Predictive analyses of QT prolongation from ECG monitoring in STREAM Stage 1

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Introduction

- STREAM Stage 1
- Phase 3 non-inferiority RCT for rifampicin-resistant TB
- Short 9-11 month regimen (n=282) *versus* Long 20+ month WHO 2011 control regimen (n=142)
- Sites in Ethiopia, Mongolia, South Africa and Vietnam
- Patients with a QT or corrected QT (QTcF) interval ≥500ms at screening were excluded
- Regular ECG monitoring was undertaken up to 52 weeks

Why focus on ECG data?

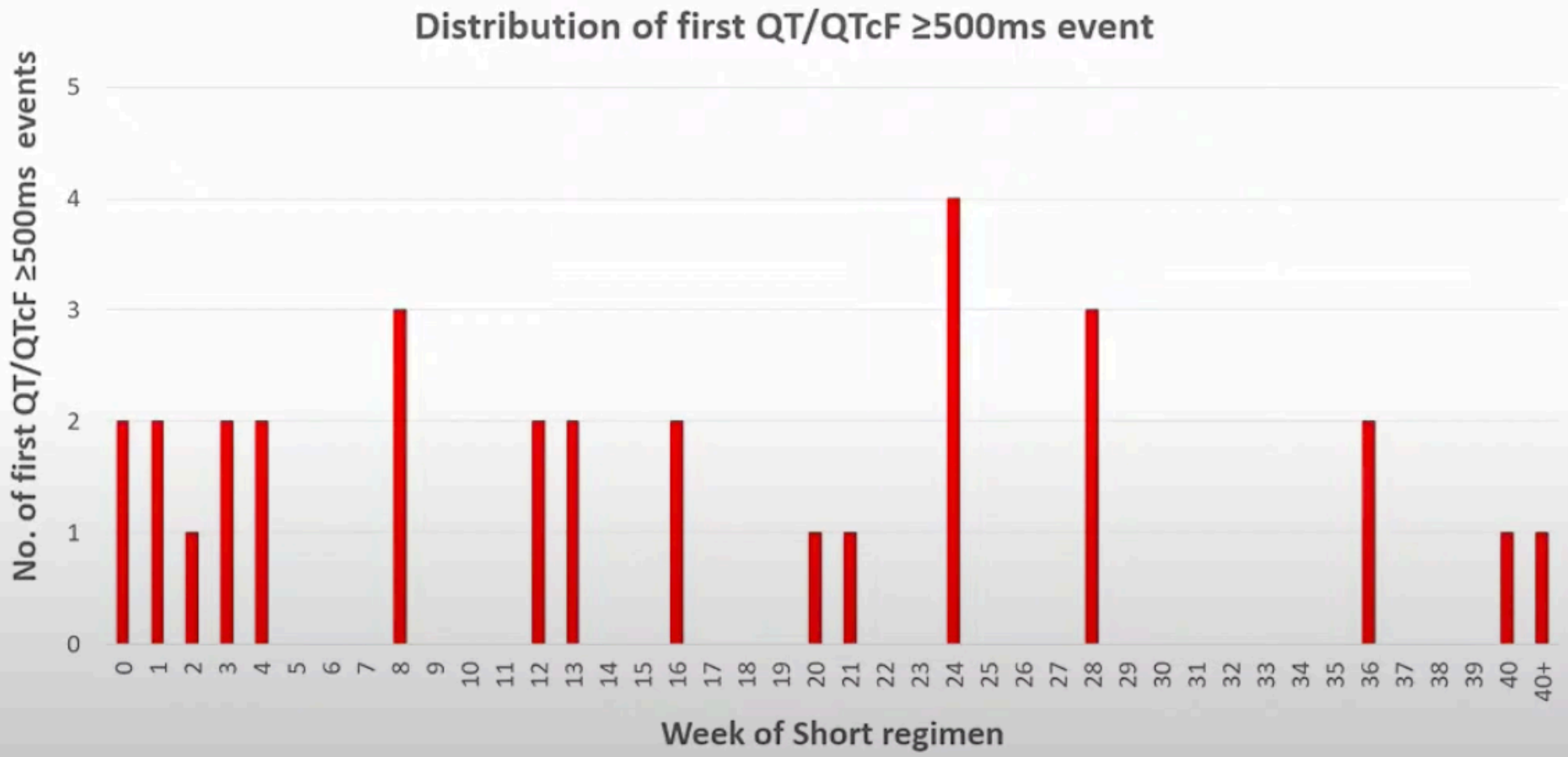
- Short regimen includes 2 drugs known to prolong QT interval (moxifloxacin and clofazimine)
- QT or QTcF interval prolongation ≥500ms occurred in 11% of Short regimen participants *versus* 6.4% Long regimen (P=0.14)
- We have previously presented results of trial and analysis of risk factors for QT prolongation (baseline >450ms and recruitment from the Mongolia site)
- This analysis aimed to identify a simplified monitoring strategy for programmatic settings

Objective

- To use results of QTcF monitoring in the first few weeks of treatment (change from baseline and absolute values) to identify patients requiring more intensive ECG monitoring

Distribution of first QT/QTcF ≥500ms event in Short regimen

N=31



Methods

- Change from baseline in QTcF of 5,10,15,20 and 40ms at each time point were examined
- Absolute QTcF values at each time point were categorised as less than, or greater than/equal to 415, 425, 430, 435 and 445ms
- The most promising time points and absolute QTcF cut-off values were combined to try and optimise the sensitivity and specificity

Results

- 31 of 275 patients on the Short regimen developed QT/QTcF ≥500ms

- The best single predictor for change from baseline value was an increase of ≥40ms at the majority of time points examined but many patients were still missed

Time point	Change from baseline	Total (n=274)	Prolongation ≥500ms (n=30)*	P-value
4 Hours	<40ms	260	26 (10.0%)	0.030
	≥40ms	14	4 (28.6%)	
Week 12	<40ms	198	15 (7.6%)	<0.001
	≥40ms	66	16 (24.2%)	

Results – Absolute QTcF at 4 hours and week 3

Time point post randomisation	QTcF	Total	Prolongation ≥500ms	Sensitivity	Specificity	PPV	NPV
4 hours	<425ms	169	5 (3.0%)	83.3%	67.2%	23.8%	97.0%
	≥425ms	105	25 (23.8%)				
Week 3*	<430ms	129	1 (0.8%)	83.3%	79.0%	12.8%	99.2%
	≥430ms	39	5 (12.8%)				
Combined				96.7%	52.9%	20.8%	99.2%

**Week 3 data only included patients with QTcF <425ms at 4 hours*

Summary

- By combining absolute values ≥425ms at 4 hours and ≥430ms at week 3 it was possible to identify patients who developed QT/QTcF prolongation ≥500ms with 97% sensitivity and 99% negative predictive value (NPV)
- If implemented prospectively this might limit the number of ECG monitoring visits required in almost half the patients receiving the Short regimen
- Such a targeted monitoring strategy could be useful in programmatic settings with limited resources and large geographic spread
- These results need validation in a different data set and planned for STREAM Stage 2

The Stream Collaboration

STREAM Stage 1 involved investigators, staff and participants from:
Armauer Hansen Research Institute, Ethiopia; King Dinuzulu Hospital, Durban, South Africa; Liverpool School of Tropical Medicine, UK; MRC CTU at UCL, UK; National Center for Communicable Diseases, Mongolia; Pham Ngoc Tach Hospital, Ho Chi Minh City, Vietnam; Sizwe Tropical Diseases Hospital, Johannesburg, South Africa; St Peter's Tuberculosis Specialized Hospital, Ethiopia; Think Tuberculosis & HIV Investigative Network, Doris Goodwin Hospital, South Africa; Institute of Tropical Medicine, Belgium and The Union/Vital Strategies