Prolonged QTc interval in adults with diabetic ketoacidosis: is it only electrolyte disturbance?

Osama A. Khalil, Ghada M. Samir, Ayman M.E.M. Sadek

Department of Internal Medicine, Zagazig University, Zagazig, Sharkia Governorate, Egypt

Correspondence to Ayman M.E.M. Sadek, MD, Shoubak Basta, Zagazig 44519, Sharkia Governorate, Egypt. Tel: +20 122 138 7405/ +20 111 448 0339; e-mails: amedms@gmail.com, ayman.sadek@zu.edu.eg

Received 10 December 2018
Accepted 16 January 2019

The Egyptian Journal of Internal Medicine
2019, 31:136–141

Context
Cardiac arrhythmia in diabetic ketoacidosis (DKA) is a well-known complication that is usually a result of electrolyte imbalance. Another frequently missed cause of arrhythmia is the QT interval prolongation, which is not always attributed to electrolytes disturbance.
Aim
We aimed to explore the frequency of QTc interval prolongation among patients with DKA in the medical ICU, the association with serum electrolytes and pH, and the implication on the outcome.
Patients and methods
We carried out a cross-sectional cohort study on patients with DKA admitted to medical ICU. We had worked on 72 patients with DKA by performing the routine investigation including ECG follow-up during the hospital stay. Maximum QT interval in all measured leads (QTmax) and heart rate-corrected QTmax (QTmaxc) were calculated in milliseconds according to Bazett's formula. We used SPSS, version 20.0, with the following statistical tests: Shapiro–Walk, Student's *t*, Pearson's correlation, logistic regression, receiver operating characteristic curve analysis, and relative risk.
Results
The frequency of QTmaxc interval prolongation without electrolyte imbalance was seen in 46 (63.9%) patients. pH revealed to be the most significant independent risk factor for QTmaxc interval prolongation (odds ratio=8.39, 95% confidence interval: 1.67–18.06) with a cutoff value less than 7.03, with sensitivity of 56% and specificity of 44%. QTmaxc prolongation carried a relative risk of ~1.7-fold for mortality in patients with DKA.
Conclusion
Acidosis carries an independent risk for QTmaxc interval prolongation in the absence of electrolytes abnormalities, with related poor ICU outcome in patients with DKA.

Keywords:
diabetic ketoacidosis, ICU, QT interval

Egypt J Intern Med 31:136–141

1110-7782

Introduction

Egypt has the highest prevalence of type 1 diabetes mellitus in middle-income Arabian countries, with diabetic ketoacidosis (DKA) frequency ranging from 17 to 61% [1].

Cardiac arrhythmia and cardiac arrest have been attributed to electrolyte abnormalities during DKA treatment [2].

During DKA, ketosis or acidosis may directly affect cardiac repolarization with prolongation of QTc interval, leading to arrhythmia and cardiac arrest [3].

Previous studies had reported prolongation of QTc interval in children during DKA with a suggestion of whether ketosis or acidosis may directly affect cardiac repolarization and cause arrhythmia and cardiac arrest during DKA, but to our knowledge, few data were reported in adult [3–6].

We aimed to explore the frequency of QTc interval prolongation among patients with DKA in the medical ICU, the association with serum electrolytes and pH, and the implication on the outcome.

Patients and methods

Study design and settings

We conducted a prospective observational cohort study in the period from August 2016 to March 2018 on patients with DKA who were selected from medical

ICU as presented in the flowchart diagram (Supplementary 1).

Patients

A total of 72 patients with DKA were recruited, including 26 patients who were newly diagnosed with diabetes, whereas the other 46 patients were known diabetic cases. The estimated sample size was 72 patients at 80% power and 95% confidence interval (Open Epi, Open Source Epidemiologic Statistics for Public Health, Atlanta, Georgia, USA).

Ethical clearance

Written informed and oral consents were taken from the relatives of patients who participated in the study in addition to the approval for performing the study that was obtained from medical ICU of Internal Medicine Department after taking the Institutional Review Board (IRB) approval (IRB:871/8-5-2013). We performed the study according to the Helsinki declaration guidelines.

Inclusion criteria and exclusion criteria

We considered patients admitted to medical ICU for DKA, of either sex, with age above 13 years old. DKA was diagnosed by all of the following criteria: blood glucose more than 250 mg/dl, arterial pH of less than or equal to 7.30, bicarbonate level of less than or equal to 18 mEq/l, and an anion gap of more than 12 (adjusted for albumin) [7]. We excluded patients having any underlying condition that may predispose to the prolongation of the QTc interval, for example, structural heart disease (left ventricular hypertrophy, heart failure, myocardial ischemia), hyperthyroidism, hypercholesterolemia, and BMI more than 30 kg/m^2. In addition, we omitted patients who were taking medications known to affect QTc.

Process

We subjected the patients to history taking and clinical examination, and routine laboratory investigations (urine analysis, complete blood picture, blood gases and electrolytes, kidney function tests, liver chemistry, lipid profile, thyroid-stimulating hormone, C-reactive protein, and HbA1c). We recorded resting ECG in the first 6 h of admission and after the control of DKA episode. QT interval was measured manually from at least 8-leads. At least two consecutive QT intervals were measured in each lead. Maximum QT interval in all measured leads (QTmax) and heart rate-corrected QTmax (QTmaxc) were calculated in milliseconds. $QTmaxc = QTmax/\sqrt{R\text{-}R}$ interval according to Bazett's formula [8], where QTmaxc equal to or above 450 ms in men or equal to or above 460 ms in women was considered a sign for prolonged QT interval. We calculated Acute Physiology and Chronic Health Evaluation (APACHE) II score within 48 h from admission.

Statistical analysis

We used the SPSS program (version 20.0) for Windows (SPSS Inc., Chicago, Illinois, USA). Data were expressed in the form of mean±SD for continuous variables, and we tested it for normality by using Shapiro–Wilk test. The data were normally distributed, and we interpreted it by independent Student's *t*-test. We used Pearson's correlation coefficient to assess the correlation between QTmaxc interval and study parameters, as the data was parametric. (+) sign as an indication for direct correlation, that is, increase in the frequency of independent leads to increase in the frequency of dependent, and (–) sign as an indication for inverse correlation, that is, increase in the frequency of independent leads to decrease in the frequency of dependent. Moreover, we consider values near to 1 as strong correlation and values near 0 as weak correlation. We used receiver operating characteristic curve analysis to establish the optimal cutoff value of pH with maximum sensitivity and specificity for the differentiation of patients with QTmaxc prolongation from those without. A two-sided (α=2) *P* value less than 0.05 was considered significant.

Results

This study included 72 patients with age ranging from 14 to 57 years old. A total of 32 patients were males and 40 of patients were females, with ICU stay ranging from 4 to 13 days. We found that 46 (63.9%) patients had a prolonged QTmaxc at the time of admission. All the demographic, clinical, and laboratory data are demonstrated in Table 1.

Comparison of the data between the patients with prolonged QTmaxc and patients without revealed that pH, anion gap, heart rate, white blood cell, and Acute Physiology and Chronic Health Evaluation II score were the statistically significant factors (Table 2).

Multivariate logistic regression was used after Pearson's correlation (Supplementary 3) to purify the most significant independent risk factor for QTmaxc prolongation, which was pH (Table 3).

We tried to figure out a cutoff value for pH that may predict the occurrence of QTmaxc prolongation by constructing a receiver operating characteristic curve model (Fig. 1), which showed that pH below 7.03 had a sensitivity of 56% and specificity of 44% in prediction.

We found that QTmaxc prolongation carried a relative risk of ~1.7-fold for mortality in patients with DKA (Table 4).

Mortality in prolonged QTmaxc group was mainly owing to sudden cardiac arrest because of malignant ventricular tachycardia captured on the monitors, except for one patient who died from cerebral edema (Supplementary 2).

The study showed a significant resolution of QTmaxc interval prolongation after treatment of DKA (Fig. 2).

Table 1 Demographic and laboratory parameters of the studied patients at the time of admission

Parameters	Mean	SD	Range
Age (years)	25.11	10.2	14–57
RBG (mg/dl)	394.15	64.21	280–537
pH	7.09	0.16	6.52–7.32
Serum Na (mEq/l)	141.03	4.99	135–150
Serum K (mEq/l)	4.03	0.42	3.5–5
Serum Ca (mg/dl)	9.07	0.63	8.4–11
Serum Mg (mg/dl)	2.09	0.37	1.3–3.2
Serum creatinine (mg/dl)	0.99	0.36	0.4–2.6
HbA1c (%)	9.38	2.44	7–16
C-reactive protein (mg/l)	24.44	11.92	6–48
WBC ($\times 10^3$)	12.24	6.01	4.2–36.7
QTmaxc (ms)	502.65	62.87	388–626
Anion gap (mEq/l)	29.98	7.34	19–48
Heart rate (bpm)	83.63	18.295	50–130
TSH (mIU/l)	2.61	1.04	0.8–6
BMI (kg/m^2)	22.13	3.86	16–30
Cholesterol (mg/dl)	178.94	23.44	145–220
TG (mg/dl)	118.79	18.53	85–148.4
HDL-C (mg/dl)	49.32	5.92	35–66
LDL-C (mg/dl)	87.97	19.49	60–140
APACHE II score	11.5	3.78	5–19
Duration of stay in ICU (days)	7	2.55	4–13

APACHE, Acute Physiology and Chronic Health Evaluation; Ca, calcium; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; K, potassium; LDL-C, low-density lipoprotein cholesterol; Mg, magnesium; Na, sodium; QTmaxc, heart rate-corrected maximum QT interval in all measured leads; RBG, random blood glucose; TG, triglyceride; TSH, thyroid-stimulating hormone; WBC, white blood cell.

Discussion

The main results of our study can be summarized that the frequency of QTmaxc interval prolongation without electrolyte imbalance was seen in 46 (63.9%) patients. pH revealed to be the most significant independent risk factor for QTmaxc interval prolongation (odds ratio=8.388, 95% confidence interval: 1.673–18.057) with a cutoff value less than 7.03 with sensitivity 56% and specificity 44%. QTmaxc prolongation carried a relative risk of ~1.7-fold for the development of adverse outcome in patients with DKA.

None of the enrolled patients experienced hypoglycemia, hypokalemia, hypocalcemia, or hypomagnesemia, during DKA treatment, which could account for QTmaxc prolongation, embracing the findings of multiple studies [3,6,9–11]. Therefore, the role of ketoacidosis in causing such prolongation

Table 3 Multivariate logistic regression for Independent predictors of heart rate-corrected maximum QT interval in all measured leads prolongation

	Wald	*P*	OR	95% CI	
				Lower	Upper
pH	5.127	**0.017**	8.388	1.673	18.057
Anion gap (mEq/l)	1.254	0.214	1.012	0.847	1.854
WBC ($\times 10^3$)	0.604	0.437	1.055	0.922	1.207
APACHE II	2.210	0.137	1.098	0.971	1.241

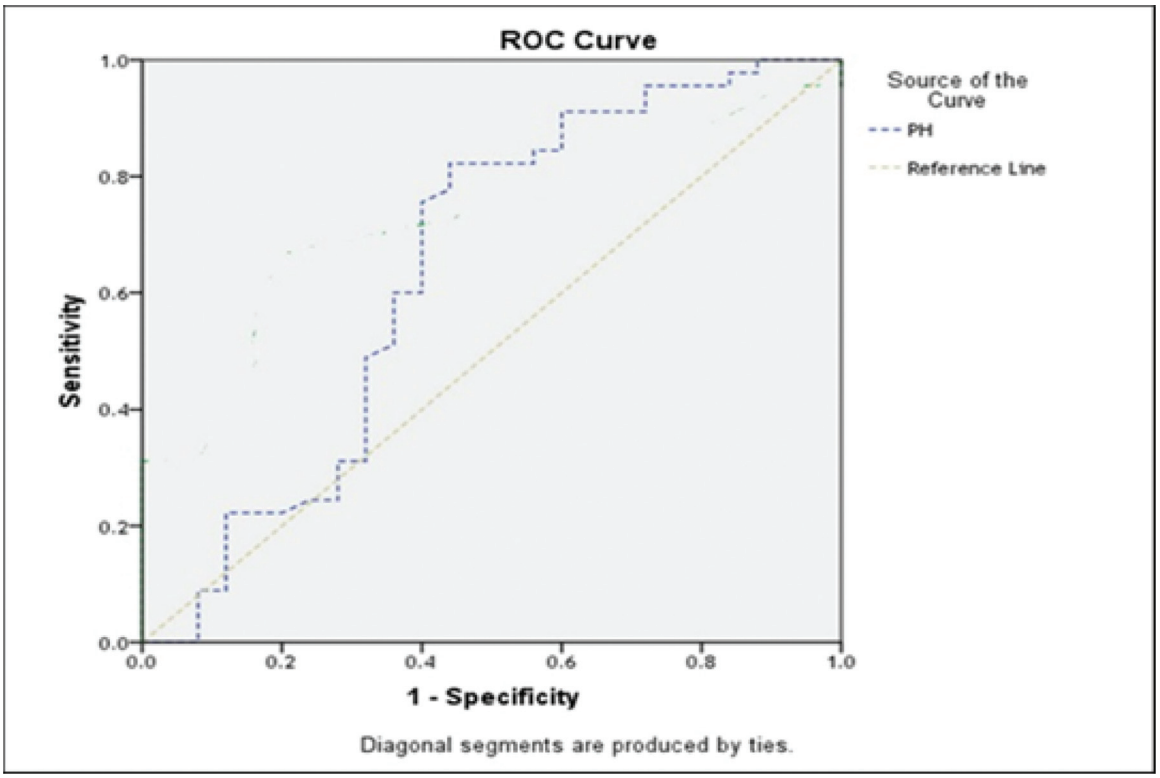
APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; OR, odds ratio; WBC, white blood cell.

Table 2 Comparison between nonprolonged heart rate-corrected maximum QT interval in all measured leads (ms) cases and prolonged ones regarding the laboratory data and Acute Physiology and Chronic Health Evaluation II score at the time of admission

	Nonprolonged (*N*=26) (mean±SD)	Prolonged (*N*=46) (mean±SD)	Student's *t*-test	*P*
RBG (mg/dl)	385.19±68.88	399.25±61.61	0.889	0.377
Serum Na (mEq/l)	140.21±3.88	141.49±5.51	1.044	0.300
Serum K (mEq/l)	4.07±0.35	4.01±0.46	–0.558	0.579
Serum Ca (mg/dl)	9±0.52	9.05±0.71	0.246	0.807
Serum Mg (mg/dl)	2.04±0.32	2.097±0.42	0.660	0.512
Serum creatinine (mg/dl)	0.94±0.27	1.01±0.41	0.807	0.423
pH	7.12±0.11	6.96±0.36	–2.846	**0.006**
Anion gap (mEq/l)	25.64±4.61	33.75±5.15	11.325	<**0.001**
Heart rate (bpm)	75.96±9.7	87.96±20.56	2.798	**0.007**
WBC ($\times 10^3$)	10.29±3.24	13.35±6.91	2.127	**0.037**
C-reactive protein (mg/l)	24±10.995	24.71±12.62	0.202	0.840
HbA1c (%)	9.65±2.31	9.23±2.52	–0.696	0.489
APACHE II	10.35±3.08	12.152±3.999	2.190	**0.030**

APACHE, Acute Physiology and Chronic Health Evaluation; Ca, calcium; HbA1c, glycated hemoglobin; K, potassium; Mg, magnesium; Na, sodium; RBG, random blood glucose; WBC, white blood cell. The bold values means the significant *p* values.

Figure 1



The specificity and sensitivity in the receiver operating characteristic (ROC) curve considering pH as a predictor of mortality.

Table 4 Relative risk of heart rate-corrected maximum QT interval in all measured leads prolongation for adverse outcome in diabetic patients admitted with diabetic ketoacidosis

	Mortality	Favorable outcome	Total
Prolonged QTmaxc	6	40	46
Nonprolonged QTmaxc	2	24	26
Total	8	64	72
Relative risk		6/(6+40)/2/(2+24)=1.6956	

QTmaxc, heart rate corrected-maximum QT interval in all measured leads.

and delayed cardiac repolarization is considered. In contrast, Glaser *et al.* [2] claimed that the prolongation of QTc interval, cardiac arrhythmias, and arrest presumed to be solely attributed to the electrolyte abnormalities during DKA.

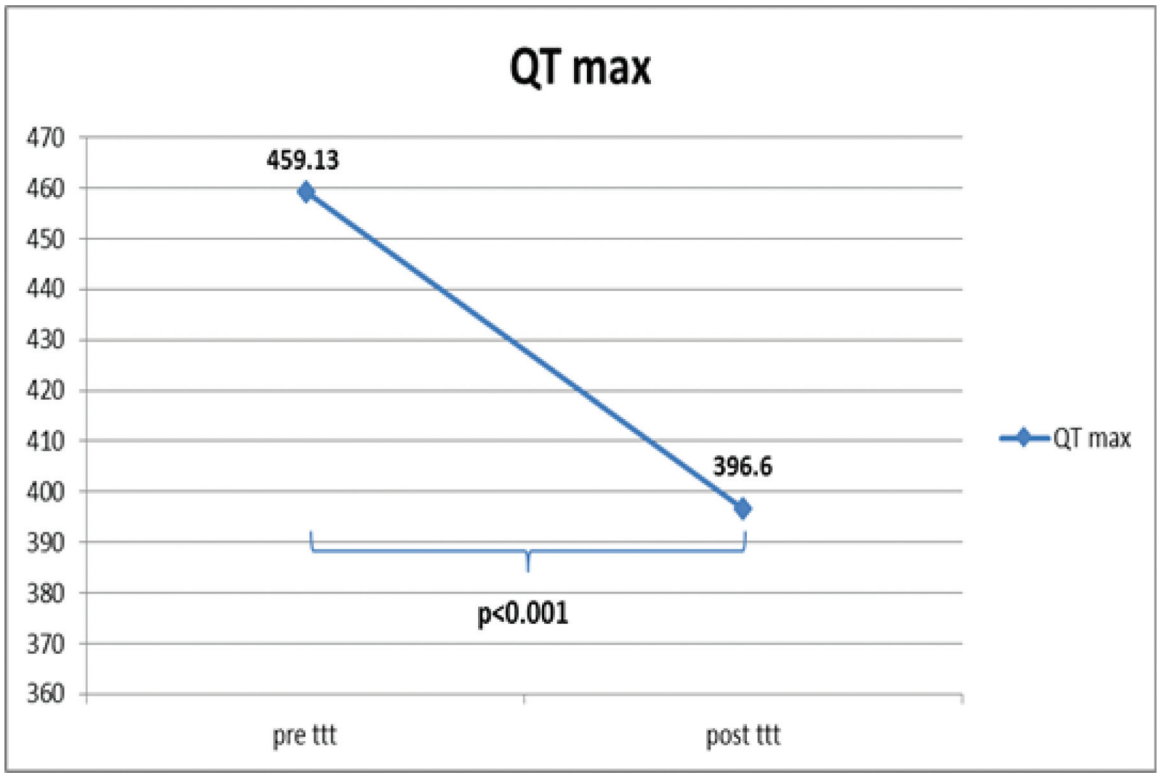
Regarding the heart rate, it had been significantly higher in prolonged QTmaxc cases, which is convenient with the results of Kuppermann *et al.* [3] and Burkett *et al.* [12], which considered the heart rate as a strongest independent variable for QTmaxc prolongation. However, Pearson's correlation in our study abolished this finding and revealed an absence of correlation between QTmaxc and heart rate.

Patients with prolonged QTmaxc in our study had a significantly lower pH at presentation compared with those with nonprolonged QTmaxc values, with a significant positive correlation between QTmaxc and Anion gap, and a significant negative correlation between QTmaxc and pH. The QTmaxc interval prolongation in the current study was significantly decreased ($P<0.001$) with the recovery from DKA in 35 patients; meanwhile, 11 patients had persistent prolonged QTmaxc even after recovery from DKA, which had returned to normal after one week of hospital discharge. This illustrated the effect of acidosis that may precipitate arrhythmias such as re-entry, pulsus alternans, and early/delayed afterdepolarization, supporting the findings of several studies [3,6,9,13].

Leukocytosis, which is common in patients with DKA, was noted in the current study to have a significant positive correlation with QTmaxc. It may not be indicative of an infectious process, particularly when total white blood cell counts are below 25 000. The reason for this elevation has not been established, and leukocytosis more than 25 000 requires further assessment for an underlying infection [14].

We performed a multivariate logistic regression analysis to confirm that pH was a significant independent predictor for QTmaxc prolongation,

Figure 2



The mean pretreatment heart rate-corrected maximum QT interval in all measured leads (QTmaxc) values were significantly decreased after resolution of diabetic ketoacidosis.

with a cutoff value of 7.03, enforcing the results of Adeva-Andany *et al.* [15].

We found a significant positive correlation between QTmaxc prolongation and APACHE II score in our patients. Furthermore, prolongation of QTmaxc increases the relative risk of mortality in diabetic patients with DKA by 1.7-fold, confirming the findings of some studies [16,17].

To our knowledge, the present study is the first to address QTmaxc interval prolongation in adults with DKA, yet we need to compare these results with patients having acidosis owing to other causes, to reach the definite cause of QTc prolongation without electrolytes imbalance: is it the acidosis or ketone bodies?

Therefore, our study concluded that acidosis carries an independent risk for QTmaxc interval prolongation in the absence of electrolytes abnormalities, with a related poor ICU outcome in patients with DKA. We recommend a strict continuous cardiac monitoring during DKA management.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 Zayed H. Epidemiology of diabetic ketoacidosis in Arab patients with type 1 diabetes: a systematic review. Int J Clin Pract 2016; 70:186–195.

2 Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, *et al.* Risk factors for cerebral oedema in children with diabetic ketoacidosis. N Engl J Med 2001; 344:264–269.

3 Kuppermann N, Park J, Glatter K, Marcin JP, Glaser NS. Prolonged QT interval corrected for heart rate during diabetic ketoacidosis in children. Arch Pediatr Adolesc Med 2008; 162:544–549.

4 Suys B, Heuten S, de Wolf D, Verherstraeten M, de Beeck LO, Matthys D, *et al.* Glycemia and corrected QT interval prolongation in young type 1 diabetic patients: what is the relation? Diabetes Care 2006; 29:427–429.

5 Szabo A, Andrássy G. Prolonged QT interval corrected for heart rate during diabetic ketoacidosis in children: psychological stress could be another explanation. Arch Pediatr Adolesc Med 2009; 163:92.

6 Youssef OI, Farid SM. QTc and QTd in children with type 1 diabetes mellitus during diabetic ketoacidosis. ISRN Pediatr 2012; 2012:619107.

7 Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009; 32:1335–1343.

8 Bazett HC. An analysis of the time-relations of electrocardiograms. Ann Noninvasive Electrocardiol 1997; 2:177–194.

9 Best TH, Franz DN, Gilbert DL, Nelson DP, Epstein MR. Cardiac complications in pediatric patients on the ketogenic diet. Neurology 2000; 54:2328–2330.

10 Stevens A, Robinson DP, Turpin J, Groshong T, Tobias JD. Sudden cardiac death of an adolescent during dieting. South Med J 2002; 95:1047–1049.

11 George TK, Chase D, Peter JV, Satyendra S, Kavitha R, George LR, *et al.* Association between a prolonged corrected QT interval and outcomes in patients in a Medical Intensive Care Unit. Indian J Crit Care Med 2015; 19:326–332.

12 Burkett E, Keijzers G, Lind J. The relationship between blood glucose level and QTc duration in the critically ill. Crit Care Resusc 2009; 11:8–13.

13 Orchard CH, Cingolani HE. Acidosis and arrhythmias in cardiac muscle. Cardiovasc Res 1994; 28:1312–1319.

14 Nyenwe EA, Kitabchi AE. The evolution of diabetic ketoacidosis: an update of its aetiology, pathogenesis and management. Metabolism 2016; 65:507–521.

15 Adeva-Andany MM, Fernández-Fernández C, Mouriño-Bayolo D, Castro-Quintela E, Domínguez-Montero A. Sodium bicarbonate therapy in patients with metabolic acidosis. ScientificWorldJournal 2014; 2014:627673.

16 Rossing P, Breum L, Major-Pedersen A, Sato A, Winding H, Pietersen A, *et al.* Prolonged QTc interval predicts mortality in patients with type 1 diabetes mellitus. Diabet Med 2001; 18:199–205.

17 Straus SMJM, Kors JA, de Bruin ML, van Der Hooft CS, Hofman A, Heeringa J, *et al.* Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. J Am Coll Cardiol 2006; 47:362–367.