

# Are women more susceptible than men to drug-induced QT prolongation? Concentration–QT<sub>c</sub> modelling in a phase 1 study with oral rac-sotalol

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## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Women have a longer QT<sub>c</sub> interval and an increased risk for pro-arrhythmias caused by drug-induced delayed cardiac repolarization.
- This increased risk cannot be explained by gender differences in plasma concentration of the drug.
- This study evaluated the QT<sub>c</sub>–plasma concentration relationship after dosing of rac-sotalol in men and women.

## WHAT THIS STUDY ADDS

- When given a therapeutic dose of rac-sotalol, the slope of the relationship between rac-sotalol concentration and change in QT<sub>c</sub> interval was steeper in women.
- This indicates a greater sensitivity in women as compared with men for rac-sotalol-induced QT prolongation, which may contribute to the greater pro-arrhythmic risk in women.

## AIM

To study the differences in QT<sub>c</sub> 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–QT<sub>c</sub> 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 (QT<sub>cl</sub>) most effectively removed the heart rate dependency of the QT<sub>c</sub> interval. Mean QT<sub>cl</sub> was 10 to 15 ms longer in women at all time points on the baseline day. Rac-sotalol significantly prolonged QT<sub>cl</sub> in both genders. The largest mean change in QT<sub>cl</sub> ( $\Delta$ QT<sub>cl</sub>) 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 C<sub>max</sub> 1.8  $\mu$ g ml<sup>-1</sup> (range 1.1–2.8) vs. 1.4  $\mu$ g ml<sup>-1</sup> (range 0.9–1.9), *P* = 0.0009). The slope of the concentration– $\Delta$ QT<sub>cl</sub> relationship was steeper in women (30 ms per  $\mu$ g ml<sup>-1</sup> vs. 23 ms per  $\mu$ g ml<sup>-1</sup> 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.

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## Introduction

Prolongation of the corrected QT ( $QT_c$ ) 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  $QT_c$  intervals exceeding 500 ms [2]. Premenopausal women have on average a 10 to 20 ms longer  $QT_c$  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  $QT_c$  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  $QT_c$  effect, which would lead to more pronounced  $QT_c$  prolongation at high plasma concentrations. This idea gains support from the finding that patients who experience drug-induced TdP, demonstrate a much more pronounced  $QT_c$  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  $QT_c$  prolongation, we undertook this analysis with the objective of assessing gender differences in the concentration– $QT_c$  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<sup>-1</sup> (validated using a 0.50 ml sample volume) and the inter-day precision (coefficient of variation, CV) was <8.4%. The 10 ng ml<sup>-1</sup> 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<sup>-1</sup> 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<sup>-1</sup>) and to ±15% at medium (300 ng ml<sup>-1</sup>) to high (1500 ng ml<sup>-1</sup>) 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<sup>-2</sup> (18 to 31 kg m<sup>-2</sup>). Based on discontinuation criteria (change from baseline  $QT_cF$  ( $\Delta QT_cF$ ) > 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 Pharmacia 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, AMPS-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

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 ( $QT_cF = QT/RR^{1/3}$ ) and Bazett's ( $QT_cB = QT/RR^{1/2}$ ) correction methods. Study population-specific QT correction ( $QT_cN = QT/RR^N$ ) and individual QT correction ( $QT_cI = QT/RR^I$ ) were also obtained by a log-linear regression model using all drug-free ECGs from all study subjects. Linear regression analysis was performed between  $QT_cI$  and the RR interval by each of the correction methods to identify the best correction method for the data from this study.

The time-matched baseline values on day 0 were used to obtain change from baseline in ECG intervals at corresponding time points after rac-sotalol administration on day 1. Repeated-measures ANCOVA was performed using a mixed effect linear model with gender, time and gender-by-time interaction as fixed effects, baseline  $QT_c$  value as a covariate and subject as a random effect. Least-squares mean (LS mean) and two-sided 95% confidence intervals (CIs) for change from baseline  $QT_c$  ( $\Delta QT_c$ ) for each post-dose time point were estimated. The effect of rac-sotalol on heart rate and differences between males and females were compared using repeated measures ANOVA.

Concentration- $QT_c$  analyses were performed on the  $\Delta QT_cI$  values using a linear mixed-effects model. Both linear and log-linear concentration- $\Delta QT_c$  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 (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-centred baseline  $QT_cI$  and gender as a covariate on the intercept and gender as a covariate on the slope. Median-centred baseline  $QT_cI$  for the population was calculated using the median of all baseline  $QT_cI$  values from all subjects. Individual median-centred baseline values were obtained by subtracting each baseline  $QT_cI$  value from this median value. Using these models, regression lines for concentration vs.  $\Delta QT_cI$  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  $\Delta QT_c$  and plasma concentration in males and females were evaluated by testing gender and gender  $\times$  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  $\Delta QT_cF$  (median-centred baseline  $QT_cF$  was substituted as a covariate for this analysis).

## 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)  $C_{max}$  1.8 (0.4)  $\mu g ml^{-1}$ , range 1.1 to 2.8) than in men (1.4 (0.3)  $\mu g ml^{-1}$ , range 0.9 to 1.9;  $P = 0.0009$ ), as was the extent of exposure in plasma (mean  $AUC(0,\infty)$  17.1  $\mu g ml^{-1} h$  in women (SD 2.7) vs. 14.6  $\mu g ml^{-1} h$  in men (SD 3.3),  $P = 0.028$ ).

### Effect on heart rate and $QT_c$

**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  $min^{-1}$

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  $\text{min}^{-1}$  as compared with women, both at baseline (17.3% vs. 3.8%) and after dosing of rac-sotalol (53.3% vs. 29.6%).

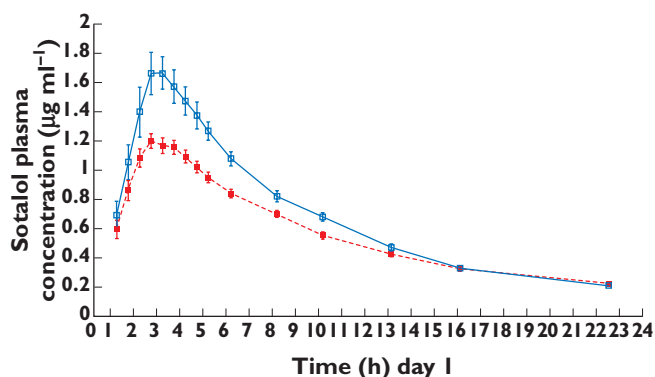
### Correction for heart rate changes

**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  $\text{QT}_c/\text{RR}$  pairs from the dosing day, i.e. using on-drug data only.  $\text{QT}_c\text{B}$  (Bazett) resulted in a negative slope of  $0.037 \text{ ms ms}^{-1} \text{ RR}$ , i.e. an under-correction of 4.9 ms per 10 beats  $\text{min}^{-1}$  reduction of HR.  $\text{QT}_c\text{F}$  (Fridericia),  $\text{QT}_c\text{I}$  (individualized) and

$\text{QT}_c\text{N}$  (study population) resulted in similar positive slopes ( $\text{QT}_c\text{F}$  0.035;  $\text{QT}_c\text{I}$  0.016 and  $\text{QT}_c\text{N}$ :  $0.030 \text{ ms ms}^{-1} \text{ RR}$ ; Figure 3), which will give an overcorrection of 2.1 to 4.7 ms per 10 beats  $\text{min}^{-1}$  HR reduction. Based on this evaluation, results will be given for  $\text{QT}_c\text{I}$  since it eliminated most of the bias inherent in the uncorrected QT-RR relationship, and for  $\text{QT}_c\text{F}$  since this is commonly used in studies on drug-induced QT prolongation.

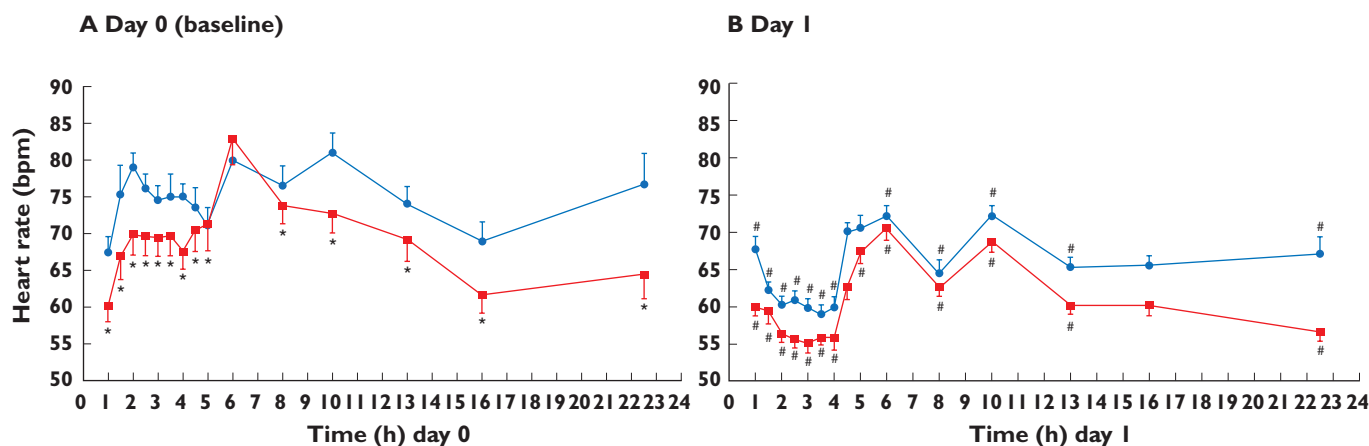
**The effect of rac-sotalol on  $\text{QT}_c$**  For all HR correction methods, women had a higher  $\text{QT}_c$  than men at all time points at baseline by app. 10 to 15 ms (Figure 4).  $\text{QT}_c\text{I}$  values on day 0 ranged between 398 and 412 ms in women and between 384 and 394 ms in men. The corresponding values for  $\text{QT}_c\text{F}$  were 393 ms and 410 ms in women and between 380 ms and 396 ms in men. Rac-sotalol caused a significant  $\text{QT}_c$  prolongation with all heart rate correction methods in both women and men at all time points (Figure 5). The mean  $\text{QT}_c$  prolongation after rac-sotalol reached a peak at 3.5 h after dosing in men and women. The mean  $\text{QT}_c\text{I}$  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  $\text{QT}_c\text{F}$ , the mean prolongation in women was 72 ms and 31 ms in men ( $P < 0.0001$ ).  $\text{QT}_c\text{I}$  and  $\text{QT}_c\text{F}$  prolongation were significantly larger than that observed in men at all post-dose time points (Figure 5).

The larger  $\text{QT}_c$  prolongation observed in women resulted in a higher proportion of ECGs with  $\text{QT}_c$  values above 480 and 500 ms and with more than 60 ms change from baseline. At baseline, no subject had a  $\text{QT}_c\text{F}$  exceeding 450 ms. On day 1, six of 11 women had a  $\text{QT}_c\text{F}$  value exceeding 480 ms, of which one exceeded 500 ms. Similarly,  $\text{QT}_c\text{I}$  exceeded 480 ms in six women and 500 ms in two. None of the men had a  $\text{QT}_c\text{F}$  or  $\text{QT}_c\text{I}$  value above



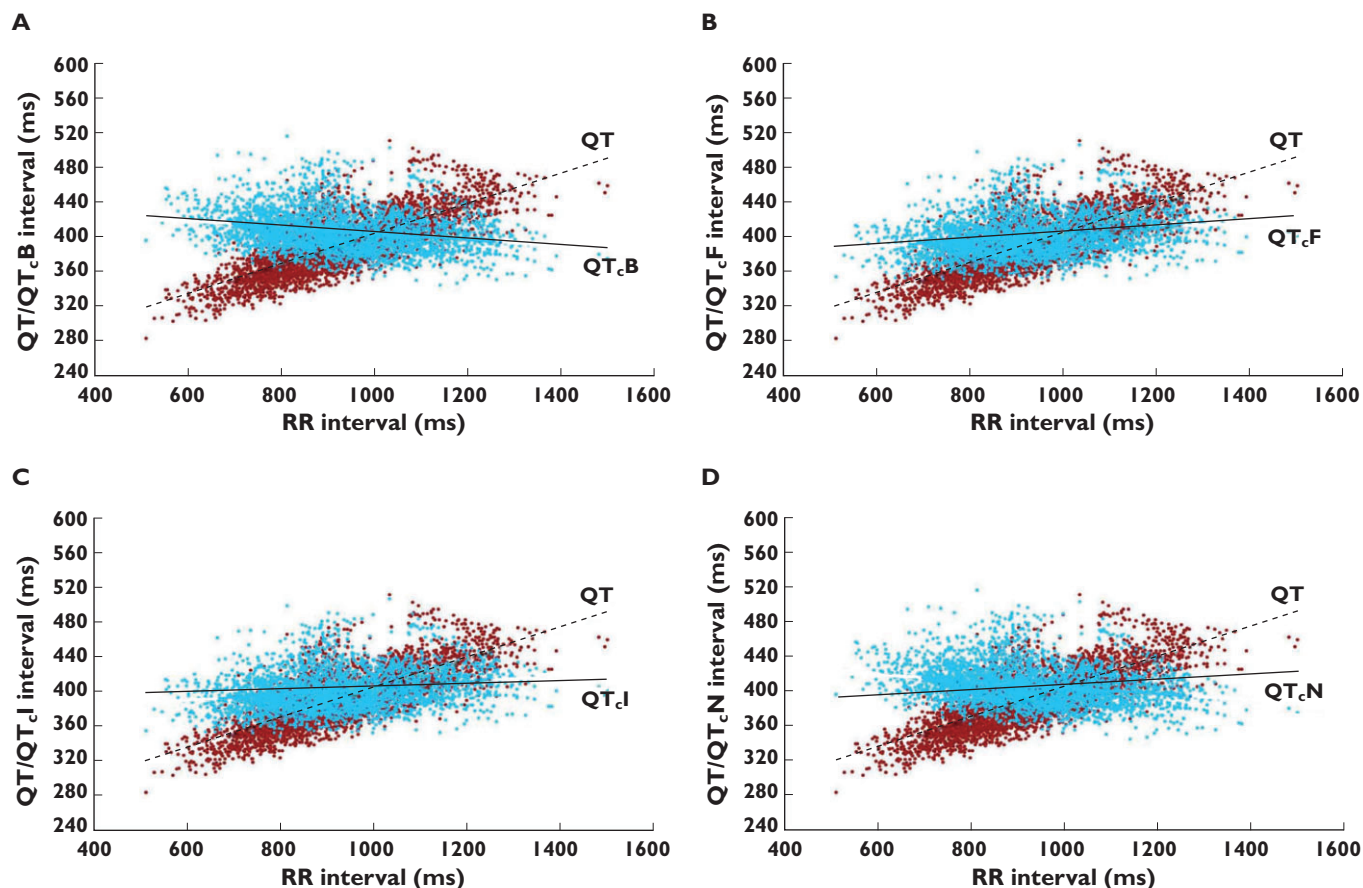
**Figure 1**

Mean plasma concentration–time profile in women ( $n = 11$ ) and in men ( $n = 28$ ) after oral administration of 160 mg rac-sotalol. Rac-sotalol was given at 08.00 h (hour 0). Values are mean and SEM.  $\text{---}\blacksquare\text{---}$ , males;  $\text{---}\blacksquare\text{---}$ , females



**Figure 2**

Heart rate at baseline (day 0, A) and after oral administration of 160 mg rac-sotalol (day 1, B). Time points on day 0 correspond to post-dosing time points on day 1, on which rac-sotalol was given at 08.00 h (hour 0). The mean heart rate at baseline was lower in men as compared with women. Rac-sotalol caused a significant reduction in heart rate for both genders. #: significant change ( $P < 0.05$ ) from the corresponding time point at baseline; \*: significant difference between men and women.  $\text{---}\bullet\text{---}$ , females;  $\text{---}\blacksquare\text{---}$ , males



**Figure 3**

Scatter plots demonstrating the relation of QT (in red, black) and QT<sub>c</sub> (blue, grey) versus heart rate using all QT/QT<sub>c</sub>/RR pairs at baseline and after dosing of rac-sotalol. The slope of the regression line was 0.17 for the uncorrected QT interval (shown in all panels), -0.037 for Bazett's method (QT<sub>cB</sub>, A), 0.035 for Fridericia's method (QT<sub>cF</sub>, B), 0.016 for the individual correction method (QT<sub>cI</sub>, C) and 0.030 for the study population correction method (QT<sub>cN</sub>, D)

480 ms. Ten of 11 (91%) women had at least one ECG recording (12% of all recordings) with a change in  $\Delta$ QT<sub>cF</sub> exceeding 60 ms. Four men (14%) had six recordings (1%) exceeding this cut-off. For QT<sub>cI</sub>, 10 (91%) of 11 women and two (7%) of 28 men had at least one ECG with  $\Delta$ QT<sub>cI</sub> exceeding 60 ms.

### Concentration–effect analysis

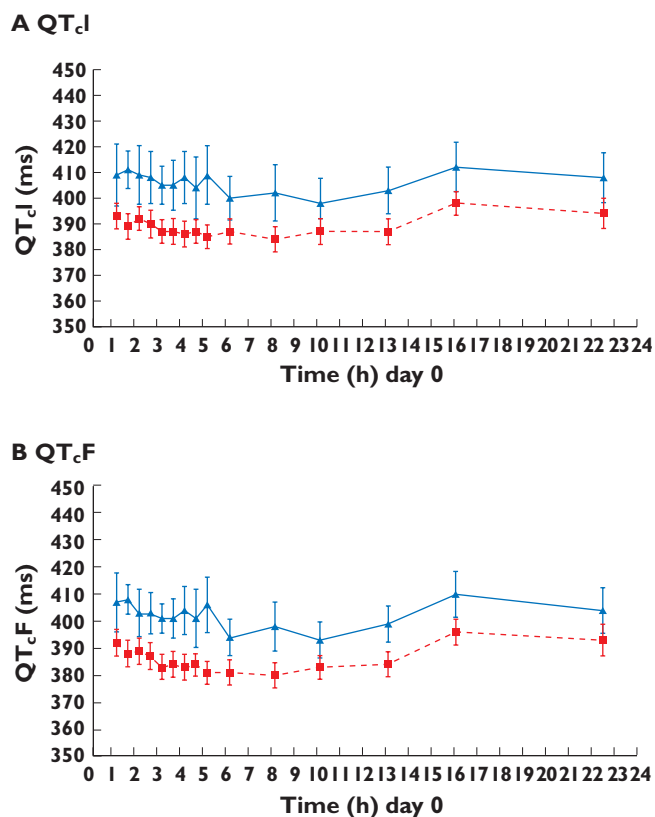
A linear concentration- $\Delta$ QT<sub>cI</sub> model structure including fixed and random effects on slope and intercept was found to describe the observed data best. Using this base structure, gender and baseline centred QT<sub>cI</sub> were identified as a significant covariate on the intercept and gender was identified as a significant covariate on the slope. The slope of the concentration- $\Delta$ QT<sub>cI</sub> relationship was 30 ms per  $\mu\text{g ml}^{-1}$  in women and 23 ms per  $\mu\text{g ml}^{-1}$  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  $\Delta$ QT<sub>cI</sub> in women would be around 58 ms at the geometric mean concentration observed in

this study ( $1.8 \mu\text{g ml}^{-1}$ ) and around 88 ms at the upper range ( $2.8 \mu\text{g ml}^{-1}$ ). Corresponding  $\Delta$ QT<sub>cI</sub> values for men would be approximately 25 ms at the geometric mean concentration observed in this study ( $1.4 \mu\text{g ml}^{-1}$ ) and 37 ms at the upper range ( $1.9 \mu\text{g ml}^{-1}$ ).

A similar concentration–QT<sub>c</sub> relationship, including similar significant covariates, was obtained when the analysis was performed using  $\Delta$ QT<sub>cF</sub>. The slope of the regression line for  $\Delta$ QT<sub>cF</sub> was 31 ms per  $\mu\text{g ml}^{-1}$  in women and 24 ms per  $\mu\text{g ml}^{-1}$  in men ( $P = 0.0189$ ) (Figure 6B and Table 1).

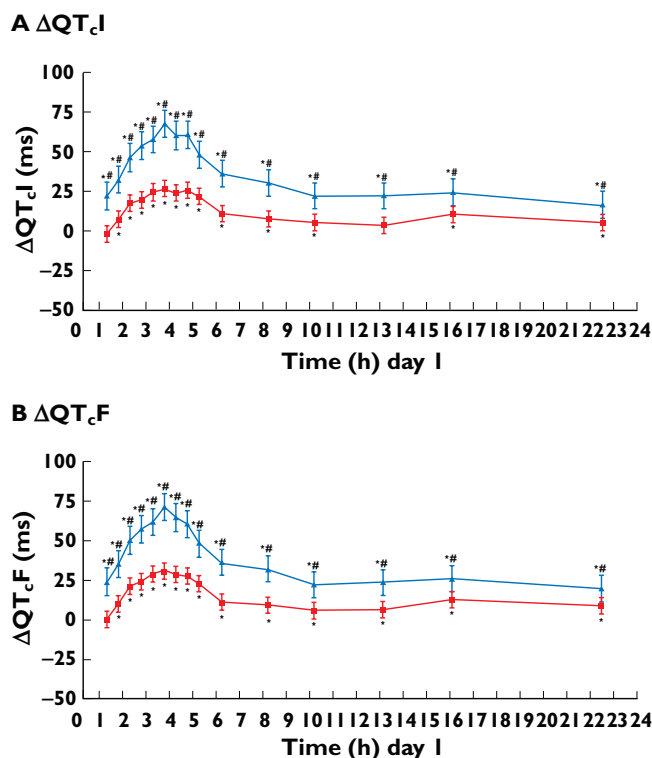
## Discussion

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 QT<sub>c</sub> interval prolongation was also significantly larger in female healthy subjects. The mean peak rac-sotalol plasma concentration

**Figure 4**

QT<sub>c</sub> in men and women in the drug free state at baseline (day 0). For all heart rate correction methods, women had longer baseline QT<sub>c</sub> than men. A) QT<sub>cI</sub>; B) QT<sub>cF</sub>. —●—, females; -■-, males

was 1.8 µg ml<sup>-1</sup> (SD 0.4) in women compared with 1.4 µg ml<sup>-1</sup> (0.3) in men and the overall rac-sotalol exposure (AUC<sub>(0,∞)</sub>) was also larger in women (17.1 vs. 14.6 µg ml<sup>-1</sup> h). At baseline, men had a lower resting heart rate and irrespective of heart rate correction method, 15 to 20 ms shorter QT<sub>c</sub> than women (around 390 ms in men and 410 ms in women, Figure 4). Expectedly, rac-sotalol caused a pronounced and significant QT<sub>c</sub> prolongation in both genders with a largest mean ΔQT<sub>cI</sub> of 68 ms and ΔQT<sub>cF</sub> of 72 ms in female subjects and a significantly less pronounced effect in males (mean ΔQT<sub>cI</sub> of 27 ms and mean ΔQT<sub>cF</sub> of 31 ms) (Figure 5). Interestingly, this difference in ΔQT<sub>cI</sub> and ΔQT<sub>cF</sub> cannot entirely be explained based on gender differences in plasma concentration. The model-based concentration-ΔQT<sub>c</sub> relationship was significantly steeper in female subjects (slope of 30 ms per µg ml<sup>-1</sup> for ΔQT<sub>cI</sub> and 31 ms per µg ml<sup>-1</sup> for ΔQT<sub>cF</sub>) as compared with males (slope of 23 ms per µg ml<sup>-1</sup> for ΔQT<sub>cI</sub> and 24 ms per µg ml<sup>-1</sup> for ΔQT<sub>cF</sub>). The projected ΔQT<sub>cI</sub> and ΔQT<sub>cF</sub> based on the concentration-ΔQT<sub>c</sub> model were generally consistent with the time-matched analysis with an effect of approximately 58 ms for ΔQT<sub>cI</sub> and 60 ms for ΔQT<sub>cF</sub> at the geometric mean peak concentration in women and 25 ms for ΔQT<sub>cI</sub> and 28 ms for ΔQT<sub>cF</sub> in men.

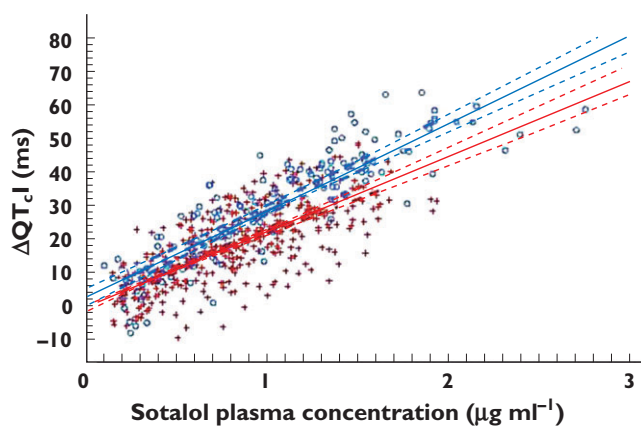
**Figure 5**

Change from baseline in QT<sub>c</sub> (ΔQT<sub>c</sub>) in men and women after dosing of 160 mg rac-sotalol on day 1. The QT<sub>c</sub> prolongation was consistently larger in women than in men at all time points after dosing. A) QT<sub>cI</sub>; B) QT<sub>cF</sub>. # Significant change (*P* < 0.05) from the corresponding time point at baseline; \* Significant difference between men and women. —●—, females; -■-, males

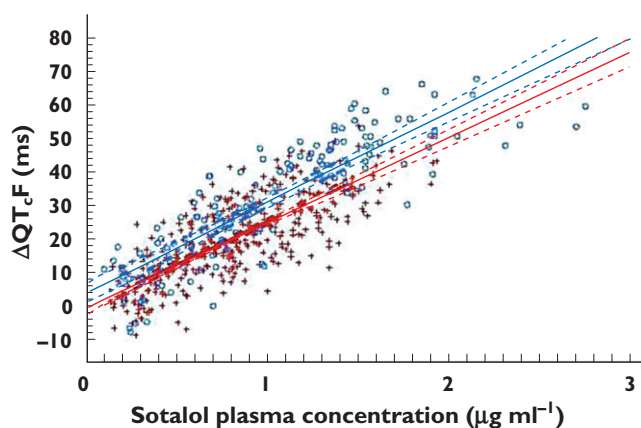
It is well described that women are at a higher risk than men for the development of the feared consequence of delayed repolarization, torsades de pointes ventricular tachycardia (TdP). In a meta-analysis of 332 patients who developed TdP on cardiovascular drugs known to prolong the QT<sub>c</sub> interval (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 QT<sub>c</sub> 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

A  $\Delta QT_c I$



B  $\Delta QT_c F$



**Figure 6**

A): Concentration vs.  $\Delta QT_c I$  using a linear mixed effects model. The slope of the model based concentration- $\Delta QT_c I$  relationship was significantly different ( $P = 0.0135$ ) in women as compared with men:  $\Delta QT_c I = -3.2 - 0.7 \times \text{centred baseline } QT_c I + 23 \times \text{rac-sotalol concentration } (\mu\text{g ml}^{-1})$  in men and  $\Delta QT_c I = 7.9 - 0.7 \times \text{centred baseline } QT_c I + 30 \times \text{rac-sotalol concentration } (\mu\text{g ml}^{-1})$  for women. B) Concentration vs.  $\Delta QT_c F$  using a linear mixed-effects model. The slope of the model based concentration- $QT_c F$  relationship was significantly different ( $P = 0.0189$ ) in women as compared with men:  $\Delta QT_c F = -2.5 - 0.7 \times \text{centred baseline } QT_c F + 24 \times \text{rac-sotalol concentration } (\mu\text{g ml}^{-1})$  in men and  $\Delta QT_c F = 8.1 - 0.7 \times \text{centred baseline } QT_c F + 31 \times \text{rac-sotalol concentration } (\mu\text{g ml}^{-1})$  for women.  $++$ , males;  $oo$ , females

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

**Table 1**

Estimates from the concentration- $\Delta QT_c$  relationship model

Variable	Estimate	Standard error	P value
<b>QT<sub>c</sub>F</b>			
Intercept (ms)	-2.5	2.0	0.22
Plasma concentration of rac-sotalol (ms per $\mu\text{g ml}^{-1}$ )	24	1.7	<0.0001
Female gender (ms)	10.6	3.8	0.005
Concentration $\times$ Female gender interaction (ms per $\mu\text{g ml}^{-1}$ )	7	2.8	0.019
Centred baseline QT <sub>c</sub> F (ms)	-0.70	0.05	<0.0001
<b>QT<sub>c</sub>I</b>			
Intercept (ms)	-3.2	2.0	0.12
Plasma concentration of rac-sotalol (ms per $\mu\text{g ml}^{-1}$ )	23	1.7	<0.0001
Female gender (ms)	11.1	3.8	0.004
Concentration $\times$ Female gender interaction (ms per $\mu\text{g ml}^{-1}$ )	7	2.8	0.01
Centred baseline QT <sub>c</sub> I (ms)	-0.70	0.05	<0.0001

effect at similar concentrations of a drug. In addition, the longer baseline  $QT_c$  in women may be a contributing factor. Limited data from multiple small studies support that women may have greater  $QT_c$  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 ( $3 \text{ mg kg}^{-1}$ ). Peak plasma concentrations were comparable in women ( $0.87 \mu\text{g ml}^{-1}$ ) and in men ( $1.0 \mu\text{g ml}^{-1}$ ), but the  $QT_c I$  prolongation was greater in females with the largest effect observed 2 h after the infusion:  $33 \pm 16 \text{ ms}$  in women and  $24 \pm 17 \text{ ms}$  in men ( $P = 0.037$ ) [26]. Twelve women and 12 men received a single i.v. dose of quinidine ( $4 \text{ mg kg}^{-1}$ ) 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 ( $3.7 \pm 0.13$  vs.  $2.8 \pm 0.87 \mu\text{g ml}^{-1}$ ,  $P = 0.07$ ) but the concentration- $QT_c B$  slope was more than 40% steeper in women:  $42.2 \pm 3.4 \text{ ms per } \mu\text{g ml}^{-1}$  in women vs.  $29.3 \pm 2.6 \text{ ms per } \mu\text{g ml}^{-1}$  in men;  $P < 0.001$ . Results were similar with  $QT_c F$ . 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 ( $4 \text{ mg kg}^{-1}$ ) or saline and the QT interval was measured serially after the infusion and corrected using  $QT_c B$ . The concentration-effect relationship was analyzed by means of a non-linear  $E_{\text{max}}$  model. Female Caucasian subjects ( $n = 6$ ) had substantially lower peak plasma concentrations than males ( $2.46 \pm 0.33 \text{ mg l}^{-1}$  vs.  $3.69 \pm 0.60 \text{ mg l}^{-1}$ ), but due to the small sample size, plasma concentration differences across gender or ethnicity were not statistically significant. Quinidine-induced  $QT_c B$  prolongation was in general higher in Caucasian subjects as compared with Koreans and significantly higher in

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 QT<sub>c</sub> 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 QT<sub>c</sub> 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<sup>-1</sup> vs. 2.1 µg ml<sup>-1</sup>, *P* < 0.001) and a statistically significant larger peak QT<sub>c</sub>F effect with a placebo-corrected ΔQT<sub>c</sub>F 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–QT<sub>c</sub>F relationship, which indicates that the observed difference in QT<sub>c</sub>F prolongation can be explained by differences in plasma concentrations.

It has been clearly shown that TdP is preceded by a pronounced and exaggerated QT<sub>c</sub> prolongation [2, 9, 21, 24, 30] and that patients who experience TdP exhibit a larger degree of QT<sub>c</sub> 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<sub>c</sub> 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<sup>-1</sup>) 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<sup>-1</sup>) than in men (563 (291) pg ml<sup>-1</sup>). Greater ΔQT<sub>c</sub>B 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 QT<sub>c</sub>

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<sup>-1</sup> i.v. over 10 min), ΔQT<sub>c</sub>B 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 QT<sub>c</sub> 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 (QT<sub>c</sub> 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 QT<sub>c</sub> interval [36], as demonstrated by the slope of the QT<sub>c</sub>/RR regression lines (Figure 3). Even so, our findings were essentially the same for a population-derived method, QT<sub>c</sub>F, a study-specific method, QT<sub>c</sub>N and for a method based on each subject's QT/RR pairs, QT<sub>c</sub>I. The use of ECGs recorded at 180 Hz is another limitation. To overcome this limitation, we upsampled 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 QT<sub>c</sub> 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 QT<sub>c</sub> prolongation than males at given plasma concentrations with a steeper concentration–ΔQT<sub>c</sub> 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](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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