Are women more susceptible than men to drug-induced QT prolongation? Concentration–QTc modelling in a phase 1 study with oral rac-sotalol

Borje Darpo,1 Dilip R. Karnad,2 Fabio Badilini,3 Jeff Florian,4 Christine E Garnett,5 Snehal Kothari,2 Gopi Krishna Panicker2 & Nenad Sarapa6

1Karolinska Institute, Department of Clinical Sciences, Danderyd’s Hospital, Division of Cardiovascular Medicine, Stockholm, Sweden, 2Quintiles Cardiac Safety Services, Mumbai, India, 3AMPS-LLC, New York, 4Division of Pharmacometrics, US Food and Drug Administration, Silver Spring, MD, 5Certara, St Louis, MT and 6Clinical Pharmacology, Hoffmann-La Roche, Inc., Nutley, NJ, USA

AIM
To study the differences in QT, interval on ECG in response to a single oral dose of rac-sotalol in men and women.

METHODS
Continuous 12-lead ECGs were recorded in 28 men and 11 women on a separate baseline day and following a single oral dose of 160 mg rac-sotalol on the following day. ECGs were extracted at prespecified time points and upsampled to 1000 Hz and analyzed manually in a central ECG laboratory on the superimposed median beat. Concentration–QTc analyses were performed using a linear mixed effects model.

RESULTS
Rac-sotalol produced a significant reduction in heart rate in men and in women. An individual correction method (QTcI) most effectively removed the heart rate dependency of the QTc interval. Mean QTcI was 10 to 15 ms longer in women at all time points on the baseline day. Rac-sotalol significantly prolonged QTcI in both genders. The largest mean change in QTcI (ΔQTcI) was greater in females (68 ms (95% confidence interval (CI) 59, 76 ms) vs. 27 ms (95% CI 22, 32 ms) in males). Peak rac-sotalol plasma concentration was higher in women than in men (mean Cmax 1.8 μg ml⁻¹ (range 1.1–2.8) vs. 1.4 μg ml⁻¹ (range 0.9–1.9), P = 0.0009). The slope of the concentration–ΔQTcI relationship was steeper in women (30 ms per μg ml⁻¹ vs. 23 ms per μg ml⁻¹ in men; P = 0.0135).

CONCLUSIONS
The study provides evidence for a greater intrinsic sensitivity to rac-sotalol in women than in men for drug-induced delay in cardiac repolarization.
Introduction

Prolongation of the corrected QT (QTc) interval in the surface ECG is regarded as a biomarker for pro-arrhythmias caused by delayed cardiac repolarization [1] and a vast majority of patients who experience torsades de pointes (TdP) while on QT prolonging drugs have QTc intervals exceeding 500 ms [2]. Premenopausal women have on average a 10 to 20 ms longer QTc interval than men [3–5] and it is well described that women are at higher risk for the development of pro-arrhythmias caused by drugs with an effect on cardiac repolarization, i.e. drugs that further prolong the QTc interval [6–8].

Even though plasma concentration of some drugs may be higher in women than in men, these differences in plasma concentrations cannot fully explain the increased pro-arrhythmic susceptibility of women. Another reason for the observed increased pro-arrhythmic risk for women may be an increased sensitivity to QT prolongation compared with men, i.e. a steeper relationship between drug plasma concentration and the QTc effect, which would lead to more pronounced QTc prolongation at high plasma concentrations. This idea gains support from the finding that patients who experience drug-induced TdP, demonstrate a much more pronounced QTc prolongation at similar plasma concentrations than those who do not develop the pro-arrhythmia [9, 10].

To explore further whether women are more sensitive than men to drug-induced QTc prolongation, we undertook this analysis with the objective of assessing gender differences in the concentration–QTc relationship after a single oral, therapeutic dose of rac-sotalol in healthy volunteers.

Methods

Study outline

Healthy young adult subjects were enrolled in a previously reported study [5] exploring electrocardiographic identification of drug-induced QT prolongation following treatment with rac-sotalol. The study was open-label, non-randomized with a fixed treatment sequence on 3 consecutive days: a separate baseline day (day 0), a single oral 160 mg dose of rac-sotalol (Betapace®, Berlex Laboratories) on day 1 and a single 320 mg dose of rac-sotalol on day 2. Rac-sotalol was given at 08.00 h in the fasted state and ECGs were serially recorded post-dosing and at corresponding time points on day 0. Subjects met typical inclusion criteria for phase 1 studies and the experimental conditions were strictly standardized. Subjects rested quietly in the supine position for 5 min before the nominal time point of each ECG extraction, had the same standardized meals at the same time across study days and the same lead electrode positioning was used on all days. Rac-sotalol plasma concentration was determined at each of the 15 time points at which ECGs were extracted and blood samples were drawn after the ECG recording. Blood samples for rac-sotalol plasma concentrations were drawn in 5.0 ml K3-EDTA Vacutainer® tubes. Extraction was done with ethyl acetate and measurements were performed with a validated HPLC assay (PPD Development, Middleton, WI, USA). Calibration standard responses were linear over the concentration range of 10–2000 ng ml$^{-1}$ (validated using a 0.50 ml sample volume) and the inter-day precision (coefficient of variation, CV) was <8.4%. The 10 ng ml$^{-1}$ value was used as the lower limit of quantification (LLOQ) for the assay in the current study. The error for the mean of the standard value at the LLOQ was 2.0% (CV 2.3%). Reproducibility of the assay over the range of 10.0 to 2000 ng ml$^{-1}$ was tested in triplicate on 3 separate days. The average CV for all levels of the standard curve was 1.4%. The acceptable control range in the assay was set to ±20% at low range (30 ng ml$^{-1}$) and to ±15% at medium (300 ng ml$^{-1}$) to high (1500 ng ml$^{-1}$) range. The long term matrix stability in plasma stored at or below −20°C was 53 months.

Thirty-nine healthy adult subjects (11 women and 28 men) with a mean age of 27 years (range 18 to 45 years) were enrolled. Their mean weight was 74 kg (range 47 to 108 kg) with a mean body mass index of 24 kg m$^{-2}$ (18 to 31 kg m$^{-2}$). Based on discontinuation criteria (change from baseline QTcF (∆QTc,F) > 60 ms), all women were excluded from dosing on day 2. ECG data from both genders on day 0 (baseline) and on day 1 (rac-sotalol 160 mg) were therefore used for this analysis.

The study was conducted at the Pharmacial Clinical Research Unit in Kalamazoo, MI, USA according to the Good Clinical Practice and Declaration of Helsinki principles. All subjects gave written informed consent to the study protocol approved by an independent Institutional Review Board of the Bronson Methodist Hospital in Kalamazoo, MI, USA (BMH-2001-0039).

ECG assessment

A continuous digital 12-lead ECG was recorded by Holter (H12, Mortara Instrument, Milwaukee, WI, USA) at 180 Hz sampling rate for 22.5 h at baseline (day 0) and on day 1. For the purpose of this study, ECGs were extracted and remeasured in the following way. Triplicate 10 s ECG strips were extracted at 15 matched time points (1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 13, 16 and 22.5 h post-dosing) on day 0 (baseline) and at corresponding times on day 1 after dosing of 160 mg rac-sotalol. Holter tracings were reviewed by one trained reader at AMPS-LLC, NY, USA to exclude distortion and other sources of inadequate ECG signal quality. ECG strips were extracted from the continuous recordings by a commercial software application (Antares 2.0.0, AMPH-LLC, New York, NY, USA) using optimized extraction criteria based on heart rate stability and ECG signal noise content [11]. The software provided a set of parameters to customize the extraction procedure, such as the number of extractions to obtain at each time

[Image 505x738 to 554x758]
point and the length of the time window in the Holter tracing where the ECG strip should be identified for extraction. Strips were extracted from a segment of the recording at which a stable heart rate (i.e., comparable RR duration in consecutive cardiac cycles) was identified by Antares for at least 1 min before the point of extraction of the first ECG. All segments with stable heart rate were contained within a 5 min window centred around the nominal time point. Each extracted ECG strip was up-sampled at 1000 Hz by AMPS-LLC, converted to the HL7 v.3.0 XML format and transferred to the central ECG laboratory (Quintiles Cardiac Safety Services, Mumbai, India) for QT and RR interval measurement. Fully manual measurements were made using a commercial digital on-screen measurement software (CalECG 2.3 from AMPS, New York, NY, USA) on the globally presented, superimposed median beat after ungrouping [12] to ensure QT measurement from the earliest Q wave onset to the latest T wave offset in any lead. The T wave offset was determined by visual determination of the intersection between the end of T wave and the isoelectric line.

Statistical analysis
Statistical analysis was performed using SAS software package (9.2, SAS Institute Inc., Cary, NC, USA). For each ECG time point, the QT and RR intervals were the average of measurements from the triplicate ECGs for each subject recorded at that time point. The QT intervals were corrected for the effect of heart rate using Fridericia’s (QTcF = QT/RR\(^{1/3}\)) and Bazett’s (QTcB = QT/RR\(^{1/2}\)) correction methods. Study population-specific QT correction (QTcI) was estimated by each of the correction methods to identify the best correction method for the data from this study. Strips were extracted from a segment of the recording which a stable heart rate (i.e., comparable RR duration in consecutive cardiac cycles) was identified by Antares for at least 1 min before the point of extraction of the first ECG. All segments with stable heart rate were contained within a 5 min window centred around the nominal time point. Each extracted ECG strip was up-sampled at 1000 Hz by AMPS-LLC, converted to the HL7 v.3.0 XML format and transferred to the central ECG laboratory (Quintiles Cardiac Safety Services, Mumbai, India) for QT and RR interval measurement. Fully manual measurements were made using a commercial digital on-screen measurement software (CalECG 2.3 from AMPS, New York, NY, USA) on the globally presented, superimposed median beat after ungrouping [12] to ensure QT measurement from the earliest Q wave onset to the latest T wave offset in any lead. The T wave offset was determined by visual determination of the intersection between the end of T wave and the isoelectric line.

Results
A total of 3456 ECGs from 39 healthy adult subjects (11 women and 28 men) were included in this analysis. There were 33 missing ECGs and the QT interval could not be measured in 49 ECGs (1.9%). The missing ECGs were evenly distributed across time points.

Rac-sotalol pharmacokinetic profile
Plasma concentration–time profiles after dosing with rac-sotalol 160 mg for men and women are shown in Figure 1. The peak plasma concentration was observed on average 2.8 h (SD 0.86) after dosing in men as compared with 2.9 h (SD 0.63) in women (P = NS) and was higher in women (mean (SD) C\(_{\text{max}}\) 1.8 (0.4) µg ml\(^{-1}\), range 1.1 to 2.8) than in men (1.4 (0.3) µg ml\(^{-1}\), range 0.9 to 1.9; P = 0.0009), as was the extent of exposure in plasma (mean AUC(0,\(\infty\)) 17.1 µg ml\(^{-1}\) h in women (SD 2.7) vs. 14.6 µg ml\(^{-1}\) h in men (SD 3.3), P = 0.028).

Effect on heart rate and QT.
Heart rate At baseline, men had a lower resting heart rate (HR) than women (Figure 2). The mean HR in men varied between 60 and 71 beats min\(^{-1}\) across all time points until 6 h, with slightly higher values between 6 and 10 h. In women, mean HR was on average 3 to 9 f beats min\(^{-1}\) with additive between-subject variability associated with slope and (iii) estimated slope and intercept fixed to zero with additive between subject variability associated with slope and intercept. The model structure best describing the observed data based on Akaike Information Criterion (AIC) was then used as the final structural model for covariate exploration. Covariates evaluated in this final step included median-centered baseline QTcI and gender as a covariate on the intercept and gender as a covariate on the slope. Median-centred baseline QTcI for the population was calculated using the median of all baseline QTcI values from all subjects. Individual median-centred baseline values were obtained by subtracting each baseline QTcI value from this median value. Using these models, regression lines for concentration vs. ΔQTcI and their 90% two-sided confidence limits were plotted for males and females [13]. To compare the regression lines in males and females, a hypothesis of coincidence, that is, the relationships between ΔQTcF and plasma concentration in males and females were evaluated by testing gender and gender × concentration interaction effects at a two-sided alpha of 0.05. A statistically significant gender–concentration interaction rejects the hypothesis that the slopes of the two regression lines are equal and a significant gender effect rejects the hypothesis that the two intercepts are equal [14, 15]. The same analysis was also performed for ΔQTcF (median-centred baseline QTcF was substituted as a covariate for this analysis).

Concentration–QTc analyses were performed on the ΔQTcI values using a linear mixed-effects model. Both linear and log-linear concentration–ΔQTcI relationships were considered. Three base model structures were evaluated: (i) slope and intercept as fixed effects with additive between-subject variability associated with slope and intercept, (ii) estimated slope and intercept fixed to zero with additive between-subject variability associated with slope and intercept. The model structure best describing the observed data based on Akaike Information Criterion (AIC) was then used as the final structural model for covariate exploration. Covariates evaluated in this final step included median-centered baseline QTcI and gender as a covariate on the intercept and gender as a covariate on the slope. Median-centred baseline QTcI for the population was calculated using the median of all baseline QTcI values from all subjects. Individual median-centred baseline values were obtained by subtracting each baseline QTcI value from this median value. Using these models, regression lines for concentration vs. ΔQTcI and their 90% two-sided confidence limits were plotted for males and females [13]. To compare the regression lines in males and females, a hypothesis of coincidence, that is, the relationships between ΔQTcF and plasma concentration in males and females were evaluated by testing gender and gender × concentration interaction effects at a two-sided alpha of 0.05. A statistically significant gender–concentration interaction rejects the hypothesis that the slopes of the two regression lines are equal and a significant gender effect rejects the hypothesis that the two intercepts are equal [14, 15]. The same analysis was also performed for ΔQTcF (median-centred baseline QTcF was substituted as a covariate for this analysis).

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higher for most time points. Rac-sotalol caused a significant HR reduction at most time points, and the level of this effect was similar in males and females. Since males had slower heart rates at baseline, a higher proportion of the ECGs recorded in males had HRs below 60 beats min\(^{-1}\) as compared with women, both at baseline (17.3% vs. 3.8%) and after dosing of rac-sotalol (53.3% vs. 29.6%).

**Correction for heart rate changes**

**Correction for heart rate changes** All heart rate correction methods were tested for their ability to correct adequately for differences in heart rate using all QTc/RR pairs from the dosing day, i.e. using on-drug data only. QTcB (Bazett) resulted in a negative slope of 0.037 ms ms\(^{-1}\)RR, i.e. an under-correction of 4.9 ms per 10 beats min\(^{-1}\) reduction of HR. QTcF (Fridericia), QTcI (individualized) and QTcN (study population) resulted in similar positive slopes (QTcF 0.035; QTcI 0.016 and QTcN: 0.030 ms ms\(^{-1}\)RR; Figure 3), which will give an overcorrection of 2.1 to 4.7 ms per 10 beats min\(^{-1}\) HR reduction. Based on this evaluation, results will be given for QTcI since it eliminated most of the bias inherent in the uncorrected QT-RR relationship, and for QTcF since this is commonly used in studies on drug-induced QT prolongation.

The effect of rac-sotalol on QTc For all HR correction methods, women had a higher QTc than men at all time points at baseline by app. 10 to 15 ms (Figure 4). QTcI values on day 0 ranged between 398 and 412 ms in women and between 384 and 394 ms in men. The corresponding values for QTcF were 393 ms and 410 ms in women and between 380 ms and 396 ms in men. Rac-sotalol caused a significant QTc prolongation with all heart rate correction methods in both women and men at all time points (Figure 5). The mean QTc prolongation after rac-sotalol reached a peak at 3.5 h after dosing in men and women. The mean QTcI change from baseline at this time point was 68 ms (95% CI 59, 76 ms) in women and 27 ms (95% CI: 22, 32 ms) in men (\(P < 0.0001\)). With QTcF, the mean prolongation in women was 72 ms and 31 ms in men (\(P < 0.0001\)). QTcI and QTcF prolongation were significantly larger than that observed in men at all post-dose time points (Figure 5).

The larger QTc prolongation observed in women resulted in a higher proportion of ECGs with QTc values above 480 and 500 ms and with more than 60 ms change from baseline. At baseline, no subject had a QTcI exceeding 450 ms. On day 1, six of 11 women had a QTcF exceeding 480 ms, of which one exceeded 500 ms. Similarly, QTcI exceeded 480 ms in six women and 500 ms in two. None of the men had a QTcF or QTcI value above
480 ms. Ten of 11 (91%) women had at least one ECG recording (12% of all recordings) with a change in ΔQTcF exceeding 60 ms. Four men (14%) had six recordings (1%) exceeding this cut-off. For QTcI, 10 (91%) of 11 women and two (7%) of 28 men had at least one ECG with ΔQTcI exceeding 60 ms.

### Concentration–effect analysis

A linear concentration–ΔQTcI model structure including fixed and random effects on slope and intercept was found to describe the observed data best. Using this base structure, gender and baseline centred QTcI were identified as a significant covariate on the intercept and gender was identified as a significant covariate on the slope. The slope of the concentration–ΔQTcI relationship was 30 ms per μg ml⁻¹ in women and 23 ms per μg ml⁻¹ in men (P = 0.0135). The fits of these relationships to the observed data are shown in Figure 6A and model parameters are summarized in Table 1. Using this full model, it can be projected that the mean ΔQTcI in women would be around 58 ms at the geometric mean concentration observed in this study (1.8 μg ml⁻¹) and around 88 ms at the upper range (2.8 μg ml⁻¹). Corresponding ΔQTcI values for men would be approximately 25 ms at the geometric mean concentration observed in this study (1.4 μg ml⁻¹) and 37 ms at the upper range (1.9 μg ml⁻¹).

A similar concentration–QTc relationship, including similar significant covariates, was obtained when the analysis was performed using ΔQTcF. The slope of the regression line for ΔQTcF was 31 ms per μg ml⁻¹ in women and 24 ms per μg ml⁻¹ in men (P = 0.0189) (Figure 6B and Table 1).

### Discussion

The current study demonstrated that a single therapeutic oral dose of 160 mg rac-sotalol resulted in higher mean peak plasma concentrations of the drug in women as compared with men and that the observed QTc interval prolongation was also significantly larger in female healthy subjects. The mean peak rac-sotalol plasma concentration...
Gender differences in rac-sotalol-induced QT prolongation

Figure 4
QTc, in men and women in the drug free state at baseline (day 0). For all heart rate correction methods, women had longer baseline QTc than men.
A) QTcI; B) QTcF.

Figure 5
Change from baseline in QTc (ΔQTc) in men and women after dosing of 160 mg rac-sotalol on day 1. The QTc prolongation was consistently larger in women than in men at all time points after dosing. A) QTcI; B) QTcF.

It is well described that women are at a higher risk than men for the development of the feared consequence of delayed repolarization, torsades de pointes ventricular tachycardia (TdP). In a meta-analysis of 332 patients who developed TdP on cardiovascular drugs known to prolong the QTc interval (procainamide, disopyramide, amiodarone, quinidine, rac-sotalol, bepridil or prenylamine), 70% of patients were women [8]. The same observation has been made with other anti-arrhythmic drugs [9, 16], and also in patients treated with non-cardiovascular drugs with an effect on the QTc interval, like terfenadine [17], erythromycin [18], cisapride [19] and probucol [20].

More specifically, female gender as a risk factor for TdP has also been described for rac-sotalol [21, 22] as well as for d-sotalol in the large SWORD trial which was conducted in patients with a prior myocardial infarction [23]. Lehman and co-workers analyzed a database containing clinical trials with rac-sotalol in 3135 adult patients. TdP was observed in 44 (1.9%) of 2336 men and in 33 (4.1%) of 799 women (P < 0.001) [21]. When adjusted for observed risk factors (congestive heart failure, sustained VT/VF as the presenting arrhythmia and rac-sotalol dose > 320 mg), women had a three times higher risk of developing TdP.
than men. In 22 patients, ECG recordings were available and demonstrated a pronounced prolongation of the uncorrected QT interval to 640 ms (range 500 to more than 840 ms) immediately before the pro-arrhythmic event.

Based on these and other studies [24, 25], it appears evident that women are at a higher risk for the development of drug-induced TdP. The basis for this could be that women are exposed to higher plasma concentrations of the QT prolonging drugs administered without regard to body size, or have greater sensitivity for the QT prolonging effect at similar concentrations of a drug. In addition, the longer baseline QTc in women may be a contributing factor. Limited data from multiple small studies support that women may have greater QTc prolongation compared with men at similar drug plasma concentrations, though this has primarily been observed with anti-arrhythmics in older studies without robust ECG monitoring. In a study with 48 healthy volunteers (21 females), an i.v. infusion of quinidine was given at a body weight adjusted dose (3 mg kg\(^{-1}\)). Peak plasma concentrations were comparable in women (0.87 μg ml\(^{-1}\)) and in men (1.0 μg ml\(^{-1}\)), but the QTc prolongation was greater in females with the largest effect observed 2 h after the infusion: 33 ± 16 ms in women and 24 ± 17 ms in men (P = 0.037) [26]. Twelve women and 12 men received a single i.v. dose of quinidine (4 mg kg\(^{-1}\)) or placebo in a single-blind, randomized crossover trial [27]. There was a trend toward higher quinidine peak plasma concentrations in men than in women (3.7 ± 0.13 vs. 2.8 ± 0.87 μg ml\(^{-1}\), P = 0.07) but the concentration–QTcB slope was more than 40% steeper in women: 42.2 ± 8.6 ms per μg ml\(^{-1}\) in women vs. 29.3 ± 2.6 ms per μg ml\(^{-1}\) in men; P < 0.001. Results were similar with QTcF. In another study by the same group, 24 Korean (12 male and 12 female) and 13 Caucasian subjects (seven male and six female) were given a 20 min infusion of quinidine (4 mg kg\(^{-1}\)) or saline and the QT interval was measured serially after the infusion and corrected using QTcB. The concentration–effect relationship was analyzed by means of a non-linear E\(_{max}\) model. Female Caucasian subjects (n = 6) had substantially lower peak plasma concentrations than males (2.46 ± 0.33 mg l\(^{-1}\) vs. 3.69 ± 0.60 mg l\(^{-1}\)), but due to the small sample size, plasma concentration differences across gender or ethnicity were not statistically significant. Quinidine-induced QTcB prolongation was in general higher in Caucasian subjects as compared with Koreans and significantly higher in

![Figure 6](image)

**Table 1**

Estimates from the concentration–ΔQTc relationship model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>P value</th>
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<td>QTcF Intercept (ms)</td>
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<td>2.0</td>
<td>0.22</td>
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<tr>
<td>Plasma concentration of rac-sotalol (ms per μg ml(^{-1}))</td>
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<td>1.7</td>
<td>&lt;0.001</td>
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<tr>
<td>Female gender (ms)</td>
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<td>3.8</td>
<td>0.005</td>
</tr>
<tr>
<td>Concentration × Female gender interaction (ms per μg ml(^{-1}))</td>
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<td>2.8</td>
<td>0.019</td>
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<tr>
<td>Centred baseline QTcF (ms)</td>
<td>−0.70</td>
<td>0.05</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 2**

A): Concentration vs. ΔQTc using a linear mixed effects model. The slope of the model based concentration–ΔQTc relationship was significantly different (P = 0.0135) in women as compared with men: ΔQTc = −3.2 − 0.7 × centred baseline QTc + 23 × rac-sotalol concentration (μg ml\(^{-1}\)) in men and ΔQTc = 7.9 − 0.7 × centered baseline QTc + 30 × rac-sotalol concentration (μg ml\(^{-1}\)) for women.B) Concentration vs. ΔQTcF using a linear mixed-effects model. The slope of the model based concentration–ΔQTcF relationship was significantly different (P = 0.0189) in women as compared with men: ΔQTcF = −2.5 − 0.7 × centred baseline QTcF + 24 × rac-sotalol concentration (μg ml\(^{-1}\)) in men and ΔQTcF = 8.1 − 0.7 × centred baseline QTcF + 31 × rac-sotalol concentration (μg ml\(^{-1}\)) for women. ++, males; +++ females
female Caucasian subjects. The difference was most pronounced during the first 2 h post-dosing, i.e. at high quinidine plasma concentrations.

For drugs with only a mild effect on the QT interval, it has been more difficult to demonstrate a gender difference in sensitivity for the drug-induced QTc prolongation. In a pooled analysis of data from two studies in healthy Japanese and Caucasian volunteers who were dosed with levofloxacin, age and gender did not have an effect on the level of QT prolongation when analyzed with a linear concentration–effect model [28]. Gender differences in QTc prolongation for moxifloxacin were investigated in a pooled analysis of 20 TQT studies that used moxifloxacin as a positive control [29]. All 20 studies were performed in healthy volunteers and 17 enrolled both genders, two enrolled only men and one enrolled only women. Women had approximately 40% higher moxifloxacin peak plasma concentrations than men (mean: 2.9 μg ml⁻¹ vs. 2.1 μg ml⁻¹, P < 0.001) and a statistically significant larger peak QTcF effect with a placebo-corrected ΔQTcF of 12.4 ms (95% CI 11.1–13.7 ms) compared with 9.1 ms (95% CI 8.1–10.1 ms) in men. There was no difference in slope estimate for the concentration–QTcF relationship, which indicates that the observed difference in QTcF prolongation can be explained by differences in plasma concentrations.

It has been clearly shown that TdP is preceded and exaggerated QTc prolongation [2, 9, 21, 24, 30] and that patients who experience TdP exhibit a larger degree of QTc prolongation than patients without pro-arrhythmic events at comparable plasma concentrations [9, 10]. Our data and other studies with potent QT prolonging drugs [27, 31] suggest that women can be more sensitive to delay in cardiac repolarization induced by some drugs, as previously suggested by Woolsey’s group [27], supported by in vitro experiments with quinidine [32] and with erythromycin [18]. Such a gender-based difference in sensitivity can be caused by hormonal effects, or differences in regard to the expression or activity of ion channels that regulate repolarization in the cardiomyocyte. The baseline QT interval is generally the same in boys and girls before puberty but then shortens in males, returning to prepuberty levels at the age of 50 to 60 years [33], which indicates a hormonal influence. In this context, the study by Rodriguez and co-workers is interesting. Fifty-eight healthy volunteers (38 men and 20 women) were given a body weight adjusted dose (0.003 mg kg⁻¹) of ibutilide as a 10 min infusion [34]. Female subjects were dosed three times in relation to the menstrual cycle. Resulting peak plasma concentrations were somewhat lower in women (mean (SD): 507 (160) pg ml⁻¹) than in men (563 (291) pg ml⁻¹). Greater ΔQTcB prolongation was seen in women during menstruation (63 (13) ms) and during the ovulatory phase (59 (17) ms) as compared to the luteal phase (53 (14) ms) and compared with men (46 (16) ms; P = 0.02 menses vs. men and P = 0.07 ovulatory phase vs. men). Data suggested a hormonal influence on the QTc response, but concentration–effect modelling was not performed, which to some extent limits the conclusiveness of the study. In a more recent, relatively large study in which 253 (153 women) healthy subjects were dosed with body weight adjusted ibutilide (10 μg kg⁻¹ i.v. over 10 min), ΔQTcB was similar in men and women and the findings could thus not be confirmed [35]. In the present study, women were in different phases of the menstrual cycle when participating in the study. It could be argued that the QTc response would have been even more pronounced if all women in our study were administered rac-sotalol during the menstrual and ovulatory phase.

**Study limitations**

The study used commercially available rac-sotalol (Betapace®, Berlex Laboratories), which has both a class III effect (QTc prolongation) and a bradycardic effect, based on its β-adrenoceptor blocking properties. A limitation of the study is the methodology used for heart rate correction of the QT interval. For drugs with a pronounced effect on the heart rate such as rac-sotalol, standard correction methods may not completely remove the heart rate dependence of the derived QTc interval [36], as demonstrated by the slope of the QTc/RR regression lines (Figure 3). Even so, our findings were essentially the same for a population-derived method, QTcF, a study-specific method, QTcN and for a method based on each subject’s QT/RR pairs, QTcI. The use of ECGs recorded at 180 Hz is another limitation. To overcome this limitation, we upsamplled the digital ECGs to 1000 Hz using modern mathematical functions, thereby permitting more accurate measurement of the QT interval [37]. It should also be acknowledged that the study should have been placebo-controlled, in line with modern thorough QT studies. Given the effect size of rac-sotalol-induced QTc prolongation in this study (30 to 70 ms) as compared with what is normally seen in thorough QT studies on placebo (a few ms) and that exposure response analysis was used to study the gender effect, it does however not seem likely that this would have impacted on the results.

In conclusion, this study showed that female healthy subjects experienced higher peak plasma concentrations of rac-sotalol after a single 160 mg oral dose and a significantly larger QTc prolongation than males at given plasma concentrations with a steeper concentration–ΔQTc relationship. More studies are needed to ascertain whether women have greater intrinsic sensitivity to the actions of other QT prolonging drugs too. If confirmed, this may be an important factor that could explain the observed increased risk for women for the development of pro-arrhythmias with drugs that delay cardiac repolarization.

**Competing Interests**

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (avail-
able on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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