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LETTER

Prolonged corrected QT interval is associated with short-term and long-term mortality in critically ill patients: results from the FROG-ICU study

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Dear Editor,

Prolonged corrected QT interval (QTc) is common in the intensive care unit (ICU) [1, 2]. It is associated with higher mortality in general population [3] and with higher in-hospital mortality in critically ill patients ICU [1, 4], while the association with long-term mortality is unclear. The benefit of beta-blockers is confirmed in congenital long QT syndrome [5], but not evaluated in ICU patients with QTc prolongation. Our aim was to investigate the association between prolonged QTc and both short- and long-term outcome in ICU patients and to assess the effect of beta-blockers on outcome in patients with prolonged QTc.

The FROG-ICU study (NCT 01367093) is a prospective, observational study conducted in 21 ICUs in 14 university hospitals in France and Belgium. The study was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki. In this sub-study, patients with at least one 12-lead ECG available within 3 days of ICU admission were included. ECGs were recorded with a high-resolution electrocardiograph (CarTouch®, Cardionics). QT interval was measured from overlapped averaged 12-lead ECG data using Cardionics® QT analysis software, and it was corrected for heart rate using Bazett's formula. Prolonged QTc was defined as QTc ≥ 500 ms [5]. ECGs with atrial fibrillation ($n=271$) and with QRS-duration ≥ 120 ms ($n=160$) were excluded from this study. Multivariable Cox regression models included Charlson Comorbidity Index, Simplified Acute Physiology Score II (SAPS II), gender and cardiac arrest or cardiogenic shock as cause for ICU admission.

Of 2087 FROG-ICU patients, 1467 were included in this sub-study. Prolonged QTc was found in 209 (14%) patients within 3 days. Patients with prolonged QTc were older (63 ± 16 vs. 58 ± 16 years, $p<0.001$), had higher Charlson Comorbidity Index (4 ± 3 vs. 3 ± 2, $p<0.001$) and higher SAPS II (51 ± 17 vs. 48 ± 19, $p=0.018$) than patients with normal QTc. Heart rate was similar in the two groups (91 ± 19 vs. 90 ± 19 bpm, $p=0.48$).

Thirty-day mortality [30% ($n=63$) vs. 17% ($n=216$), $p<0.001$, Fig. 1a] and 1-year mortality [45% ($n=94$) vs. 31% ($n=386$), $p<0.001$, Fig. 1a] were higher in patients with prolonged QTc compared to normal QTc. In adjusted mortality analysis, prolonged QTc was associated with the risk of 30-day (HR 1.55, 95% CI 1.16–2.06, $p=0.003$) and 1-year death (HR 1.31, 95% CI 1.04–1.65, $p=0.02$).

Among patients with prolonged QTc, 34 (16%) were treated with beta-blockers during the ICU stay. Of these patients, 15 had beta-blocker as chronic treatment. Patients with beta-blocker therapy during the ICU stay had lower 30-day [12% ($n=4$) vs. 34% ($n=59$), $p=0.001$, Fig. 1b] and 1-year mortality [29% ($n=10$) vs. 48% ($n=84$), $p=0.001$, Fig. 1b] when compared to patients without beta-blockers. Among patients with prolonged

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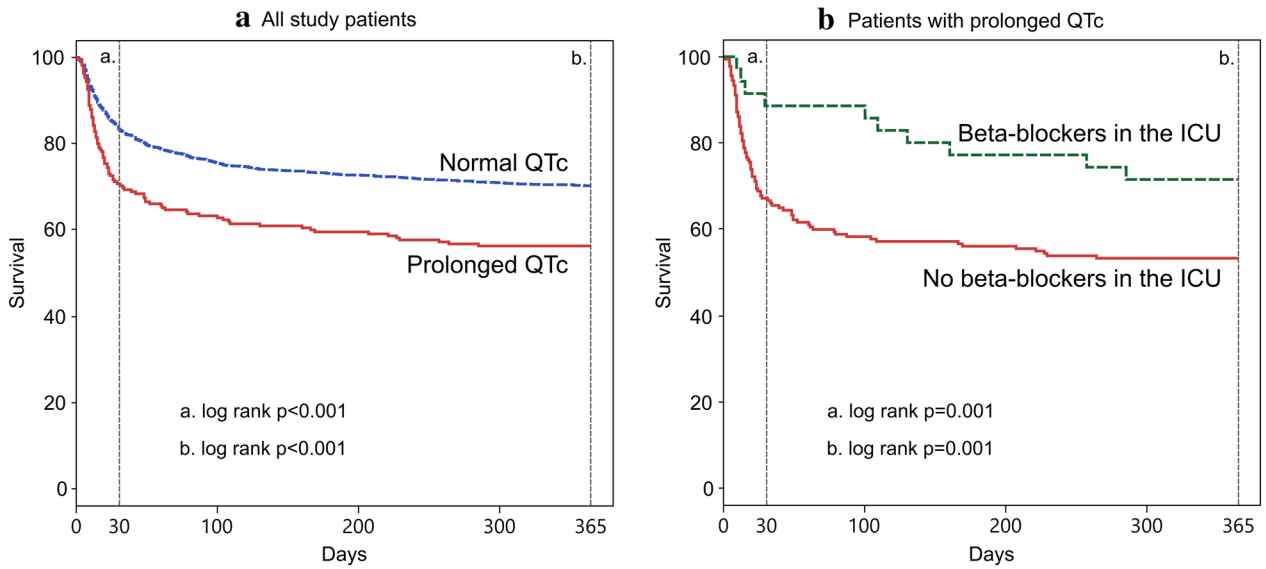

Fig. 1 Kaplan-Meier survival curves. **a** Patients with prolonged QTc had higher 30-day and 1-year mortality rates when compared to patients with normal QTc. **b** Among patients with prolonged QTc, patients with beta-blocker therapy during the course of the ICU stay had lower mortality rates that patients without beta-blockers

QTc, beta-blocker therapy was associated with lower risk of 30-day (HR 0.29, 95% CI 0.11–0.82, $p = 0.019$) and 1-year death in adjusted mortality analysis (HR 0.46, 95% CI 0.24–0.89, $p = 0.040$).

In conclusion, prolonged QTc was associated with worse outcome in ICU patients and beta-blocker therapy among patients with prolonged QTc was associated with lower mortality. Indeed, these results reveal many questions. To name but one, it was not possible to explore if the outcome would be different in patients with acquired prolonged QTc and pre-existing QTc prolongation as the data for QT-prolonging medications was not available in this cohort. Further studies are needed to answer this question and to confirm our results.

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Compliance with ethical standards

Ethical approval
The study was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki.

Conflicts of interest
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