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ORIGINAL RESEARCH ARTICLE

Prevalence and Risk Factors of Drug-Associated Corrected QT Prolongation in Elderly Hospitalized Patients: Results of a Retrospective Analysis of Data Obtained Over 6 Months

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Abstract

Objectives Little information exists on the frequency and determinants of drug-associated long QT syndrome in older adults. The objectives of this study were to assess the prevalence and identify risk factors of drug-associated long QT syndrome in a population of elderly hospitalized patients.

Methods This was a retrospective study performed over 6 months in hospital geriatric medicine. Various QT-correction equations were fitted to the individual QT-RR data to evaluate the most appropriate equation. Long QT syndrome was defined as corrected QT ≥450 ms. Available data were compared in patients with and without long QT syndrome. Logistic regression and classification and regression tree analysis were performed to identify determinants of long QT syndrome.

Results Thirty-three of 152 patients (22%) exhibited corrected QT ≥450 ms. The different QT correction equations provided similar results, except the Bazett equation. In patients with long QT syndrome, there was a higher proportion of male subjects (58 vs. 33%, $p = 0.009$) and a higher number of QT-prolonging drugs than in patients without long QT syndrome. Male sex (odds ratio, 3.25) and the number of prescribed QT-prolonging agents (odds ratio, 1.77) were significantly associated with the probability of long QT syndrome. The number of QT-prolonging drugs had a stronger influence on the risk of long QT syndrome in men than in women.

Conclusion Male sex was found to be a significant risk factor of corrected QT prolongation in elderly hospitalized patients. The risk also increased with the number of QT-prolonging agents, especially in men. Those findings may help to mitigate the risk of long QT syndrome in elderly patients in clinical practice.

Key Points

Drug-associated long QT syndrome is not rare in older adults: 22% of patients exhibited this effect in this observational study of 152 patients.

Male sex was found to be a risk factor of QT prolongation.

The risk of QT prolongation also increased with the number of QT-prolonging drugs.

1 Introduction

Long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by a prolonged QT interval on the electrocardiogram (ECG) [1, 2]. Long QT interval has

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been associated with an increased risk of the life-threatening ventricular arrhythmia known as Torsades de pointes (TdP). Long QT syndrome can be either congenital or acquired. Drug therapy is most frequent risk factor of acquired LQTS [1–3]. Other reported risk factors of prolonged QT and/or TdP include female sex, advanced age, hypokalemia, history of heart failure, and an additional use of QT-prolonging drugs [1, 4, 5]. However, most of those risk factors have been identified in young subjects.

Many drugs have been reported to cause QT prolongation, including cardiovascular agents (class III anti-arrhythmic agents, diuretics) but also antipsychotics, antidepressants, anti-infectives, antihistamines, and others drugs [6, 7]. Elderly patients are widely exposed to QT-prolonging drugs as they often need multiple drugs for treating several co-morbidities. A recent study performed in a large cohort of more than 130,000 patients in Germany reported that 58.7 and 22.1% of older patients received at least one QT-prolonging drug and two or more of such agents, respectively [8]. Thus, a large number of patients are routinely exposed to QT-prolonging drugs. In addition, geriatric patients are likely to cumulate other known risk factors of drug-induced LQTS and TdP such as bradycardia, hypokalemia, or congestive heart failure. In a large study performed in Columbia, 98% of patients aged older than 65 years who received a QT-prolonging drug also had another risk factor for LQTS or TdP [9].

Because the QT interval increases with an increasing RR interval, and thus with a decreasing heart rate (HR), it is necessary to correct the QT interval to interpret the QT value regardless of HR changes. Many equations have been proposed for QT interval correction [10, 11], the most widely used being the Bazett and Fridericia equations [12, 13]. Little is known about the influence of a QT-correction equation on the identification of corrected QT (QTc) prolongation in elderly individuals.

Clinical management of the risk of QT prolongation in geriatric patients requires prior evaluation of the frequency and identification of risk factors of this problem. However, limited data are available in this group of patients. The objectives of the present study were: (1) to investigate the prevalence of drug-associated QTc prolongation in elderly hospitalized patients; (2) to assess the QT correction for HR provided by various equations; and (3) to identify the determinants of drug-associated LQTS in this group of patients.

2 Methods

2.1 Data Collection

This was a retrospective study based on data collected from 1 January to 30 June, 2013, in a single unit of geriatric medicine of the University Hospitals of Lyon, France. All inpatients with at least one ECG as well as clinical chemistry results [including the most common tests: serum electrolytes (sodium, potassium, chloride, bicarbonate, calcium), blood glucose, serum creatinine] and a full drug prescription at the time of the ECG were included. All data were retrieved from the electronic and paper patient files. As this was a non-interventional study without any additional procedure, no institutional review board or ethics committee approval was required, in accordance with the French regulation on biomedical research (articles L 1121-1 and R 1121-2 of the French Code of Public Health).

All patients underwent standard 12-lead ECG using the same Nihon Kohden Cardiofax M 1350 (Nihon Kohden, Tokyo, Japan) machine. The ECG consistency was checked by a physician at the bedside in all cases. The individual values of HR, QT, and QTc were obtained from the original ECG of each patient, as provided by the machine report, which uses an automated algorithm to determine the T wave end, as described elsewhere [14]. All QT values were double checked by visual examination of the ECG trace using an ECG ruler. The QT interval was measured from the beginning of the QRS complex to the end of the T-wave in the derivation where the QT interval was the most visible.

By default, the corrected QT provided by the machine was calculated based on the ECAPs (Nihon Koden's electrocardiogram analysis program system) equation (QTcE) [14], which is a linear equation as follows:

$$\mathrm{QTcE\ (ms)} = \mathrm{QT(ms)} + [1000 - \mathrm{RR(ms)}]/7.$$

Some patients underwent several ECGs during their hospital stay. Those multiple ECGs ($n = 226$) were only used for the analysis of the QT-RR relationship (see below), while only the first ECG of each patient ($n = 152$) on admission was used for subsequent statistical analysis.

2.2 Analysis of the QT-RR Relationship

We examined the QT-RR relationship by fitting several equations to the observed values of RR and uncorrected QT:

- Bazett equation [12]: $\mathrm{QT} = A_\mathrm{B} \cdot \mathrm{RR}^{1/2}$.
- Fridericia equation [13]: $\mathrm{QT} = A_\mathrm{F} \cdot \mathrm{RR}^{1/3}$.
- Power function: $\mathrm{QT} = A_\mathrm{P} \cdot \mathrm{RR}^{\alpha}$.
- ECAPs equation [14]: $\mathrm{QT} = A_\mathrm{E} + (1/7) \times \mathrm{RR}$.
- Linear equation: $\mathrm{QT} = A_\mathrm{L} + B \times \mathrm{RR}$.

In those regression equations, A_X represents a constant (intercept) to be estimated. In the power and linear regression equations, a second parameter was estimated, the exponent α and the slope B, respectively. Then, we plotted the fitted curve from each equation over the QT-RR scatter plots and calculated the R^2 coefficient of

determination to identify the best fit. All regressions and plots were performed using the MATLAB software (Version 2011b; The MathWorks, Natick, MA, USA). Finally, we compared the proportion of QTc values ≥450 ms obtained with each equation.

2.3 Analysis and Classification of Prescribed Drugs According to QT prolongation risk

For each subject, all the drugs that were administered to the patient at the time of the ECG were retrieved, for each ECG. We used the so-called 'QT drugs lists' proposed by the Arizona Center for Research and Education on Therapeutics to classify drugs according to their QT/TdP risk [15]. There are three risk categories: "known" for drugs that prolong the QT interval and are clearly associated with clinical evidence of TdP even when taken as recommended, "possible" for drugs that can cause QT prolongation but currently lack evidence for a risk of TdP when taken as recommended and "conditional" for drugs associated with TdP but only under certain conditions of their use or by creating conditions that facilitate or induce TdP. Drugs considered without risk by the Arizona Center for Research and Education on Therapeutics were not considered in the analysis.

2.4 Study of Factors Associated with Prolonged Corrected QT and Statistical Analysis

We performed a case–control analysis of drug-associated long QTc. Subjects were divided into two groups according to their QTc value as provided by the machine (i.e., QT corrected with the ECAPs equation, QTcE) on admission. Prolonged QTcE interval was defined as QTcE ≥450 ms, in accordance with the US Food and Drug Administration guidance for thorough QT/QTc studies [16]. The case group included patients with QTcE ≥450 ms, while the control subjects were defined as QTcE <450 ms.

Then, we compared the demographic, biological, clinical, and therapeutic characteristics of patients between the case and the control groups. Continuous variables were compared using the Mann–Whitney test, while categorical variables were compared using the Chi-squared test or the Fisher exact test (in case of $n < 5$). Statistical significance was set at a p value <0.05 for all comparisons.

The influence of available variables on the probability of prolonged QTcE (i.e., QTcE ≥450 ms) was analyzed by univariate and multivariate logistic regression using the Statview software (Version 5.0; SAS Institute Inc., Cary, NC, USA). Variables were introduced in the regression as continuous, categorical, or both for clinical chemistry and drug therapy data. The influence of each variable was assessed by the estimated odds ratio (OR) along with its confidence interval, and the likelihood ratio test that evaluates the influence of the variable on the goodness of fit of the statistical model. Statistical significance was set at 5% in the univariate analysis. Variables that were significant in the univariate analysis were then tested in a multivariate model. The final model was identified by backward deletion, using again the likelihood ratio test as goodness-of-fit criterion. Statistical significance was set at 0.025 in the final model selection.

We then used classification and regression tree (CART) analysis within the MATLAB software (Version 2011b; The MathWorks) to identify variables that were the most predictive of QTcE prolongation. Only the variables identified as significant in the multivariate logistic regression were used in the CART analysis as predictors to create a decision tree for predicting the outcome, i.e., QTcE ≥450 ms, as a function of those predictors. CART analysis is a nonparametric data mining and machine-learning approach. It is a binary partitioning technique, splitting predictors at nodes into two groups of maximum homogeneity. The partitioning is done automatically through all possible predictors and values to identify the most significant variables and the optimal cut-off value for continuous variables at each node. CART analysis was performed within the MATLAB software. We set a minimal number of observations per tree leaf of five. Pruning was set on to compute the full tree and the optimal sequence of pruned subtrees. The Gini's diversity index was used as a criterion for optimal splitting. In addition, the Fisher exact test was used to compare the rates of prolonged QTc and to derive ORs associated with the tree nodes produced by the CART analysis.

3 Results

A total of 210 medical files were initially retrieved over the 6-month period. Fifty-eight subjects were excluded because ECGs were not available in the patients' file. A total of 152 subjects were included, and 226 ECGs were available from these patients. There were 52 values of QTcE ≥450 ms (23%, including eight values >500 ms) and 174 QTcE < 450 ms among the 226 ECGs. There was a similar proportion of prolonged QTcE in the subset of ECGs obtained on admission, 33 of 152 subjects [22%, including six values (4%) >500 ms]. No patient experienced TdP during the study.

Characteristics of patients with and without QTcE ≥450 ms are summarized in Table 1. In the case group, there was a greater proportion of male subjects. Additionally, patients with prolonged QTcE had significantly higher body weight, lower HR, lower rate of atrial fibrillation, and a higher number of QT-prolonging drugs than patients with normal QTcE.

Table 1 Comparative characteristics of patients with and without prolonged corrected QT (QTc) on admission

Variable[a]	Patients with QTc <450 ms ($n = 119$)	Patients with QTc ≥450 ms ($n = 33$)	P-value[b]
Number of female/male subjects (% female)	80/39 (67%)	14/19 (42%)	0.009
Age (years)	86 ± 6	88 ± 5	0.07
Body weight (kg)	65 ± 15	71 ± 15	0.05
Serum creatinine (μmol/L)	98 ± 57	110 ± 56	0.19
Serum potassium (mmol/L)	3.8 ± 0.5	3.8 ± 0.5	0.64
Serum calcium (mmol/L)	2.3 ± 0.2	2.3 ± 0.3	0.26
Uncorrected QT (ms)	383 ± 37	463 ± 40	<0.0001
QTc (ms, ECAPs formula)	414 ± 22	480 ± 26	<0.0001
Heart rate (bpm)	80 ± 18	72 ± 17	0.04
Bradycardia (heart rate <60 bpm)	11 (9%)	6 (18%)	0.26
History of heart failure	2 (2%)	2 (6%)	0.21
Sinus rhythm on ECG	79 (66%)	12 (36%)	0.002
History or ECG signs of atrial fibrillation	39 (33%)	17 (52%)	0.05
Number of prescribed QT-prolonging drugs	0.8 ± 0.8	1.1 ± 0.8	0.02

Continuous variables are given as mean ± standard deviation, other variables are given as numbers and percentages

ECAPs electrocardiogram analysis program system, *ECG* electrocardiogram

[a] Body weight was not available for one patient in the prolonged QTc group. Serum calcium was available for 101 and 31 patients in the normal and prolonged QTc groups, respectively

[b] The Mann–Whitney test was used for continuous variables, while the Chi-squared test or the Fisher exact test (in the case of $n < 5$) was used for categorical variables

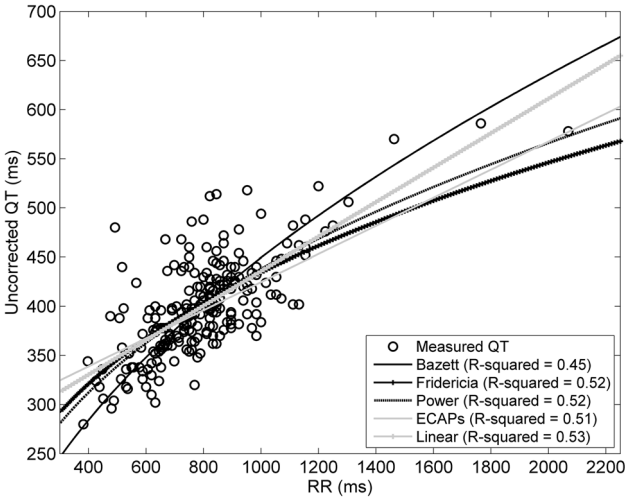

Fig. 1 Scatter plot of QT and RR pairs and the fit of various QT-correction equations. The *circles* indicate the values of uncorrected QT and RR observed in the 226 electrocardiograms (152 patients). The *curves* indicate the regression obtained with the various QT-correction equations. The estimated exponent (α) and slope (B) parameters of the power and linear equations were 0.37 and 0.18, respectively. *ECAPs* electrocardiogram analysis program system

Figure 1 shows the scatter plot of uncorrected QT and RR paired values observed in the 226 ECG (152 patients), as well as the fit of the data regression obtained with the different QT-correction equations. The Fridericia, power, ECAPs, and linear equations provided a very similar fit, while the Bazett equation appeared to be the least appropriate fitting method. No method provided a very good fit, suggesting that RR (or HR) only explains part of the variability of the QT, whatever the assumed QT-RR relationship was. The number of QTc values ≥450 ms obtained were 102, 59, 64, 52, and 60 for the Bazett, Fridericia, power, ECAPs, and linear equations, respectively. Thus, the Bazett equation would have identified substantially more prolonged QTc than any other equation. The proportions of prolonged QT identified by all equations except Bazett were not significantly different ($p = 0.63$, Chi-squared test). Because the ECAPs equation provided results similar to those from other equations except Bazett's, and because this was the reference equation in the ECG machine used, we decided to keep the QT values corrected by the ECAPs equation (denoted QTcE) in the subsequent analyses.

A majority of patients were prescribed at least one QT-prolonging agent at the time of the first ECG: 94 out of 152 patients (61.8%). In detail, 58 (38.2%), 67 (44%), 22 (14.5%), 4 (2.6%), and 1 (0.7%) patients were prescribed zero, one, two, three, and four QT-prolonging agents, respectively. The proportions of patients with at least one QT-prolonging drug were similar in male (32/58, 55%) and female patients (62/94, 66%). Table 2 displays the number, therapeutic class, and risk category of QT-prolonging drugs prescribed in the 152 patients at the time of the first ECG. There were a total of 127 prescriptions of QT-prolonging drugs. The top five of the most prescribed QT-prolonging

Table 2 Prescribed QT-prolonging drugs stratified by risk and therapeutic use

Drugs	Number of prescriptions	QT risk category[a]
Cardiovascular	61 (48%)	
Furosemide	31	Conditional
Hydrochlorothiazide	9	Conditional
Indapamide	3	Conditional
Amiodarone	8	Known
Nicardipine	7	Possible
Ivabradine	1	Conditional
Flecainide	2	Known
Psychiatric		
Antidepressants	39 (31%)	
Escitalopram	20	Known
Venlafaxine	5	Possible
Paroxetine	3	Conditional
Citalopram	1	Known
Fluoxetine	1	Conditional
Sertraline	2	Possible
Antipsychotics		
Risperidone	5	Possible
Clozapine	1	Possible
Olanzapine	1	Possible
Anti-infectives	15 (12%)	
Ofloxacin	8	Possible
Ciprofloxacin	2	Conditional
Fluconazole	2	Conditional
Levofloxacin	2	Possible
Clarithromycin	1	Known
Others	12 (9%)	
Alfuzosine	6	Possible
Domperidone	4	Known
Galantamine	2	Conditional

Known risk, $n = 36$ (28%); possible risk, $n = 37$ (29%); conditional risk, $n = 54$ (43%)

[a] Risk categories as defined by the Arizona Center for Education and Research in Therapeutics [15]

drugs was as follows: furosemide (conditional risk) > escitalopram (known risk) > hydrochlorothiazide (conditional risk) > amiodarone (known risk) = ofloxacine (possible risk). The three most frequently prescribed drugs with known risk were escitalopram, amiodarone, and domperidone.

Results from the logistic regression analysis are shown in Table 3. In the univariate analysis male sex, increasing body weight, and number of QT-prolonging drugs were significantly associated with an increased risk of QTcE prolongation. The influence of drugs was also significant when the variable was introduced as a categorical variable, a number of QT-prolonging drugs (≥2) being associated with a 2.6-fold greater risk of prolonged QTcE. Of note, none of the serum electrolyte levels was found to influence QTcE prolongation. In the multivariate analysis, only male sex and the number of prescribed QT-prolonging agents were found to independently influence the probability of the outcome, with an estimated OR of 3.25 and 1.77, respectively.

The CART analyses provided additional results regarding the relative importance of these two variables (sex and number of QT-prolonging drugs) and the differential effects of QT-prolonging drugs in each sex. The tree is shown in Fig. 2. Sex was found to be the most important predictor of QTcE prolongation, with men having a greater proportion of this outcome than women (32.8 vs. 14.9%, $p = 0.01$). This was in accordance with findings from descriptive statistics and logistic regression. Yet, the influence of the number of QT-prolonging drugs on LQTS risk appeared to be different in men and women. In men, the prescription of at least one QT-prolonging drug was associated with a significant increase in the risk of QT-prolongation compared with no QT-prolonging drug: 46.9 vs. 15.4% [$p = 0.01$; OR = 4.7, 95% confidence interval 1.2–23.2, Fisher exact test for count data]. The prescription of at least two QT-prolonging drugs also appeared to increase the risk compared with only one agent based on the observed proportions (66.7 vs. 39.1%), but the difference was not statistically significant, probably because of the scarcity of data ($p = 0.24$, OR = 3.00, 95% confidence interval 0.49–23.5, Fisher exact test for count data). In women, the risk of QTc prolongation seemed to increase when at least two QT-prolonging drugs were prescribed: 22.2% of women with at least two agents had QTcE ≥450 ms compared with 13.2% of women with zero or one agent. However, this difference was not statistically significant ($p = 0.46$). By contrast with men, the proportions of QTcE prolongation were not different between women who were prescribed zero and one QT-prolonging drug.

4 Discussion

Although considered as rare, drug-induced LQTS and TdP are important safety issues for clinicians, drug companies, and regulatory agencies [17]. The QT interval increases with age [18], and elderly patients are common users of QT-prolonging drugs [8, 9]. Thus, elderly patients have a special risk of this adverse drug reaction. It is desirable to quantify this risk and identify risk factors in this special population. Our study provided several original findings on this question.

First, we found that drug-associated LQTS was relatively frequent in elderly hospitalized patients, as more than one-fifth of patients (22%) presented with QTcE

Table 3 Logistic regression analysis of determinants of QTcE ≥450 ms

Variable	OR	95% CI	*P* value[a]
Univariate analysis			
Male sex	2.78	1.26–6.13	0.01
Age	1.07	1.00–1.15	0.06
Body weight	1.03	1.00–1.06	0.04
Serum creatinine	1.00	1.00–1.01	0.31
Serum potassium	0.91	0.43–1.96	0.82
Hypokalemia[b]	0.80	0.33–1.95	0.62
Serum calcium	0.57	0.08–4.00	0.56
Hypocalcemia[c]	1.67	0.7–3.97	0.25
History or ECG signs of atrial fibrillation	2.18	1.00–4.77	0.051
Bradycardia (heart rate <60 bpm)	2.18	0.74–6.43	0.17
History of heart failure	3.74	0.51–27.6	0.21
Number of QT-prolonging drugs	1.59	1.00–2.51	0.047
At least one QT-prolonging drug	2.26	0.94–5.44	0.057
At least two QT-prolonging drugs	2.61	1.06–6.43	0.04
Multi-variate analysis			
Male sex	3.11	1.29–7.51	0.01
Body weight	1.02	0.99–1.05	0.25
Number of QT-prolonging drugs	1.87	1.14–3.06	0.01
Final model			
Male sex	3.25	1.43–7.41	0.004
Number of QT-prolonging drugs	1.77	1.10–2.85	0.019

CI confidence interval, *ECG* electrocardiogram, *OR* odds ratio

[a] Likelihood ratio test

[b] Defined as serum potassium <3.5 mmol/L

[c] Defined as serum calcium <2.2 mmol/L

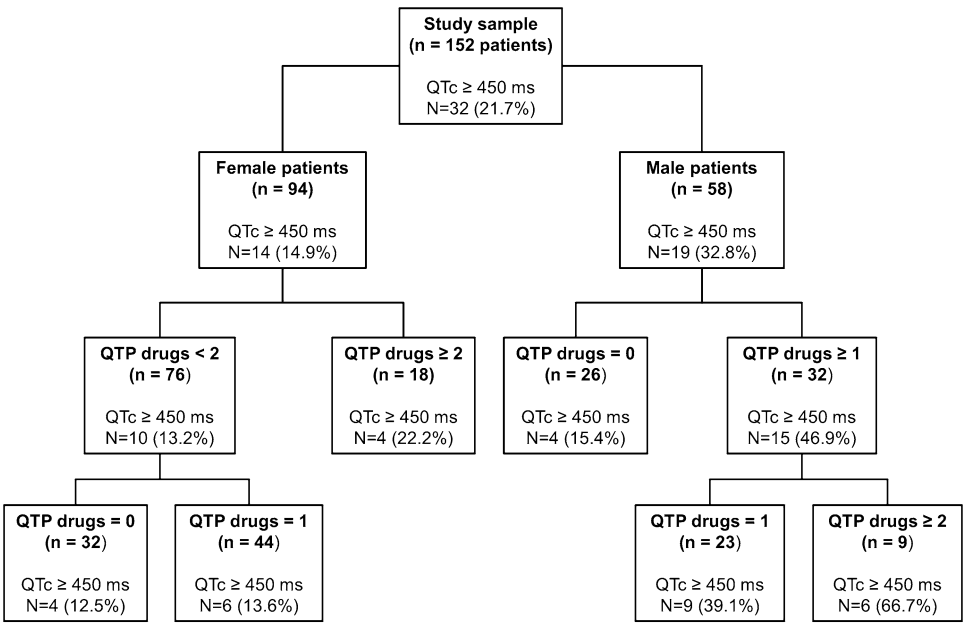

Fig. 2 Influence of sex and the number of prescribed QT-prolonging drugs (QTP drugs) on the outcome (QTcE ≥450 ms) as estimated from classification and regression tree analysis. *QTc* corrected QT

≥450 ms on admission. In a study conducted in a tertiary hospital in Canada, patients with QTc prolongation (defined as QTc >500 ms or a 60-ms increase from the baseline) were significantly older than patients without QTc prolongation [3].

Second, this study shows that the equation used for adjusting QT for HR may have an influence on QTc assessment and the identification of LQTS. The Bazett equation was found to be the least appropriate equation for QT correction in this elderly population, while the other linear and power functions evaluated provided comparable results. The use of the Bazett equation was associated with a proportion of QTc ≥450 ms larger than that obtained with any other equation. Many studies have compared various methods for correcting the QT for HR, and the Bazett equation has often been criticized for its poor performance in fitting the QT-RR relationship and providing rate-independent QTc values [10, 19, 20]. Our study results confirm that the use of the Bazett equation should be discouraged in elderly patients. As QTc is often provided directly by the ECG machine, clinicians should be aware of the equation used by default, and select the most appropriate equation for their patients. Although the use of QT-correction equations is convenient in clinical practice, thorough electrophysiology studies have shown that no universal equation exists. The QT-RR relationship is highly individual and any QT-correction equation only provides an average population-based adjustment, and does not adjust the QT for other determinants [10, 19].

Next, this study confirmed that elderly patients are often prescribed drugs with risks of prolonged QT and TdP. More than six of ten patients (61.8%) were prescribed at least one drug with a risk, and 17.8% received two or more QT-prolonging drugs. Those results are remarkably consistent with those from a recent large German cohort study, which found that 58.7 and 22.1% of elderly patients were prescribed one and two or more QT-prolonging drugs, respectively [8]. We also found that a limited number of drugs accounted for most of the prescribed QT-prolonging agents in patients with LQTS. The five most prescribed QT-prolonging drugs, namely furosemide, escitalopram, hydrochlorothiazide, amiodarone, and ofloxacin accounted for approximately 60% of prescriptions of QT-prolonging drugs (76 out of 127). This is also consistent with the German study results, which also reported that only 20 drug–drug combinations accounted for more than 90% of co-prescriptions of drugs with risk [8]. This suggests that a special focus on a limited number of drugs could be very relevant in the clinical management of the risk of drug-associated LQTS. Diuretics are widely prescribed drugs with risk of LQTS. While the risk of QT prolongation associated with the use of diuretic drugs such as furosemide and hydrochlorothiazide is considered to be low and related to electrolyte imbalance, several studies have reported the use of diuretics as an independent risk factor for LQTS or TdP [4, 21].

Male sex was found to be a significant predictor of QTc prolongation. As female sex has been frequently reported as a risk factor of LQTS and TdP in most publications, one may be surprised by this result at first sight. However, there is epidemiological and physiological evidence that could explain this finding. As reported elsewhere, the mean QTc interval is longer in adult women than in adult men, and this sex difference holds true from adolescence until the sixth decade [18, 22]. However, this difference tends to vanish in patients aged over 60 years. While the QTc still increases with increasing age in the elderly, the slope appears to be greater in men and the men's curve almost crosses the women's curve in patients aged over 80 years [22]. Sex hormones, especially testosterone, appear to be the major cause of these sex- and age-related patterns of QTc variation. Several studies have confirmed that differences in QTc correlated with testosterone levels [23–25]. Testosterone appears to modify the dynamics of cardiac ion channels. Testosterone and changes in its levels over a lifetime explain well both the sex difference and the age-related pattern of the QTc profile. While the QTc is not different in young boys and girls, the QTc decreases in adolescent boys, but not in girls. The age difference is significant in adults, but progressively decreases in elderly patients, in relation to hormonal aging [22]. This phenomenon should result in a similar risk of QTc prolongation in octogenarian men and women, but not an increased risk in men.

We further examined the risk profile of QT-prolonging drugs prescribed in women and men, as an imbalanced use of drugs with a higher risk of QT prolongation might have explained this sex difference. We calculated the proportion of women and men who received at least one drug with a known and possible risk of TdP/LQTS. Actually, women were prescribed more drugs with known and possible risks than men: 43 of 96 (45%) vs. 19 of 58 (33%). Thus, the greater risk of QT prolongation observed in men was not related to a greater use of high-risk drugs and remains unexplained. Further research is needed to clarify this point.

The probability of prolonged QT was found to increase with the number of prescribed QT-prolonging agents. This result was expected and it is in accordance with previously published results [3, 4]. The OR for the number of QT-prolonging drugs estimated by logistic regression was 1.77 (95% confidence interval 1.10–2.85), which means that each addition of a QT-prolonging drug is associated with a 1.8-fold increase in the risk of LQTS, regardless of sex. However, the CART analysis suggested that the influence of QT-prolonging drugs was somewhat different in men

and women. Men appeared to be more sensitive to the effect of QT-prolonging drugs on QTc prolongation. The use of at least one QT-prolonging agent was associated with a significant 4.7-fold increase in the rate of QTc ≥450 ms in men, while this seemed to have no significant effect in women. To our knowledge, this is the first study showing a sex difference in the effect of drugs on QT prolongation in the elderly. The reason for this potential sex difference in older subjects is unclear. Using a mathematical model of cardiac ion channels, Gonzalez et al. have shown that, in conditions of reduced repolarization reserve and treatment by a QT-prolonging agent (dofetilide), young male cardiac cells had longer action potentials and higher susceptibility to early after depolarization than young female cardiac cells [26]. We may hypothesize that such conditions might also occur in the elderly. In addition, the influence of another variable not observed in this study cannot be ruled out and might explain this apparent sex difference. This is an area for further research.

This study has a number of limitations. It was performed in a limited number of elderly hospitalized patients in a single medical unit. Thus, the generalizability of the results is uncertain. However, such a design had the advantage of reducing inter-individual variability in ECG measurements. We did not investigate the presence of congenital LQTS in the study population. Congenital LQTS is uncommon, with an estimated prevalence of 1/2500 [27]. Although such a condition was not retrieved in any patient's file, it cannot be totally ruled out.

Pre-admission and post-discharge ECGs were not available. It has been shown that QTc values were significantly greater on hospital admission compared with before and after hospitalization [3]. This may be owing to reduced repolarization reserve caused by acute illnesses. This suggests that the risk of QTc prolongation may be reduced in an outpatient setting.

Regarding the analysis of the QT-RR relationship, only a few QT-RR paired values were available for each patient. As highlighted in previous studies [19], this precludes a thorough analysis of the true individual QT-RR relationships. The conditions of ECG and QT values collection were not fully standardized, which may introduce variability in the results. However, these bedside conditions are closer to the routine clinical practice of ECG monitoring and QTc assessment. We did not integrate the risk level of QT-prolonging drugs or the drug dose in our analysis because of the limited sample size and lack of data on the relationship between drug dose and QT prolongation, respectively.

The ECAPs equation was used as the reference for QTc calculation in this study. While this equation has been rarely used in previous studies, it provided results comparable to those from other equations, except the Bazett formula. Many equations have been proposed and there is no general agreement regarding the equation to be used. Additionally, we used 450 ms as the cut-off for defining prolonged QTc. Although this threshold has been recommended by the US Food and Drug Administration [16], this remains somehow arbitrary. There is no consensus regarding how long is too long for QTc. The classical approach relies on the statistical analysis of QTc distribution and the use of some upper quantiles as cut-off values [22]. Another approach is the use of a QTc cut-off associated with clinical events. In a previous study, we identified that an uncorrected QT value of 550 ms was the optimal predictor of TdP in elderly patients [28]. However, defining a value associated with negligible risk is challenging because of limited data on cardiac events and the potential influence of other determinants on the risk.

5 Conclusion

In this study performed in elderly hospitalized patients, 22% of patients had a QTc interval ≥450 ms. Male sex and the number of prescribed QT-prolonging drugs were significantly associated with the probability of QTc prolongation. The use of at least one QT-prolonging agent was associated with a significant increase in the risk of QTc ≥450 ms in men. Those findings may help to mitigate the risk of QTc prolongation in clinical practice, as these risk factors are easily identifiable.

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Compliance with Ethical Standards

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Conflict of interest Ophélie Maison, Blandine de la Gastine, Laurent Dayot, and Sylvain Goutelle declare they have no conflicts of interest that might be directly relevant to the contents of this manuscript.

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