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QTc Interval Prolongation Is a Proxy for Increased Short-Term Mortality

Severe QT prolongation is associated with poor long-term outcome in the general population and in high-risk diseases (e.g., diabetes and rheumatoid arthritis); however, little is known about the relationship between QT prolongation and short-term mortality. Because of the lack of data, and erring on the side of safety, physicians often admit patients with QT prolongation for telemetry (1). The present study aimed to describe the association between the corrected QT (QTc) interval and short-term mortality.

We included consecutive adult patients with an electrocardiogram (ECG) recorded within 4 h of arrival at 2 community-based and 2 academic emergency departments in Sweden and Denmark. We excluded patients with atrial fibrillation or flutter patterns, paced rhythms, and QRS intervals >120 ms.

We collected patient data on pharmaceutical treatment before inclusion, blood test values, and data from national health registries on prior illnesses and outcome. The primary endpoint was 7-day mortality.

We performed Cox proportional hazard regression with 3 levels of adjustments for the potential confounders: 1) sex and age; 2) level 1, site, Charlson comorbidity index, prior relevant diagnoses (e.g., long QT syndrome), and prior pharmacological treatment (e.g., beta-blockers, selective serotonin reuptake inhibitors, and any drugs with QT-prolonging potential); and 3) level 2 and C-reactive protein. As a sensitivity analysis, we reran all regressions excluding patients with heart rate >100 beats/min. Our data support the assumptions for performing Cox regression (data not shown).

QTc was defined according to Framingham's formula with 450 to 499 ms for men and 460 to 499 ms for women as moderate prolongation and ≥500 ms as severe prolongation for both sexes. As sensitivity analyses, we repeated all specified analyses using Bazett's and Fridericia's formulae for QTc. For patients with QTc prolongation, we identified the cause of in-hospital death. The study was approved by ethics review boards in Sweden and Denmark.

We included 103,075 (82.9%) patients with ECGs in the final analysis, 93.0% of whom had normal QTc, 6.5% moderate, and 0.6% severe QTc prolongation. Median age was 60 years (interquartile range: 43 to 73 years), 47.5% were men, and 1,326 (1.3%) died within 7 days. Patients with QTc prolongation were older, had more comorbidity, used more medication (including QT-prolonging drugs), and had more cardiovascular morbidity than patients with normal QTc intervals.

Seven-day all-cause mortality was 1.2% in patients with normal QTc, 2.4% in moderately and 4.3% in severely prolongated QTc. Multivariate analyses decreased HRs at all levels of adjustment, but all estimates remained statistically significant (Table 1). Our sensitivity analysis did not change the estimates (data not shown). Most patients with in-hospital fatality died of infection (23% with moderate vs. 35% with severe QTc prolongation), cardiac causes (14% vs. 22%), and stroke (26% vs. 14%).

When using Bazett's formula, the number of patients with moderate and severe QTc prolongation increased, whereas Fridericia's formula gave similar proportions. Seven-day mortality rates were virtually unaffected with Fridericia's formula but were slightly higher in patients with severe QTc prolongation when Bazett's formula was used.

We found that 7-day mortality increased with both moderate and severe QTc prolongation, but that fewer than a quarter of the patients died from cardiac causes, and especially few among those with moderate QTc prolongation. Also, the strength of the association

TABLE 1 Association Between QTc Duration and 7-Day Mortality

			Framingham			
	n	Events	HR, Crude	HR, Level 1	HR, Level 2	HR, Level 3
QTc normal	95,822	1,137	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
QTc moderate	6,663	164	2.20 (1.84–2.62)	1.24 (1.04–1.48)	1.22 (1.02–1.46)	1.35 (1.13–1.62)
QTc severe	588	25	3.72 (2.41–5.73)	2.14 (1.39–3.30)	1.88 (1.22–2.90)	1.90 (1.23–2.94)

HR, Crude = unadjusted; HR, Level 1 = adjusted for sex and age; HR, Level 2 = level 1, site, Charlson comorbidity index, prior relevant diagnoses (e.g., long QT syndrome), and prior pharmacological treatment (e.g., beta-blockers, selective serotonin reuptake inhibitors, and any drugs with QT-prolonging potential); HR, Level 3 = level 2 and C-reactive protein. QTc normal = interval of <450 ms for men and <460 ms for women; QTc moderate = interval of 450 to 499 ms for men and 460 to 499 ms for women. QTc severe = interval of ≥500 ms for all.

HR = hazard ratio; QTc = corrected QT interval.

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decreased as we adjusted our analyses. We used Framingham's formula, but found only slightly different results using Bazett's and Fridericia's.

Most of our patients with QTc prolongation died due to infection, but adjusting for C-reactive protein in the analyses had little impact. This could be a coincidence, but previous research has shown an association between infection and malignant dysrhythmias (2). Whether this is due to pharmacological treatment of infection (3) or systemic inflammation (4) is unclear. In any case, admitting patients with isolated QTc prolongation for telemetry, particularly when a concomitant infection is present, may be useful to intercept early life-threatening arrhythmias but should not be done automatically but on clear clinical indication.

Our study has high generalizability, and because of our Nordic nationwide registries, we had access to complete follow-up and reliable data on prescription drugs and comorbidities. As QTc prolongation is dynamic, and we used only the initial ECG, we could have missed patients who later developed QTc prolongation. Also, as all medical records were not manually reviewed, we may have missed patients who deteriorated but were resuscitated during admission, which might have led to a higher complication rate.

***Mikkel Brabrand, MD, PhD**
Helene K. Jensen, MD
Ulf Ekelund, MD, PhD
Jakob L. Forberg, MD, PhD
Annmarie Lassen, MD, PhD, DMSc
Anton Pottegård MscPharm, PhD

*Department of Emergency Medicine
Hospital of South West Jutland
Finsensgade 35
DK-6700 Esbjerg
Denmark
E-mail: mikkel.brabrand@rsyd.dk
Twitter: @MBrabrand

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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Healthy Diet and Cardiovascular Prevention

Time to Go Further With a Precision Medicine Approach?

We immediately read with great interest the significant and well-presented large, nonrandomized observational analysis by Guasch-Ferré et al. (1). The study reports findings from 3 seminal Harvard cohorts prospectively assessing olive oil consumption in relation to cardiovascular disease. The collected data provide robust evidence of the association between olive oil consumption and lower cardiovascular risk in a non-Mediterranean country, such as the United States. We would like to take this opportunity to

TABLE 1 Continued

Bazett				Fridericia			
HR, Crude	HR, Level 1	HR, Level 2	HR, Level 3	HR, Crude	HR, Level 1	HR, Level 2	HR, Level 3
1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
2.31 (2.03–2.64)	1.44 (1.27–1.65)	1.39 (1.21–1.58)	1.38 (1.21–1.57)	2.45 (2.08–2.88)	1.40 (1.19–1.65)	1.39 (1.18–1.64)	1.51 (1.28–1.78)
6.96 (5.77–8.41)	3.69 (3.05–4.47)	3.38 (2.78–4.10)	3.02 (2.49–3.67)	4.31 (2.98–6.23)	2.41 (1.66–3.49)	2.13 (1.47–3.09)	2.12 (1.46–3.08)