitriptyline patient developed right bundle-branch block and was discontinued from therapy
Astemizole	255	12 M healthy volunteers	Itraconazole, 100 mg twice daily × 14 d; astemizole, 10 mg × 1 on d 11	Double-blind, placebo-controlled, randomized crossover with 2 study phases; 4-wk washout period between doses	Bazett	Itraconazole	B/L 2, 4, 8, and 24 h postdrug	2 h postdrug	402	−17	−17													
Astemizole	256	18 (9 M, 9 F) healthy volunteers	Dirithromycin, 500 mg every AM, astemizole, 30 mg	Randomized 2-way crossover, dirithromycin × 10 d ± single dose astemizole on d 4; 4-wk washout period	Not specified	Dirithromycin	B/L; 10-12 h after astemizole and on final d of dirithromycin or PBO	12 h after AM dose	453 452	−19	8	16.7	50 (9/18)	0	22.2 (4/18)	0	11.1 (2/18)	11.1	16.7	0	0			
Bepridil	257	24 (12 M, 12 F) healthy volunteers	Digoxin, 0.375 mg/d for 12 d after 0.75 mg on d 1 and 2; bepridil, 300 mg 3 × daily	Randomized double-blind design with parallel treatment groups, 12 subjects each, balanced for gender; each of 2 periods was 1 wk	Bazett	Digoxin	B/L, d 7, 14	Same time of day	406	33														
Bepridil	258	21 (18 M, 3 F)	3 mg/kg IV over 10 min (2 patients, 300 mg PO)	Open	Bazett		Immediately before and 30 min after	30 min after therapy	423	32														1 patient on PO med died suddenly; 1 patient on PO med died of progressive heart failure
Bepridil	259	13 M	400 mg PO daily	Randomized, double-blind, placebo-controlled crossover × 4 wk after a 2-wk single-blind placebo period	Not specified	Placebo	At end of each treatment period	Not further specified	420	30														

Table 9. (Continued)

Drug	Reference	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms)			QTc (ms; %)						QTc Change (ms; % with increased QTc value)						Comments
												>450		>480		>500		>30		>60		>75		
									B/L	Change Preinh Con Med	Change Postinh Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	
Cisapride	260	12 healthy volunteers	Cisapride, 10 mg 4 × d; clarithromycin, 500 mg 2 × d	Open randomized 2-way crossover with washout periods of 1 wk, cisapride therapy × 10 d with con clarithromycin from d 6-10 or clarithromycin × 10 d with con cisapride from d 6-10	Bazett plus individual AUEC/ duration, summed and averaged	Clarithromycin	B/L and daily; on d 5 and 10: ECGs obtained "regularly" for 24 h	24 h mean at B/L and on d 5 and 10	400	6	25													
Cisapride	261	19 Children	Not specified	Open label	Not specified	None	Before drug and at least 4 d after starting drug	Not specified	393	6														Age range, 32 wk gestational age to 17 yr (mean, 44 mo)
Cisapride	262	10 M healthy volunteers	200 ml GFJ or water 3 × d × 3 d; cisapride, 10 mg on d 3	Randomized 2-period crossover	Bazett	GFJ	B/L and 2, 5, 8 and 12 h after cisapride	Peak QTc (5 h after cisapride)	389	18	17													
Cisapride	263	16 M healthy volunteers	Cisapride, 20 mg ± pantoprazole, 40 mg daily × 3 d starting 1 h before cisapride or PBO; washout period at least 1 wk	Randomized open-label 2-period crossover	Not specified	Pantoprazole	B/L and 1, 2, 4, 8, 12, 24, 36, 48 and 72 h after cisapride (72 h done only for combined therapy)	Mean changes reported	403	4	3													
Cisapride	264	12 Infants (5 M, 7 F) 4 d-6 mon	Cisapride dose at least 0.2 mg/kg/ dose 4 × d	Open-label prospective trial	Not specified	None	B/L and 3 d after treatment	Not specified	414	10														
Cisapride	265	8 Infants *v* age-matched controls (average age, 3 wk)	Cisapride, 0.2 mg/kg/dose	Open label	Bazett	None	Active group: 3 separate measurements for all subjects, each after a dose of cisapride; age-matched controls underwent 24 h monitoring	Cisapride No drug	460 440			50												50% had QTc >470 ms

Table 9. (Continued)

Drug	Reference	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms)			QTc (ms; %)						QTc Change (ms; % with increased QTc value)						Comments
												>450		>480		>500		>30		>60		>75		
									B/L	Change Preinh Con Med	Change Postinh Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	
Cisapride	266	20 Children; mean age 6 yr	Cisapride, 0.8-1.2 mg/kg/d	Open label	Bazett	None	B/L and 3, 7 d and 1 mon after initiating therapy	Time after initiating therapy, 7 d, 1 m	406 7 d 1 mon	 6 22		10												
Cisapride	267	160 Infants; 73, <3 mon; 42, 3-6 mon; 45, 6-12 mon	Not specified	Open	Bazett	None	After a minimum of 4 d on cisapride therapy	3 Consecutive beats taken each h for 8 h and the 24 values averaged	ND <3 mon 3-6 mon 6-12 mon	 31 10 5														QTc-subjects on cisapride *v* cohort not on therapy
Cisapride	268	35 Children (0.4-18 yr)	Mean dose of cisapride, 0.19 mg/kg; mean daily dose of cisapride, 0.67 mg/kg/d	Open	Bazett	None	Single ECG	Not specified	ND	10		31												Mean age, 5.2 yr *v* 1,000 children not on medications
Cisapride	269	30 Children	Not specified	Open	Bazett	None	B/L and 2 and 7 d after starting cisapride	1-2 h after cisapride dosing	394	15.5														12/101 had QTc >440 ms on cisapride therapy
Cisapride	270	49 Neonates (25-41 wk gestation)	0.42-1.6 mg/kg/d	Not specified	Bazett	None	B/L and a mean of 2.9 d after starting therapy	Not specified	395	23		14		2		2								
Clarithromycin	260	12 Healthy volunteers	Cisapride, 10 mg qid; clarithromycin 500 mg bid	Open randomized 2-way crossover with washout periods of 1 wk; cisapride therapy × 10 d with con clarithromycin from d 6-10 or clarithromycin × 10 d with con cisapride from d 6-10	Bazett plus individual AUEC/duration, summed and averaged	Cisapride	B/L and daily; on d 5 and 10, ECGs obtained "regularly" for 24 h	24 h mean at B/L and on d 5 and 10	400	3	26													
Clomipramine	271	47	Variable	Literature search	Not specified	None	Not specified	Not specified	399	20														
Desipramine	254	Depressed population 26 (12 M, 14 F)	W1: 100 mg qhs W2: 150 mg qhs W3: 200 mg qhs	Randomized and blinded to either desipramine or amitriptyline	Not specified	None	B/L and every wk	Not specified. Performed at wk 3	408	24														
Desipramine	271	271	Variable	Literature search	Not specified	None	Not specified	Not specified	415	12														

Table 9. (Continued)

Drug	Reference	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms)			QTc (ms; %)						QTc Change (ms; % with increased QTc value)						Comments
												>450		>480		>500		>30		>60		>75		
									B/L	Change Preinh Con Med	Change Postinh Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	
Doxepin	272	Ventricular arrhythmias 10 (2 M, 8 F)	Doxepin 1-3.5 mg/kg/d	48 h antiarrhythmic drug washout; dose increased from 1 to a maximum of 3.5 mg/kg/d by 1 mg/kg/d increments every third d	Bazett	None	Continuous during dose ranging	2-3 h after AM dose	436	23		57.1 (4/7)		20 (2/10)		10 (1/10)		30		10		10		
Doxepin	273	8 (2 M, 6 F)	150-275 mg qd	Open label 3 × d schedule for drug for 14-120 d	Not specified	None	B/L and during therapy	B/L and on therapy	NA	1								12.5 (1/8)						
Erythromycin	274	49 (26 M, 23 F)	Mean dose, 42 mg/kg/d	Retrospective chart review	Bazett	None	B/L; and drug infusion	During drug infusion	432	51														
Erythromycin	275	22 M healthy volunteers	Loratidine, 10 mg every d, erythromycin, 500 mg every 8 h	Randomized blinded placebo controlled crossover with 36 h initial washout and 14 d washout between study arms of loratadine or erythromycin or both for 10 d	Bazett	None	B/L, 7, 8, 9, 10, 11 AM and 1, 3, 7 and 11 PM during treatment and at hours 1, 2, 3, 4, 6, 8, 12, 16, 24, and 48 after the 7 AM dose on d 10 of each treatment period	Change from maximum QTc interval to d 10 maximum QTc	414	2														
Erythromycin	276	6 Healthy volunteers	Terfenadine, 60 mg twice daily; erythromycin 500 mg 3 × d	Specific design not specified. Terfenadine, 60 mg twice daily × 14 d; erythromycin, d 9-14; washout period of 1-2 mon; 6 of 9 subjects returned and received erythromycin, 500 mg 3 × d × 1 wk	Bazett	None	B/L; d 8-15 AM trough	Pre-AM drug on d 8 and 15	389	10														All extensive metabolizers, 3 of 9 subjects acoumulated terfenadine after erythromycin therapy (associated with mean QTc change of 64 ms)

Table 9. (Continued)

Drug	Reference	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms)			QTc (ms; %)						QTc Change (ms; % with increased QTc value)						Comments
												>450		>480		>500		>30		>60		>75		
									B/L	Change Preinh Con Med	Change Postinh Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	
Erythromycin	277	Target population 36	Not specified	Not specified	Bazett	Sparfloxacin	Not specified	Not specified	NA	13.8	5.9													Erythromycin was used as comparator agent in a sparfloxacin clinical trial in which the latter prolonged the QT interval by 5.9 ms (n = 30)
Grepafloxacin	278	48	600 mg every d for 7 d	Open label, nonrandomized, parallel group study	Bazett	None	7 d before treatment, eve of treatment; and d 4 and 3 d after treatment ended	C_{max}	NA	10.4						0								Using Fridericia, the change in QTc was 1.8 ms
Halofantrine	279	8 (4 M, 4 F)	Mefloquine, 250 mg every wk × 5; halofantrine, 500 mg every 6 h × 3	Open label	Not specified	Mefloquine	Not specified	Not specified	NA		99													
Halofantrine	280	Target population 12	Halofantrine, 1 mg/kg every 8 h × 3	Open label	Not specified	None	B/L immediately before/ after each drug infusion, 24 h after admission and at discharge	After dose 2	410	30														Convalescent group received halofantrine, 1 mg/kg IV × 1; no change in QTc was reported
Haloperidol	281	42 (32 M, 10 F) Tourette patients	Haloperidol, maximum dose 10 mg/d and pimozide, maximum dose 20 mg/d	21-wk randomized double-blind crossover comparing haloperidol, pimozide, and placebo (6 wk each) after a 3-wk placebo run in	Bazett	Pimozide	B/L and every 3 wk	End point of each treatment	384	4	20													

Table 9. (Continued)

Drug	Reference	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms)			QTc (ms; %)						QTc Change (ms; % with increased QTc value)						Comments
												>450		>480		>500		>30		>60		>75		
									B/L	Change Preinh Con Med	Change Postinh Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	
Haloperidol	282	57 (44 M, 13 F) Tourette patients	Maximum: pimozide, 20 mg daily; haldol, 10 mg daily	Double-blind, parallel, cross-over design, initial single-blind 3-wk placebo period, then randomized to haloperidol, pimozide, or placebo for 6 wk, followed by cross-over for 6 more wk	Not specified	Pimozide	B/L and every 3 wk	End point of each drug	388	4	24													
Haloperidol	283	325	Variable, 4-20 mg/d, all dosing 2 × d		Not specified	None						2.8												
Imipramine	271	181	Variable	Literature search	Not specified	None	Not specified	Not specified	393	39														
Moxifloxacin	284	Not specified	400 mg PO (IV)	Not specified	Not specified	None	Not specified	Expected QTc max		6 (12)														
Moxifloxacin	284	787	400 mg PO			None			NA	6						0.4		12		1.3				Mean QTc prolongation with comparator (n = 759) = 1 ms and QTc >500 ms of 0.1%; 13 patients had atrial fibrillation during moxifloxacin therapy or within 30 d (2 with comparator)
Moxifloxacin	284	4,008	400 mg every d	"Controlled" trials, not otherwise specified	Not specified	None			NA	6														Comparators with mean QTc increase of 1 ms (clarithromycin, cephalexin, cefuroxime, axetil, amoxicillin, doxycycline, metronidazole)

Table 9. (Continued)

Drug	Reference	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms)			QTc (ms; %)						QTc Change (ms; % with increased QTc value)						Comments
												>450		>480		>500		>30		>60		>75		
									B/L	Change Preinh Con Med	Change Postinh Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	
Nortriptyline	273	20 (6 M, 14 F)	75-400 mg every d	Open label 3 × d schedule for drug for 14-120 d	Not specified	None	B/L and during therapy	At or after 14 d of therapy	NA	20								20 (4/20)	5 (1/20)					
Nortriptyline	271	119	Variable	Literature search	Not specified	None	Not specified	Not specified	406	16														
Pimozide	285	12 (7 M, 5 F) Healthy volunteers	Pimozide, 6 mg; clarithromycin, 500 mg every 12 h	Double-blind, randomized, placebo-controlled, 2-period crossover study of the effect of clarithromycin (5 d) or placebo with single-dose pimozide	Fridericia	Clarithromycin	B/L; serial ECGs done over 12 h on d 1 and 15	QTc max at Tmax (QTc mean)	NA	13 (9)	15 (10)	0	8.5			0	0							5 Poor metabolizers, 7 extensive metabolizers
Pimozide	281	42 (32 M, 10 F) Tourette patients	Haloperidol, maximum dose of 10 mg/d; pimozide, maximum dose of 20 mg/d	21-wk, randomized, double-blind crossover comparing haloperidol, pimozide, and placebo (6 wk each) after a 3-wk placebo run in	Bazett	Haloperidol	B/L and every 3 wk	End point of each treatment	384	19	4													
Pimozide	282	57 (44 M, 13 F) Tourette patients	Maximum of pimozide, 20 mg every d, haldol, 10 mg every d	Double-blind, parallel, crossover design, initial single-blind 3-wk placebo period, then randomized to haloperidol, pimozide, or placebo for 6 wk followed by crossover for 6 more wk	Not specified	Haloperidol	B/L and every 3 wk	End point with each drug	388	24	4													
Quetiapine	286	698				None						0				1.4								2.3% chlorpromazine patients and 0% haloperidol patients reached 500 ms

Table 9. (Continued)

Drug	Reference	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms)			QTc (ms; %)						QTc Change (ms; % with increased QTc value)						Comments
												>450		>480		>500		>30		>60		>75		
									B/L	Change Preinh Con Med	Change Postinh Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	
Risperidone	287	Target population 167	7.2 mg/d mean, modal olanzapine, 17.2 mg/d	Antipsychotic drug washout period; 28 W treatment. Double-blind, parallel group	Not specified	None	B/L; 4, 8, 28 wk	Not specified	NA	4.4														
Risperidone	283	1,429				None						4.3												
Risperidone	283	385				None						2.1												
Sertindole	288	1,446	12, 20 and 24 mg/d	Not specified	Not specified	None	Not specified	Not specified	NA	21						4								4 with QTc >500 ms died
Sertindole	288	497	Sertindole, 12, 20, 24 mg; haloperidol, 4, 8, 16 mg	8 wk inpatient study in neuroleptic responsive or naive pts; doses titrated every 3rd day	Not specified	None	Not specified	Not specified	NA							7-8								Dose response for QT interval with 13 ms up to 22 ms of prolongation
Sertindole	288	438	Sertindole, 20, 24 mg; haloperidol, 16 mg	8 wk inpatient study	Not specified	None	Not specified	Not specified	NA							2-6								High dose of sertindole had a 25-30 ms increase
Sparfloxacin	289	90 M healthy volunteers	Sparfloxacin, 200-800 mg every d; 3 dosing regimens, each 4 days; low, 200 mg d 1, 100 mg d 2-4; medium, 400 mg d 1, 200 mg d 2-4; high, 800 mg d 1, 400 mg d 2-4	Double-blind, randomized, placebo-controlled	Bazett	None	30 min before and 1.5, 3, 4, and 5 h after drug dosing.	QTc max (mean) d 1	NA	Low 10 (9) medium 19 (16), high 31 (28)														
Sparfloxacin	290	23 (12 M, 11 F) Healthy volunteers	400 mg × 1	Double-blind, randomized, placebo-controlled, 14-d washout between arms	Bazett	None	B/L; 1.5, 3, 4, 5, 8, 10, 14, 24, 36, 48 h postdrug	QTc mean max change (QTc mean change)	398	16 (16)						4.3						8.7		
Sparfloxacin	290	23 (12 M, 11 F)	800 mg × 1	Double-blind, randomized, placebo-controlled, 14-d washout between arms	Bazett	None	B/L, 1.5, 3, 4, 5, 8, 10, 14, 24, 36, 48 h postdrug	QTc mean max change (QTc mean change)	398	29 (33)						0						0		

Table 9. (Continued)

Drug	Reference	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms)			QTc (ms; %)						QTc Change (ms; % with increased QTc value)						Comments
												>450		>480		>500		>30		>60		>75		
									B/L	Change Preinh Con Med	Change Postinh Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	
Sparfloxacin	290	23 (12 M, 11 F)	1,200 mg × 1	Double-blind, randomized, placebo-controlled, 14-d washout between arms	Bazett	None	B/L; 1.5, 3, 4, 5, 8, 10, 14, 24, 36, 48 h postdrug	QTc mean max change (QTc mean change)	398	51 (49)						9.9						4.5		
Sparfloxacin	290	23 (12 M, 11 F)	1,600 mg × 1	Double-blind, randomized, placebo-controlled, 14-d washout between arms	Bazett	None	B/L; 1.5, 3, 4, 5, 8, 10, 14, 24, 36, 48 h postdrug	QTc mean max change (QTc mean change)	397	60 (55)						14						17.4		
Sparfloxacin	291	15 M healthy volunteers	Cisapride, 10 mg 3 × d; sparfloxacin, 400 mg × 1	Open, randomized, triple-crossover study; 1 wk washout between arms	Not specified	Cisapride	5 h after sparfloxacin in cisapride group	5 h after sparfloxacin (cisapride patients only)	376		29													
Sparfloxacin	277	336	400-mg loading dose; 200 mg every d		Bazett	None		Mean QTc change	381	10.3-11														
Sparfloxacin	292-294	Target population 1,489	400 mg PO d 1, 200 mg PO daily up to 10 d	Analysis of 6 sites (controlled studies)	Not specified	None	B/L, d 4	On treatment	408	10						0.7	None							Comparator groups with mean QTc increase of 3 ms with 0.2% of subjects with QTc >500 ms (n = 1,215)
Sparfloxacin	293	357	400 mg loading dose followed by 200 mg daily (once per day) up to 10 d	Double-blind, double-dummy, randomized, comparative, multicenter trial with ofloxacin as comparator drug	Not specified	None	B/L (visit 1), d 4 ± 1, d 20 ± 3 (posttreatment), and d 38 ± 7 (posttreatment)	QTc max on d 4 of therapy	409	11														Ofloxacin mean QTc change = 1 ms
Sparfloxacin	293	228	400 mg loading dose followed by 200 mg daily up to 10 d	Double-blind, randomized, comparative, multicenter trial with clarithromycin as comparator drug	Not specified	None	B/L (visit 1), d 4 ± 1, d 20 ± 3 (posttreatment), and d 38 ± 7 (posttreatment)	d 4 of therapy	405	5														Clarithromycin change in QTc = 3 ms
Sparfloxacin	295	15 M healthy volunteers	Sparfloxacin, 200 and 400 mg	Controlled, randomized, 3-period crossover, single-dose sparfloxacin; washout period, 1 wk	Sarma	None	Every 30 sec during progressive increase in rate from 60-150 beats/min	5 h after drug at rate of 60/min	362	200 mg, 15; 400 mg, 14														Clarithromycin change in QTc = 3 ms

Table 9. (Continued)

Drug	Reference	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms)			QTc (ms; %)						QTc Change (ms; % with increased QTc value)						Comments
												>450		>480		>500		>30		>60		>75		
									B/L	Change Preinh Con Med	Change Postinh Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	
Terfenadine	296	12 (9 M, 3 F)	Terfenadine, 60 mg 2 × d × 6 d	Randomized parallel design with either simultaneous or delayed GFJ with AM terfenadine	Bazett	GFJ	Before AM drug	Steady state	410 433	10	12	0	16.7			0	0							
Terfenadine	297	6 (3 M, 3 F) Healthy volunteers	Terfenadine 60 mg 2 × d; GFJ, 240 mL; double strength.	Single-arm run-in with terfenadine × 14 d and GFJ added 2 × d on d 9-14.	Bazett	GFJ	Pre-AM drug at B/L and d 8-15; d 8 and 15 also with testing at 1, 2, 4, 6, and 12 h after drug.	Pre-AM drug on d 8 and 15	415	15	19	0	33			0	0	16.7	33.3	0	0			All subjects were known to be poor metabolizers of terfenadine based on data from a 1-wk screening protocol
Terfenadine	276	9 (4 M, 5 F) Healthy volunteers	Terfenadine 60 mg 2 × d, erythromycin, 500 mg 3 × d	Specific design not specified; terfenadine, 60 mg 2 × d × 14 d; erythromycin, d 9-14 washout period of 1-2 mos; 6 of 9 subjects returned and received erythromycin 500, mg 3 × d × 1 wk	Bazett	Erythromycin	B/L; d 8-15 AM trough	Pre-AM drug on d 8 and 15	NA	18	39												All extensive metabolizers; 3 of 9 subjects accumulated terfenadine after erythromycin therapy (associated with mean QTc change of 64 ms)
Terfenadine	298	12 (7 M, 5 F) Healthy volunteers	Terfenadine, 120 mg; atorvastatin, 80 mg every d	Terfenadine, 120 mg × 1 on d 1 and 15 (4-h fast after drug) with atorvastatin from 7 d before to 2 d after the terfenadine dose 2; design not otherwise specified	Not specified	Atorvastatin	B/L 1-2 h after terfenadine on d 1 and 15 and 6 h after terfenadine on d 15	B/L; 1-2 h after terfenadine on d 1 and immediately before and 1-2 h after terfenadine on d 15	399	3	−8												

Table 9. (Continued)

Drug	Reference	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms)			QTc (ms; %)						QTc Change (ms; % with increased QTc value)						Comments
												>450		>480		>500		>30		>60		>75		
									B/L	Change Preinh Con Med	Change Postinh Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	
Terfenadine	299	12 M healthy volunteers	Terfenadine, 60 mg 2 × d; paroxetine, 20 mg every d	Randomized, open-label, 2-period (14 d apart), steady-state crossover; terfenadine d 8-15 and paroxetine d 1-15.	Bazett	Paroxetine	B/L; predrug and 4, 8 and 12 h after AM dose and 2 h after PM dose, each after resting supine for 15 min; also q 1-2 h for 12 h on the final day of terfenadine dosing. (either d 8 or d 15)	QTc max on last d of dosing over 12 h Mean of all values attained on the last d of dosing over the 12-h period	381 381	24 6	23 5						0						
Terfenadine	300	12 (9 M, 3 F) Healthy volunteers	Terfenadine, 60 mg 2 × d, cimetidine, 600 mg 2 × d; ranitidine, 150 mg 2 × d	Not specified; all subjects received terfenadine for 14 d with 6 receiving cimetidine and 6 receiving ranitidine from d 9-14	Bazett	Cimetidine	B/L; d 8-15 AM trough	AM trough levels	405	5	11													Data excludes 1 subject with accumulation of parent compound
Terfenadine	300	12 (9 M, 3 F) Healthy volunteers	Terfenadine, 60 mg 2 × d; cimetidine, 600 mg 2 × d; ranitidine, 150 mg 2 × d	Not specified; all subjects received terfenidine for 14 d with 6 receiving cimetidine and 6 receiving ranitidine from d 9-14	Bazett	Ranitidine	B/L; d 8-15 AM trough	AM trough levels	401	4	4													Data excludes 1 subject with accumulation of parent compound
Terfenadine	301	24 M healthy volunteers	Terfenadine, 60 mg 2 × d; azithromycin 500 mg × 1, then 250 mg daily	24 subjects randomized to terfenadine (12 d) ± azithromycin (d 9-12)	Bazett	Azithromycin	B/L; pre AM dose d 1-6 and at 4 and 7 h and immediately after PM dosing on d 8-11; continuous ECG d 7 and 12	Mean QTc over 12 h postdose d 7 and 12	390 392	10	11													
Terfenadine	302	8 M healthy volunteers	Terfenadine, 60 mg 2 × d; zafirlukast, 160 mg daily.	Terfenadine × 16 d with zafirlukast d 8-16; open-label steady state	Not specified	Zafirlukast	B/L and 2 h after AM dosing.	2 h after AM dosing d 7 and 16	383	−5	15													
Terfenadine	303	6 M healthy volunteers	GFJ, 300 mL, terfenadine, 120 mg	Terfenadine, 120 mg ± GFJ 30 min before	Bazett	GFJ	B/L, 1.5, 3, 6 h postdrug	at C_{max}	NA	0	10							16.7	33.3	0	0			

Table 9. (Continued)

Drug	Reference	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms)			QTc (ms; %)						QTc Change (ms; % with increased QTc value)						Comments
												>450		>480		>500		>30		>60		>75		
									B/L	Change Preinh Con Med	Change Postinh Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	
Terfenadine	304	16 M healthy volunteers	Terfenadine, 60 mg 2 × d; zileuton, 600 mg every 6 h	Double-blind, randomized, placebo-controlled, 2-period crossover study, 2-wk washout.	Bazett	Zileuton	B/L, d 1 and d 7 (0, 1, 2, 4, 6, 8, 12 h after dosing) and daily 30 min before dosing	Not specified	413	4	5													
Terfenadine	305	6 M healthy volunteers	Terfenadine, 60 mg 2 × d; dirithromycin, 500 mg daily	3 d washout, then terfenadine × 8 d; dirithromycin added × 10 d; final 2 d with dirithromycin alone	Bazett	Dirithromycin	2 × d, 4 h after each terfenadine dose	Reported mean QTc for each period	365	4	2													
Terfenadine	306	6 (2 M, 4 F) Healthy volunteers	Terfenadine, 120 mg; itraconazole, 200 mg daily	Terfenadine × 1; itraconazole × 7 d, then repeat terfenadine × 1, prospective cohort	Bazett	Itraconazole	B/L, 1, 2, 4, 6, 8, 12 h after dosing	Maximum QTc	376	14	41	0	0	0	0	0	0	16.7 (1/6)	66.7	0	33.3	0	0	
Terfenadine	307	4 M, 2 F	Terfenadine, 60 mg 2 × d × 6 d, add erythromycin, 500 mg, every 8 h	Randomized prospective study cohort	Bazett	Erythromycin	B/L, 1, 2, 4, 6, 8, 12 h after dosing	Maximum QTc	394	14	34													3 of 6 subjects with accumulation of terfenadine associated with QTc prolongation
Terfenadine	307	5 M, 1 F	Terfenadine, 60 mg 2 × d × 6 d; clarithromycin 500 mg every 12 h	Randomized prospective study cohort	Bazett	Clarithromycin	B/L, 1, 2, 4, 6, 8, 12 h after dosing	Maximum QTc	409	1	21													4 of 6 subjects with accumulation of terfenadine associated with QTc prolongation
Terfenadine	307	4 M, 2 F	Terfenadine, 60 mg 2 × d × 6 d; azithromycin, 250 mg daily for 500 load × 1,250 every d × 4	Randomized prospective study cohort	Bazett	Azithromycin	B/L, 1, 2, 4, 6, 8, 12 h after dosing	Maximum QTc	419	1	1													
Terfenadine	3	6 (4 M, 2 F) Healthy volunteers	Terfenadine, 60 mg 2 × d; ketoconazole, 200 mg 2 × d	Terfenadine for 14 d; ketoconazole begun on d 9 through 14	Bazett	Ketoconazole	B/L and pre AM dosing ECG on d 7, 9-12, and 14-17	Before AM dosing on d 7 and d 4-7 of terfenadine and ketoconazole	408	8	82	0	88	0	67	0	16.7	0	100	0	83.7	0	66.7	

Table 9. (Continued)

Drug	Reference	Sample Size	Dose	Design	QTc Correction Factor	Inh or Con Med	ECG Schedule	Reported Time Point	QTc (ms)			QTc (ms; %)						QTc Change (ms; % with increased QTc value)						Comments
												>450		>480		>500		>30		>60		>75		
									B/L	Change Preinh Con Med	Change Postinh Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	No Inh/ Con Med	Inh/ Con Med	
Terfenadine	4	28 (24 M, 4 F) Healthy volunteers 28 (24 M, 4 F) Stable cardiovascular disease	Terfenadine, 60, 180, or 300 mg 2 × d	Double-blind, PBO-controlled, 4-period crossover, dose escalation; Four 8-d treatments with 2 wk washout between periods	Bazett	None	B/L (d 0) and d 5 at 8, 9, 10, 11, 12 noon; 2, 4, 6, 8 PM d 1: midnight, 8, 9, 10, 11, 12 noon; 2, 4, 6 PM d 2-4: 8, 10, 12 noon; 4 PM d 6: midnight 8 AM, 8 PM d 7: 8 AM	Mean QTc on d 5 compared to mean QTc on d 0 (B/L)	60 mg 2 × d; healthy, 403 cardiovascular, 416 180 mg 2 × d healthy, 407 cardiovascular, 417	6 12 19 26													300 mg 2 × d dose also in study design but halted because of a death (presumed arrhythmic); another patient had asymptomatic U waves at this dose
Terodiline	308	9 Healthy volunteers	Terodiline, 200 mg racemic or 100 mg of either R(+) or R(−) terodiline or PBO as a single dose	Randomized, placebo-controlled, crossover with washout periods of 1 mon	Bazett	None	B/L; 1, 2, 4, 8 and 24 h and 4, 7 and 14 d after single-dose administration	8 h after drug dosing (QTc max)	ND Racemic R(+) R(−)	−3 23 19 0														
Thioridazine	309	9 M healthy volunteers	Thioridazine, 10 mg, 50 mg	Randomized, double-blind, placebo-controlled crossover of single-dose, low- and high-dose thioridazine; each period separated by 1 wk; Fast of 5 h before drug	Bazett	None	B/L; 1, 2, 4, 6, 8, 24, 48, 72 h after drug	QTc max (4 h after drug) high dose thioridazine (low dose)	388	22 (9)														
Trimethoprim	245	8 M healthy volunteers	Procainamide, 500 mg every 6 h; trimethoprim, 200 mg daily	7-d washout; procainamide × 7 d; trimethoprim begun on d 4 through d 7; 3-day washout; followed by 3 d trimethoprim	Bazett	Procainamide	d 1: B/L; 1, 3 h after drug; d 2: random ECG; d 3, 4, 7, 14 (last d): every h × 6 h after drug; d 5, 6 single ECG after drug	Mean QTc from a total of 4 ECGs taken within 6 h of drug therapy	NA	NA	30														Change in QTc *v* trimethoprim

Note. Some data were extrapolated from available figures.

Abbreviations: F, female; GFJ, grapefruit juice; M, male; NA, not available; Inh, inhibitor; con med, concomitant medication; B/L, baseline; PO, oral; IV, intravenous; ND, not done; PBO, placebo; AUEC, area under the time-effect curve; C_{max}, maximum drug concentration; T_{max}, time when measured drug concentration is maximal.

These reports prompted a series of changes in product labeling, most recently in January 2000 (recommendations regarding measurement of baseline ECG and electrolytes before initiating therapy).[317]

Mibefradil. This antihypertensive and/or antianginal agent primarily blocks calcium channel ion influx (T > L).[318] Mibefradil inhibits both I_{Kr} and I_{Ks}, and although its effects on QTc and morphology were difficult to interpret, administration of the drug was associated with rare reports of TdP. In addition, mibefradil is metabolized by and is a potent inhibitor of CYP3A4,[318] as well as CYP2D6 and CYP1A2.[319,320] This metabolic profile led to an increased incidence of adverse events when the drug was coadministered with other CYP3A4 substrates, and for this reason, the drug was subsequently withdrawn from use.[321,322]

Antipsychotics. The arrhythmogenic effects of the first-generation (so called typical) antipsychotics were first described in 1963 in a report outlining an association between ECG abnormalities and sudden death after thioridazine administration.[323] Since that time, a number of reports have been published that support an association between phenothiazine administration and arhythmias and/or sudden death,[324] and thioridazine, chlorpromazine, olanzapine, risperidone, and ziprasidone have been shown to block I_{Kr}.[325-328] In a study of healthy men, thioridazine doses of 10 and 50 mg prolonged the mean QTc by 9 and 22 ms, respectively.[309] In addition, in a literature review of 97 cases of thioridazine overdose, Buckley et al[324] reported a 60% incidence of QTc greater than 450 ms. Although phenothiazines have focused attention on cardiac events in association with antipsychotic therapy, QTc prolongation has been associated with a wide range of agents, including haloperidol and pimozide, as well as with the newer generation of atypical compounds (Table 10, Bazett correction, when specified).

Amiodarone. Amiodarone is a class III antiarrhythmic with multiple mechanisms of action,[332] including inhibition of the fast sodium current, calcium current, and potassium currents (I_{Kr} and I_{Ks}). It is also a noncompetitive blocker of β-adrenergic receptors. Although amiodarone is well known for its ability to markedly prolong QTc, it is also evident that this very potent antiarrhythmic has a low incidence of TdP and cardiac arrest.[333,334] Although the reason for this discrepancy is unclear, it has been suggested that this may relate to the broad profile of ion channel activity. "Moreover, the malignant arrhythmias associated with abnormal repolarization are not simply linked to QT durations longer than some fixed threshold" (R.R. Fenichel, MD, PhD, and J. Koemer, MD, PhD, personal communication, 2000).

Conclusion

The precise relationship between prolongation of cardiac repolarization and risk for serious ventricular arrhythmias remains unresolved. The clinical measurement of repolarization, QTc, is a highly variable parameter that does not closely correlate with risk for sudden death, perhaps because prolongation may occur by a number of different mechanisms of variable proarrhythmic potential. However, existing data suggest that the magnitude of QTc prolongation and characteristics of the population (in particular, the presence of heart disease) are the most important determinants of risk for TdP and sudden death. Population characteristics associated with increased risk include

Table 10. Incidence of QTc Prolongation With Recently Approved Atypical Antipsychotics in Short-Term Fixed-Dose Studies

	Patients With QTc Prolongation* (ms)					
	Active Drug		Placebo or Haloperidol Control			
Antipsychotic	>450	>500	Placebo >450	Placebo >500	Haloperidol >450	Haloperidol >500
Risperidone[283,329]	2.1 (8/380)		0 (0/120)		2.4 (3/126)	
Olanzapine[330]	0.8 (2/248)		None reported			
Quetiapine[286]	4.8 (18/377)	1.4 (10/698)	3.5 (5/144)	1.3 (2/151)		
Ziprasidone[331]	2.4 (16/660)	0 (0/660)	0.8 (2/251)		0 (0/76)	0 (0/76)

* Values expressed as percent (number/total number).

heart disease, female sex, bradycardia, hypokalemia, and other electrolyte abnormalities.

In addition to these established risk factors, concomitant administration of I_{Kr} blockers may markedly increase the risk for drug-induced TdP in all patient populations. Finally, it is possible that genetic heterogeneity in I_{Kr} or I_{Na} expression (regardless of whether expressed phenotypically as a prolonged QTc) may be responsible for increased susceptibility to TdP in some individuals and that these individuals may in the future be identified through genetic screening.[204,205,335]

QTc therefore is an important but imprecise marker of cardiovascular risk. There is concern that drugs with only minor effects on QTc may under some circumstances be associated with the rare occurrence of TdP. The use of such agents must be governed by the balance between the best estimate of TdP risk and the benefits of the drug. This balance will be influenced importantly by the morbidity and mortality of the underlying disease, the patient populations in which the drug is used, the full range of therapeutic benefits attributable to the drug, and the efficacy and safety of alternative therapies. The breadth of therapeutic agents that affect cardiac repolarization underscores the need to advance our understanding of the relationship between QTc prolongation and risk for TdP.

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