



Online article and related content  
current as of July 19, 2010.

## What Clinicians Should Know About the QT Interval

Sana M. Al-Khatib; Nancy M. Allen LaPointe; Judith M. Kramer; et al.

*JAMA*. 2003;289(16):2120-2127 (doi:10.1001/jama.289.16.2120)

<http://jama.ama-assn.org/cgi/content/full/289/16/2120>

### Correction

Correction is appended to this PDF and also available at  
<http://jama.ama-assn.org/cgi/content/full/jama;290/10/1318>  
Contact me if this article is corrected.

### Citations

This article has been cited 132 times.  
Contact me when this article is cited.

### Related Articles published in the same issue

Long QT Syndrome  
Arthur J. Moss. *JAMA*. 2003;289(16):2041.

Electrocardiograms  
Sharon Parmet et al. *JAMA*. 2003;289(16):2166.

### Related Letters

Medications That Prolong the QT Interval  
Mori J. Krantz et al. *JAMA*. 2003;290(8):1025.  
John A. Gillespie et al. *JAMA*. 2003;290(8):1025.  
Carol Cappuccio. *JAMA*. 2003;290(8):1026.

### Subscribe

<http://jama.com/subscribe>

### Permissions

[permissions@ama-assn.org](mailto:permissions@ama-assn.org)  
<http://pubs.ama-assn.org/misc/permissions.dtl>

### Email Alerts

<http://jamaarchives.com/alerts>

### Reprints/E-prints

[reprints@ama-assn.org](mailto:reprints@ama-assn.org)

# What Clinicians Should Know About the QT Interval

Sana M. Al-Khatib, MD, MHS

Nancy M. Allen LaPointe, PharmD

Judith M. Kramer, MD, MS

Robert M. Califf, MD

**T**HE QT INTERVAL ON THE ELECTROCARDIOGRAM (ECG) has gained clinical importance, primarily because prolongation of this interval can predispose to a potentially fatal ventricular arrhythmia known as torsades de pointes. Multiple factors have been implicated in causing QT prolongation and torsades de pointes. Among these, improper use of QT interval-prolonging medications deserves special attention. Recently, cisapride and grepafloxacin were removed from the US drug market because of the risk for QT prolongation and fatal arrhythmias.<sup>1,2</sup> The need to remove these agents from the market was related not just to the inherent properties of the drugs but also to the demonstrated failure of government-mandated black box warnings and "Dear Doctor" letters to mitigate inappropriate prescribing by physicians.<sup>3</sup>

To reduce the risk of torsades de pointes, health care providers must understand what is known about the QT interval. In this article, we address the meaning and measurement of the QT interval, describe factors that affect the QT interval, and assess the balance of risks and benefits of QT-prolonging medications. We also evaluate the steps that have been taken to enhance proper management of risk emanating from the use of QT interval-prolonging medications.

**See also p 2041 and Patient Page.**

**Context** Of the several factors implicated in causing QT interval prolongation and torsades de pointes, errors in the use of medications that may prolong this interval deserve special attention.

**Objective** To systematically summarize the available clinical data on the QT interval and to offer improved recommendations for the use of QT-prolonging medications.

**Data Sources** We searched MEDLINE from 1966 through 2002 for all English-language articles related to the QT interval. Additional data sources included bibliographies of articles identified on MEDLINE, a survey of experts, and data presented at a meeting of experts on long QT syndrome.

**Study Selection** We selected for review registries and case series examining clinical outcomes of patients with prolonged QT interval and the effect of different methods of measurement of the QT interval on patient outcomes. Ten studies were identified, of which 6 were included in the analysis.

**Data Extraction** Data quality was determined by publication in the peer-reviewed literature.

**Data Synthesis** Optimal measurement of the QT interval is problematic because of lack of standardization and lack of data regarding the best way to adjust for heart rate. Reliable information on the proper use of QT-prolonging medications is scarce. Although a QT interval of at least 500 milliseconds generally has been shown to correlate with a higher risk of torsades de pointes, there is no established threshold below which prolongation of the QT interval is considered free of proarrhythmic risk. The risk of torsades de pointes should be assessed in patients who are about to begin taking a QT-prolonging medication. Although inadequate clinical studies preclude prediction of absolute risk for individual patients, particularly high-risk situations can be defined based on clinical variables. We propose recommendations on proper monitoring of the QT interval in patients receiving QT-prolonging medications.

**Conclusion** Although the use of QT-prolonging medications can predispose to torsades de pointes, there is a relative paucity of information that can help clinicians and patients make optimal informed decisions about how best to minimize the risk of this serious complication.

JAMA. 2003;289:2120-2127

www.jama.com

## METHODS

Literature for this review was systematically identified by searching MEDLINE for all English-language articles published from 1966 through

2002 related to the QT interval (search terms: *long QT syndrome, death, outcomes, registries, case series, QT interval, and measurement*), reviewing bibliographies of articles identified on

**Author Affiliations:** Duke Center for Education and Research on Therapeutics, Duke Clinical Research Institute, Durham, NC.

**Financial Disclosures:** AstraZeneca and GlaxoSmith-Kline (GSK) have contributed unrestricted funds to projects of the Duke Center for Education and Research on Therapeutics. Dr Al-Khatib is involved in a research project sponsored and funded by GSK. This project is not related to the QT-prolonging drugs made by GSK. Dr Califf has received research funding from

Johnson & Johnson, Pfizer, and Eli Lilly, which all sell QT-prolonging drugs described in the article. None of these research grants pertain to QT-prolonging drugs.

**Corresponding Author and Reprints:** Sana M. Al-Khatib, MD, MHS, Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715 (e-mail: alkha001@mc.duke.edu).

**Clinical Cardiology Section Editor:** Michael S. Lauer, MD, Contributing Editor.

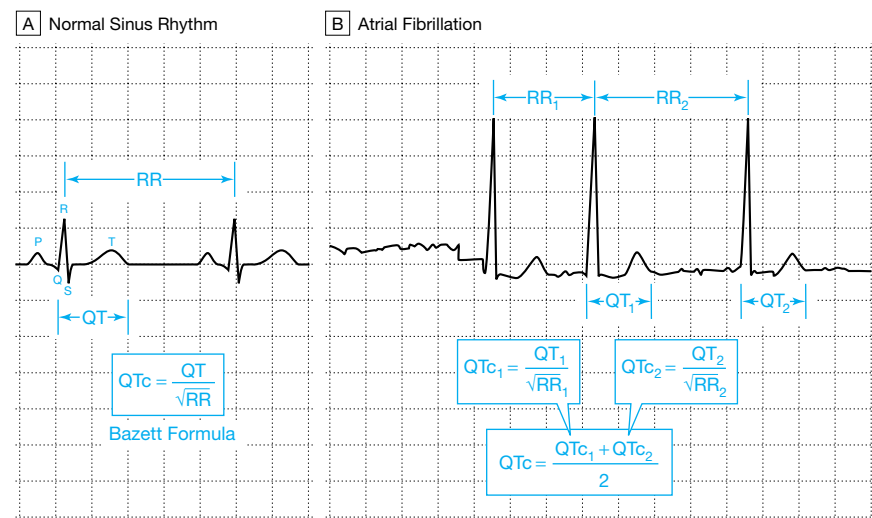
MEDLINE, surveying experts, and reviewing data presented at a meeting of experts on long QT syndrome (LQTS). We selected for review registries and case series examining clinical outcomes of patients with prolonged QT interval and the effect of different methods of measurement of the QT interval on patient outcomes. Ten studies were identified by the search, of which 6 were included in the analysis.<sup>4-9</sup> Data quality was determined by publication in the peer-reviewed literature.

### WHAT IS THE QT INTERVAL AND HOW SHOULD IT BE MEASURED?

The QT interval on the surface ECG is measured from the beginning of the QRS complex to the end of the T wave. Thus, it is the electrocardiographic manifestation of ventricular depolarization and repolarization. This electrical activity of the heart is mediated through channels, complex molecular structures within the myocardial cell membrane that regulate the flow of ions in and out of cardiac cells. The rapid inflow of positively charged ions (sodium and calcium) results in normal myocardial depolarization. When this inflow is exceeded by outflow of potassium ions, myocardial repolarization occurs. Malfunction of ion channels leads to an intracellular excess of positively charged ions by way of an inadequate outflow of potassium ions or excess inflow of sodium ions. This intracellular excess of positively charged ions extends ventricular repolarization and results in QT interval prolongation.<sup>10</sup>

In the clinical setting, it is now widely recognized that typical measurement of the QT interval is subject to substantial variability, which can cloud interpretation.<sup>11,12</sup> This variability in QT interval measurement results from biological factors, such as diurnal effects, differences in autonomic tone, electrolytes, and drugs; technical factors, including the environment, the processing of the recording, and the acquisition of the ECG recording; and intraobserver and interobserver variabil-

**Figure.** Measuring the QT Interval in Different Clinical Scenarios



QTc indicates corrected QT interval; RR, R-R interval. A, Normal sinus rhythm; the Bazett formula is used to correct the QT interval for the heart rate. B, Atrial fibrillation; QT interval is calculated by taking the average of QT intervals with shortest and longest preceding R-R intervals.

ity, resulting from variations in T-wave morphology, noisy baseline, and the presence of U waves. Interobserver variability also results from the lack of agreement among experts about standardizing approaches to measure the QT interval.<sup>11,12</sup> Although experts on the QT interval argue that intraobserver and interobserver variability and measurement error are higher when the corrected QT (QTc) interval is taken from computerized ECG algorithms rather than from careful high-resolution manual measurements, automated readings may be useful for rapid assessment of patient safety.<sup>13</sup> Unfortunately, there is no credible empirical evidence to support this view. In addition, as demonstrated by a recent survey of health care practitioners, many clinicians simply do not know how to measure the QT interval. Whereas 61% of respondents were able to identify what the QT interval represented on an ECG, only 36% correctly measured it.<sup>14</sup>

Although it is standard practice to measure the QT interval from the beginning of the QRS complex to the end of the T wave, the actual methods of measurement have not been standardized. Because the QT interval is pro-

longed at slower heart rates and shortened at faster heart rates, many formulas have been proposed to adjust for these variations. Yet differences of opinion exist regarding the most useful correction for heart rate.<sup>15-18</sup> One of the commonly used formulas is the Bazett formula, in which the QT interval is adjusted for heart rate by dividing it by the square root of the R-R interval (FIGURE, A). However, this formula has been criticized for being inaccurate at fast heart rates.<sup>19</sup> Other formulas are the Fridericia cube-root correction (QT interval divided by the cube root of the R-R interval) and the Framingham linear regression equation.<sup>16,17</sup> From an epidemiological perspective, the Framingham approach is the most sound because it is based on empirical data from a large population sample rather than on hypothetical reasoning. Unfortunately, none of these corrections has been examined comparatively to determine the most effective formula in predicting which patients are at greatest risk for torsades de pointes.

A group of experts on LQTS recently acknowledged the lack of empirical data in determining the best approach to measuring the QT interval.

This group convened in August 2000 to discuss the current knowledge of LQTS (see Acknowledgment). As a result of this meeting, the panel proposed the following 4 guidelines<sup>13</sup> for measuring the QT interval, based on expert opinion:

1. The QT interval should be measured manually, preferably by using one of the limb leads that best shows the end of the T wave on a 12-lead ECG.

2. The QT interval should be measured from the beginning of the QRS complex to the end of the T wave and averaged over 3 to 5 beats. U waves possibly corresponding to the late repolarization of cells in the mid myocardium should be included in the measurement only if they are large enough to seem to merge with the T wave.

3. The QT interval should be measured during peak plasma concentration of a QT-prolonging medication.

4. The QT interval should be adjusted for heart rate. Because the best way to adjust for heart rate has not been determined by prospective studies, the panel could not make a definitive recommendation in this regard.

Measurement of the QT interval is particularly challenging if the patient is in atrial fibrillation because the QT interval varies from beat to beat depending on the interval between successive R waves. Unfortunately, there is no consensus on how to measure the QT interval in this circumstance. Some clinicians suggest using the same steps in the aforementioned recommendations but further advise averaging the measured QT interval over 10 beats. Others prefer to measure the QT intervals that follow the shortest and longest R-R intervals and divide each by the square root of the R-R interval preceding it. The average of these intervals would then be used as the adjusted QT interval (Figure, B).

Measurement of the QT interval is also difficult in the setting of a wide QRS complex related to either ventricular conduction defects or a paced QRS complex. This is primarily because of the lack of a standard method to mea-

sure the QT interval in this setting; data on the best way to make this measurement do not exist. The Pfizer Tikosyn program specifies that while the QTc should be no more than 440 milliseconds (ms) to start dofetilide in the setting of a narrow QRS complex, the QTc should be no more than 500 ms in the setting of ventricular conduction abnormality.<sup>20</sup> This guidance may be used with other QT-prolonging medications until a standard method to measure the QT interval in the setting of ventricular conduction abnormality is identified.

Some argue that the QT interval should be measured only by cardiologists, but this suggestion is impractical. In light of the number of medications that could prolong the QT interval, other health care practitioners, especially internists, family practitioners, and psychiatrists, should either learn how to measure the QT interval or develop systematic approaches to ensuring that accurate measurements are being made at the appropriate time by specialists. Indeed, nurses, physician assistants, and clinical pharmacists may play an important role in this regard; if properly trained, it is likely that they can be relied on to measure the QT interval. However, the use of multiple health care practitioners in measuring the QT interval for clinical decision making needs to be tested in prospective studies.

It is important to realize that the methods proposed to correct the QT interval have primarily been evaluated for their correlation with heart rate. The formula with the best correlation with heart rate is believed to be the most accurate. It would be of great clinical importance if these formulas were validated prospectively and then compared with each other in adequately sized prospective studies. In this way, it could be determined which one most strongly correlates with an increased risk of adverse clinical events (especially death). However, this endeavor would be challenging because it might be difficult to identify a patient population with an event rate high enough to provide ad-

equate statistical power. In the absence of such studies, practitioners must be aware of the ongoing uncertainty about the best way to adjust the QT interval.

## FACTORS THAT AFFECT THE QT INTERVAL

Although it is convenient to think of QT prolongation as occurring because of either congenital or acquired abnormalities, the phenomenon probably most often involves a gene-environment interaction. Pure congenital prolongation characterized by lifelong, ambient QT prolongation is rare but does carry a high risk of sudden death. Several forms of congenital LQTS have been reported, and 3 forms (*LQT1*, *LQT2*, and *LQT3*) have been well characterized in previous studies.<sup>21</sup> These forms have been found to have distinctly different clinical outcomes and clinical manifestations, including factors that trigger clinical events and ECG features.<sup>6,22</sup> For example, physical activity tends to trigger events in *LQT1*, auditory stimuli in *LQT2*, and rest or sleep in *LQT3*.<sup>7,23,24</sup> Each form has also been characterized electrocardiographically by a specific pattern of T waves.<sup>25</sup> The T wave is of long duration in *LQT1*, is small and/or notched in *LQT2*, and has an unusually long onset in *LQT3*.<sup>22</sup> More important, the genotype of LQTS seems to have a significant impact on outcome.<sup>4</sup> In a study using a large international registry of LQTS, it was noted that although the risk of cardiac events was significantly higher among patients with *LQT1* and *LQT2* than with *LQT3*, the frequency of lethal cardiac events was significantly higher in the *LQT3* group.<sup>6</sup>

When exposed to QT-prolonging medications, individuals without lifelong QT prolongation may develop QT prolongation with or without torsades de pointes or may not develop QT prolongation at all. Even after adjustment for other factors that could prolong QT interval, some patients seem to be more likely than others to have QT prolongation at a given dose of a drug. This observation led researchers to hypoth-

**Box. Potential of Selected Medications for Causing QT Prolongation Based on a Survey of Expert Opinion\*****VERY PROBABLE****Antiarrhythmics**

Amiodarone  
Disopyramide  
Dofetilide  
Ibutilide  
Procainamide  
Quinidine  
Sotalol

**Antipsychotics**

Thioridazine

**PROBABLE****Antipsychotics**

Pimozide  
Ziprasidone

**POSSIBLE IN HIGH-RISK PATIENTS****Anti-infectives**

Clarithromycin  
Erythromycin  
Gatifloxacin  
Pentamidine  
Sparfloxacin

**Antipsychotics**

Chlorpromazine  
Haloperidol  
Olanzapine  
Risperidone

**Antidepressants**

Amitriptyline  
Desipramine  
Imipramine  
Sertraline  
Venlafaxine

**Other**

Droperidol

**IMPROBABLE****Anti-infectives**

Fluconazole  
Levofloxacin  
Trimethoprim-sulfamethoxazole

**Antidepressants**

Fluoxetine  
Paroxetine

**Migraine Drugs**

Sumatriptan  
Zolmitriptan

**Other**

Methadone

**VERY IMPROBABLE****Anti-infectives**

Azithromycin  
Ciprofloxacin  
Clindamycin

**Other**

Isradipine  
Nicardipine

**UNKNOWN****Antipsychotics**

Mesoridazine  
Quetiapine

**Antidepressants**

Doxepin

**Other**

Chloroquine  
Domperidone  
Felbamate  
Foscarnet  
Fosphenytoin  
Indapamide  
Moexipril/hydrochlorothiazide  
Octreotide  
Ondansetron  
Quinine  
Tacrolimus  
Tamoxifen  
Vasopressin

\*"Very probable" indicates more than 50% of respondents stated they would always check an electrocardiogram (ECG) when starting this medication; "probable," 40%-49% of respondents stated they would always check an ECG when starting this medication; "possible in high-risk patients," more than 40% of respondents stated they would always check an ECG in high-risk patients; "improbable," 40%-49% of respondents stated they would never check an ECG when starting this medication; "very improbable," more than 50% of respondents stated they would never check an ECG when starting this medication; and "unknown," survey responses did not fit any of the other categories.

esize that patients with acquired QT prolongation may have a genetic predisposition for it.<sup>8,10,26</sup> Recent investigations suggest that such patients may have clinically silent gene mutations that lead to overt QT prolongation only with exposure to QT-prolonging medications.<sup>8,10,26</sup>

It is important to note that the majority of patients with documented acquired LQTS never experience torsades de pointes, and many patients with torsades de pointes have a normal QT interval shortly before the event. It appears that a variety of coincident circumstances, including genetic predisposition and a prolonged QT interval (which may occur precipitously and transiently), are required to precipitate torsades de pointes.

Factors that predispose to QT prolongation and higher risk of torsades de pointes include older age, female sex, low left ventricular ejection fraction, left ventricular hypertrophy, ischemia, slow heart rate, and electrolyte abnormalities including hypokalemia and hypomagnesemia.<sup>5,27-34</sup> Certain drugs also predispose to QT prolongation (BOX). An extensive list of these drugs can be found at <http://www.torsades.org>. Regarding antiarrhythmic QT-prolonging drugs, the risk of torsades de pointes seems to be highest within the first few days of initiating therapy.<sup>35-37</sup> For this reason, physicians should consider admitting patients to the hospital when starting such drugs, a practice most warranted among patients with structural heart disease. Hospitalized patients can be better monitored for the warning signs that precede torsades de pointes. In a rigorous study of patients with supraventricular tachycardias, investigators reported that a 72-hour hospitalization for initiation of antiarrhythmic therapy appeared to be cost-effective.<sup>38</sup>

Several noncardiac medications can cause torsades de pointes, either by directly blocking potassium currents or by interacting with other medications (TABLE). These interactions could be purely pharmacodynamic (both drugs block outward potassium currents), purely pharmacokinetic (one drug in-

**Table.** Pharmacokinetic Interactions With Selected QT-Prolonging Drugs\*

QT-Prolonging Drugs	Drugs Possibly Affecting Pharmacokinetics
Antiarrhythmics	
Disopyramide	Erythromycin
Dofetilide	Cimetidine, ketoconazole, megestrol, prochlorperazine, trimethoprim, verapamil, thiazide diuretics
Procainamide	Amiodarone, cimetidine, trimethoprim
Quinidine	Amiodarone, cimetidine, possibly erythromycin and verapamil
Antipsychotics	
Haloperidol	Fluoxetine, venlafaxine
Pimozide	Erythromycin
Thioridazine	Paroxetine
Ziprasidone	Fluconazole, itraconazole, ketoconazole
Antidepressants	
Amitriptyline	Cimetidine, fluconazole, fluoxetine, ritonavir
Desipramine	Venlafaxine
Anti-infectives	
Erythromycin	Ritonavir
Sparfloxacin	Cisapride
Other	
Bepridil	Ritonavir
Cisapride	Clarithromycin, erythromycin, fluconazole, indinavir, itraconazole, ketoconazole, nefazodone, ritonavir

\*Drugs from the "very probable," "probable," and "possible in high-risk patients" categories of the Box are included in this table. This is not an all-inclusive list of all pharmacokinetic drug-drug interactions with these agents but, rather, some interactions that could lead to increased serum concentrations of the QT-prolonging drug. New drug-drug interactions may be identified in the future. Pharmacodynamic interactions are not included in this table; however, combinations of QT-prolonging drugs such as macrolide antibiotics and quinolones are strongly discouraged.<sup>39-42</sup>

terferes with the clearance of another), or of mixed pharmacodynamic and pharmacokinetic origin. An example of a purely pharmacodynamic interaction is that of quinidine and sotalol—both block outward potassium currents. The interaction between cisapride and ketoconazole provides an example of a purely pharmacokinetic interaction. Ketoconazole inhibits the cytochrome P-450 3A4 isoenzyme that metabolizes cisapride, and this inhibition results in increased cisapride levels that may augment QT prolongation and result in torsades de pointes. An example of a mixed interaction is that of erythromycin and cisapride. Not only do both drugs block potassium currents, but erythromycin also inhibits cytochrome P-450 3A4.

### ASSESSING THE BALANCE OF RISK AND BENEFIT OF QT INTERVAL-PROLONGING MEDICATIONS

When drugs that can prolong the QT interval are used, physicians should ensure that the potential benefits are clinically important and the risks are

minimized. Specifically, they should determine whether the likely benefit justifies the potential risk and should do so in light of the treated condition, the specific circumstances of the patient, and other available therapeutic options. For example, a QT interval-prolonging medication is the appropriate choice if it has a proven salutary effect on survival. However, the majority of these medications have not been proven to improve survival. Another strong reason to use such a medication is if it will significantly improve symptoms and morbidity relative to other treatment options. In this regard, medications that commonly cause significant QT prolongation must be used only if no other medications have a comparable beneficial effect in treating the same condition, if they are known to be or are potentially superior to other available medications, or if other medications carry other more significant risks.

The benefit of antiarrhythmic therapy, for example, is clearest when it results in the immediate termination of a sustained ventricular arrhythmia. When antiarrhythmic therapy is used for pa-

tients with symptoms of chronic arrhythmias, the risk may outweigh the benefit because few studies have shown a significant effect of antiarrhythmic therapy in this situation.<sup>43</sup> The risks are particularly disconcerting with antiarrhythmic medications that have been shown to worsen survival.<sup>44-46</sup>

The risk of torsades de pointes should be assessed for patients who are about to begin taking a QT-prolonging medication. Although inadequate clinical studies preclude prediction of absolute risk for individual patients, particularly high-risk situations can be defined based on clinical variables. This estimate requires knowledge of the drug's properties, including route of elimination and drug interactions, familiarity with factors that predispose to torsades de pointes, and baseline measurement of the QT interval. For example, sotalol and dofetilide are renally cleared; thus, it is important to monitor the renal function of patients starting these medications and to reduce the dose if renal function is impaired. To avoid risk of torsades de pointes, physicians should be aware that dofetilide has significant interactions with commonly used drugs such as verapamil and trimethoprim-sulfamethoxazole.

Among the factors that could predispose to torsades de pointes, hypokalemia and hypomagnesemia are particularly significant and remediable. Physicians should monitor potassium and magnesium levels in patients who start antiarrhythmic QT-prolonging medications and supplement them as needed, especially in patients taking other medications that can cause hypokalemia or hypomagnesemia.

Measurement of the baseline QT interval may also be of critical importance when assessing the risk of torsades de pointes in a particular patient. However, with many drugs that can cause QT interval prolongation, the risk of torsades de pointes is so low that the majority of experts do not consider measurement of the QT interval to be cost-effective. For some of these drugs, the QT interval must be measured in thou-

sands of patients to identify 1 person at risk of significant QT prolongation. The cost of this practice, in our opinion, outweighs the benefits. In a survey completed by LQTS experts, the majority would always check an ECG before and after starting an antiarrhythmic medication, one third to half would always check an ECG before and after starting an antipsychotic drug, and less than one third would always check an ECG before and after starting an anti-infective or antidepressant (Box). Based on the results of this survey, we propose the following recommendations on the proper monitoring of the QT interval in patients receiving QT-prolonging medications. First, an ECG should be routinely checked before and after starting an antiarrhythmic agent that can prolong the QT interval (Table 1). If the patient has a prolonged QTc at baseline (>450 ms in men and >460 ms in women in the absence of interventricular conduction defects), it is important to try to avoid all QT-prolonging medications.<sup>47</sup> Although this is not an absolute contraindication to starting QT-prolonging drugs, expert opinion should be sought before such drugs are started. If the patient is already taking an antiarrhythmic agent with this potential and another drug needs to be added, it is important to know whether the new drug may also prolong the QT interval (Box) or can interact with the antiarrhythmic medication (Table). If one of these events is a possibility, an alternative agent should be considered. If no alternative is available and the drug being added is necessary, an ECG should be performed to monitor the QT interval before and after starting the new drug. Indeed, concurrent prescribing of QT-prolonging drugs is common in the outpatient setting; however, the clinical consequences of this practice are not known.<sup>48</sup>

Second, an ECG should be checked before and after starting a drug if the drug is one that has been deemed by the LQTS experts to have very probable, probable, or possible potential for causing QT prolongation (Box). If the drug was deemed by the LQTS experts to

have improbable or very improbable potential for causing QT prolongation, checking an ECG before and after starting the drug, especially in low-risk patients, may not be necessary (Box).

Despite these recommendations, uncertainty remains regarding the specific relationship between the degree of QT prolongation and the risk of life-threatening arrhythmias with each individual drug. A QT interval of at least 500 ms generally has been shown to correlate with a higher risk of torsades de pointes, but there is no established threshold below which prolongation of the QT interval is considered free of proarrhythmic risk.<sup>9,49</sup> Thus, physicians are left with great uncertainty regarding when to stop a QT-prolonging medication. Respondents to the survey on LQTS were more likely to stop a QT-prolonging medication for a QT of 520 ms than for a QT of 500 ms. However, it should be emphasized that there is no clear-cut consensus on the degree of drug-induced QT prolongation that should require drug discontinuation.

Despite the clinical importance of the QT interval, definitive information on the clinical epidemiology of the QT interval and its prolongation by medications is surprisingly lacking. Few studies have evaluated the relationship between the QT interval and patient outcomes. Even for commonly used antiarrhythmic drugs like sotalol and amiodarone, this relationship has not been adequately explored. The newly marketed compound dofetilide is the only medication for which such a relationship has been extensively explored and reported.<sup>20,50</sup> It has been demonstrated that a linear relationship exists between the plasma concentration of dofetilide and the mean change from baseline QTc. It has also been shown that a relationship exists between the dose and concentration of dofetilide and its efficacy as well as the risk of torsades de pointes associated with its use.<sup>20</sup> A direct correlation between rate of torsades de pointes and increase from baseline QTc has also been proven for dofetilide.<sup>20</sup> Knowl-

edge of these relationships should enable an astute clinician to make a semi-quantitative decision about the use and dosing of dofetilide by weighing the risks and the proposed benefits of preventing recurrent atrial fibrillation or flutter. Likewise, detailed dosing and monitoring recommendations are part of the product labeling for the 2 most recently approved antiarrhythmic agents, dofetilide and sotalol. The product labeling for medications that could prolong the QT interval contains warnings regarding their effect on the QT interval that clinicians who prescribe these drugs should be aware of.

Some antipsychotic drugs have been shown to prolong the QT interval.<sup>51,52</sup> A recent clinical epidemiological study has demonstrated a direct relationship between the dose of the older antipsychotic drugs and the risk of sudden death, but the QT interval was not measured in this study to examine its correlation with sudden death.<sup>53</sup> More recently, a population-based study confirmed that antipsychotic drugs known to produce greater QT prolongation than other antipsychotic drugs were associated with a higher risk of cardiovascular death.<sup>54</sup> Of note, no consensus exists about the relative likelihood of torsades de pointes among patients treated with different antipsychotic drugs, nor is there a prospective study delineating the absolute risk of arrhythmia. This paucity of data leaves the practitioner in a lurch concerning therapeutics: the need for antipsychotic therapy cannot be ignored, and the patients with the most severe psychoses may need the highest doses of drugs. These same patients are also at higher risk of nonadherence to prescribed therapies (including omitting and taking excessive amounts of needed therapies) and to the development of other conditions, such as electrolyte depletion or sympathetic overactivity, that may predispose to torsades de pointes.

Furthermore, no data exist on how and when to monitor the QT interval when various antipsychotic drugs are used. Until more data are obtained, the Box should provide some guidance in

this regard. Of note, because of the concern raised about risk of QT prolongation with ziprasidone, a trial has been launched that will randomly assign more than 15 000 patients with schizophrenia to ziprasidone and olanzapine. This trial's primary end point is all-cause mortality (Brian Strom, MD, unpublished data, 2002).

Quinolone antibiotics also pose a difficult dilemma. They are used on a wide scale for common infections without checking the ECG, an approach generally agreed on by the aforementioned LQTS experts (Box). Yet, sporadic episodes of torsades de pointes have been reported in association with quinolones,<sup>55</sup> and there is evidence that quinolones are commonly coprescribed with other QT-prolonging drugs.<sup>48</sup> Because of the immense uncertainty surrounding the effects of concurrent use of QT-prolonging drugs, no preventive approach is currently recommended other than trying to avoid quinolones in patients taking other QT-prolonging drugs or with other risk factors.

### RISK MANAGEMENT OF QT INTERVAL-PROLONGING MEDICATIONS

We have thus far discussed the role of health care practitioners in management of the risk of QT-prolonging medications in treating individual patients. The scope of risk management, however, extends beyond health care practitioners and includes regulators, pharmaceutical companies, and investigators. For example, regulators came to realize the potential of noncardiovascular drugs to prolong the QT interval and potentially result in life-threatening arrhythmias. Thus, regulatory guidances on drug development advise that all new drugs be evaluated for possible effects on cardiac repolarization.<sup>56</sup>

Guidance in that regard had until recently been sketchy. The US Food and Drug Administration's (FDA's) International Conference on Harmonization (ICH) S7A guidance included only a general mention of cardiovascular testing of new drugs, which led to a lack of

standardization of preclinical and clinical cardiovascular drug testing.<sup>57</sup> For example, it was not specified whether drug testing should explore the effect of the drug on the QTc or the uncorrected QT interval. The label for dofetilide relies on the QTc (using the Bazett formula), whereas the label for sotalol uses the uncorrected QT interval.

In February 2002, the ICHS7B guidance was proposed and, although it has not been finalized, provides more specific direction for cardiac safety testing of new drugs.<sup>56</sup> The ICHS7B specifies that new drugs should be tested in 3 preclinical assays: the human ether-a-go-go-related gene channel assay to check for blockade of the IKr channel, the action potential duration (APD) assay that uses canine Purkinje fibers to check for significant APD prolongation, and an in vivo rodent ECG with a detailed description of test methods. The guidance also suggests that if the tested drug is shown in preclinical assays to cause some blockade of the IKr channel or prolongation of the APD, its potential clinical risks should be evaluated in carefully designed clinical trials. Those studies must have adequate sample sizes and should ensure frequent recording of ECGs.

Although the preliminary ICHS7B guidance lacks data on the standards of clinical evaluation, it is hoped that the final version will provide specific information on the clinical evaluation standards for compounds with and without hazardous QT signals in preclinical testing. It is well known that many companies are screening compounds and discontinuing those in which a flag is raised at the preclinical level. The potential advantage of this approach is obvious: it prompts stopping the drug's development before the complex clinical manifestations become an issue. However, the list of QT-prolonging drugs includes several that provide substantial health benefits, and it would be unfortunate if drugs with the potential for a highly positive overall impact were dropped early in development.

The ICHS7B is one of many initiatives recently developed to improve the

cardiac safety of new drugs. In November 2001, the FDA announced that as of the fall of 2002, sponsors must submit ECG raw data in digital format with annotations to enable the FDA to independently assess the cardiac safety profile of new drugs.<sup>58</sup> The FDA is also working with Health Canada to develop guidance on the assessment of QT prolongation during clinical trials.<sup>47</sup> The final guidance is still pending. Through these initiatives, regulators are hoping to standardize preclinical and clinical cardiovascular testing of all drugs, an important endeavor in enhancing efforts at risk management of QT-prolonging medications. Equally important, however, is the clear dissemination of these guidelines and clear labeling of drugs with QT-prolonging potential, specifically as they relate to interactions that could augment prolongation.

In this article, we present an update of the current knowledge of the QT interval and proposed ways to enhance risk management of QT-prolonging medications. As more knowledge about this important topic is gained, it is critical that this knowledge be disseminated in a timely fashion and in a style that is easily comprehended by clinicians. Perhaps the most surprising finding of our review is the relative paucity of information that can help clinicians and patients make informed decisions about drugs that can prolong the QT interval.

**Author Contributions:** *Study concept and design:* Al-Khatib, Allen LaPointe, Kramer, Calif.

*Acquisition of data:* Al-Khatib, Allen LaPointe.

*Analysis and interpretation of data:* Al-Khatib, Allen LaPointe, Kramer.

*Drafting of the manuscript and obtaining funding:* Al-Khatib, Calif.

*Critical revision of the manuscript for important intellectual content:* Allen LaPointe, Kramer, Calif.

*Administrative, technical, or material support:* Al-Khatib, Allen LaPointe, Calif.

*Study supervision:* Kramer.

**Funding/Support:** This study was supported in part by grant U18HS10548 from the Agency for Healthcare Research and Quality, Rockville, Md.

**Acknowledgment:** The following persons participated in a survey and convened in August 2000 to discuss the current knowledge of LQTS. Academic participants: Mark E. Anderson, John T. Bigger, Jr, Robert M. Califf, Robert R. Fenichel, David A. Flockhart, Augustus O. Grant, Ralph Lazzara, Kerry L. Lee, Marek Malik, Joel Morganroth, Arthur J. Moss, Milton Packer, Ileana L. Pina, Eric N. Prystowsky, Dan M. Roden, Jeremy N. Ruskin, Michael Sanguinetti, Gordon F. To-

maselli, Raymond L. Woosley; participants from the FDA: Stephen Fredd, Maryann Gordon, Abraham Karkowsky, John Koerner, Raymond J. Lipicky, Anthony Proakis, Shari Targum, Robert J. Temple; participants from European regulatory agencies: Ursula Hoppe, Rashmi Shah; participants from industry: Leif Carlsson, Borje Darpo, Paul R. Eisenberg, Karen Frank, Alan S. Hollister, J. Heyward Hull, Lewis Kinter, John H. Lawrence, Leslie Lipka, Eric Michelson, Steven J. Miller, Andrew Nicholls, Gunnar Olsson, Ihor W. Rak, Stots B. Relle, David T. Roberts, Pierre A. Wicker.

## REFERENCES

- MedWatch. Glaxo Wellcome voluntarily withdraws Raxar (grepafloxacin) [press release]. Rockville, Md: US Food and Drug Administration; October 1999. Available at: <http://www.fda.gov/medwatch/safety/1999/raxar.html>. Accessed October 22, 2002.
- FDA Talk Paper. *Janssen Pharmaceutica Stops Marketing Cisapride in the US*. Rockville, Md: US Food and Drug Administration; March 2000. Available at: <http://www.fda.gov/bbs/topics/answers/ans01007.html>. Accessed October 22, 2002.
- Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride: impact of Food and Drug Administration regulatory action. *JAMA*. 2000;284:3036-3039.
- Moss AJ, Zareba W, Kaufman ES, et al. Increased risk of arrhythmic events in long QT syndrome with mutations in the pore region of the human ether-a-go-go-related gene potassium channel. *Circulation*. 2002;105:794-799.
- Locati EH, Zareba W, Moss AJ, et al. Age- and sex-related differences in clinical manifestations in patients with congenital long QT syndrome: findings from the international LQTS Registry. *Circulation*. 1998;97:2237-2244.
- Zareba W, Moss AJ, Schwartz PJ, et al. Influence of the genotype on the clinical course of the long-QT syndrome. *N Engl J Med*. 1998;339:960-965.
- Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation*. 2001;103:89-95.
- Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome: clinical impact. *Circulation*. 1999;99:529-533.
- Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome: prospective longitudinal study of 328 families. *Circulation*. 1991;84:1136-1144.
- Viskin S. Long QT syndromes and torsade de pointes. *Lancet*. 1999;354:1625-1633.
- Morganroth J, Brozovich FV, McDonald JT, Jacobs RA. Variability of the QT measurement in healthy men, with implications for selection of an abnormal QT value to predict drug toxicity and proarrhythmia. *Am J Cardiol*. 1991;67:774-776.
- Molnar J, Zhang F, Weiss J, Ehler FA, Rosenthal JE. Diurnal pattern of QTc interval: how long is prolonged? possible relation to circadian triggers of cardiovascular events. *J Am Coll Cardiol*. 1996;27:76-83.
- Anderson ME, Al-Khatib SM, Roden DM, Califf RM. Cardiac repolarization: current knowledge, critical gaps, and new approaches to drug development and patient management. *Am Heart J*. 2002;144:769-781.
- Allen LaPointe N, Al-Khatib SM, Kramer JM, Battle J, Califf RM. Deficits in knowledge related to the QT interval that could impact patient safety [abstract]. *J Am Coll Cardiol*. 2002;39:125A.
- Funck-Brentano C, Jaillon P. Rate-corrected QT interval: techniques and limitations. *Am J Cardiol*. 1993;72:17B-22B.
- Hnatkova K, Malik M. "Optimum" formulae for heart rate correction of the QT interval. *Pacing Clin Electrophysiol*. 1999;22:1683-1687.
- Aytemir K, Maarouf N, Gallagher MM, Yap YG, Waktare JE, Malik M. Comparison of formulae for heart rate correction of QT interval in exercise electrocardiograms. *Pacing Clin Electrophysiol*. 1999;22:1397-1401.
- Malik M. Problems of heart rate correction in assessment of drug-induced QT interval prolongation. *J Cardiovasc Electrophysiol*. 2001;12:411-420.
- Milne JR, Ward DE, Spurrell RA, Camm AJ. The ventricular paced QT interval: the effects of rate and exercise. *Pacing Clin Electrophysiol*. 1982;5:352-358.
- Dofetilide product monograph and confirmation of education. New York, NY: Pfizer Inc; March 2000.
- Chiang CE, Roden DM. The long QT syndromes: genetic basis and clinical implications. *J Am Coll Cardiol*. 2000;36:1-12.
- Moss AJ, Zareba W, Benhorin J, et al. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. *Circulation*. 1995;92:2929-2934.
- Wilde AA, Jongbloed RJ, Doevendans PA, et al. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KV-LQT1-related patients (LQTS1). *J Am Coll Cardiol*. 1999;33:327-332.
- Schwartz PJ, Priori SG, Locati EH, et al. Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na<sup>+</sup> channel blockade and to increases in heart rate: implications for gene-specific therapy. *Circulation*. 1995;92:3381-3386.
- Zhang L, Timothy KW, Vincent GM, et al. Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. *Circulation*. 2000;102:2849-2855.
- Donger C, Denjoy I, Berthet M, et al. KVLQT1 C-terminal missense mutation causes a forme fruste long-QT syndrome. *Circulation*. 1997;96:2778-2781.
- Reardon M, Malik M. QT interval change with age in an overtly healthy older population. *Clin Cardiol*. 1996;19:949-952.
- Ahnve S. QT interval prolongation in acute myocardial infarction. *Eur Heart J*. 1985;6(suppl D):85-95.
- Rebeiz AG, Al-Khatib SM. A case of severe ischemia-induced QT prolongation. *Clin Cardiol*. 2001;24:750.
- Khan IA. Clinical and therapeutic aspects of congenital and acquired long QT syndrome. *Am J Med*. 2002;112:58-66.
- Kay GN, Plumb VJ, Arciniegas JG, Henthorn RW, Waldo AL. Torsade de pointes: the long-short initiating sequence and other clinical features: observations in 32 patients. *J Am Coll Cardiol*. 1983;2:806-817.
- Roden DM. Risks and benefits of antiarrhythmic therapy. *N Engl J Med*. 1994;331:785-791.
- Roden DM. Mechanisms and management of proarrhythmia. *Am J Cardiol*. 1998;82:491-571.
- Makkar RR, Fromm BS, Steinmen RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. *JAMA*. 1993;270:2590-2597.
- Maisel WH, Kuntz KM, Reimold SC, et al. Risk of initiating antiarrhythmic drug therapy for atrial fibrillation in patients admitted to a university hospital. *Ann Intern Med*. 1997;127:281-284.
- Chung MK, Schweikert RA, Wilkoff BL, et al. Is hospital admission for initiation of antiarrhythmic therapy with sotalol for atrial arrhythmias required? yield of in-hospital monitoring and prediction of risk for significant arrhythmia complications. *J Am Coll Cardiol*. 1998;32:169-176.
- Torp-Pedersen C, Moller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. *N Engl J Med*. 1999;341:857-865.
- Simons GR, Eisenstein EL, Shaw LJ, Mark DB, Pritchett EL. Cost effectiveness of inpatient initiation of antiarrhythmic therapy for supraventricular tachycardias. *Am J Cardiol*. 1997;80:1551-1557.
- Clinical Pharmacology [database online]. Tampa, Fla: Gold Standard Multimedia Inc; 2002. Available at: <http://cp.gsm.com>. Accessed September 17, 2002.
- USPDI advice for the patient. MICROMEDEX [database online]. Stamford, Conn: Thomson Corp. Healthcare Series Vol 114. Expiration: December 2002. Available at: <http://www.micromedex.com>. Accessed April 2, 2003.
- Tatro DS, ed. *Drug Interaction Facts*. St Louis, Mo: Facts and Comparisons; 2002.
- Hansten PD, Horn JR. *Hansten and Horn's Drug Interactions Analysis and Management*. St Louis, Mo: Facts and Comparisons; 2002.
- Pacifico A, Hohnloser SH, Williams JH, et al. Prevention of implantable-defibrillator shocks by treatment with sotalol. *N Engl J Med*. 1999;340:1855-1862.
- Morganroth J, Goin J. Quinidine-related mortality in the short-to-medium-term treatment of ventricular arrhythmias: a meta-analysis. *Circulation*. 1991;84:1977-1983.
- Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion: a meta-analysis of randomized control trials. *Circulation*. 1990;82:1106-1116.
- Waldo AL, Camm AJ, de Ruyter H, et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet*. 1996;348:7-12.
- The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs*. Available at: <http://www.fda.gov/cder/calendar/meeting/qt4jam.pdf>. Accessed March 25, 2003.
- Curtis LH, Østbye T, Sendersky V, et al. Prescription of QT-prolonging drugs in a large, national outpatient population. *Am J Med*. 2003;114:135-141.
- Bednar MM, Harrigan EP, Anziano RJ, Camm AJ, Ruskin JN. The QT interval. *Prog Cardiovasc Dis*. 2001;43:1-45.
- Demolis JL, Funck-Brentano C, Ropers J, Ghad-anfar M, Nichols DJ, Jaillon P. Influence of dofetilide on QT-interval duration and dispersion at various heart rates during exercise in humans. *Circulation*. 1996;94:1592-1599.
- Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SH. QTc interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet*. 2000;355:1048-1052.
- Glassman AH, Bigger JT. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry*. 2001;158:1774-1782.
- Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry*. 2001;58:1161-1167.
- Hennessy S, Bilker WB, Knauss JS, et al. Cardiac arrest and ventricular arrhythmias in patients taking antipsychotic drugs: cohort study using administrative data. *BMJ*. 2002;325:1070-1074.
- Anderson ME, Mazur A, Yang T, Roden DM. Potassium current antagonist properties and proarrhythmic consequences of quinolone antibiotics. *J Pharmacol Exp Ther*. 2001;296:806-810.
- ICH57B Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals*. Washington, DC: US Food and Drug Administration; 2002.
- ICH57A Safety Pharmacology Studies for Human Pharmaceuticals*. Washington, DC: US Food and Drug Administration; 2001.
- Center for Drug Evaluation and Research home page. Available at: <http://www.fda.gov/cder>. Accessed March 25, 2003.

features of this case. It is unclear whether the nearly simultaneous extrusion of these 2 foreign bodies 60 years after the injury was a coincidence or whether it was related to some underlying systemic or environmental factor. Explosive fragments are sometimes discovered as incidental findings during radiological examinations. This case underscores the fact that such fragments may pose a lifelong risk of migration and should be considered in the differential diagnosis of patients who were present in war zones.

Pierre-Dominique Ghislain, MD  
Department of Dermatology  
Université Catholique de Louvain  
Bruxelles, Belgium

1. Wittich AC. Diagnosis and removal of a grenade fragment from the Vietnam war 35 years after injury. *Mil Med.* 2002;167:519-520.
2. Mitchell R, Kerr R, Barton J, Schmidt A. Biliary obstruction secondary to shrapnel. *Am J Gastroenterol.* 1991;86:1531-1534.
3. Symonds RP, Mackay C, Morley P. The late effect of grenade fragments. *J R Army Med Corps.* 1985;131:68-69.
4. Lee JH, Kim DG. Brain abscess related to metal fragments 47 years after head injury: case report. *J Neurosurg.* 2000;93:477-479.
5. Coupland RM. Hand grenade injuries among civilians. *JAMA.* 1993;270:624-626.
6. Karger B, Zwiheoff RF, DuChesne A. Injuries from hand grenades in civilian settings. *Int J Legal Med.* 1999;112:372-375.
7. Cooper GJ, Ryan JM. Interaction of penetrating missiles with tissues: some common misapprehensions and implications for wound management. *Br J Surg.* 1990;77:606-610.

## CORRECTIONS

**Incorrect Data in Table:** In the article entitled "Neurologic Manifestations and Outcome of West Nile Virus Infection" published in the July 23/30, 2003, issue of THE JOURNAL (2003;290:511-515), on page 513, Table 1, the following data are incorrect: row "Days from illness onset to presentation, median (range)," column "West Nile Encephalitis (n=8)," 1.5 (-3 to -14) should be 1.5 (-3 to 14); row "Headache," column "West Nile Virus Seronegative Controls (n=23)," 22 (96) should be 22 (100); row "Nausea," column "West Nile Encephalitis (n=8)," 5 (62) should be 5 (63) and column "West Nile Virus Seronegative Controls (n=23)," 17 (74) should be 17 (77); row "Neck pain," column "West Nile Virus Seronegative Controls (n=23)," 17 (74) should be 17 (77); row "Bradykinesia," column "Acute Flaccid Paralysis (n=3)," 2 (67) should be 2 (66); and row "Nuchal rigidity," column "West Nile Encephalitis (n=8)," 5 (63) should be 5 (71).

**Incorrect Author Contact and Reference Information:** In the Original Contribution entitled "Breast Cancer Following Radiotherapy and Chemotherapy Among Young Women With Hodgkin Disease" published in the July 23/30, 2003, issue of THE JOURNAL (2003;290:465-475), author Lois B. Travis' affiliation in the "Corresponding Author and Reprints" footnote should be Division of Cancer Epidemiology and Genetics, and her e-mail address should be TravisL@mail.nih.gov. Also, the date, volume number, and page number for reference 20 should be 2003;95:971-980.

**Incomplete Acknowledgment:** In the Clinical Cardiology article entitled "What Clinicians Should Know About the QT Interval" published in the April 23/30, 2003, issue of THE JOURNAL (2003;289:2120-2127), the following individuals participated in a survey conducted in 2002 and/or in a meeting held in August 2000 and should have been listed as academic participants in the Acknowledgment: John Camm, Peter J. Schwartz, Craig January, Michael Kilborn, Christian Funck-Brentano, JoAnn Lindenfeld, Stefan H. Hohnloser, Pedro Brugada, Robert J. Myerburg, Nabil E. El-Sherif, Michael Ackerman, John DiMarco, Sylvia Priori, Lemuel A. Moye, Charles Antzelevitch, Michael R. Franz, and Victoria Vetter.

Long experience has taught us that it is dangerous in the interest of truth to suppress opinions and ideas; it has further taught us that it is foolish to imagine that we can do so. It is far easier to meet an evil in the open and defeat it in fair combat in people's minds, than to drive it underground and have no hold on it or proper approach to it. Evil flourishes far more in the shadows than in the light of day.

—Jawaharlal Nehru (1889-1964)