Determination of Prolonged QT Interval and Their Contribution to Sudden Death Risk in Coronary Artery Disease
The Oregon Sudden Unexpected Death Study

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Background—In a recent cohort study, prolongation of the corrected QT interval (QTc) was associated with an independent increased risk of sudden cardiac death (SCD). We evaluated determinants of prolonged QTc and the relationship of prolonged QTc to SCD risk among patients with coronary artery disease in the general population.

Methods and Results—A case-control design was used. Cases were SCD patients with coronary artery disease among a metropolitan area of 1 000 000 residents (2002 to 2006); controls were area residents with coronary artery disease but no history of SCD. All cases were required to have an ECG suitable for QTc analysis before and unrelated to the occurrence of SCD. A total of 373 cases and 309 controls met criteria for analysis. Mean QTc was significantly longer in cases than in controls (450 ± 45 versus 433 ± 37 ms; \( P < 0.0001 \)). In a multivariate model, gender, diabetes mellitus, and QTc-prolonging drugs were significant determinants of QTc prolongation in controls. In a logistic regression model predicting SCD, diabetes mellitus (odds ratio, 1.97; 95% confidence interval, 1.32 to 2.96) and use of QTc-prolonging drugs (odds ratio, 2.90; 95% confidence interval, 1.92 to 4.37) were significant predictors of SCD among subjects with normal or borderline QTc. However, abnormally prolonged QTc in the absence of diabetes and QT-prolonging medications was the strongest predictor of SCD (odds ratio, 5.53; 95% confidence interval, 3.20 to 9.57).

Conclusions—Diabetes mellitus and QTc-affecting drugs determined QTc prolongation and were predictors of SCD in coronary artery disease. However, idiopathic abnormal QTc prolongation was associated with 5-fold increased odds of SCD. A continued search for novel determinants of QTc prolongation such as genomic factors is likely to enhance risk stratification for SCD in coronary artery disease. (Circulation. 2009;119:663-670.)

Key Words: coronary disease ■ death, sudden ■ epidemiology ■ population ■ diabetes mellitus ■ prescription drugs ■ risk

A mechanistic link between the prolonged corrected QT interval (QTc) and increased risk of fatal arrhythmogenesis is well established by the detailed investigation of the relatively rare, monogenic long-QT syndromes.\(^1\)\(^2\) However, QTc prolongation also has been associated with increased risk of sudden cardiac death (SCD) in a non–long-QT syndrome community-based cohort of unrelated individuals.\(^3\)\(^4\) The potential of prolonged cardiac repolarization as a stratifier of risk among unrelated individuals in the general population merits further evaluation.

Clinical Perspective p 670
Coronary artery disease (CAD) is the condition most commonly associated with sudden cardiac death (SCD). At present, severe left ventricular (LV) systolic dysfunction is an established predictor of SCD, but fewer than one third of all SCD cases will have severe LV dysfunction.\(^5\)\(^6\) Enhancement of risk stratification among CAD patients is likely to have a significant impact on SCD prevention. QTc prolongation has emerged as a possible candidate, but determinants of QTc prolongation among individuals with CAD remain unclear. In general, QTc prolongation is more common among diabetics,\(^7\) with a good correlation reported between prolonged QTc and overall cardiac mortality in diabetes.\(^8\)\(^9\) QT-prolonging noncardiac medications also have been implicated as contributors to SCD risk.\(^10\)

The Oregon Sudden Unexpected Death Study (Ore-SUDS) is an ongoing investigation of SCD among all residents of a
large US community. Based on the hypothesis that diabetes and QT-prolonging medications can cause QTc prolongation, analyses were conducted to evaluate the determinants of QTc among patients with CAD. We also evaluated whether prolonged QTc was a predictor of SCD risk in this population.

Methods

Ascertainment of Subjects

Detailed methods were published earlier. Briefly, the ongoing Ore-SUDS prospectively identified all cases of SCD that occurred among residents of the Portland, Ore, metropolitan area (population ~1,000,000) from February 2002 to January 2005 from the Emergency Medical Response system, the Medical Examiner’s office, and local hospitals. From February 2005 to January 2006, identification was limited to the majority subset identified by first responders or investigated by the medical examiner. SCD was defined as a sudden unexpected pulseless condition of likely cardiac origin. If unnoticed, SCDs were those in which patients were found dead within 24 hours of having last been seen alive and in normal state of health. Subjects with likely SCD were assigned a diagnosis of SCD after a review of available medical records and the circumstances of arrest; survivors of SCD were included. Subjects with chronic terminal illnesses (eg, cancer), known noncardiac causes of sudden death (eg, pulmonary embolism, cerebrovascular accident), traumatic deaths, and overdoses were excluded. Cases also were required to have documented significant CAD or, if ≥50 years of age, were assumed to have CAD (based on 95% likelihood of CAD in SCD cases ≥50 years of age). CAD was defined as ≥50% stenosis of a major coronary artery or history of myocardial infarction (MI), coronary artery bypass grafting, or percutaneous coronary intervention.

During the same time period, a control group of subjects from the same geographic region who had CAD but no history of SCD were identified. They had been transported by the Emergency Medical Response system for complaints suggestive of ongoing coronary ischemia, were recruited from clinics of participating health systems, or had received a coronary angiogram revealing significant CAD. After consent was obtained, medical records for each potential control were reviewed; those with documented CAD (as defined above) were enrolled.

Measurement of QTc Interval From the 12-Lead ECG

All cases and controls were required to have a 12-lead ECG in sinus rhythm. For SCD cases, the most recent ECG available in the medical records, before and unrelated to the cardiac arrest, was used. For control subjects, ECGs were obtained from the postenrollment medical records, before and unrelated to the cardiac arrest, was used. A standard 12-lead ECG tracing at 25-mm/s paper speed and 10-mm/mV amplitude was used, with measurements conducted manually with calipers. The QT interval was measured from the beginning of the earliest onset of the QRS complex to the end of the T wave. The end of the T wave was defined as the return of the descending limb to the TP baseline when not followed by a U wave or if distinct from the following U wave. If a second low-amplitude repolarization wave interrupted the terminal portion of the T wave, the T-wave offset was measured as the nadir between the T and U waves. After measurements in all precordial and limb leads, the longest QT interval was recorded. Two trained personnel performed separate, blinded measurements on a subset of ECGs. The QT interval was corrected with the Bazett formula. Data were analyzed by use of gender-specific QTc categories as defined in the Rotterdam study (men: normal, ≤430 ms; borderline, 431 to 450 ms; and abnormal, >450 ms; women: normal, ≤450 ms; borderline, 451 to 470 ms; and abnormal, >470 ms). LV ejection fraction was used to assess the association of LV function and QTc interval for the subset of patients with ejection fraction measured before arrest (cases) or ascertainment (controls) by echocardiogram, angiogram, or multigated acquisition. To identify drugs that prolong the QT interval and/or induce torsades de pointes ventricular arrhythmia, we used the exhaustive set of lists from the Arizona Center for Education and Research on Therapeutics (http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm).

Statistical Analysis

Independent-samples t tests and Pearson’s χ² tests were used for bivariate case-control comparisons of continuous and categorical variables, respectively. A general linear model was used for ANCOVA to evaluate significant independent predictors of QTc interval length in controls and potential interaction among covariates. Potential predictors of the QTc interval were age, gender, history of MI, diabetes, obesity, and use of QT-prolonging medications. All 2-way interactions between significant main effects terms were evaluated. A model also was run for the subgroup of control patients with LV function assessment available.

Finally, univariate logistic models were used to estimate the association between SCD and QTc, diabetes, and QT-prolonging medications, and a multiple logistic regression model was used to estimate odds ratios (ORs) for SCD associated with abnormal QTc (versus normal or borderline QTc) adjusted for age, gender, history of MI, diabetes, obesity, and use of QT-prolonging medications. Abnormal QTc was compared with the normal and borderline QTc groups combined on the basis of initial results showing that borderline QTc had no elevation in risk compared with normal QTc. Two-way interactions also were evaluated between all covariates and abnormal QTc and between diabetes and QT-prolonging medications. Main effects terms were retained in the logistic model for any factors with significant interaction. When significant interactions were identified, we used the full model to estimate ORs for SCD for relevant patient subgroups.

For all analyses, main effects terms were considered significant at values of P<0.05. For identification of interaction, values of P<0.20 were considered potentially significant; probability values for each interaction term were reported.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

In the 4-year period of February 1, 2002, to January 31, 2006, 1678 adult cases of SCD (>18 years of age) were identified in the Portland, Ore, metropolitan area. Of these, 682 (41%) had ECGs available. Of the 682 cases, 403 (59%) had ECGs before arrest with sinus rhythm and QRS <120 ms. Reasons for exclusion of case ECGs were timing (n=29), abnormal rhythms (n=81), and QRS ≥120 ms (n=69). In the same time period, 400 control subjects were identified; 379 (86%) had an ECG performed, and 309 (82%) had an ECG with sinus rhythm and QRS <120 ms. Control ECGs were excluded as a result of abnormal rhythms (n=24) and QRS interval ≥120 ms (n=46). For both cases (51%) and controls (87%), the majority of ECGs were done within a year of the SCD occurrence or control ascertainment, respectively.

Among the 403 cases with ECGs meeting criteria, 373 also had documented CAD or assumed CAD based on age. All control subjects had documented CAD (n=309). Basic demographics and clinical characteristics of cases and controls are summarized in Table 1. Cases were older and had a higher frequency of diabetes, medications that prolong the QT interval, and severe LV dysfunction (Table 1).

Reliability of QT Measurement

ECGs for a subset of patients in this analysis (197 cases, 276 controls) were randomly selected to be read by a second
Mean QTc was 17 ms longer in cases (\(P<0.0001\); Table 2). In a final multivariate model, only gender (\(P=0.01\)), diabetes (\(P=0.0007\)), use of QT-prolonging medications (\(P=0.0003\)), and the interaction between diabetes and medications were significant (\(P=0.08\)). The adjusted (least-squares) mean QTc interval was longer in women than men (534 versus 446 ms; Table 3). Use of QT-prolonging medications and diabetes were significantly associated with the QTc interval, and their effects depended on each other (test for interaction \(P=0.08\)). Diabetics using QT-prolonging medications had a significantly longer adjusted mean QTc interval compared with other patients (\(P=0.01\); Table 3). Because age has been associated with QTc in previous studies, we repeated the analyses, retaining age in the ANCOVA model, and obtained very similar results (data not shown). In the subset of individuals with measurement of LV ejection fraction available (188 cases, 116 controls), severe LV dysfunction was nonsignificantly associated with a longer QTc (452 versus 439 ms; \(P=0.21\)).

**Use of QTc-Interval-Prolonging Medications**

Cases were significantly more likely to be taking QT-prolonging medications than controls (\(P<0.0001\); Table 4). The vast majority of QTc drugs prescribed in either group were noncardiac. For both groups, the majority of patients were taking a single QT-prolonging medication (Table 4). We were able to establish that for 160 (43%) of the 373 cases in this analysis, the date the medications were noted was within 45 days of the ECG. Similarly, 144 (39%) of the 373 cases were on the listed medications within the 45 days before arrest.

**QTc Remained a Significant Predictor of SCD Among Subjects Not Taking QT-Prolonging Medications**

In the univariate logistic model, abnormal QTc and borderline QTc were compared with normal QTc. Abnormal QTc was significantly associated with SCD (OR, 2.5; 95% CI, 1.7 to 3.6), whereas borderline QTc was not (OR, 1.0; 95% CI, 0.7 to 1.6). In univariate models, diabetes (OR, 1.4; 95% CI, 1.0 to 1.9) and QT-prolonging medications (OR, 2.0; 95% CI, 1.5 to 2.8) also were associated with SCD.

In the initial multiple logistic regression models, borderline QTc had ORs close to 1.0; thus, the normal and borderline QTc categories were combined as a reference category. History of MI and obesity were not associated with SCD and were removed from the model, as was the interaction term for diabetes and QT-prolonging medications (\(P=0.36\)). The final model included age (\(P<0.0001\)), gender (\(P=0.42\)) (retained on the basis of an a priori decision to adjust for gender), abnormally prolonged QTc (\(P<0.0001\)), QT-prolonging medications (\(P<0.0001\)), and diabetes (\(P=0.001\)) as main effects terms, as well as interaction terms for diabetes and abnormal QTc (\(P=0.007\)) and for QT-prolonging medications and abnormal QTc (\(P=0.0009\)).

Table 5 presents ORs for SCD from the multivariable model. Among subjects without diabetes who were not using QT-prolonging medications (idiopathic QTc prolongation), an abnormally long QTc quintupled the odds of SCD (OR, 5.53; 95% CI, 3.20 to 9.57). In subjects with diabetes who were not using QT-prolonging medications, an abnormally prolonged QTc remained associated with SCD, but the magnitude of the effect was attenuated (OR, 2.04; 95% CI, 1.08 to 3.85). In subjects using QT-prolonging medications, no significant association was found between abnormal QTc and SCD, whether diabetes was present or absent (\(P>0.14\)).

From the same multivariable models, we also estimated the adjusted effects of diabetes and QT-prolonging drugs on odds of SCD. Because of the interaction between both of these

**Table 1. Demographics and SCD Risk Factors in Cases and Controls**

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=373)</th>
<th>Controls (n=309)</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70±13</td>
<td>64±12</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Male, %</td>
<td>60</td>
<td>64</td>
<td>0.24</td>
</tr>
<tr>
<td>History of MI, %</td>
<td>33</td>
<td>28</td>
<td>0.23</td>
</tr>
<tr>
<td>History of diabetes mellitus, %</td>
<td>40</td>
<td>33</td>
<td>0.06</td>
</tr>
<tr>
<td>Obese, † %</td>
<td>35</td>
<td>38</td>
<td>0.37</td>
</tr>
<tr>
<td>Severe LV dysfunction (EF ≤35%), ‡ %</td>
<td>22</td>
<td>9</td>
<td>0.004</td>
</tr>
<tr>
<td>Using medication with risk of causing torsades de pointes (qtdrugs.org list 1), %</td>
<td>7.5</td>
<td>3.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Using medication that may prolong QT interval (qtdrugs.org list 2 or 3), %</td>
<td>38</td>
<td>26</td>
<td>0.0005</td>
</tr>
<tr>
<td>Any medication from qtdrugs.org lists 1–3, %</td>
<td>43</td>
<td>27</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(^*\)P value from \(t\) tests for continuous variables and \(\chi^2\) tests for categorical variables.

†Body mass index ≥30 kg/m\(^2\). Body mass index was available for 309 cases and 291 controls.

‡Ejection fraction (EF) from echocardiogram, angiogram, or multigated acquisition for 188 cases and 116 controls.

reader. The intraclass correlation coefficient comparing the first and second readers for the QT interval was 0.92 (95% CI, 0.90 to 0.93); for the RR interval, it was 0.94 (95% CI, 0.93 to 0.95), indicating excellent reliability in the method of reading ECGs.

**Greater Prolongation of QTc Interval in Cases of SCD**

Cases were significantly more likely than controls to have an abnormally prolonged QTc interval (\(P<0.0001\); Table 2). Mean QTc was 17 ms longer in cases (\(P<0.0001\); Table 2). The Figure shows the distribution of QTc in cases and controls. Prolongation of the QTc interval was consistently associated with SCD status across demographic and clinical characteristics except in subjects using QT-prolonging drugs, subjects with diabetes, and subjects with severe LV dysfunction (Table 2).

**Determinants of QTc Interval Prolongation**

In the ANCOVA model, age, history of MI, and obesity did not significantly predict QTc interval when the other variables were controlled for (\(P=0.43\)). In a final multivariate model, only gender (\(P=0.01\)), diabetes (\(P=0.0007\)), use of QT-prolonging medications (\(P=0.0003\)), and the interaction between diabetes and medications were significant (\(P=0.08\)). The adjusted (least-squares) mean QTc interval was longer in women than men (534 versus 446 ms; Table 3). Use of QT-prolonging medications and diabetes were significantly associated with the QTc interval, and their effects depended on each other (test for interaction \(P=0.08\)).
factors and the QTc interval, we present estimates for their effects by QTc interval category (normal/borderline QTc and abnormal QTc; Table 5). Both diabetes and use of QT-prolonging medications doubled or nearly tripled the odds of SCD, but only in subjects with normal or borderline QTc. Neither diabetes nor QT-prolonging medications were related to SCD among subjects with an abnormally prolonged QTc ($P>0.30$).

Finally, the full logistic regression model in the subset of patients with data on ejection fraction (188 cases, 116 controls) showed that severe LV dysfunction was significantly associated with SCD ($P<0.0001$) and that significant interaction was found between LV dysfunction and the QTc interval ($P<0.005$). Among patients with normal or borderline QTc, severe LV dysfunction was strongly associated with SCD (OR, 5.11; 95% CI, 1.83 to 14.22); this association was not observed in subjects with abnormal QTc ($P=0.86$).

### Discussion

#### Summary of Main Findings

In this population-based sample of subjects with CAD, QTc interval duration was significantly greater in cases (those who suffered SCD) compared with controls (those who did not have a history of SCD). Gender, diabetes, and use of QT-prolonging medications were significant predictors of QT interval prolongation. In multiple logistic regression analyses, abnormally prolonged QTc in the absence of diabetes and without the use of QT-prolonging medications was an important determinant of SCD risk (OR, 5.53; 95% CI, 3.20 to 9.57).

The vast majority (at least 80%) of all cases of SCD are associated with significant CAD. At present, the only available predictor of SCD risk used in clinical practice is severe LV systolic dysfunction. However, recent population-based studies have reported that only a minority of patients...
(20% to 30%) are found to have LV systolic dysfunction before SCD.\textsuperscript{5,6,16} In fact, the majority have either normal or mildly to moderately decreased LV systolic dysfunction.\textsuperscript{6} As a consequence, there is an urgent need to identify additional novel and clinically relevant predictors of SCD in patients with coronary disease. In early small case-control studies, QTc prolongation was identified as a predictor of SCD in patients who suffered MI.\textsuperscript{17} Most recently, the Rotterdam Heart Study provided strong evidence of a doubling of SCD risk with abnormal QTc prolongation among middle-aged and older members of this large cohort.\textsuperscript{3,4,18} Therefore, abnormal QTc prolongation has significant potential for use in enhancing risk stratification and future prevention of SCD.

However, before this potential can be exploited, it is important to understand the cause of QTc prolongation among patients with CAD. In the present study, diabetes and QT-prolonging drugs were independent determinants of QTc prolongation in the control population. In addition, patients with both of these factors had a significantly longer QT interval than patients with neither or only one of these factors.

Both diabetes and QT-prolonging drugs have previously been associated with increased SCD risk. The association of diabetes with SCD risk was first identified in the Paris Prospective Study from an analysis performed among patients with CAD and event. QTc duration was significantly longer in patients with diabetes compared with those without diabetes. However, the independent contribution of diabetes to QTc prolongation in the presence of other risk factors was not assessed in this study.

Table 3. Predictors of QTc Duration Among Controls in Multivariate ANCOVA Model\textsuperscript{*}

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=373)</th>
<th>Controls (n=309)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>161 (43)</td>
<td>84 (27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>212 (57)</td>
<td>225 (73)</td>
<td></td>
</tr>
<tr>
<td>Diabetes-by–QT-prolonging medications interaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes mellitus and no QTmeds</td>
<td>428</td>
<td>446</td>
<td>0.08</td>
</tr>
<tr>
<td>With diabetes mellitus and no QTmeds</td>
<td>437</td>
<td>436</td>
<td></td>
</tr>
<tr>
<td>No diabetes mellitus and use of QTmeds</td>
<td>462‡</td>
<td>462‡</td>
<td></td>
</tr>
<tr>
<td>With diabetes mellitus and use of QTmeds</td>
<td>462‡</td>
<td>462‡</td>
<td></td>
</tr>
</tbody>
</table>

QTmeds indicates QT-prolonging medications.

\textsuperscript{*}Model predicting QTc in controls (with CAD but no SCD) included age, gender, history of MI, diabetes mellitus, obesity, and use of QT medications.\textsuperscript{†}P value from ANCOVA F statistic.

\textsuperscript{‡}Mean differs from 3 other groups (P<0.01) in posthoc test with Tukey-Kramer adjustment for multiple comparisons.

Table 4. Use of QT-Prolonging Medications Among Cases and Controls

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=373)</th>
<th>Controls (n=309)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any QT-prolonging medication\textsuperscript{*}</td>
<td>161 (43)</td>
<td>84 (27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Type of QT-prolonging medications</td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>Cardiac†</td>
<td>16 (10)</td>
<td>7 (8)</td>
<td></td>
</tr>
<tr>
<td>Noncardiac</td>
<td>145 (90)</td>
<td>77 (92)</td>
<td></td>
</tr>
<tr>
<td>QT-prolonging medications, n</td>
<td></td>
<td></td>
<td>0.0002</td>
</tr>
<tr>
<td>0</td>
<td>212 (57)</td>
<td>225 (73)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>133 (36)</td>
<td>73 (24)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>25 (6)</td>
<td>11 (3)</td>
<td></td>
</tr>
<tr>
<td>3 or 4</td>
<td>3 (1)</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{*}QT-prolonging medications included antiarrhythmics, antibiotics, antidepressants, antihypertensives, antipsychotics, antiepileptic medications, bronchodilators, diuretics, lithium, and methadone.

\textsuperscript{†}Cardiac QT-prolonging medications are antiarrhythmic agents that prolong QT interval; all others are defined as noncardiac.
Table 5. Factors Independently Associated With SCD From the Full Multiple Logistic Regression Model: QTc Prolongation,* Diabetes Mellitus, and Use of QT-Prolonging Medications

<table>
<thead>
<tr>
<th>Patient Subgroup From Full Model</th>
<th>OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal QTc vs Normal/Borderline QTc (reference)</td>
<td></td>
</tr>
<tr>
<td>No diabetes mellitus and no QTmeds</td>
<td>5.53 (3.20–9.57)</td>
</tr>
<tr>
<td>With diabetes mellitus and no QTmeds</td>
<td>2.04 (1.08–3.85)</td>
</tr>
<tr>
<td>No diabetes mellitus and use of QTmeds</td>
<td>1.60 (0.83–3.05)</td>
</tr>
<tr>
<td>With diabetes mellitus and use of QTmeds</td>
<td>0.59 (0.29–1.19)</td>
</tr>
<tr>
<td>Diabetes vs no diabetes (reference)</td>
<td></td>
</tr>
<tr>
<td>Normal/borderline QTc</td>
<td>1.97 (1.32–2.96)</td>
</tr>
<tr>
<td>Abnormal QTc</td>
<td>0.73 (0.39–1.34)</td>
</tr>
<tr>
<td>Use of QTmeds vs no use (reference)</td>
<td></td>
</tr>
<tr>
<td>Normal/borderline QTc</td>
<td>2.90 (1.92–4.37)</td>
</tr>
<tr>
<td>Abnormal QTc</td>
<td>0.84 (0.45–1.54)</td>
</tr>
</tbody>
</table>

*QTc categories: men: ≤ 430 ms (normal), 431 to 450 ms (borderline), and >450 ms (abnormal); women: ≤ 430 ms (normal), 451 to 470 ms (borderline), and >470 ms (abnormal).
†From full multiple logistic regression model adjusting for age (P<0.0001), gender (P=0.42), abnormal QT interval vs normal or borderline QTc (P<0.0001), use of QT medications (yes/no) (P<0.0001), diabetes mellitus (yes/no) (P=0.001), and interaction terms for QT interval by diabetes mellitus (P=0.007) and QT interval by use of QT medications (P=0.0009).

middle-aged, healthy male Parisian civil servants who were enrolled and followed up for >23 years.19,20 The US Nurses Study and the Physicians Health Study,21,22 as well as a retrospective clinical database analysis from a health cooperative in Seattle,23 have reported similar findings. Although these observations implicate diabetes as an important factor in the pathogenesis of SCD, our findings indicate that this relationship may be complex. Diabetes appears to confer risk of SCD only in subjects with normal or borderline QTc interval. The association between noncardiac QT-prolonging drugs and SCD was evaluated from a large longitudinal observational database in the Netherlands, and use of a noncardiac QT-prolonging drug was associated with a significantly increased risk of SCD (adjusted OR, 2.7; 95% CI, 1.6 to 4.7), nearly identical to the findings reported in the present study. However, the present study evaluated all QTc-prolonging drugs, cardiac and noncardiac. The fact that QT-prolonging drugs were associated with SCD occurrence in the absence of QTc prolongation has potential implications for their clinical use and follow-up of patients. A potential mechanistic explanation has recently been reported by Hintsere et al.24 This report noted that in some patients with drug-induced torsades, beat-to-beat or short-term variability of the QT interval may be more useful as a predictor of arrhythmic risk than absolute value of the QTc.

The most interesting and somewhat unexpected finding of the present study is that abnormally prolonged QTc of unknown etiology was a powerful independent predictor of SCD. When 2 groups, both of which have coronary disease and similar comorbidities, are compared, a 5-fold increase in odds is a significant finding. If not diabetes or drugs, what are the potential causes of prolonged QTc in coronary disease? It has been postulated that heart failure could be a form of acquired, abnormally prolonged ventricular repolarization.25 In the present study, however, although a strong association (5-fold increased risk) was found between severe LV dysfunction and SCD in patients with normal QTc, it was not observed for patients with borderline/abnormally prolonged QTc. Although this observation appears contrary to some observations published in the literature, these findings likely relate to the nature of the population. Both cases and controls have significant coronary disease and a high prevalence of diabetes and other conditions that indicate high risk. Individuals with QT prolongation who also have diabetes and are using QT-prolonging medications may have additional risk for SCD conferred by comorbidities. In the present study, 2 other comorbidities, chronic renal insufficiency and chronic obstructive pulmonary disease, were significantly more common in subjects with prolonged QTc, diabetes, and QT-prolonging medications than in subjects with idiopathic prolonged QTc (data not shown). With many competing risks, the SCD risk attributable to QTc prolongation may become attenuated.

Our findings of SCD cases with prolonged QTc in the absence of diabetes, QT-prolonging drugs, or severe LV dysfunction suggest that genetic factors may contribute to QTc prolongation. A growing body of literature is available on the contribution of common genetic variants to cardiac repolarization. Bezzina and colleagues26 demonstrated that a common polymorphism in the KCNH2 gene influenced QT interval length in healthy individuals in the Monitoring of Trends and Determinants in Cardiovascular Disease study 3 (Augsburg MONICA). Further evidence of the influence of common gene variants on the QT interval came from a linkage disequilibrium–based single-nucleotide polymorphism association study of the Cooperative Health Research in the Region of Augsburg (KORA) population in Germany.27 More recently, Arking and coworkers28 performed a genome-wide association study on subjects from the KORA cohort and identified a common genetic variant in NOS1AP (CAPON), a regulator of neuronal nitric oxide synthase, as a new target that modulates cardiac repolarization. Several other studies have since been published that have confirmed the role of this common genetic variant as a determinant of the QT interval.29–31 Newton-Cheh and colleagues,32 using a candidate gene variation approach in the Framingham Heart Study population, found that 2 common genetic variants at the KCNH2 locus were associated with continuous QT interval duration and were able to replicate these observations in an independent sample of the same population. Albert and coworkers33 recently evaluated the role of repolarization-prolonging SCN5A gene variants in 113 SCD cases from 2 large prospective cohorts of women (Nurses’ Health Study) and men (Health Professional Follow-Up Study). Found at a significantly higher frequency in cases than controls (10% versus 1.6%), functionally significant mutations and rare variants in SCN5A are likely to have contributed to SCD risk among women but not among men. Taken together, published studies and the present study suggest that abnormally prolonged ventricular repolarization may be a causative factor in the pathophysiology of SCD in patients with CAD, and not just a marker of increased
morbidity. Therefore, the continued identification of gene variants that determine QT interval duration has become an important scientific priority in the field.

This study has some potential limitations. Approximately half of the cases (47%) had medically documented CAD, but the remainder were assumed to have CAD on the basis of prior studies showing that >95% of SCD patients ≥50 years of age have significant CAD at autopsy.12,13 However, sensitivity analyses showed that the results were very similar when the analysis was restricted to cases with documented CAD. Although all ECGs with QRS ≥120 ms were excluded from analysis, we also considered possible confounding of the QTC-SCD association by QRS duration and did not find evidence of any. Finally, in a population-based study of this nature, the exact timing of medications can be difficult to determine. However, we were able to determine that for 160 (43%) of the 373 case subjects in this analysis, the date the medications were noted was within 45 days of the ECG. In addition, the large proportion (up to 50%) of patients with sudden death as a first cardiac event may have infrequent visits to their healthcare provider. For some of these patients, medications noted more remotely from the ECG may represent the medications taken when the ECG was performed. Similarly, we were able to establish that 144 (39%) of the 373 cases were on the listed medications within the 45 days before arrest, indicating that a substantial number of patients were likely to be on the listed medications during the time of cardiac arrest.

Conclusions
These findings underscore the importance of prolonged QTc as an independent predictor of SCD risk in the general population, even in the presence of CAD and diabetes. Idiopathic QTc prolongation was a strong, significant predictor, resulting in a 5-fold increased risk of SCD. Because common and rare genetic variants are likely to be important contributors to cardiac ventricular repolarization, continued identification of these factors is likely to enhance risk stratification and prevention of SCD in patients with coronary disease.

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Disclosures
None.

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**CLINICAL PERSPECTIVE**

In this population-based study, determinants of QT interval prolongation were evaluated among patients with coronary disease. These patients were compared with cases of sudden cardiac death who also had coronary disease to identify risk predictors of sudden cardiac death. Gender, diabetes mellitus, and QT-prolonging drugs were determinants of QT prolongation in coronary artery disease. In addition, diabetes mellitus and QT-prolonging drugs were identified as significant predictors of sudden cardiac death risk. However, QT interval prolongation of unknown origin (in the absence of diabetes or QT-prolonging drugs) was an even stronger predictor of sudden death risk, resulting in a 5-fold increase in sudden death risk among patients with coronary disease. These findings have significant implications for improvement of sudden death risk stratification among patients with coronary artery disease. Risk stratification with the prolonged corrected QT interval may allow us to extend beyond the left ventricular ejection fraction, which we are learning is, at best, a modest predictor of risk of sudden death. Other recent research suggests that relatively common gene variations may contribute to the idiopathic QT prolongation observed among patients with coronary artery disease. Therefore, to optimize the effectiveness of the prolonged QT interval as a risk stratification tool, a continued search for novel determinants of QTc prolongation such as genomic factors is warranted.

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