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ARTICLE

Models of Variability and Circadian Rhythm in Heart Rate, Blood Pressure, and QT Interval for Healthy Subjects Who Received Placebo in Phase I Trials

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This work characterized the time-course, circadian rhythm, and inherent variability in key cardiovascular variables (heart rate, corrected QT interval, and systolic and diastolic blood pressure) that are routinely collected as part of safety monitoring in phase I trials. Longitudinal data from 1,035 healthy volunteers who received placebo in 65 single-dose and multiple-dose phase I trials conducted by AbbVie were compiled and analyzed using nonlinear mixed-effects modeling. An independent nonlinear mixed-effects model was developed for each variable, and combinations of cosine functions were used to capture circadian oscillations. Gender, race, age, and body weight were significant covariates for variability in baseline measures, and the contributions of these covariates were quantitatively characterized. Based on the extensive data set analyzed, the developed models represent valuable tools to help contextualize and differentiate inherent variability that can be expected in a typical phase I setting from true drug-related cardiovascular safety signals. In addition, these placebo models can be used to support exposure–response analyses that estimate treatment-related effects on the evaluated cardiovascular measures.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Cardiovascular variables are routinely measured in healthy volunteers in a phase I research setting as part of the safety assessment. Small sample size always poses a limitation in understanding placebo vs. drug-related effects.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ Our goal was to characterize the inherent variability in heart rate, QT interval, and systolic and diastolic blood pressure in subjects receiving placebo to facilitate differentiation of placebo variability from true drug-related effects.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ We developed nonlinear mixed-effects models of the cardiovascular variables incorporating subject demographics, circadian rhythms, other time-related effects, and random between-subject and residual variabilities. These analyses used a large data set from subjects randomized to placebo across 65 phase I trials.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ This work can provide reference to aid differentiation of true drug-related cardiovascular safety signals from inherent variability in the early phases of drug development. The developed placebo models can also support exposure–response analyses of cardiovascular safety parameters from phase I trials.

Early phase I trials typically evaluate single and/or multiple escalating doses of an investigational new drug using blinded (single or double), randomized, placebo-controlled designs in healthy volunteers. In addition to evaluating the pharmacokinetics, the key objective of this early phase of development is to characterize the initial safety and tolerability profiles of the evaluated compound over a wide dose range. However, given the small sample size of most phase I studies (typically 8–12 subjects per dose group randomized to active or placebo using an unbalanced ratio), certainty in ascribing an apparent safety signal to the drug under investigation vs. being just a chance finding or an artifact is always limited and needs to be supported by larger data sets to clearly delineate what can be expected in the absence of drug treatment.[1] Therefore, there is a need to robustly characterize the inherent variability in some of the routine safety variables collected in the early phase I trials and to assess the potential impact of study design elements and baseline participant demographics in such a setting.

Heart rate, QT interval, and blood pressure (BP) are among the key cardiovascular safety parameters monitored in

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early-phase clinical trials. The development of a drug candidate is usually halted if evidence of a clinically relevant effect on these parameters is observed in the early phase of development (with some exceptions when the potential benefit may justify the risk), especially for treatments intended for chronic administration. It is not uncommon to observe large intersubject variability (ISV) and/or within-subject variability in these key cardiovascular safety variables even in a well-controlled phase I setting, making data interpretation more challenging. Diurnal variations, changes in the environment, ingestion of meals, and stress associated with study activities are known to influence some of these parameters.[2,3]

Because the study design characteristics, baseline demographics, and random unexplained variability can confound interpretation of the cardiovascular safety signal and potentially delay or halt development of otherwise effective medicines, the objective of this work was to use a model-based approach to quantitatively characterize the time-course and inherent variability in key cardiovascular measures and identify the sources of variability using data from subjects who received placebo in 65 single-dose and multiple-dose phase I trials conducted by AbbVie. These analyses were envisioned to aid physicians in understanding the range of what can be observed on placebo in terms of cardiovascular parameters in the phase I setting. They were also designed to serve as robust placebo models that anchor and support nonlinear mixed-effects exposure–response analyses of cardiovascular parameters from small individual studies with limited placebo information.

METHODS

Longitudinal data from healthy subjects who received single or multiple administrations of placebo in 65 phase I studies (conducted between 2007 and 2014) for systolic and diastolic BP and 63 studies for heart rate and QT interval were included in the analyses. A majority of the analyses were conducted in 2015. All studies were conducted in accordance with Good Clinical Practice guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The protocols and informed consent forms were approved by the institutional review boards at each site, and all participants provided written informed consent before any study-related procedures were performed.

Model development

The TIME variable in non-linear mixed effects modeling (NONMEM) (version 7.3; Icon, Ellicott City, MD) was adjusted to time since midnight (12:00 AM clock time) prior to the first record of measurement (including screening). In the cases of single-dose and multiple-dose studies, the TIME variable was continuous starting with the midnight prior to the first record of measurement through the end of the study. In the case of crossover studies, the event identification (ID) variable in the NONMEM data set was set to four at the start of each study period within the subject. The QT interval was corrected for heart rate using Fridericia's formula as shown in Eq. 1:

$$QTcF = QT/((RR/1{,}000)^{(1/3)}). \quad (1)$$

The models for each cardiovascular variable were developed using the first-order conditional estimation method with INTERACTION.

The final model had the following structure as shown in Eq. 2; each component is defined separately:

$$P_{ij} = (BL_i + CIRC_{k,ij} + TE_i) + \text{residual random error}. \quad (2)$$

where P_{ij} is the estimate of the selected cardiovascular variable for the ith individual at the jth time, BL_i is the baseline estimate of the ith subject, $CIRC_{k,ij}$ is the kth (24, 12, 6, or 3 hours) circadian rhythm ($CIRC_k$) for subject i at the jth time, and TE_i is the additional time effect for subject i.

The starting model for each variable estimated only the baseline (at 12:00 midnight) and the associated ISV in baseline (in standard deviation (SD) scale) as described in Eq. 3:

$$\begin{aligned} BL_i = {} & TVBL \times (CON_i/CON_{ref})^{CON}_{factor} \\ & + CAT_i \times (CAT_{factor,q}) + (\eta_i) \times \Theta_1, \end{aligned} \quad (3)$$

where TVBL is the population baseline estimate, η_i is the additive difference between BL_i and TVBL, assumed to be normally distributed with a mean of 0 and a variance of ω^2 fixed to 1, and Θ_1 is the scaling factor for ISV estimated as a fixed effect for ease of interpretation of variability of baseline in the SD scale.

A stepwise inclusion of covariates was performed. The continuous covariates were evaluated as a power model, normalized at the reference covariate value (CON_{ref}; 70 kg for body weight and 30 years for age) as shown in Eq. 3, where CON_i is the body weight or age of the ith subject and CON_{factor} is the estimated slope of the relationship between log TVBL and the log of (CON_i/CON_{ref}). The categorical covariates of gender and race (black, white, Asian, and others) were evaluated with an additive function (Eq. 3), where the CAT_{factor} is the parameter that describes the additive difference estimated for the effect of selected categorical covariates on the evaluated variable where CAT_i takes the value of zero for the most frequent category.

Following estimation of baseline and inclusion of significant covariates, the circadian rhythm components were incorporated in the model in a stepwise manner starting with 24 hours followed by 12, 6, and 3 hours using a cosine function for each as shown in Eq. 4:

$$CIRC_{k,ij} = AMP_{k,i} \times COS(2 \times 3.14(T_j - PS_{k,i})/k), \quad (4)$$

where $AMP_{k,i}$ and $PS_{k,i}$ represent the individual estimate of the amplitude and phase shift (relative to 12:00 AM) of the kth (24, 12, 6, or 3 hours) circadian rhythm ($CIRC_k$) for the ith subject relative to midnight.

Following inclusion of the significant circadian oscillations to the model, an additive time drift modeled as a linear or a nonlinear function was also explored as shown in Eqs. 5 and 6, respectively.

$$TE = (SLP * (TIME/24)), \quad (5)$$

$$TE = MAX * (1 - EXP(-(TIME/24) \times SLP)), \quad (6)$$

where TE is the time drift with a linear (Eq. 5) or an exponential slope (Eq. 6) of SLP reaching a maximum effect (MAX) over time.

Residual random error was modeled using a proportional or an additive error term as described in Eqs. 7 and 8, respectively.

$$P_{ij} = (\mathrm{BL}_i + \mathrm{CIRC}_k + \mathrm{TE}_i) \times (1 + \epsilon_{ij}), \quad (7)$$

$$P_{ij} = (\mathrm{BL}_i + \mathrm{CIRC}_k + \mathrm{TE}_i) + \epsilon_{ij} \times \Theta_2, \quad (8)$$

where ϵ_{ij} is the proportional or an additive residual random error assumed to be normally distributed with a mean of zero and individual variances of σ^2. For the additive error structure, Θ_2 is the scaling factor estimated as a fixed effect with σ^2 fixed to 1 such that ϵ_{ij} was estimated in the SD scale.

The likelihood ratio test[4] was used for comparing nested hierarchical models where a decrease in NONMEM objective function value (–2 log likelihood) of 6.63 points was necessary to consider the improvement in model performance statistically significant at $P < 0.01$ at 1 degree of freedom. Other selection criteria included improved goodness-of-fit and residual plots, increased precision in parameter estimation, and reduced variance of intersubject and residual errors.

This process was repeated for each of the four cardiovascular variables heart rate, QT interval, and systolic and diastolic BP to identify the best model that described the observed data.

Model evaluation

Goodness-of-fit plots. Observed (adjusted for covariate and random between-subject variabilities) data were compared with typical model predictions for each variable. In addition, generic goodness-of-fit plots were generated to evaluate any systemic model misspecification in the structural and residual error models.

Bootstrap evaluation. Robustness of the final model was evaluated using nonparametric bootstrap. Subjects were randomly sampled with replacement from the original data set to form 500 new data sets (each with a similar number of subjects stratified by race and gender to the original data set). The model parameters were then estimated using the bootstrap data sets. The median and 95% confidence interval (2.5th to 97.5th percentiles) for each parameter were calculated from the successfully converging runs, regardless of covariance step, and compared with the point estimates from the original data set.

Xpose, Perl Speaks NONMEM (version 4.2.0; Uppsala University, Uppsala, Sweden), and the ggplot2 package in R software (version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria) were used for summary statistics and plotting the results.

RESULTS

Data sources and baseline demographics

A total of 16,509 observations for each heart rate and QT interval (corrected for heart rate using Fridericia's formula; each observation is an average of high-precision triplicate measurements at each timepoint) were available for 996 subjects (76% males (N = 754) and 24% females (N = 242)) starting from 3 days prior to placebo dose to ~ 21 days after the first placebo dose. A total of 18,807 observations for each of systolic and diastolic BP were available from 1,035 subjects starting from 3 days prior to first placebo dose to 12 weeks after the first placebo dose. The distribution of baseline demographics for all four cardiovascular variables is provided in **Table 1**.

Cardiovascular variables

Nonlinear mixed-effects models for each cardiovascular variable were developed separately. The estimated baseline values (corresponding to 12:00 AM, typical estimate ± intersubject SD) were 61 ± 7 beats per minute (bpm; heart rate), 400 ± 14 milliseconds (QT interval), 123 ± 7 mm of mercury (mmHg; systolic BP), and 78 ± 6 mmHg (diastolic BP) for a 70 kg, 30-year-old, white male as a reference. The results from the final nonlinear mixed-effects model of each variable are described later. The respective model parameter estimates are shown in **Table 2**. The NONEMEM control stream for the final heart rate model, as an example, is provided as a **Data S1**.

Heart rate. The final heart rate model is shown in Eq. 9:

$$\begin{aligned}\text{Heart Rate}_{ij} &= (\text{Baseline}_i + \text{CIR24}_{ij} + \text{CIR12}_{ij} + \text{CIR6}_{ij} \\ &\quad + \text{Time drift}) \times (1 + \text{Residual error})\end{aligned} \quad (9)$$

$$\text{Baseline}_i = 60.7\ (\text{bpm}) + 6.8\ (\text{if female}) + \eta_{\text{baseline}},$$

where ij is the estimate of the model parameter (applicable to all four cardiovascular variables) for the ith individual at the jth time, η_{baseline} represents between-subject variability in the baseline measure; CIR24, CIR12, and CIR6 represent 24-hour, 12-hour, or 6-hour circadian rhythm cycles, respectively. Of the evaluated covariates, only gender was found to be statistically significant such that when compared with males, females

Table 1 Baseline demographic summary for the analyses data set

	Heart rate and QT interval, N = 996	Systolic and diastolic blood pressure, N = 1,035
Categorical covariates	***N* (%)**	***N* (%)**
Gender		
Male	754 (76)	772 (75)
Female	242 (24)	263 (25)
Race		
Black	325 (33)	336 (33)
White	569 (57)	588 (57)
Asian	75 (8)	83 (8)
Other	27 (2)	28 (2)
Continuous covariates	**Mean (SD)**	**Mean (SD)**
Body weight, kg	75 (13)	75 (12)
Age, year	34 (10)	34 (10)

SD, standard deviation.

Table 2 Parameter estimates and the bootstrap 95% confidence interval of the final parametric models of cardiovascular variables in healthy volunteers

Parameter	Heart rate	QT interval	Systolic blood pressure	Diastolic blood pressure
Baseline for males[a]	60.7 (60.1, 61.2)	400 (398, 402)	123 (122, 125)	78.3 (76.9, 80.2)
Additive factor for female baseline[a]	6.8 (5.7, 7.9)	14.7 (12.8, 16.5)	–8.3 (–9.6, –7.2)	–4.7 (–5.7, –3.9)
Additive factor for black race[a]	NS	–3.4 (–5.4, –1.5)	3.8 (2.8, 4.9)	2.1 (1.5, 2.9)
Additive factor for Asian race[a]	NS	NS	NS	–1.5 (–1.0, –2.1)
Exponent for age; power model (normalized to 30 years)	NS	0.031 (0.025, 0.039)	NS	0.08 (0.07, 1.0)
Exponent for weight; power model (normalized to 70 kg)	NS	NS	0.09 (0.06, 0.12)	NS
24 hours circadian amplitude[a]	2.2 (2.0, 2.4)	2.6 (2.2, 2.9)	1.0 (0.7, 1.3)	1.6 (1.4, 1.9)
24 hours circadian phase shift[b]	17.6 (17.1, 17.9)	2.2 (1.9, 2.6)	19.3 (18.4, 20.3)	2.3 (1.9, 2.8)
12 hours circadian amplitude[a]	0.5 (0.4, 0.7)	2.0 (1.8, 2.3)	NS	NS
12 hours circadian phase shift[b]	NS	3.6 (3.4, 3.8)	NS	NS
6 hours circadian amplitude[a]	2.7 (2.6, 2.9)	1.2 (1.1, 1.4)	NS	NS
6 hours circadian phase shift[b]	2.8 (2.8, 2.9)	1.7 (1.5, 1.8)	NS	NS
Time drift model	0.15 x (TIME)	5.0 x (1–exp(–1.4 x TIME))	7.6 x (1–exp(–1.2 x TIME))	4.8 x (1–exp(–1.6 x TIME))
ω^2 baseline (additive model)	1 fixed	1 fixed	1 fixed	1 fixed
Scaling factor for $\omega_{baseline}$	7.1 (6.7, 7.4)	13.9 (13.1, 14.7)	7.4 (6.9, 7.8)	6.0 (5.6, 6.3)
σ^2 (additive residual error)[c]	0.004 (0.004,0.005)	1 fixed	1 fixed	1 fixed
Scaling factor for σ	NS	5.7 (5.5, 5.8)	7.5 (7.4, 7.7)	5.2 (5.1, 5.3)

Data presented as NONMEM point estimates of the final model (95% bootstrap confidence interval from successful runs).
NS, not significant and was not included in the final model; TIME, time since midnight (12:00 AM).
[a]Units are beats per minute (heart rate), milliseconds (QTcF), and mmHg (blood pressure). [b]Phase shift (hour) for cosine functions relative to 12:00 AM. [c]Proportional residual error model for heart rate.

are estimated to have a ~7 bpm higher baseline heart rate (**Table 2**). The circadian rhythm in heart rate was explained adequately by three additive cosine functions covering 24-hour, 12-hour, and 6-hour intervals. No phase shift parameter was included in the 12-hour circadian cycle because the estimate was close to 12. The addition of ISV on the 6-hour phase shift, 24-hour amplitude, 24-hour phase shift, and 12-hour amplitude was deemed necessary and was included in the model in a stepwise fashion. Visual inspection showed a shallow trend of a linear increase in the peaks and troughs of the heart rate with time (within the time frame evaluated in the analysis); hence an additive linear time drift component (typical estimate ± intersubject SD (increase of 0.15 (± 0.45) bpm/day) was added to the model. Finally, the proportional error model was found to be superior to the additive residual error structure and was included in the final heart rate model.

QT interval. The final QT interval model is shown in Eq. 10:

$$\begin{aligned} QT_{ij} &= (\text{Baseline}_i + \text{CIR24}_{ij} + \text{CIR12}_{ij} + \text{CIR6}_{ij} \\ &\quad - \text{Time drift}) + \text{Residual error} \end{aligned} \tag{10}$$

$$\begin{aligned} \text{Baseline}_i = 400\ (\text{msec}) \times \left(\frac{\text{Age}}{30}\right) 0.031 + 14.7\ (\text{if female}) \\ - 3.4\ (\text{if Black Race}) + \eta_{\text{baseline}}. \end{aligned}$$

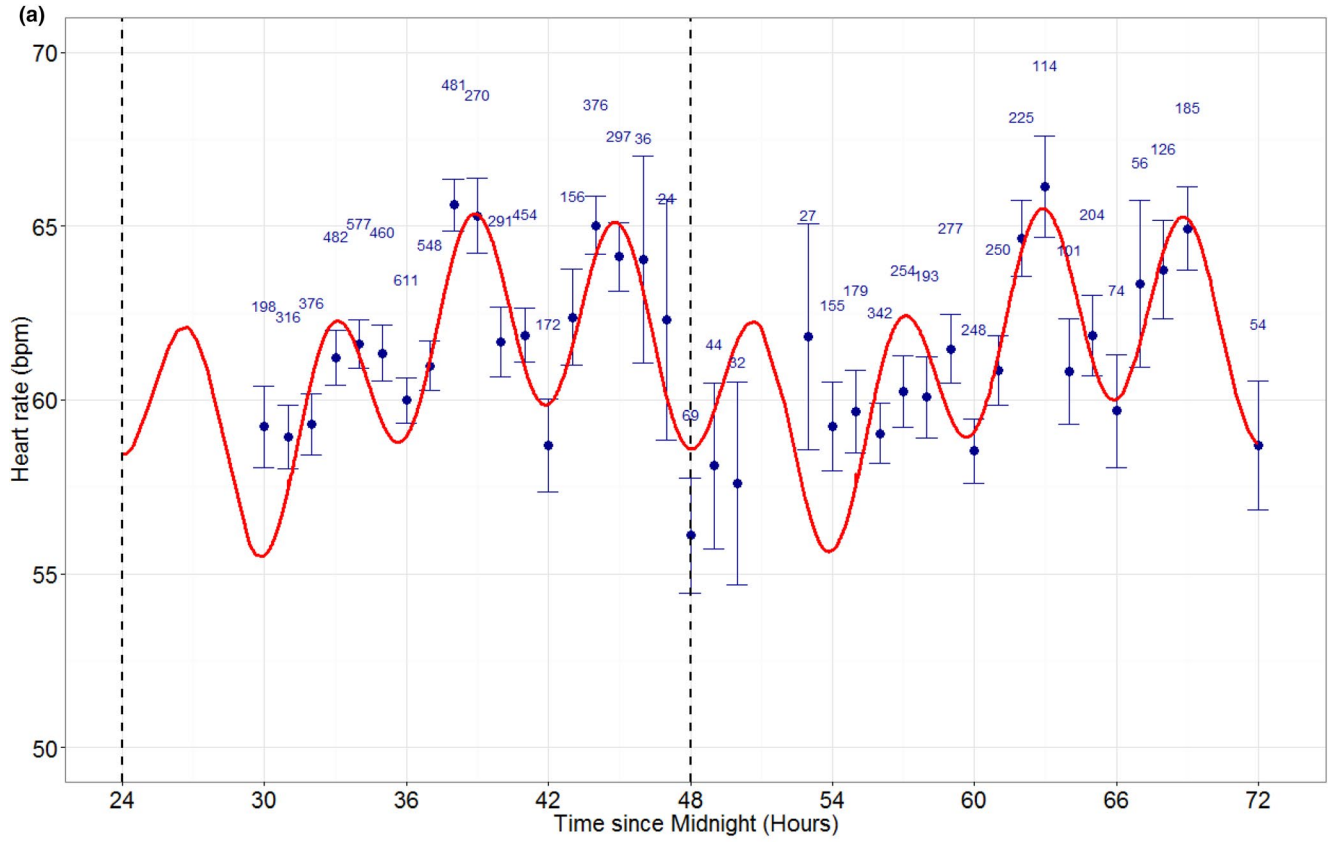
Relative to a typical male, a typical female was estimated to have a ~15 milliseconds (msec) longer baseline QT interval and, relative to a typical white male, a typical black male is estimated to have a ~3.5 shorter QT interval (**Table 2**). The inclusion of age as a covariate further improved the fit such that the QT interval increased with age (slope of relationship between log QT and log (age/30) = 0.031). Body weight was not found to be a significant covariate for the QT interval. Similar to the heart rate model, additive 24-hour, 12-hour, and 6-hour cosine functions adequately described the circadian rhythms in the QT interval. The ISV on the 24-hour, 12-hour, and 6-hour phase shifts were included in the model in a sequential manner. Visual inspection showed a trend for decline in the peaks and troughs of the QT circadian rhythms within the assessed timeframe. The model estimated an exponential drift reaching a maximum reduction of 5 msec with a first-order rate constant of 1.4 day^{-1} (half-life of ~ 12 hours). The addition of random ISV on the slope and/or maximum effect of this time drift led to model termination because of numerical errors and was not included in the final model.

Systolic BP. The final systolic BP model is shown in Eq. 11:

$$\begin{aligned} \text{Systolic BP}_{ij} &= \left(\text{Baseline}_i + \text{CIR24}_{ij} - \text{Time drift}\right) \\ &\quad + \text{Residual error} \end{aligned} \tag{11}$$

$$\begin{aligned} \text{Baseline}_i &= 123\ (\text{mmHg}) * \left(\frac{\text{WT}}{70}\right) 0.09 - 8.3\ (\text{if female}) \\ &\quad + 3.8\ (\text{if black race}) + \eta_{\text{baseline}}. \end{aligned}$$

When compared with a typical male, a typical female was estimated to have ~8 mmHg lower systolic BP, and a typical black male was estimated to have ~4 mmHg higher systolic BP (**Table 2**). Body weight was found to be positively correlated with systolic BP (slope of relationship between log systolic BP and log (body weight/70) = 0.09). Age was


(a)
Heart rate (bpm)
70
65
60
55
50
24
30
36
42
48
54
60
66
72
Time since Midnight (Hours)

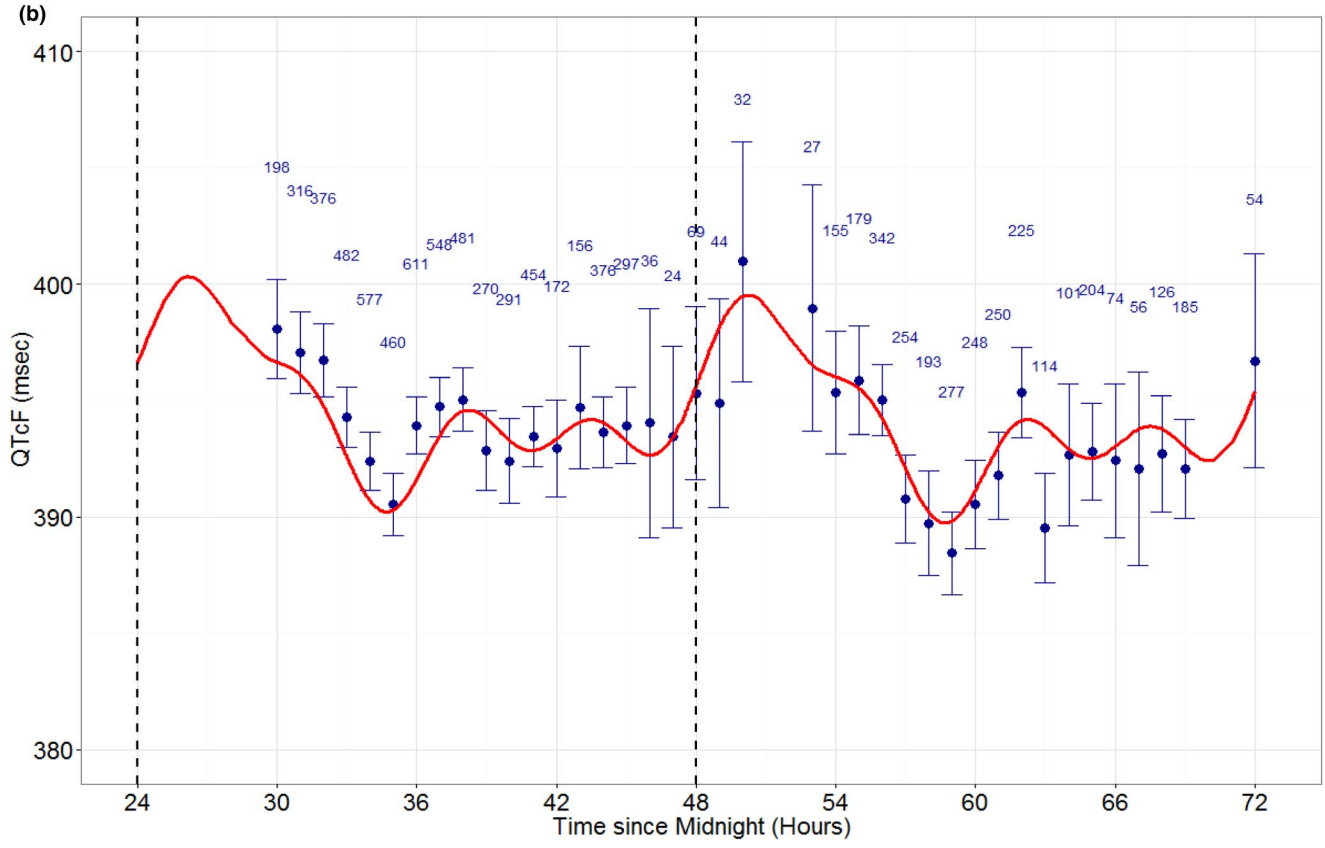

(b)
QTcF (msec)
410
400
390
380
24
30
36
42
48
54
60
66
72
Time since Midnight (Hours)

Figure 1 Observed (adjusted for covariate and random between-subject variability) and typical model-predicted (**a**) heart rate and (**b**) QT interval for a 30-year-old, 70 kg, white male. Closed circle = individual residual error + typical model predicted heart rate in or QT interval in for a white male 30 years of age and 70 kg body weight at unique times in the data set (mean ± 95% confidence interval). Solid red line = typical model predicted heart rate in or QT interval in for a white male 30 years of age and 70 kg body weight; numbers represent the number of observations at unique times in the data set. Dotted line = one cycle of 24 hours; observed data with a minimum of 20 observations are shown.

not found to be a significant covariate for the systolic BP. Of the four circadian rhythm functions evaluated (spanning 3–24 hour cycles), only the 24-hour circadian rhythm was found to be significant. The ISV parameter was found to be significant on 24-hour amplitude. The model estimated an exponential drift reaching a maximum reduction of 7.6 mmHg with a first-order rate constant of 1.2 day^{-1} (half-life of ~ 14 hours). The addition of random ISV on the maximum effect of this time drift did not improve the model fit any further.

Diastolic BP. The final diastolic BP model is shown in Eq. 12:

$$\text{Diastolic BP}_{ij} = \left(\text{Baseline}_i + \text{CIR24}_{ij} - \text{Time drift}\right) + \text{Residual error} \quad (12)$$

$$\text{Baseline}_i = 78.3\,(\text{mmHg}) \times \left(\frac{\text{Age}}{30}\right) 0.08 - 4.7\ (\text{if female}) + 2.1\ (\text{if black race}) - 1.5\ (\text{if Asian race}) + \eta_{\text{Baseline}}.$$

Relative to a typical male, a typical female is estimated to have ~5 mmHg lower diastolic BP, and a typical black male and a typical Asian male are estimated to have ~2 mmHg higher and lower diastolic BP, respectively (**Table 2**). Inclusion of age further reduced the objective function value such that the diastolic BP increased with age (slope of relationship between log diastolic BP and log (age/30) = 0.08). Body weight was not found to be a significant covariate for diastolic BP. Similar to systolic BP, a 24-hour circadian rhythm cosine function alone adequately described the data. The ISV on 24-hour amplitude and 24-hour phase shift led to further reduction in the objective function value and overall improvement of the model fit. The model estimated an exponential drift with time reaching a maximum reduction of 4.8 mmHg at a first-order rate of 1.6 day^{-1} (half-life of ~ 10 hours).

Goodness-of-fit plots (**Supplementary Figures**) and bootstrap analyses (**Table 2**) suggested adequacy of the developed models in describing the heart rate, QT interval, and systolic and diastolic BP in healthy volunteers receiving placebo in phase I trials.

Impact of subject demographics and circadian rhythm on cardiovascular variables

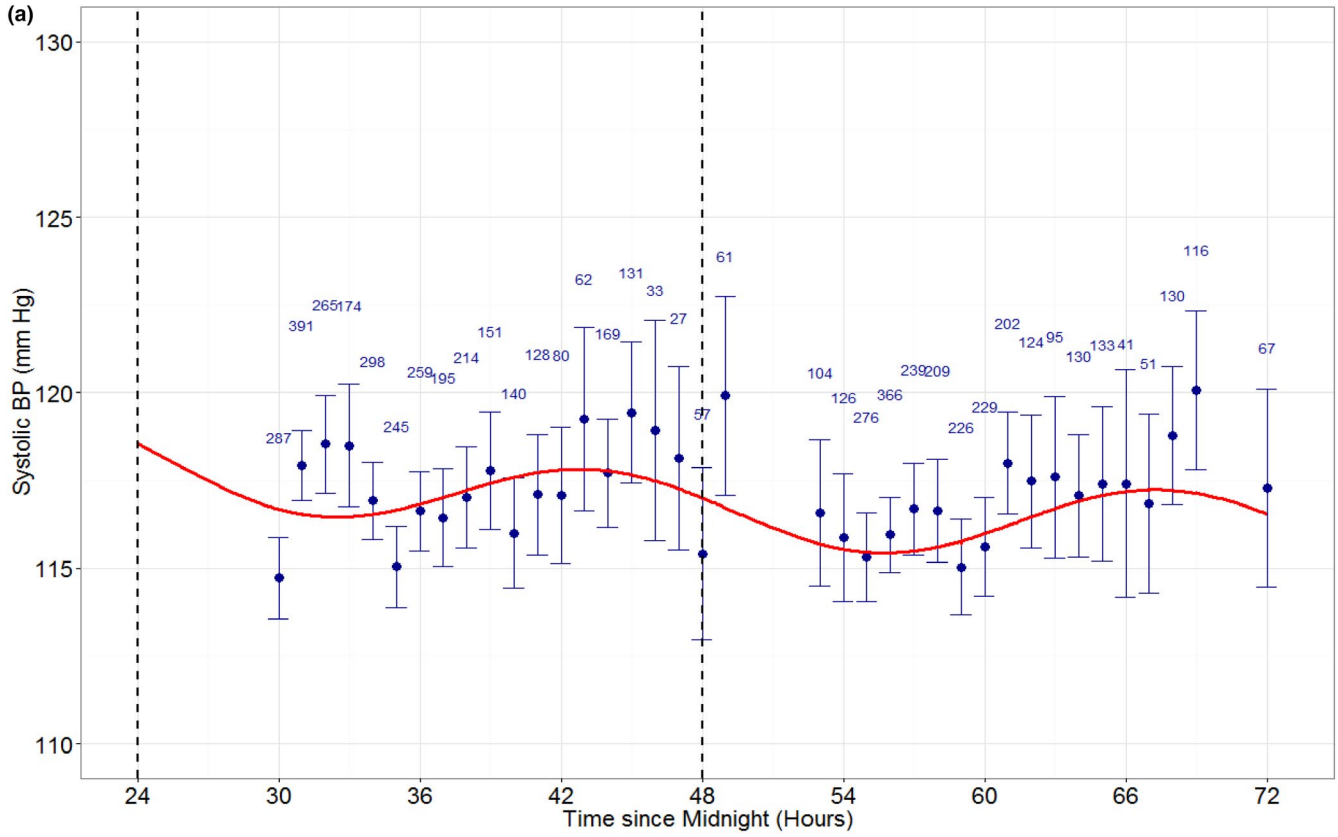
Effect of circadian rhythm. Figures 1 and 2 illustrate the observed and model-predicted time course of heart rate, QT interval, and BP in subjects who received placebo. The figures are normalized to a 30-year-old, 70 kg, white male, therefore eliminating the estimated impact of other covariates on these parameters to illustrate the circadian rhythm effect and the remaining unexplained variability in these cardiovascular measures. The peaks and troughs as a result of circadian rhythms were estimated to be, respectively, at 3:00 PM and 6:00 AM for heart rate (difference of ~10 bpm), 2:00 AM and 11:00 AM for QT interval (difference of ~10 msec), 7:00 PM and 8:00 AM for systolic BP (difference of ~ 2 mmHg), and 2:00 AM and 2:00 PM for diastolic BP (difference of ~ 3.5 mmHg).

Effect of gender and race. Box plots of model-predicted cardiovascular variables of 1,000 black male, white female, and black female subjects, each 30 years of age and weighing 70 kg, are compared with the distribution of 1,000 white males as a reference and are depicted in **Figure 3**. The summary is depicted at 11:00 AM clock time or ~ 3 hours postplacebo dose (morning dose of ~ 8:00 AM in a typical phase I study) to mimic a time close to the peak of plasma concentrations for the majority of the small molecules as assessed in phase I trials. These plots illustrate the contribution of gender and race to the overall variability in these cardiovascular measures once the age and bodyweight are taken into account.

Effect of age and body weight. Model-simulated time courses including the circadian rhythms (median and 90% prediction interval) for QT interval and diastolic BP for 1,000 white male subjects each of 18, 30, or 60 years of age (to demonstrate the impact of age) and for systolic BP of the 1,000 white male subjects each weighing 40, 70, or 120 kg (to demonstrate the impact of body weight) are depicted in **Figure 4a,b**. These figures illustrate the contribution of age and body weight to the overall variability in the QT interval and systolic BP once the age and race variables are taken into account.

DISCUSSION

This work characterized the time course and inherent variability in heart rate, QT interval, and systolic and diastolic BP in healthy volunteers using nonlinear mixed-effects modeling of longitudinal data from more than 1,000 subjects who received placebo across 65 phase I studies conducted by AbbVie from 2007–2014. A majority of these analyses were conducted in 2015. The extensive data set spread over 24-hour daily cycles enabled robust, quantitative characterization of the variability and impact of demographic characteristics, time, and circadian rhythms on cardiovascular measures that are otherwise difficult to ascertain in a single, small phase I study. The results of the current analyses expand on the initial analyses from a subset of this data set.[5] The developed models can help benchmark the expected distribution of cardiovascular parameters in a typical phase I setting and increase the power to discern artifact or chance findings from true drug-related


(a)
Systolic BP (mm Hg)
130
125
120
115
110
24
30
36
42
48
54
60
66
72
Time since Midnight (Hours)

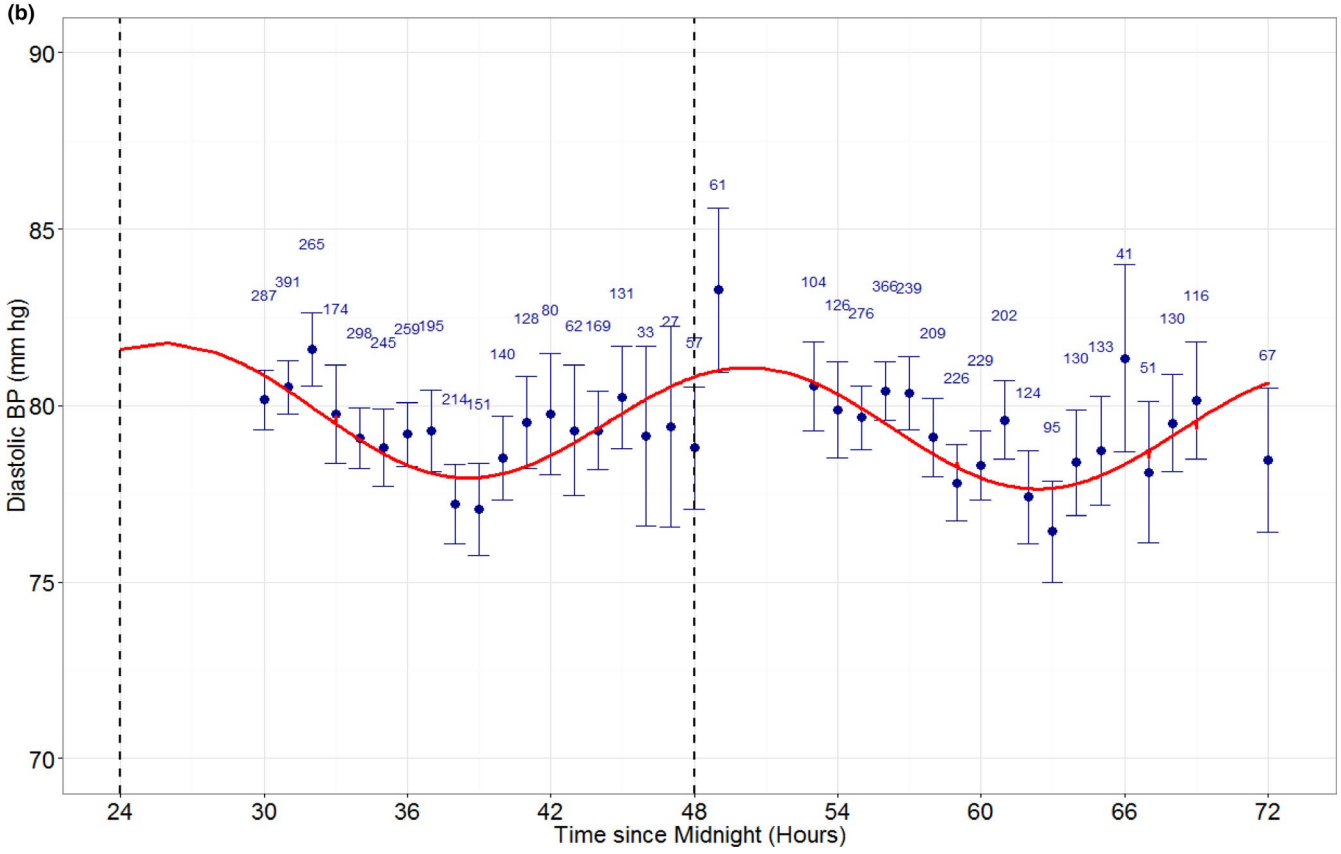

(b)
Diastolic BP (mm hg)
90
85
80
75
70
24
30
36
42
48
54
60
66
72
Time since Midnight (Hours)

Figure 2 Observed (adjusted for covariate and random between-subject variability) and typical model-predicted (**a**) systolic and (**b**) diastolic blood pressure (BP) for a 30-year-old, 70 kg, white male. Closed circle = individual residual error + typical model predicted systolic in or diastolic in BP for a white male 30 years of age and 70 kg body weight at unique times in the data set (mean ± 95% confidence interval). Solid red line = typical model predicted systolic in or diastolic in BP for a white male 30 years of age and 70 kg body weight; numbers represent the number of observations at unique times in the data set. Dotted line = one cycle of 24 hours; observed data with a minimum of 20 observations are shown.

cardiovascular safety signals. These placebo models can also be used to support the exposure–response analyses that estimate the true treatment-related effect of experimental compounds.

The effects of demographic characteristics on cardiovascular parameters have been previously evaluated, although in a less systematic fashion. Regarding gender, in an analysis of patients and healthy volunteers,[6] median heart rate and the QT interval in 20-year-old to 59-year-old females (comparable age range to the present analysis) were estimated to be 3–6 bpm higher and ~10 msec longer, respectively, relative to males in the same age range. Other reports have also noted gender-specific trends in heart rate, QT interval, and BP baseline measures.[7–12] Black race has also been shown to affect cardiovascular measures in healthy subjects. In another study that evaluated the electrocardiogram tracings of 2,686 apparently healthy subjects, the QT interval was ~5 msec shorter in black males.[13] With respect to BP, reports have shown that black men and women have higher BP than whites.[14–16] In the current analyses, an Asian male was estimated to have ~2 mmHg lower diastolic BP, although the low percentage of Asian subjects in our database (8%) may limit the interpretation of this finding. Age appeared to be strongly associated with QT interval and diastolic BP but not with heart rate or systolic BP. These findings are consistent with the longer QT interval and higher BP with increasing age.[6,11,17] Body weight was found to be correlated only with systolic BP in our analyses. Obese individuals have been reported to have higher BP than nonobese individuals.[18,19]

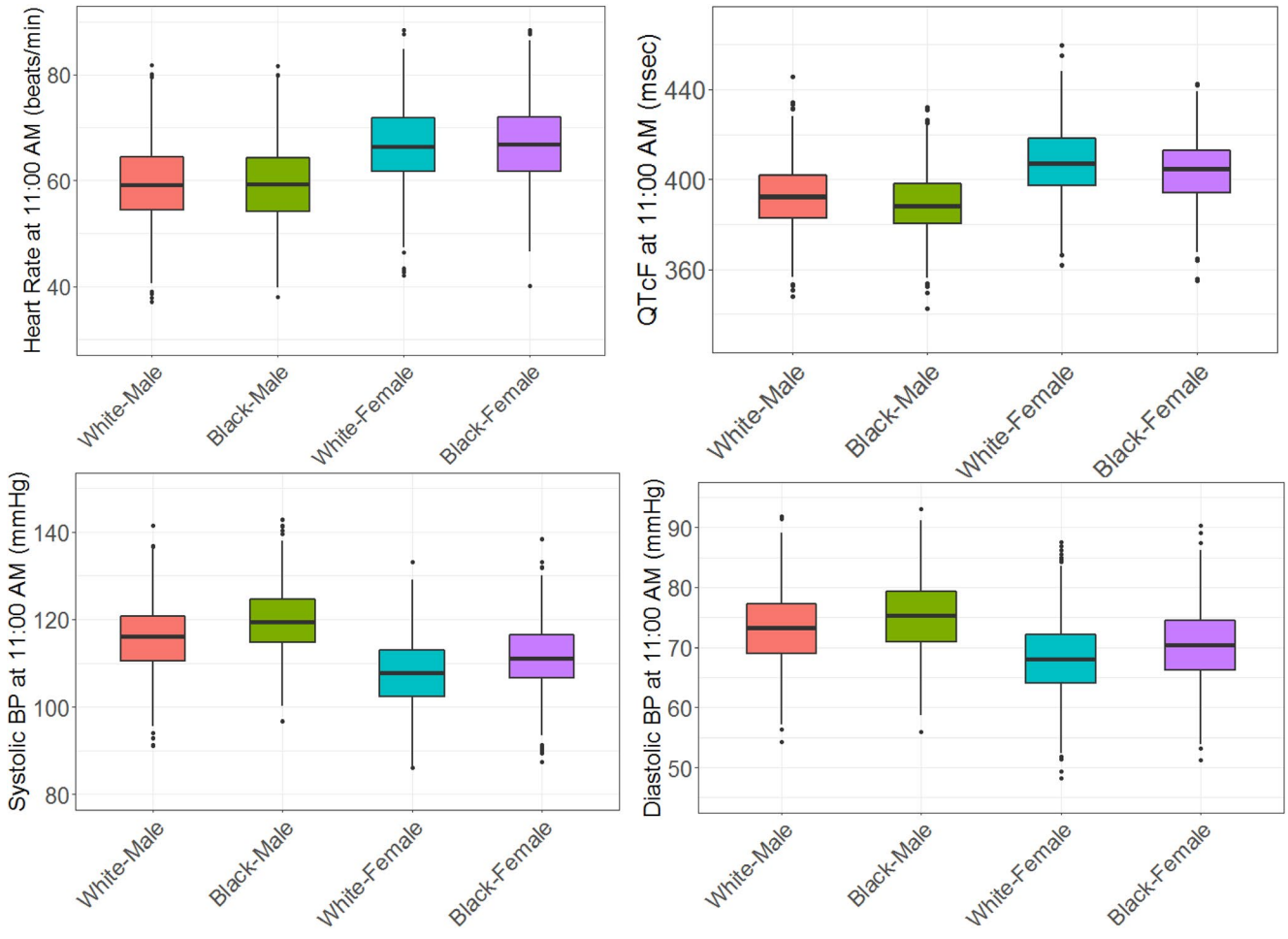


Figure 3 Impact of gender and race on cardiovascular measures: box plots for model predicted heart rate, QT interval, and systolic and diastolic blood pressure at 11:00 AM for 1,000 white or black males and white or black females who are 30 years of age and weigh 70 kg. Solid line = median; box = interquartile range, vertical bars = 1.5 times the interquartile range; circles = outliers.

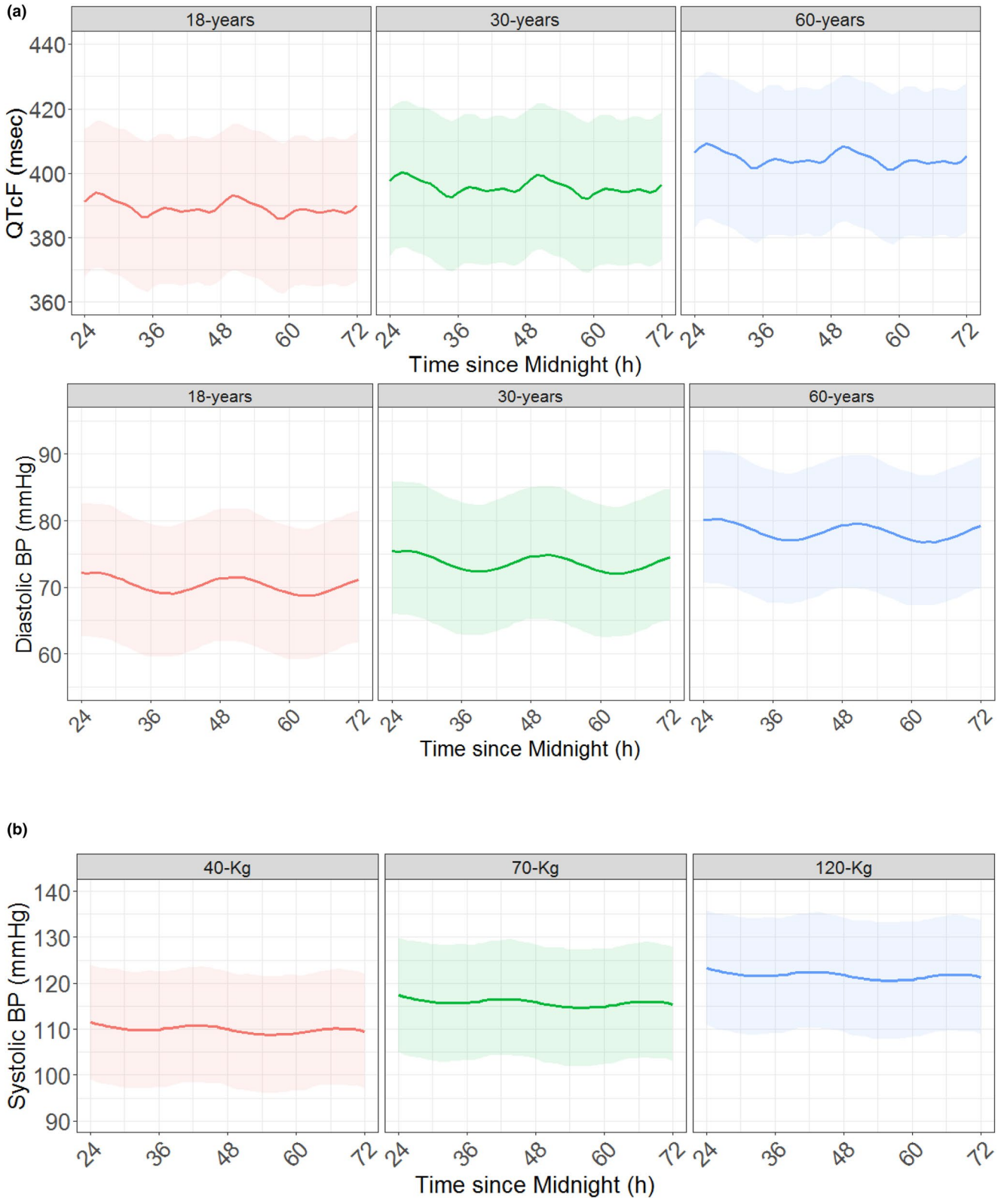


Figure 4 Simulations to demonstrate impact of (**a**) age on QT interval and diastolic blood pressure (BP) and impact of (**b**) body weight on systolic BP. For **a**, the time course (median and 90% prediction interval) for model-predicted QT interval and diastolic BP measures for 1,000 white male subjects who weigh 70 kg and are 18, 30, or 60 years of age are shown. For **b**, the time course (median and 90% prediction interval) for model-predicted systolic BP for 1,000 white male subjects who are 30 years of age and weigh 40, 70, or 120 kg are shown.

The results from the current analyses (**Table 2 and Figure 3**) provide a robust estimate for the impact of demographic characteristics on key cardiovascular variables building on the existing knowledge base. These analyses also highlight the importance of factoring in impact of imbalance (with regard to gender, race, age, and body weight) in randomization of subjects to placebo vs. an investigational compound or among different dose levels of the investigational compound when interpreting cardiovascular safety assessments from small, phase I studies.

The models for heart rate and QT interval were characterized using three cosine functions (24, 12, and 6 hours), whereas the models for systolic and diastolic BP were described using a single 24-hour circadian cycle (**Table 2**). Consistent with our analyses, Piotrovsky[20] has previously described the QT interval time course using three cosine (oscillation) functions. To our knowledge, comprehensive baseline heart rate models using circadian rhythm in adults are not currently available, although a 24-hour circadian rhythm model for heart rate in pediatrics has been reported.[21] The time course of systolic and diastolic BP in the current analyses was described using a single 24-hour circadian rhythm, consistent with that described by Conrado *et al*.[22] Other time-related effects were also observed in the baseline measures, which reached a steady state within 2–3 days. These time-related drifts cannot be clearly explained and could be attributed to the interday and intraday performances of the electrocardiogram tracings.

A study clinical investigator evaluating a deviation of a cardiovascular safety measure from an expected value faces a question of likelihood of the observation being a result of normal variability vs. a treatment effect. All potential contributing factors must be considered in evaluating observed results, but having a better understanding of what is possible on placebo provides clinicians with additional support in making well-grounded safety decisions.

In conclusion, robust nonlinear mixed-effects models incorporating subject demographics, circadian rhythms, other time-related effects, and random between-subject variability were developed to describe the normal variability in heart rate, QT interval, and BP in healthy volunteers receiving placebo in phase I studies. Gender, race, age, and body weight together with circadian rhythms were identified as significant predictors of baseline cardiovascular measures in a phase I setting. These models shed light on the inherent variability that exist among healthy subjects, even in a well-controlled setting, and can assist better differentiation of true drug-related cardiovascular safety signals from inherent subject variability in the early phases of drug development.

DATA SHARING STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets) as well as other information (e.g., protocols and clinical study reports) as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

AbbVie studies that are available for data sharing are listed on Vivli. The clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal and statistical analysis plan and execution of a data sharing agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Figure S1. Diagnostic plots of heart rate model (**a**) observed vs. population predicted heart rate; (**b**) observed vs. individual predicted heart rate; (**c**) conditional weighted residuals (CWRES) vs. population predicted heart rate; (**d**) conditional weighted residuals (CWRES) vs. time. Solid lines represent lines of identity in (**a**) and (**b**) and zero conditional residuals in (**c**) and (**d**). Dashed lines represent 3 SD in (C) and (D).
Figure S2. Diagnostic plots of QT interval model (**a**) observed vs. population predicted QT interval; (**b**) observed vs. individual predicted QT interval; (**c**) conditional weighted residuals (CWRES) vs. population predicted QT interval; (**d**) conditional weighted residuals (CWRES) vs. time. Solid lines represent lines of identity in (**a**) and (**b**) and zero conditional residuals in (**c**) and (**d**). Dashed lines represent 3 SD in (**c**) and (**d**).
Figure S3. Diagnostic plots of systolic BP model (**a**) observed vs. population predicted systolic BP; (**b**) observed vs. individual predicted systolic BP (SYS BP); (**c**) conditional weighted residuals (CWRES) vs. population predicted systolic BP; (**d**) conditional weighted residuals (CWRES) vs. time. Solid lines represent lines of identity in (**a**) and (**b**) and zero conditional residuals in (**c**) and (**d**). Dashed lines represent 3 SD in (**c**) and (**d**).
Figure S4. Diagnostic plots of diastolic BP model (**a**) observed vs. population predicted diastolic BP; (**b**) observed vs. individual predicted diastolic BP (DIA BP); (**c**) conditional weighted residuals (CWRES) vs. population predicted diastolic BP; (**d**) conditional weighted residuals (CWRES) vs. time. Solid lines represent lines of identity in (**a**) and (**b**) and zero conditional residuals in (**c**) and (**d**). Dashed lines represent 3 SD in (**c**) and (**d**).
Data S1. NONMEM control stream for the final heart rate model.

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Author Contributions. M.M., A.A.O., D.C., Y.L.C., and H.L. wrote the manuscript. M.M., A.A.O., D.C., Y.L.C., and H.L. designed the research. M.M., A.A.O., D.C., Y.L.C., and H.L. performed the research. M.M., A.A.O., Y.L.C., and H.L. analyzed the data.

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