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Randomized, Double-Blind, Crossover Study to Investigate the Effect of Rivaroxaban on QT-Interval Prolongation

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Abstract

Background: Rivaroxaban (BAY 59-7939) is a novel, oral, direct Factor Xa inhibitor in advanced clinical development for the prevention and treatment of thromboembolic disorders. Unwanted pro-arrhythmic effects are a common reason for drugs failing to gain regulatory approval; these properties can be detected by assessing the effect of the drug on the QT interval.

Objective: This study was performed, in accordance with International Conference on Harmonisation (ICH) E14 guidance, to assess whether rivaroxaban prolongs the QT interval.

Study design: This was a prospective, randomized, double-blind, double-dummy, four-way crossover study.

Setting: The study was conducted at a clinical pharmacology research unit.

Subjects: Healthy male and female subjects (n = 54) aged ≥50 years were enrolled and remained in the study unit for 3 days for each treatment. Of these, 50 patients were eligible for the QT analysis.

Intervention: Subjects received single oral doses of rivaroxaban 45 mg or 15 mg, moxifloxacin 400 mg (positive control), or placebo.

Outcome measures: Multiple ECGs were taken at frequent intervals after drug administration, and the QT interval was measured manually under blinded conditions at a central laboratory. The Fridericia correction formula (QTcF) was used to correct the QT interval for heart rate. The primary outcome was the effect of rivaroxaban or moxifloxacin on the placebo-subtracted QTcF 3 hours after administration. The frequency of outlying QTcF values and the tolerability of the treatments were also assessed.

Results: All treatments were well tolerated and had no effect on heart rate. Moxifloxacin established the required assay sensitivity; placebo-subtracted QTcF 3 hours after moxifloxacin administration was prolonged by 9.77 ms (95% CI 7.39, 12.15). Placebo-subtracted QTcF values 3 hours after rivaroxaban administration were −0.91 ms (95% CI −3.33, 1.52) and −1.83 ms (95% CI −4.19, 0.54) with rivaroxaban 45 mg and 15 mg, respectively. QTcF was not prolonged with rivaroxaban at any time, and the frequency of outlying results with rivaroxaban and placebo was similar.

Conclusion: This thorough QT study, which was performed in accordance with ICH E14 guidelines, shows that rivaroxaban does not prolong the QTc interval. Therefore, the potential of rivaroxaban for the prevention and treatment of thromboembolic disorders, including chronic cardiovascular disorders, can be investigated in appropriate clinical studies without the need for intensive monitoring of the QTc interval.

Background

Anticoagulant therapy is recommended for patients with chronic cardiovascular disorders, including atrial fibrillation and acute coronary syndromes for the prevention of stroke and myocardial infarction, respectively. Currently, vitamin K antagonists (e.g. warfarin) are the only recommended long-term anticoagulant therapy for patients with atrial fibrillation who are at high risk of stroke, and for patients with acute coronary syndromes who are at a particularly high risk of thromboembolic events.[1,2] Warfarin has various drawbacks, including a narrow therapeutic window, the need for frequent monitoring and numerous drug and food interactions.[3] Therefore, an oral anticoagulant with no major food or drug interactions and no requirement for monitoring would represent a considerable advance.[4]

Rivaroxaban (BAY 59-7939), a small molecule, is an oral, direct Factor Xa inhibitor in advanced clinical development for the prevention and treatment of thromboembolic disorders, including venous thromboembolism, and the prevention of stroke in patients with atrial fibrillation. *In vitro* and *in vivo* studies have shown that rivaroxaban has no effect on the human ether-a-go-go related gene (hERG) ion channel or on the shape of the action potential in rabbit Purkinje fibres, as well as no QT interval-prolonging effect on cardiovascular or ECG parameters in anaesthetized dogs.[5] Rivaroxaban has predictable, dose-proportional pharmacokinetics and pharmacodynamics and has been shown to be well tolerated in studies in healthy subjects, with no effect on heart rate or ECG parameters.[6,7] In recent clinical studies, rivaroxaban compared favourably with standard therapy for the prevention of venous thromboembolism after major orthopaedic surgery, and the treatment of deep vein thrombosis.[8-12] Large-scale, pivotal clinical studies of rivaroxaban for the prevention and treatment of venous thromboembolism and stroke prevention in patients with atrial fibrillation are ongoing.

Unexpected effects on cardiac repolarization are a major cause of novel drugs (not developed as antiarrhythmics) failing to gain regulatory approval, or for their withdrawal subsequent to approval. If a drug delays cardiac repolarization, it can lead to arrhythmias such as torsades de pointes (TdP), or other ventricular tachyarrhythmias. TdP can degenerate into ventricular fibrillation and, occasionally, sudden death. The effect of a drug on cardiac repolarization can be measured on an ECG as the time from the beginning of the Q-wave to the point where the T-wave returns to the isoelectric point (QT interval).[13] Numerous frequently prescribed drugs have a QT-prolonging effect, and may carry a risk of TdP; these drugs include antibacterials, such as erythromycin[14] and clarithromycin,[15] and antipsychotics, such as chlorpromazine[16] and haloperidol.[17] Furthermore, the antihistamine drugs terfenadine and astemizole have caused several sudden cardiac deaths associated with TdP when taken concomitantly with cytochrome P450 inhibitors (e.g. ketoconazole), which delay their metabolism, causing an increase in plasma drug concentrations.[18]

To address the problems associated with QT-prolonging effects of novel drugs, the International Conference on Harmonisation (ICH) guidance notes now recommend that this parameter is assessed in a dedicated clinical study early in the drug's development.[19] This may be done by measuring the effect of the drug on the QT interval, and, if a QT-prolonging effect is found, this parameter needs to be scrutinized closely in subsequent trials, along with occurrences of TdP. Although a QT-prolonging effect is currently the best available predictor of the risk of

drug-induced TdP, it is not completely reliable; therefore, the incidence of TdP and other cardiovascular adverse events should always be monitored in large-scale clinical studies.[20]

The QT interval corrected for heart rate (QTc) is a frequently used and validated method of assessing cardiac repolarization. The ICH guidance notes make several recommendations about the design of a thorough QTc study, including that the study should be randomized, double-blind, placebo-controlled and have a positive control.[19] Furthermore, it should be performed in healthy subjects, unless taking the drug would put them at unacceptable risk, and use a dose of the study drug that is higher than the likely clinical dose. This is in order to replicate circumstances that could occur if an unforeseen drug interaction caused an increase in plasma concentrations of the novel drug (e.g. as occurred with terfenadine and ketoconazole). This prospective study, designed in accordance with ICH E14, was performed with the dedicated aim of assessing whether rivaroxaban prolonged the QTc interval in healthy male and female subjects aged ≥50 years.

Materials and Methods

Subjects and Study Design

This was a single-centre, randomized, double-blind, double-dummy, four-way crossover study, conducted in accordance with the Declaration of Helsinki, and with the approval of the local ethics committee. The study was conducted at the Clinical Pharmacology Research Unit of PAREXEL International GmbH, Berlin, Germany.

Healthy male and female subjects were enrolled. Inclusion criteria included age ≥50 years old and normal body mass index (between 20 kg/m^2 and 32 kg/m^2). Subjects of this age were chosen because older patients are more likely to receive treatment with rivaroxaban. Female subjects had to be postmenopausal for >2 years or otherwise unable to become pregnant. Other exclusion criteria included: baseline QTc interval ≥440 ms, history of TdP, presence of familial long-QT-syndrome, high or low blood pressure (BP) [systolic BP <100 mmHg or >150 mmHg or diastolic BP >95 mmHg] and recent (within the last 8 weeks before the start of the study) blood donation or blood loss.

Potential subjects were screened approximately 2 weeks before commencement of the study. Enrolled subjects underwent four treatment periods: placebo, moxifloxacin 400 mg, rivaroxaban 45 mg and rivaroxaban 15 mg, in a randomized order. Each treatment period took place in-house and comprised 1 treatment day and 2 follow-up days. Study drugs were administered at 8:00 am on the treatment day with a standardized breakfast, after an overnight fast. Subjects were discharged between treatment periods, which were separated by at least 7 days, and returned for an end-of-study examination 7–14 days after the last treatment period.

The rivaroxaban doses selected for this study were chosen in accordance with ICH E14 guidance notes:[19] a previous study in healthy subjects showed that single doses of rivaroxaban of 5–60 mg had relevant pharmacodynamic effects,[7] and the 15-mg dose chosen for this study was confirmed to be clinically relevant in phase IIb studies of rivaroxaban in which a 5- to 20-mg total daily dose was clinically effective.[8,9] ICH E14 also suggests using multiples of the clinically relevant dose;[19] therefore, a 45-mg dose was also tested. A placebo control and a positive control that prolongs the QTc interval by approximately 5 ms are also recommended by ICH E14. The positive control in this study was moxifloxacin 400 mg, which has been shown to have QTc-prolonging effects of the appropriate magnitude.[21]

Study Assessments

ECGs

Subjects rested in the supine position for at least 45 minutes before drug administration. Multiple 12-lead ECG readings were taken at the time of drug administration (time 0, baseline) and at 0.5, 1, 2, 3, 4, 5, 6, 24 and 48 hours thereafter (three ECGs per timepoint, approximately 1 minute apart). Baseline readings were taken at the start of each treatment period. Subjects remained supine for 4 hours post-

administration. ECGs were examined for clinically relevant abnormalities by the investigating physician on the day of recording. All ECGs were transferred electronically to a separate centre for blinded, manual, central adjudication by one cardiologist. For each of the three ECGs taken at each timepoint, the QT interval was measured manually on-screen from three consecutive QRST complexes and averaged. Readings from lead-II were the first choice; however, if this was not possible, readings from lead-V2, and then lead-V5, were used.

The QT interval was defined as the time interval from the earliest onset of the Q wave (or RS complex, if the Q wave was not visible) to the latest offset of the T wave (the time of return to the isoelectric line). The ECG-related heart rate was calculated from the interval between the peaks of two consecutive QRS complexes (RR interval). The Fridericia correction formula for heart rate ($QTcF = QT/RR^{1/2}$) was applied to calculate QTcF – the basis of the primary analysis. Mean values for QTcF from each of the three ECGs were calculated for each timepoint. Individual corrections for heart rate were also performed (QTcI) based on log-linear regression modelling of QT and RR. All pre-dose values and post-placebo values for each subject were used to fit an individual log-regression model (equation 1):

$$1n(QT) = a + b \times 1n(RR) \quad \text{(Eq. 1)}$$

where a = the intercept of the straight line with the y-axis, b = the slope of the straight line and RR = 60/heart rate. QTcI was then calculated using the formula QT/RR^b.

The following variables for each treatment were analysed and formed the secondary analyses: QTc 3 hours after administration (including moxifloxacin in the analysis), QTc at t_{max} (the time to reach maximum plasma concentration [C_{max}] of the rivaroxaban 45 mg dose), mean of all post-administration QTc measurements (time-averaged QTc), the longest prolongation of all post-administration QTc measurements regardless of when it occurred (mean readings were calculated at each timepoint) and the drug plasma concentration at that time. For each of these variables, the absolute change from baseline was calculated by subtracting the baseline value from the measurement at the post-administration timepoint of interest (or at each timepoint for the mean of post-administration measurements).

Pharmacokinetics

Plasma concentrations of rivaroxaban and moxifloxacin were determined at the time of drug administration and 0.5, 1, 2, 3, 4, 5, 6 and 24 hours afterwards. Rivaroxaban was quantified using a fully validated high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) assay after solid-phase extraction from plasma using C_{18} cartridges. Samples above the lower limit of quantification (LLOQ; 0.5 μg/L) were determined with an accuracy of 94.8–103% and a precision of 7.28–12.5%. Plasma moxifloxacin concentrations were determined by gradient microbore HPLC with fluorescence detection after protein precipitation using an acetonitrile/phosphoric acid mixture. Samples above the LLOQ of 0.01 mg/L were determined with an accuracy of 102–106% and a precision of 4.75–5.49%. C_{max}, C_{max} normalized to dose and bodyweight ($C_{max,norm}$), and t_{max} were calculated from the plasma concentrations of each drug.

Safety and Tolerability

Safety and tolerability were assessed by questioning the subjects about the occurrence of any adverse events, or by spontaneous reporting of events. Subjects' BP and pulse rates were measured after 15 minutes in the supine position at the time of drug administration and 2, 4, 8, 24 and 48 hours afterwards. Haematology, clinical chemistry, coagulation (including the clotting tests prothrombin time and activated partial thromboplastin time) and urinalysis were also assessed.

Statistical Analyses

Vital signs, safety and pharmacokinetic data were described using appropriate summary statistics.

The primary aim of the study was to rule out an effect of rivaroxaban 45 mg on QTcF 3 hours after drug administration. For this endpoint, results were compared with placebo using null and alternative hypotheses. The null hypothesis to be tested was: absolute QTc change 3 hours after rivaroxaban 45 mg minus absolute QTc change 3 hours after placebo is ≥10 ms, which was considered to be the threshold for indicating no QTc-prolonging effect at the time this study was designed.[22] The alternative hypothesis to be tested was: absolute QTc change 3 hours after rivaroxaban 45 mg minus absolute QTc change 3 hours after placebo is <10 ms.

The absolute QTc change 3 hours after administration of the treatments was analysed assuming normally distributed data. Analysis of covariance (ANCOVA) was used to compare the effect of the treatments; point estimates (least-squares [LS]-means) and a confirmatory one-sided 95% CI were calculated. An absence of a QTc-prolonging effect could be concluded if the 95% CI for rivaroxaban 45 mg minus placebo was contained within the interval $-\infty$, 10.

Based on the primary aim of the study, the subject sample size was determined as follows: standard deviation of 15 ms for the difference between rivaroxaban and placebo was assumed. Target parameters were a type I error of 0.05, a relevant difference of 10 ms and a power of >90%, if the true difference was ≥10 ms. Using a one-sided t-test-based CI accounting for these parameters, a sample size of at least 45 subjects was required; applying a 4-fold crossover design with complete blocks of orthogonal-Latin-squares suggested around 60 subjects would be required.

For analysis of outlying results, observed absolute QTc values were sorted into the categories ≤430 ms, >430–450 ms, >450–480 ms, >480–500 ms and >500 ms, and by the absolute change from baseline into the categories ≤30 ms, >30–60 ms and >60 ms. The results were presented using appropriate summary statistics.

Results

Subjects' Disposition and Demographics

A total of 145 subjects were screened; 91 subjects either did not pass the screening procedure or were assigned to be back-ups, resulting in a total of 54 subjects (27 male and 27 female) enrolled in the study. Three subjects withdrew because of treatment-emergent adverse events that were not related to study drug (elbow fracture, sinusitis and abdominal pain), and one subject was withdrawn as a result of violation of the study protocol (the subject erroneously received one tablet fewer than planned in the last treatment period). As a result of these withdrawals, 50 subjects were valid for the QT analyses and 54 for the safety analysis.

The mean age of subjects was 62.4 years (range 51–74 years); mean weight was 74.9 kg (standard deviation [SD] ± 12.6); mean height was 168.8 cm (± 9.6); and mean body mass index was 26.2 kg/m^2 (± 3.2).

Corrected QT Interval Findings

Primary and Secondary Analyses

Compared with placebo, rivaroxaban 45 mg decreased the QTcF interval by 0.91 ms (CI −3.33, 1.52; table I) 3 hours after administration. The upper 95% CI for this value was clearly below the 10 ms change defined in the null hypothesis; indeed, values did not exceed 5 ms.

Analyses of the secondary parameters demonstrated that rivaroxaban 45 mg had no QTcF-prolonging effect (table I). No LS-means ratio exceeded 2.5 ms versus placebo for values 3 hours post-administration, at the t_{max} of rivaroxaban for the post-administration mean, or the post-administration maximum with either rivaroxaban dose. None of the upper 95% CIs were above, or close to, the predefined limit of 10 ms with either rivaroxaban dose in any of the parameters analysed. Comparison of the QTcF changes observed with the two rivaroxaban doses showed that there were no dose-dependent differences in QTcF between rivaroxaban 15 mg and 45 mg.

Table I. Treatment comparisons (95% CI) based on least-squares-mean ratios of changes in Fridericia-corrected QT interval (QTcF) from baseline for rivaroxaban 15 mg and 45 mg, and moxifloxacin 400 mg

Parameter	Treatment	Comparator	Difference	95% CI
Primary analysis[a]				
QTcF 3 hours post-administration	Rivaroxaban 45 mg	Placebo	−0.91	−3.33, 1.52
	Rivaroxaban 15 mg	Placebo	−1.83	−4.19, 0.54
	Rivaroxaban 15 mg	Rivaroxaban 45 mg	−0.92	−3.36, 1.52
Secondary analyses[b]				
QTcF 3 hours post-administration (all treatments)	Rivaroxaban 45 mg	Placebo	−1.03	−3.47, 1.42
	Rivaroxaban 45 mg	Moxifloxacin	−10.80	−13.30, −8.34
	Rivaroxaban 15 mg	Placebo	−1.49	−3.88, 0.90
	Rivaroxaban 15 mg	Rivaroxaban 45 mg	−0.47	−2.93, 2.00
	Rivaroxaban 15 mg	Moxifloxacin	−11.30	−13.60, −8,88
	Moxifloxacin	Placebo	9.77	7.39, 12.15
QTcF at time of t_{max}	Rivaroxaban 45 mg	Placebo	2.08	−0.51, 4.67
	Rivaroxaban 45 mg	Moxifloxacin	−8.04	−10.70, −5.43
	Rivaroxaban 15 mg	Placebo	−0.49	−3.05, 2.07
	Rivaroxaban 15 mg	Rivaroxaban 45 mg	−2.57	−5.18, 0.04
	Rivaroxaban 15 mg	Moxifloxacin	−10.60	−13.20, −8.05
	Moxifloxacin	Placebo	10.12	7.56, 12.68
Mean QTcF post-administration[c]	Rivaroxaban 45 mg	Placebo	−0.62	−1.93, 0.68
	Rivaroxaban 45 mg	Moxifloxacin	−6.97	−8.29, −5.65
	Rivaroxaban 15 mg	Placebo	−1.19	−2.48, 0.10
	Rivaroxaban 15 mg	Rivaroxaban 45 mg	−0.57	−1.89, 0.76
	Rivaroxaban 15 mg	Moxifloxacin	−7.54	−8.83, −6.24
	Moxifloxacin	Placebo	6.35	5.07, 7.64
Maximum QTcF post-administration[d]	Rivaroxaban 45 mg	Placebo	−0.43	−2.47, 1.61
	Rivaroxaban 45 mg	Moxifloxacin	−7.94	−10.00, −5.87
	Rivaroxaban 15 mg	Placebo	−1.43	−3.45, 0.59
	Rivaroxaban 15 mg	Rivaroxaban 45 mg	−1.00	−3.07, 1.07
	Rivaroxaban 15 mg	Moxifloxacin	−8.94	−11.00, −6.91
	Moxifloxacin	Placebo	7.51	5.50, 9.52

a ANCOVA analysis excluding results with moxifloxacin.

b ANCOVA analysis including results with moxifloxacin.

c The mean QTcF over the course of the study period, after drug administration.

d The maximum prolongation observed after drug administration, regardless of time and drug plasma concentration.

ANCOVA = analysis of covariance; $\mathbf{t_{max}}$ = time to reach maximum plasma concentration of drug.

Moxifloxacin increased QTcF >5 ms compared with placebo and both rivaroxaban doses for all parameters examined (table I). All of the lower bounds of the 95% CI exceeded 5 ms.

Analysis of the time course of QTcF showed a circadian pattern with all treatments (figure 1). With both rivaroxaban doses and placebo, QTcF decreased to a minimum level 2–3 hours after administration, and then increased again at 4–5 hours, before decreasing again. None of the mean QTcF values exceeded baseline between 0.5 and 48 hours with both rivaroxaban doses and placebo. Moxifloxacin resulted in the expected increase in QTcF and, therefore, established assay sensitivity. The mean

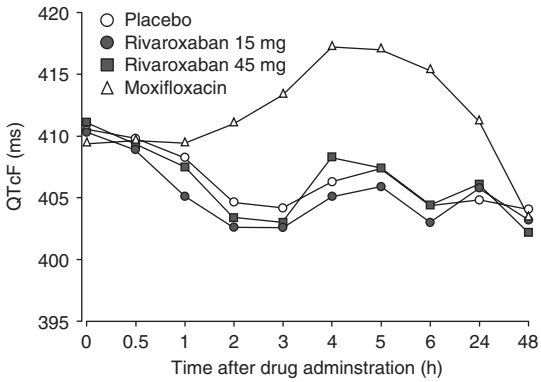

Fig. 1. Mean Fridericia corrected QT interval (QTcF) in healthy male and female subjects (n = 50) aged ≥50 years after a single dose of placebo, rivaroxaban 15 mg, rivaroxaban 45 mg or moxifloxacin 400 mg.

heart rates at baseline and over the treatment period with all four treatments were nearly identical (figure 2), indicating no effect of any of the study treatments on heart rate.

When the QT interval was corrected individually for heart rate, the results followed a similar pattern to those observed for QTcF: no evidence of QTcI prolongation with either rivaroxaban dose, no dose-dependent difference between QTcIs for rivaroxaban 45 mg and 15 mg, and a QTcI prolongation of approximately 10 ms with moxifloxacin (data available as supplementary material ['ArticlePlus'] at http://drugsafety.adisonline.com).

Outlier Analysis

Analysis of the outlying values for QTcF revealed that the majority of ECGs showed absolute QTcF values ≤430 ms (table II). Outlying results occurred at a similar frequency with both rivaroxaban doses and placebo, and were slightly higher with moxifloxacin. The only QTcF values of >480–500 ms occurred in one female subject in the rivaroxaban 15-mg group, before the dose was administered (2/1559 readings); most of the other prolongations >450 ms were also observed in this subject. All absolute QTcF changes from baseline with rivaroxaban or placebo were ≤30 ms (table II). With moxifloxacin, a small number of ECG readings showed QTcF changes from baseline of >30–60 ms. However, there were no changes from baseline exceeding 60 ms. Analysis of outliers for QTcI values showed the same patterns as for QTcF (data available as supplementary material at http://drugsafety.adisonline.com).

Correlation between Fridericia-Corrected QT Intervals and Rivaroxaban Plasma Concentrations

The plasma concentration of rivaroxaban correlated with QTcF according to the formula (equation 2):

$$QTcF = -0.003 \times \text{concentration} + 406.1 \quad \text{(Eq. 2)}$$

where –0.003 is the slope of the correlation and 406.1 is the intercept on the y-axis. The slope of the correlation was not significantly different to 0 ($p = 0.40$; figure 3), indicating no concentration-dependent effect of rivaroxaban on QTcF. Furthermore, there was no obvious difference in the correlation between the genders, except for the female subject who had a large number of outlying results (figure 3).

Pharmacokinetic Analyses

The C_{max} of rivaroxaban increased in a less than dose-proportional manner in the rivaroxaban 15 mg and 45 mg groups (table III), and this was confirmed by the $C_{max,norm}$ values. The t_{max} of rivaroxaban occurred after 4.1 hours with both 15-mg and 45-mg

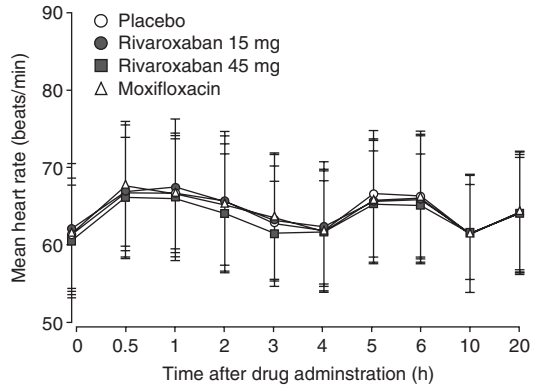

Fig. 2. Mean (± standard deviation) heart rates in healthy male and female subjects (n = 50) aged ≥50 years after a single dose of placebo, rivaroxaban 15 mg, rivaroxaban 45 mg or moxifloxacin 400 mg.

Table II. Outlying Fridericia-corrected QT interval (QTcF) results, classified by absolute values and absolute change from baseline, for 50 healthy male and female subjects aged ≥50 years receiving placebo, rivaroxaban 15 mg, rivaroxaban 45 mg or moxifloxacin 400 mg

QT interval (ms)	Placebo [n (%)]	Rivaroxaban 15 mg [n (%)]	Rivaroxaban 45 mg [n (%)]	Moxifloxacin [n (%)]
Absolute values				
≤430	1472 (91.5)	1456 (93.4)	1433 (91.8)	1316 (83.4)
>430–450	124 (7.7)	87 (5.6)	117 (7.5)	225 (14.3)
>450–480[a]	13 (0.8)	14 (0.9)	11 (0.7)	37 (2.3)
>480–500[a]	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
>500	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1609	1559	1561	1578
Absolute change from baseline				
≤30	1443 (100.0)	1404 (100.0)	1343 (100.0)	1386 (99.4)
>30–60	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.6)
>60	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1443	1404	1343	1395

a All incidences with placebo, rivaroxaban 15 mg and rivaroxaban 45 mg, and nine of the incidences observed with moxifloxacin occurred in the same subject.

n = number of electrocardiograms.

doses, and the t_{max} of moxifloxacin occurred 3.1 hours after administration (table III).

Safety and Tolerability

In total, 56 treatment-emergent adverse events were reported by 25 of the 54 subjects. There were 14 adverse events in each treatment group, of which four were considered to be related to the study drug. These were bleeding events that occurred in two subjects receiving placebo (bleeding from the catheter site and bleeding from the gums while brushing teeth), one subject receiving moxifloxacin and one subject receiving rivaroxaban 15 mg (both of these were bleeding from the catheter site). All of these drug-related adverse events were mild in severity and resolved by the final examination. There were no drug-related, treatment-emergent adverse events observed in subjects receiving rivaroxaban 45 mg.

Forty-six of the adverse events were mild in intensity, eight were moderate and two were severe. Headache was the most frequently reported adverse event and was reported a total of 17 times by 12 subjects. The two severe adverse events that occurred were appendicitis, and a fractured elbow due to a cycling accident (which occurred between treatment periods). These severe adverse events warranted withdrawal of the subjects from the study; another subject withdrew following an episode of sinusitis of moderate intensity. No adverse events were observed that were related to the cardiovascular system.

An increase in serum lipase activity in one subject receiving rivaroxaban 15 mg, and an increase in serum glutamate dehydrogenase level in another subject before receiving placebo, were reported as adverse events and resolved after 5 and 2 days, respectively. No changes in clinical chemistry were considered clinically relevant, and no changes in vital signs related to treatment were observed (other

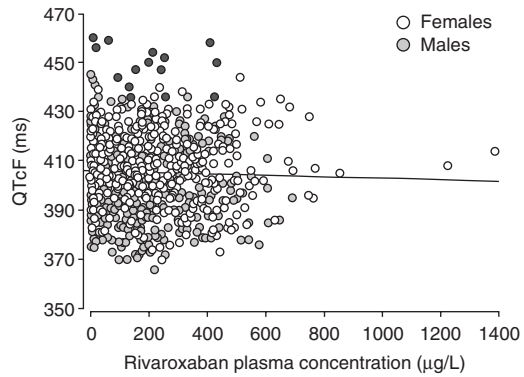

Fig. 3. Correlation between the Fridericia-corrected QT intervals (QTcF) and rivaroxaban plasma concentrations by gender. Correlations for a female subject with an increased incidence of outlying values are shown as filled black circles.

Table III. Pharmacokinetics of rivaroxaban and moxifloxacin after single doses in healthy male and female subjects aged ≥50 years

Parameter	Rivaroxaban 15 mg (n = 50)	Rivaroxaban 45 mg (n = 50)	Moxifloxacin 400 mg (n = 49)
C_{max}[a]	221.7 (28.7) μg/L	479.7 (30.5) μg/L	3.18 (25.9) mg/L
$C_{max,norm}$[a]	1095 (25.4) g/L	790 (31.6) g/L	0.589 (20.5) kg/L
t_{max} (h)[b]	4.1 (2.1–5.0)	4.1 (0.6–5.1)	3.1 (0.5–5.1)

a Values indicate geometric mean (coefficient of variation).

b Values indicate median (range).

C_{max} = maximum drug concentration in plasma; **$C_{max,norm}$** = C_{max} normalized to dose and bodyweight; **t_{max}** = time to C_{max}.

than those reported in the QTc section). Clotting times, as assessed by prothrombin time and activated partial thromboplastin time, were prolonged in a dose-dependent manner after administration of rivaroxaban, with maximum prolongation occurring approximately 3 hours after administration. Placebo and moxifloxacin had no effect on either prothrombin time or activated partial thromboplastin time.

Discussion

This study was designed and performed in accordance with the guidance notes in ICH E14 to determine whether rivaroxaban prolongs the QT interval.[19] Healthy subjects aged ≥50 years were chosen because this age group is more likely to receive rivaroxaban in clinical practice: age is a risk factor for atrial fibrillation and venous thromboembolism.[1,23] When this study was planned, the likely therapeutic dose of rivaroxaban had not yet been established. However, other phase I studies had shown that a dose of 15 mg was likely to have clinically relevant effects on coagulation,[6,7] so this was the lower dose chosen for this study. The suitability of the 15-mg dose for this study was confirmed by recently completed phase II studies of rivaroxaban for the prevention of venous thromboembolism after major orthopaedic surgery, which showed that the drug is clinically effective within the range of 5 to 20 mg daily,[8,9] and that 10 mg once daily is the optimum dose in this indication.[10] Another phase I study in a similar elderly population of healthy subjects showed that there is no increase in absorption of rivaroxaban >40 mg (Kubitza et al., manuscript submitted). As a result, a 45-mg dose of rivaroxaban was chosen as the supratherapeutic dose in this study.

Because rivaroxaban has no major circulating metabolites,[24] a relatively short half-life of between 5 and 9 hours, and no relevant accumulation after multiple doses,[6,7] a single-dose design was considered to be appropriate for this study. Furthermore, moxifloxacin is known to exert its effects on the QTc interval after one dose;[21] therefore, multiple doses of this positive control were not necessary. ECG readings were taken throughout the study, and were taken frequently in the first 6 hours after administration, to allow assessment of the effect of rivaroxaban on the QTc interval throughout the administration interval, and particularly at t_{max}. To reduce intrapatient variability and noise, multiple (three) ECG readings were taken at each timepoint; therefore, >1400 QTc values were available for analysis.

The primary analysis in this study was the effect of rivaroxaban 45 mg on QTcF 3 hours after drug administration, which is close to rivaroxaban t_{max}, as shown in this study and in a previous study.[7] Rivaroxaban reduced the QTcF by a very small amount (<1 ms) compared with placebo, and the upper limit of the 95% CI was <5 ms, thus demonstrating the absence of a QTc-prolonging effect with rivaroxaban at this supratherapeutic dose. The secondary analyses confirmed this result: a rivaroxaban dose of 15 mg did not prolong the QTc interval, and no effect on the QTc interval was evident with either rivaroxaban dose at their t_{max}, or when considering the mean post-administration QTc prolongation or the maximum post-administration prolongation. These findings were further confirmed by the correlation between rivaroxaban plasma concentrations and QTcF, which had a slope very close to zero.

Moxifloxacin was an appropriate positive control for this study, and established the required assay sensitivity. The prolongations observed with moxifloxacin are consistent with those reported previously for this dose of moxifloxacin in healthy subjects.[21,25]

The Fridericia correction formula was appropriate for correcting QT values in this study because rivaroxaban does not affect heart rate. This has been observed before,[7] and was also demonstrated in this study. Individual QT corrections were also made, and the results were similar to the QTcF findings.

Outlying QTcF and QTcI values were similar in frequency and extent of change from baseline with rivaroxaban and placebo. The majority of QTcF values >450 ms were observed in one female subject, and the only QTcF values >480 ms were observed in this same subject before administration of the rivaroxaban 15-mg dose. The incidence of prolonged QTc values after placebo administration in this subject suggests that she may experience spontaneous increases in the QT interval in the absence of drugs. However, the frequency of QT prolongations may be further increased by drugs with a known QT-prolonging effect. The change from baseline values accounts for subjects who have a naturally prolonged QTc interval, for whatever reason, and shows prolongations that may be attributed to drug administration. No absolute changes >30 ms were observed with rivaroxaban or placebo. There was a very small increase in outlier frequency and change from baseline after treatment with moxifloxacin; however, there were no increases in absolute QTcF >500 ms or changes from baseline of >60 ms with any treatment.

In this study in healthy male and female subjects aged ≥50 years, the pharmacokinetics of rivaroxaban were similar to those observed previously in healthy, young male subjects, and rivaroxaban also affected global clotting tests as expected.[6,7] There were no substantial differences in the distribution of QTcF values between the genders with rivaroxaban, except for outlying prolongations in the female subject discussed previously. The prolongations in this particular female subject did not correlate positively with the corresponding rivaroxaban plasma concentrations. All of the treatments in this study were well tolerated and, importantly, there were no adverse events related to the cardiovascular system with any treatment, as has been observed previously.[6,7]

Study Limitations

One limitation of this trial is that the study population is not highly representative of the population expected to receive rivaroxaban in clinical practice. This population is likely to include a large proportion of elderly patients. Some of these patients will be healthy, as were the subjects recruited for this study. However, a substantial proportion of elderly patients may have co-morbidities that can independently impact on QT interval. In addition, patients could be taking concomitant medications that result in prolongation of the QT interval; for example, the gastrointestinal stimulant cisapride or the antibacterial erythromycin. These factors potentially make QT interval a less relevant endpoint for assessing any effect of rivaroxaban on this parameter in patient populations. However, the results of this study are still encouraging, as the absence of any effect on QT interval suggests that rivaroxaban will not have any effect on arrhythmia risk.

Conclusions

Cardiovascular complications, including arrhythmias such as TdP, are a major reason for novel drugs in any indication failing to obtain a licence, or being withdrawn. Such a rigorous study of the effect on QT interval has not yet been published for any other novel anticoagulant. Rivaroxaban has the potential to be useful in patients with cardiovascular disorders, such as for stroke prevention in patients with atrial fibrillation and for patients with acute coronary syndromes, as well as for prevention and treatment of venous thromboembolism. Therefore, as a novel drug, it was important to determine whether rivaroxaban has arrhythmic effects. These could, of course, be serious in any patient population, but would be of particular concern in patients with cardiovascular disorders.

This thorough QT study, designed and carried out in accordance with the guidance notes in ICH E14,[19] has shown that rivaroxaban does not prolong the QTc interval. Therefore, the potential of rivaroxaban as an anticoagulant in chronic cardiovascular disorders (as well as in venous thromboembolism prevention and treatment) can be investigated in appropriate clinical studies without the need for intensive monitoring of the QTc interval.

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