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Other Types of Exposure-Response Models

Module 11: Building on PopPK – Exposure response and PK-PD

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Learning Objectives

Recognise the range of exposure response models for safety and efficacy
Analyse exposure-response data using direct, indirect and delayed response models
Defend the choice of models subject to the type of data and the research question

Lecture outline

Other Types of Exposure-Response Models

- Understand how to:
  - Model concentration-QTc relationships
  - Develop models for categorical (e.g., binary) data
  - Use a Cox proportional hazards model for time-to-event data

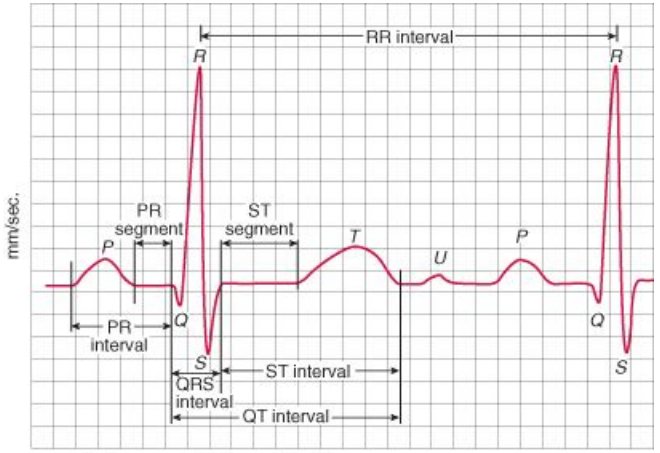
Concentration–QTc Analysis

A Special Type of PK/PD Model

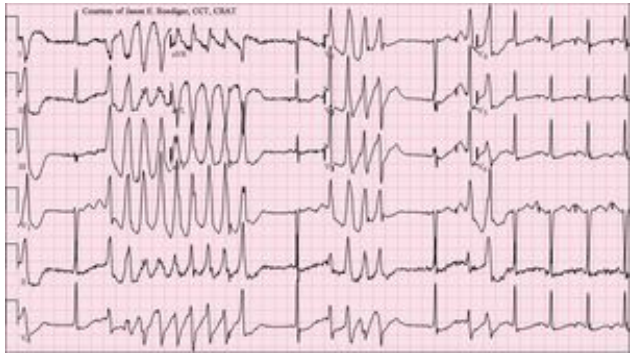
Adapted from Bill Poland's presentation **An Introduction to Concentration-QTc Analysis** (IDD Curriculum for Modern Drug Development)

Purpose: to assess QTc interval prolongation risk in new drugs

- Some drugs prolong the QT interval on the electrocardiogram (ECG)
  - Duration that ventricles depolarize and repolarize, from the beginning of the QRS complex to the end of the T wave
  - Typically around 0.4 seconds (400 milliseconds) long
- Prolongation is associated with cardiac arrhythmias such as torsade de pointes (TdP), which can degenerate into fatal ventricular fibrillation
  - Several approved drugs have been withdrawn for TdP risk
- QT naturally shortens with increased heart rate, so we correct for this with QTc
  - Most common correction (Fridericia's correction): QTcF = QT * heart rate$^{1/3}$ (heart rate in beats/sec)



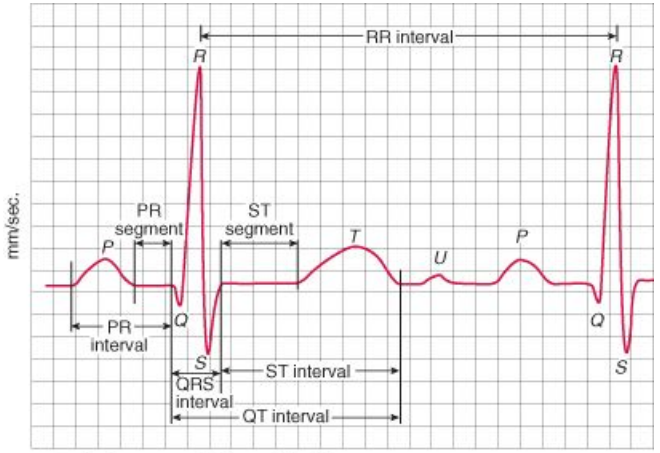
Source: https://www.timeofcare.com/segments-vs-intervals-in-an-ecg/



Source: Wikipedia: Torsades de pointes

Purpose: to assess QTc interval prolongation risk in new drugs

- Traditional approach to assessing QTc risk: Thorough QT (TQT) study
  - A study in healthy volunteers with a positive control creating a small QT prolongation
  - Typically very expensive to conduct
- International Council for Harmonisation (ICH) allows concentration-QTc (C-QTc) modeling to replace the TQT study for some drugs
- Key paper: Garnett et al. 2018, Scientific white paper on concentration-QTc modeling. J PK PD 45(3):383-397
  - Also presented by coauthor Steve Riley in “The Non-modelers Guide to the [QT] Galaxy”, 7Dec2016



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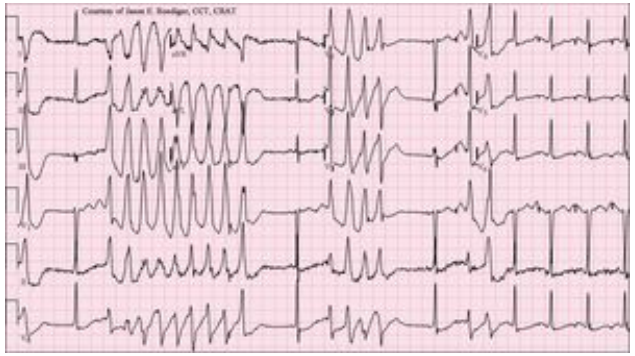
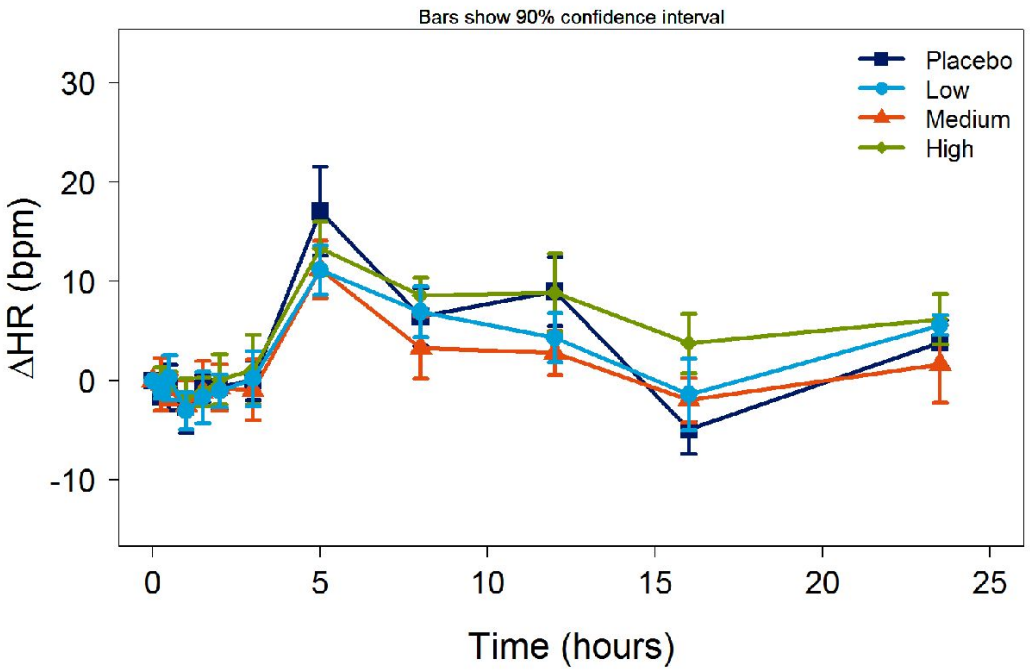


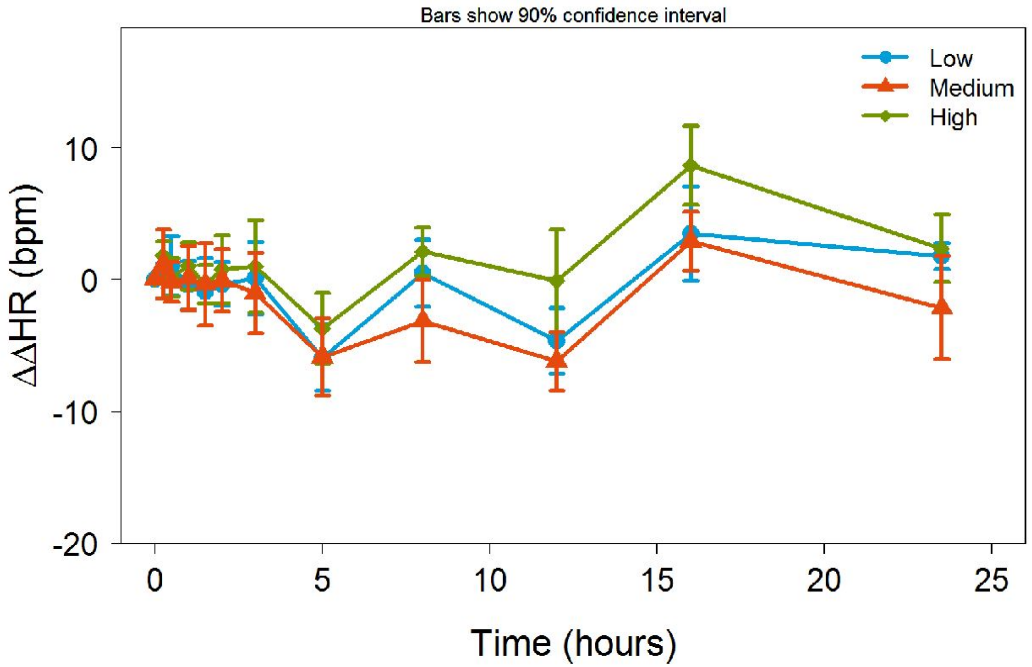
Source: Wikipedia: Torsades de pointes

Basic assumption #1: The drug does not affect heart rate (HR)

Look for consistency of ΔHR and/or ΔΔHR (placebo-corrected change from baseline HR) with time, dose, and treatment

- or the same with RR in msec = 60,000 / HR(bpm)
- Can also be plotted against concentration in a scatterplot.

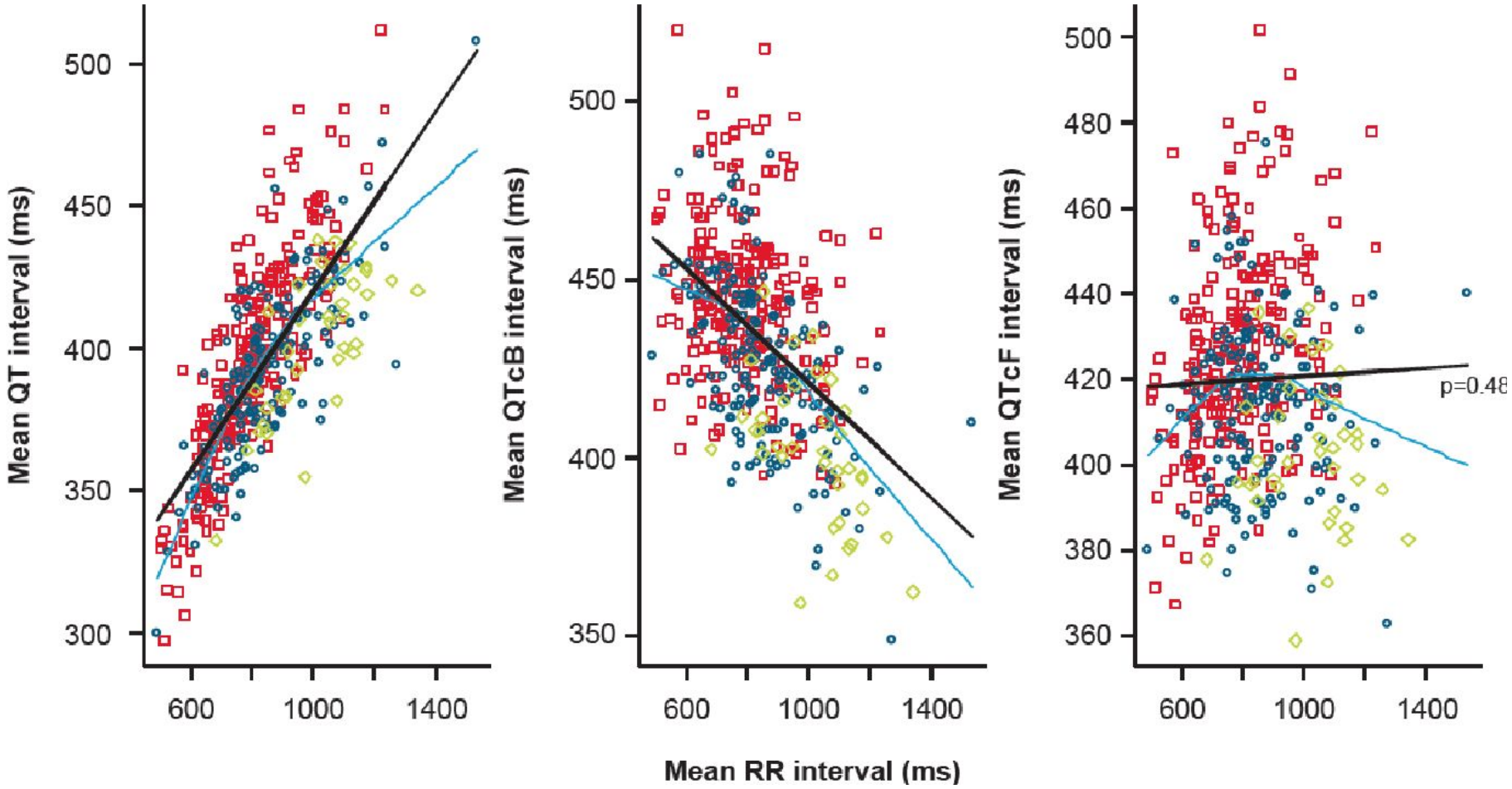




From Steve Riley, "The Non-modelers Guide to the [QT] Galaxy", 7Dec2016

Basic assumption #2: QTc is independent of HR (or its inverse, RR)

Here, QTcB ($QT \cdot HR^{1/2} = QT/RR^{1/2}$) over-corrects QT, but QTcF ($QT/RR^{1/3}$) does well. In other cases we may need a population-derived QTc (QTcP) using an estimated exponent *between* 1/3 and 1/2, or its individual-subject version (QTcI).



K. Le et al., Relationship of ivosidenib (IVO; AG-120) plasma concentration to heart rate–corrected QT interval (QTc) in patients with IDH1-mutant advanced hematologic malignancies. ASCPT, 13-16 March 2019, Washington, DC, Poster 640

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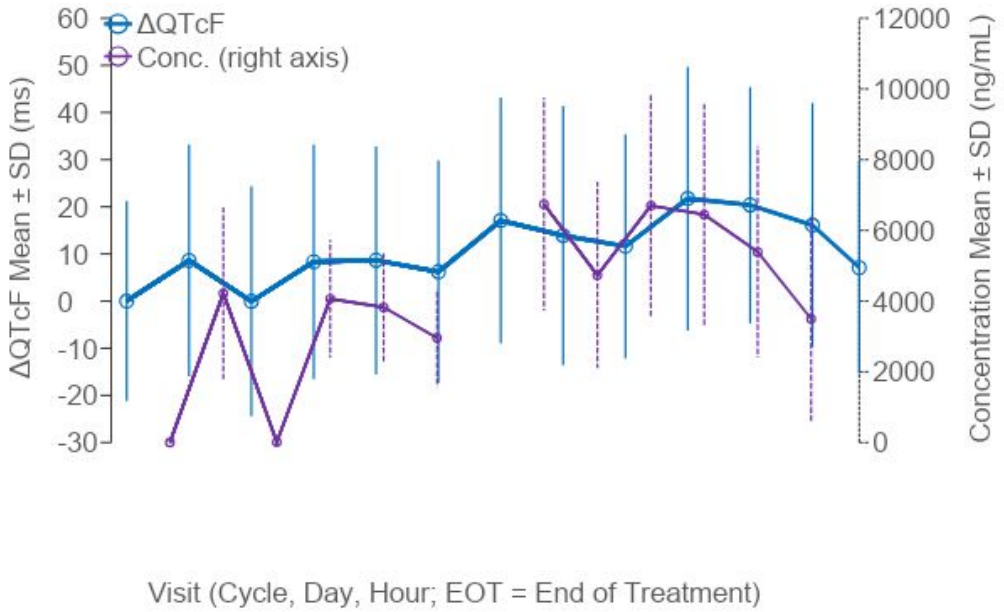
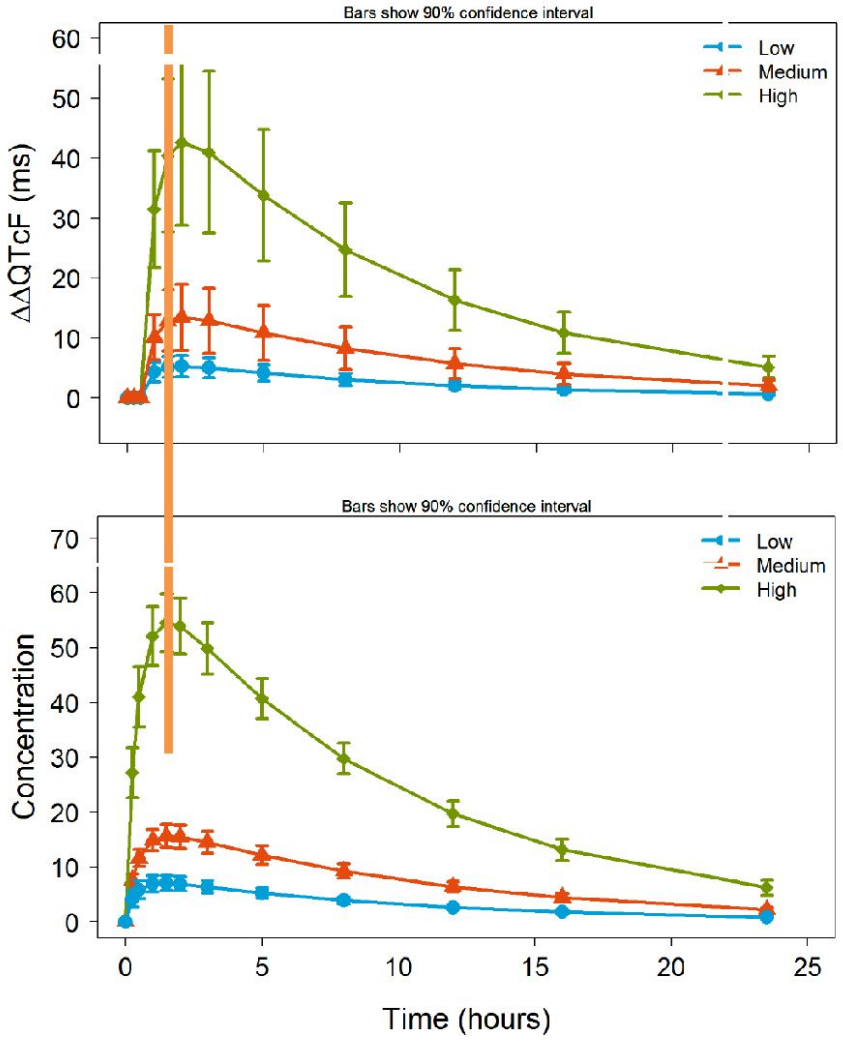
Basic assumption #3: No hysteresis (delay) between concentration and ΔQTc.

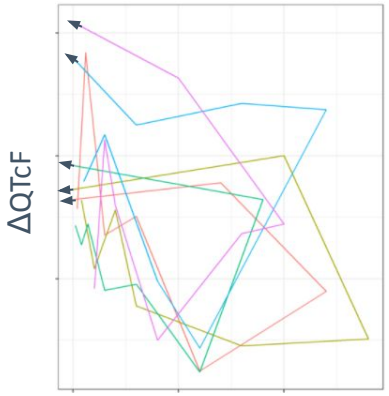
No apparent hysteresis



1-Hour Delay (Riley 2016)

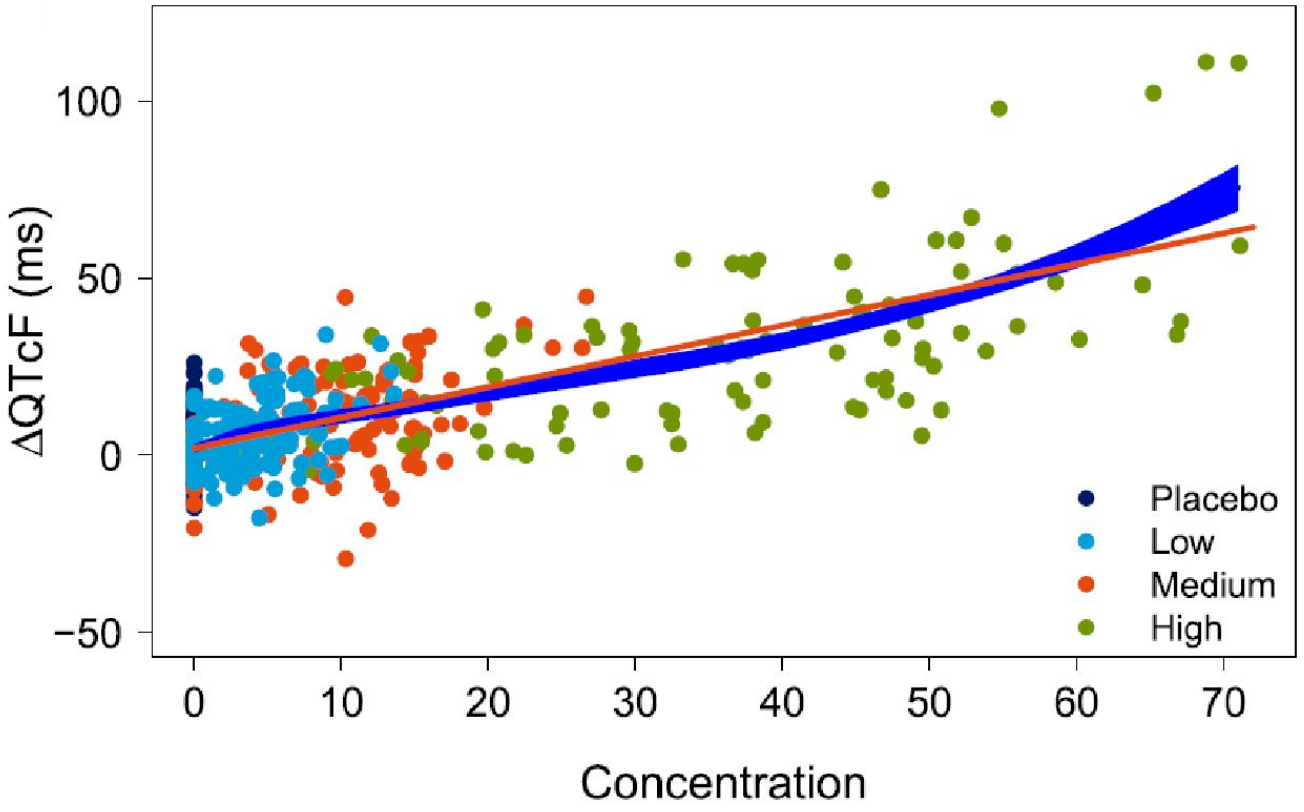


We can also check for counterclockwise hysteresis loops for individual ΔQTc vs. concentration, seen here (arrows indicate increasing time):

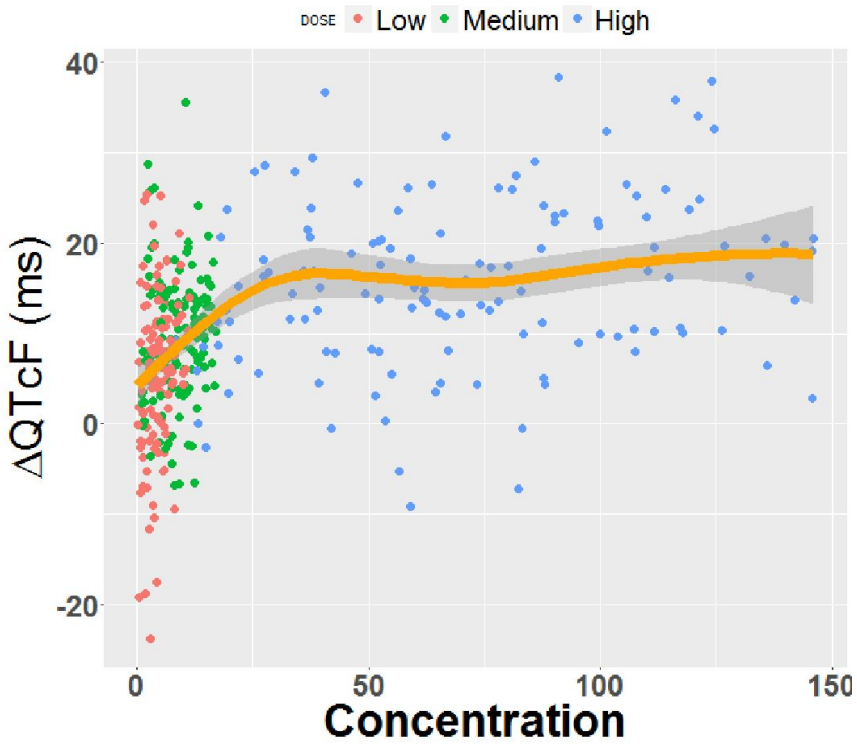


Basis assumption #4: ΔQTc is linear in concentration.

Consider the range of clinically relevant concentrations only. Left plot looks linear; on the right it depends on the range.



From Garnett et al. 2018



From Riley 2016

Here is the recommended pre-specified LME model:

$$\Delta QTc_{ijk} = (\theta_{intercept} + \theta_{TRTj} + \theta_k + \eta_{\mu,i}) + \theta_B(QTc_{i0} - mean(QTc_0)) + (\theta_C + \eta_{C,i})C_{ijk} + \varepsilon_{ijk}$$

i: subject; j: treatment (placebo or treated); k: time or time point (for θ_k).

$\theta_{intercept} + \theta_{TRT^j}$ = Treatment-specific intercept	Allows the relationship to be not perfectly linear over the entire concentration range; gives the model flexibility if misspecified.
θ_k = Intercept adjustment by time point	Accounts for diurnal variation in ΔQTc in the LME model without complex nonlinear models. Assumes the same time course of ΔQT in placebo and drug arms.
θ_B = Baseline QTc effect	Typically negative, due to regression to the mean. Shown to increase precision in parameter estimates.
θ_C = Slope in concentration	Assumes no hysteresis.
$\eta_{\mu,i}$, $\eta_{C,i}$ = Between-subject variability random effects	An unstructured covariance matrix for random effects (i.e., correlation between η_μ and η_C) is preferred because it does not constrain the variances (other random effect models based on the specific study design are acceptable).

Adapted from Riley 2016.

Notes: Garnett et al. 2018 has a similar equation, missing a "+" sign after TRT_j. ΔΔQTc (used when sufficient placebo data is available) can be derived from the equation here.

What if assumptions are not met?

- If the standard QT correction methods (e.g., QTcF) do not remove heart rate dependence derive custom corrections:
  - Population-based corrections (QTcP)
  - Individual-based corrections (QTcI): needs sufficient data from each individual
- Hysteresis use an effect compartment or indirect response to account for the delay
  - Will require development of a fit-for-purpose PK model
- Nonlinear concentration-QTc relationship Investigate mixed effects models, e.g.:
  - linear-log, i.e., use ln(Conc) as predictor variable
  - Emax models

Logistic Regression Models

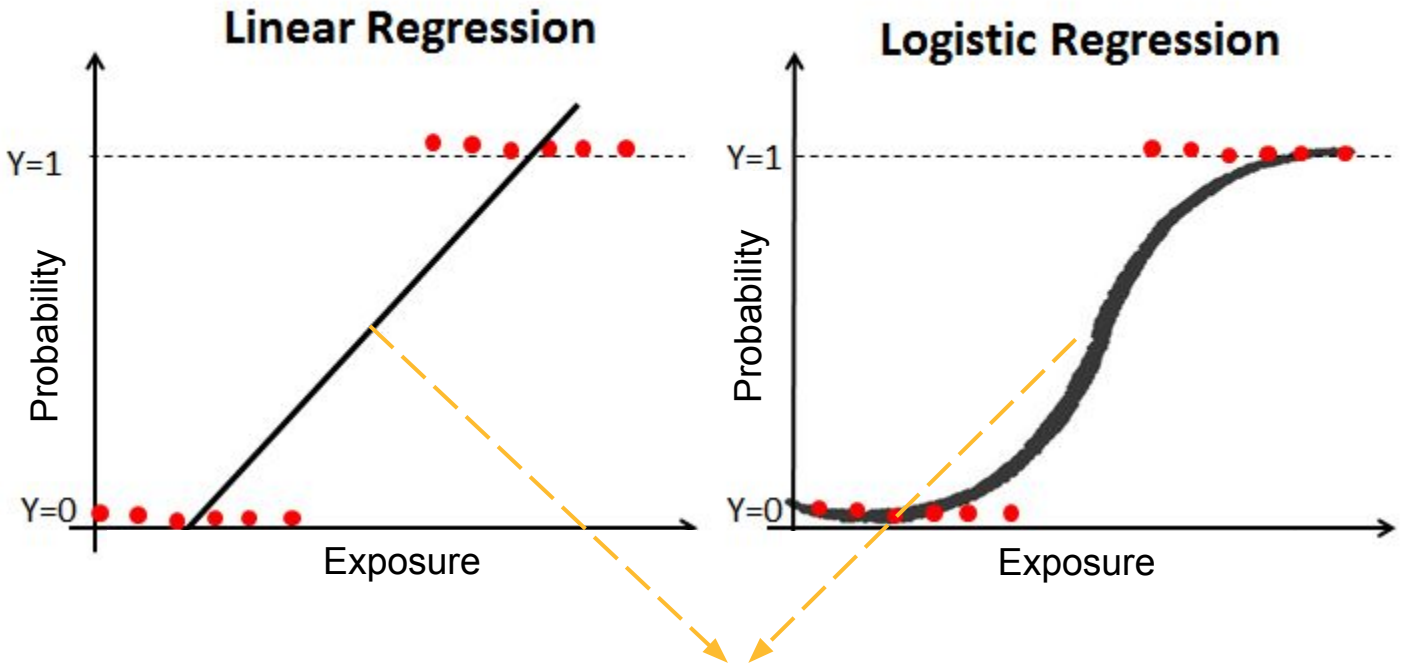
Categorical data (e.g., binary)

Binary Data

- Binary responses are categorical data representing whether an event happened or not (i.e., Yes or No). Examples: probability of an adverse event (AE) occurring, probability of objective response for anti-cancer drugs.
- The categories are represented by 0 and 1. Typically:
  - 0 is assigned to the subject if the event did not occur.
  - 1 is assigned to the subject if the event occurred.
- Logistic regression is used with binary data to model the probability of an event occurring.

Logistic regression is used to model binary data

Exploratory plots for binary data plot the occurrence of the event (0 = no, 1 = yes) on the y-axis and exposure on the x-axis



Black lines are the model prediction for the probability as a function of exposure.

- This is an idealized example - typically, there is overlap between exposures for subjects who did and did not experience the event.
- Linear regression cannot be used because it will predict impossible probability values: p < 0 and p>1.
- Therefore ,the probability is modeled on the ***logit*** scale.

$$logit(p) = lp = ln\left(\frac{p}{1-p}\right)$$

where p is the probability of the event.

- lp can take on values from -∞ to + ∞.

$$p = \frac{e^{lp}}{1+e^{lp}} = \frac{1}{1-e^{-lp}}$$

Adapted from https://medium.com/mlearning-ai/logistic-regression-60694a973bee

Slight detour: probability and likelihood

- If the probability of an event (e.g., AE) happening is p_{event}, the probability of it not happening is $(1 - p_{event})$.
  - We assume the probability is dependent on covariate(s) $\boldsymbol{x}$ (e.g., exposure) and parameter(s) $\boldsymbol{\theta}$ (e.g., exposure slope).
- If y represents whether the event happened or not (y = 1 and y = 0, respectively), then:

$$p(y|\boldsymbol{\theta},\boldsymbol{x}) = \begin{cases} p_{event}(\boldsymbol{\theta},\boldsymbol{x}), & y = 1 \\ 1 - p_{event}(\boldsymbol{\theta},\boldsymbol{x}), & y = 0 \end{cases}$$
$$= (p_{event})^{y} \, (1 - p_{event})^{1-y}$$

LIKELIHOOD:

- Suppose you already observed a measured value y_{obs}.
- That value is no longer a random variable since we know its value.
- If we insert that observed value into our probability distribution function we now refer to that function as a ***likelihood function***.
- It is the same function as before but we now view it as a ***function of the parameters given the data*** instead of as a function of the data given the parameters.

$$L(\theta|y_{obs}, x) = p(y_{obs}|\theta, x)$$

In our case, y_{obs} represents whether the event happened ($y_{obs} = 1$) or did not happen ($y_{obs} = 0$).

https://youtu.be/pYxNSUDSFH4 is a good video on probability vs. likelihood

https://www.metrumrg.com/course/mi255-exposure-response-modeling-categorical-count-time-event-data-using-bayesian-methods/: mi255Handout.pdf, slide 17/214

Logit(p) is modeled as a function of covariates

Typically (but not always), linear relationships are assumed between the explanatory variables (exposure and covariates) and logit(p).

- $$logit(p) = \ln\left(\frac{p}{1-p}\right) = \theta_0 + \theta_1 X_1 + \theta_2 X_2 + \ \ldots + \theta_n X_n$$

θ_0 is the intercept, i.e., the logit of the probability when all covariate values are equal to 0.

$X_1 \ldots X_n$ are the values of the different explanatory variables (e.g., exposure)

$\theta_1 \ldots \theta_n$ are the coefficients for the covariates

- Simplest exposure-response model:

$$logit(p) = \ln\left(\frac{p}{1-p}\right) = \theta_0 + \theta_1 \cdot Exposure$$

- Examples of exposure measures used are AUC, Cmax and trough concentration.
  - Depending on the situation, steady-state values, values at the first dose, or average values up to the time of the event (or end of treatment) can be used.

- After θ_0 and θ_1 have been estimated, then for any exposure measure, the probability of the event can be calculated as:

$$p = \frac{e^{\theta_0+\theta_1 \cdot Exposure}}{1+e^{\theta_0+\theta_1 \cdot Exposure}} = \frac{1}{1+e^{-(\theta_0+\theta_1 \cdot Exposure)}}$$

Estimation of logistic regression parameter values.

Using example of simple logistic regression model:

- $$logit(p) = \ln\left(\frac{p}{1-p}\right) = \theta_0 + \theta_1 \cdot Exposure$$

  θ_0 is the intercept, i.e., the logit of the probability when Exposure = 0

  θ_1 is the slope with respect to exposure (units = 1/(exposure units)

- The probability for subject i is $p = \frac{e^{\theta_0+\theta_1 \cdot Exposure}}{1+e^{\theta_0+\theta_1 \cdot Exposure}} = \frac{1}{1+e^{-(\theta_0+\theta_1 \cdot Exposure)}}$

- Remembering that the likelihood and probability are related as follows: $L(\boldsymbol{\theta}|y_{obs}, \boldsymbol{x}) = p(y_{obs}|\ \boldsymbol{\theta}, \boldsymbol{x})$, then the overall likelihood for *n* subjects (assuming one observation per subject and subject index *i*) is:

$$L(\boldsymbol{\theta}|y_{obs}, \boldsymbol{x}) = \prod_{i=1}^{n} p(y_{obsi}|\ \boldsymbol{\theta}, \boldsymbol{x}_i)^{y_{obsi}}\ (1\ - p(y_{obsi}|\ \boldsymbol{\theta}, \boldsymbol{x}_i))^{1-y_{obsi}}$$

The probability of independent events happening is obtained by taking the product of all the individual probabilities.

- The maximum likelihood estimates of parameters $\boldsymbol{\theta}$ are the values that maximize the likelihood (i.e., the value of the above equation).

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Odds ratio

- The quantity *p/(1-p)* is called the **odds** (ratio of probability of event happening to probability of it not happening).

$$logit(p) = \ln\left(\frac{p}{1-p}\right)$$

- Therefore, logit(p) can also be referred to as the log-odds.
- The odds ratio is the ratio of the odds of for a category relative to the reference category (e.g., males relative to females) or the fold-change change in odds for 1 unit increase of a continuous variable.
- Let OR = odds ratio. $\ln(OR) = \ln(odds_1/odds_{ref}) = \ln(odds_1) - \ln(odds_{ref}) = logit(p_1) - logit(p_{ref})$ → $OR = e^{logit(p1) - logit(pref)}$
- <u>Categorical variable</u>

  Model: $logit(p) = \theta_0 + (\theta_1\ if\ patient\ is\ diabetic)$

  OR for diabetic patient relative to non-diabetic patient = $\exp(\theta_0 + \theta_1 - \theta_0) = \exp(\theta_1)$
- <u>Continuous variable</u>

Implementation of logistic regression in R – Example Data

The *glm* (generalized linear modeling) function in R is typically used for logistic regression modeling when there is one observation per subject (i.e., not longitudinal data).

- mydata dataframe (first few rows):

id	headache	AUC	sex	age
1	0	452	M	35
2	1	440	M	60
3	0	300	F	55
4	0	320	M	22
5	1	658	F	28
6	1	399	F	70
7	1	600	F	40
8	0	500	F	21

- Observation variable is *headache* (0 = no headache, 1 = had headache)
- Covariates/explanatory variables are AUC in ng*h/mL, sex, and age in years.

Implementation of logistic regression in R – R Code

R uses Wilkinson-Rogers notation* for writing linear and generalized linear models.

The general form is y ~ …, where y is the dependent variable and … represents the explanatory variable relationships.

y ~ … □ y is a function of …

- mydata dataframe:

id	headache	AUC	sex	age
1	0	452	M	35
2	1	440	M	60
3	0	300	F	55
4	0	320	M	22

- Code for model that includes all covariates:

The intercept is implicitly included. To remove the intercept term, add " – 1"

This part is not needed – the default link function for the binomial family is the logit function.

```
mymodel <- glm(headache ~ AUC + age + sex, data = mydata, family = binomial(link = "logit"))
```

- This should not be read as an algebraic equation. It means that the probability of headache is a function of AUC, sex, and age, and that they have a linear relationship with logit(p). This is equivalent to:

$$logit(p) = \theta_{intercept} + \theta_{AUC} \cdot AUC + \theta_{age} \cdot age + (\theta_{MALE}\ if\ sex = M)$$

- In this case, F (female) is taken as the reference because it's the first in alphabetical order.
  - There are ways to select which category you want as the reference (e.g., using the *relevel function*, modifying the sex variable by adding a space before "M", etc.)

*See *Wilkinson-Rogers Notation.docx* provided in the References section this week for an explanation of Wilkinson-Rogers notation.

Logistic regression (one observation per subject) in R (left) vs. NONMEM (right)

Although R is preferred in this case, NONMEM would be better for longitudinal data or for some nonlinear relationships.

Run model:

```
mymodel <- glm(headache ~ AUC + age + sex,
data = mydata,
family = binomial)
```

View model, coefficients, get confidence intervals:

```
mymodel; coef(mymodel); confint(mymodel)
```

View parameter estimate table with standard errors and p-values:

```
summary(mymodel)
```

AIC and OFV (i.e., -2*loglikelihood:

```
AIC(mymodel); -2*logLik(mymodel)
```

Compare model to intercept only model using likelihood ratio test

```
mymodel.intonly <- glm(headache ~ 1, data =
mydata, family = binomial)
```

OR

```
mymodel.intonly <- update(mymodel, . ~ 1)
anova(mymodel.intonly, mymodel, test = "LRT")
```

```
$PRED
B1= THETA(1)  ;baseline probability of an event occurring (i.e., intercept)
SLOPAUC = THETA(2)
SLOPAGE = THETA(3)
COEFMALE = THETA(4)
LOGIT = B1 + SLOPAUC*AUC + SLOPAGE*AGE + COEFMALE*MALE
; in the dataset, MALE=0 and 1 represent female and male subjects, respectively
P=EXP(LOGIT)/(EXP(LOGIT)+1)  ;take inverse logit to get probability

IF (DV.EQ.1) THEN  ;DV of 1 indicates in this case that the event occurred
Y = P
ELSE
Y = 1-P
ENDIF

$THETA
(-2.4) ;beta
(0,1.8) ;EMAX
(0,160) ;ED50
$ESTIMATION LIKE METHOD=0
; Using the likelihood method (LIKE) tells NONMEM that in your model, Y
represents the likelihood and not a continuous observation.
```

Starting point: Mould, D., Walz, A.-C., Lave, T., Gibbs, J. and Frame, B. (2015), Developing Exposure/Response Models for Anticancer Drug Treatment: Special Considerations. CPT Pharmacometrics Syst. Pharmacol., 4: 12-27. https://doi.org/10.1002/psp4.16

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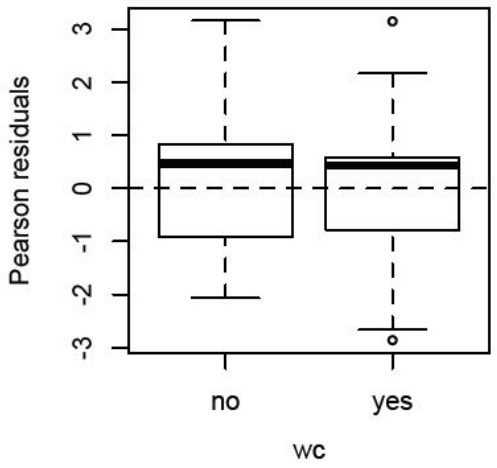
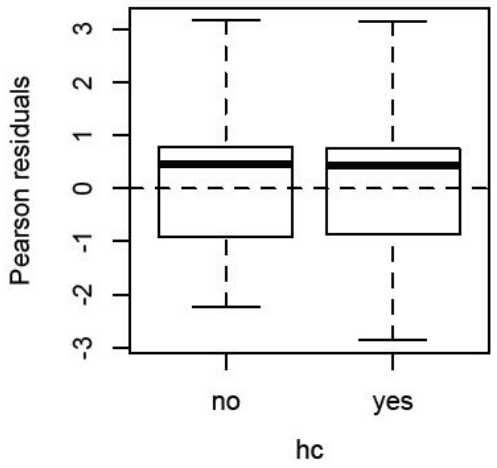
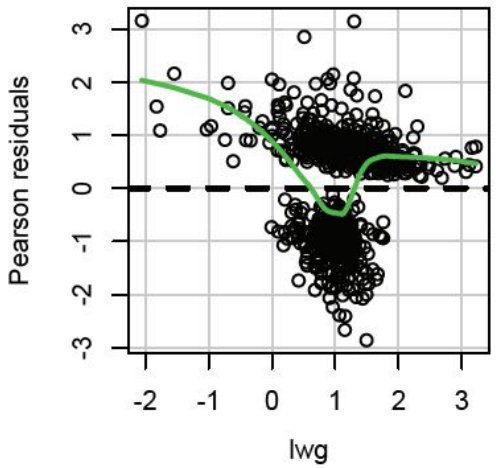
Model diagnostics for logistic regression models

Plots of Pearson's residual versus predictors can be easily generated using the *residualPlots* function in the *car* package. The plot function can also be used – look up the help in R for plot.lm ("?plot.lm" or help(plot.lm)).

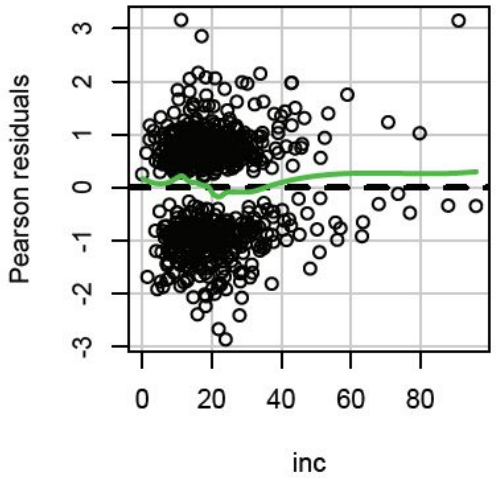


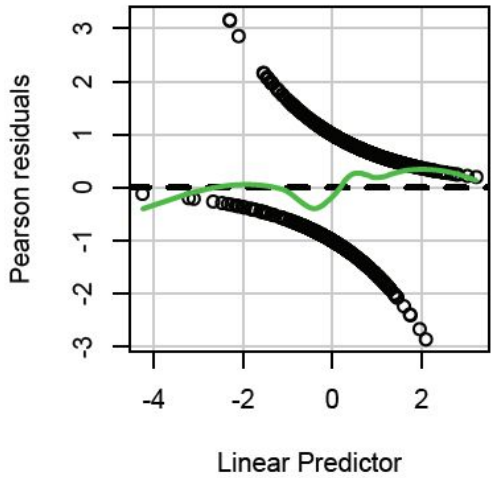




The lwg variable shows a trend. This was addressed by adding a quadratic term in lwg to the model:

```
glm(… ~ … + lwg + I(lwg^2)…)
```





Visual predictive checks can also be done: for a large number of replicates (e.g., 1000) predict the probabilities for each subject and plot summary statistics of event rate (e.g., median and 90% prediction interval) across replicates for each category or covariate quartile (for continuous covariates) and compare to observed event rates.

Other model diagnostics can be found in the paper.

Zhang Z. Residuals and regression diagnostics: focusing on logistic regression. *Ann Transl Med*. 2016;4(10):195. doi:10.21037/atm.2016.03.36v (https://atm.amegroups.com/article/view/10171/11129)

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Example: Efficacy and safety analyses for belantamab mafodotin

Separate logistic regression models were used to model the probabilities of experiencing Grade ≥2 and ≥3 corneal toxicity and of achieving partial response or better (probability of response)

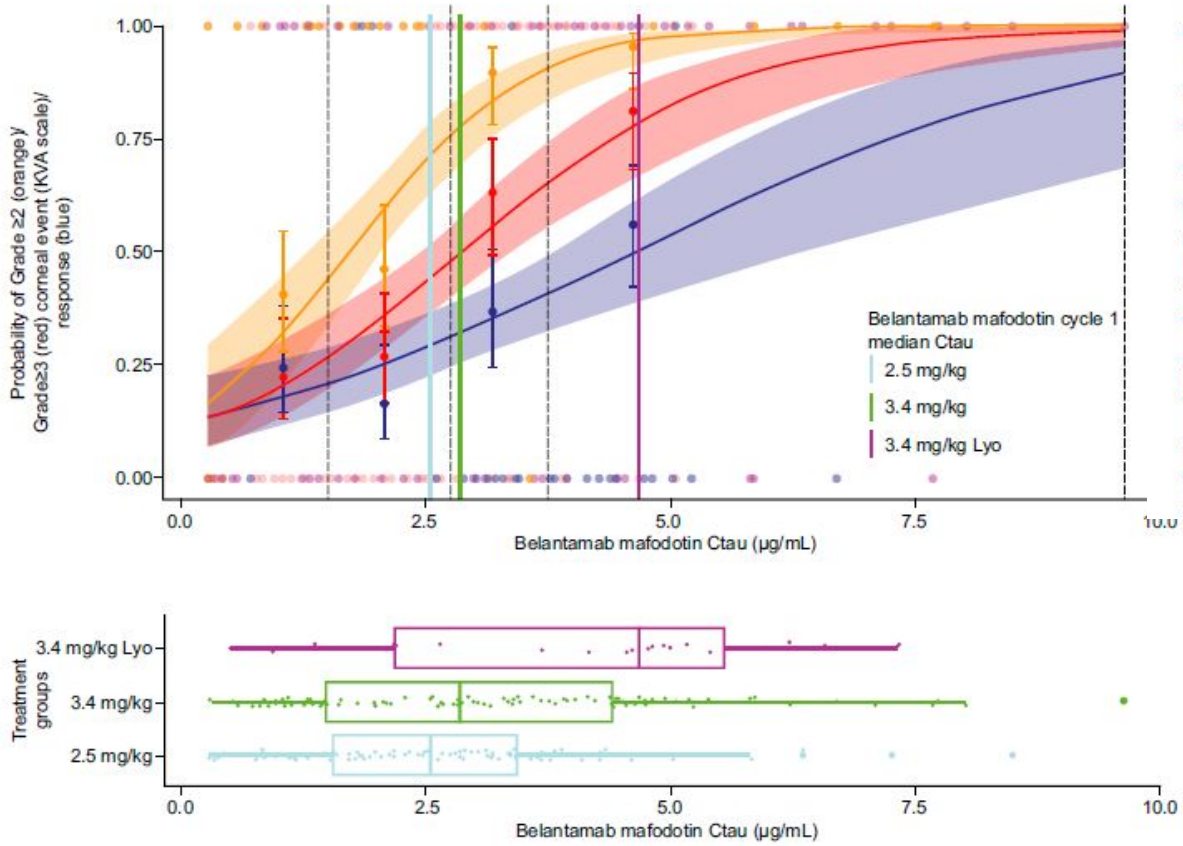


Figure 5 Integrated exposure–response analysis. Probability of grade ≥ 2 or grade ≥ 3 corneal event (KVA scale) and PoR by belantamab mafodotin C_{tau} (DREAMM-2 frozen liquid presentation), with accompanying boxplot of belantamab mafodotin C_{tau} by DREAMM-2 treatment group (frozen liquid and lyophilized presentations). C_{tau}, concentration at the end of the dosing interval (Day 21); KVA, keratopathy and visual acuity (KVA) scale; Lyo, lyophilized; PoR, probability of response.

Table 2 Probability of grade ≥ 2 or grade ≥ 3 corneal event and grade ≥ 3 thrombocytopenia - final logistic regression models

Covariate	Beta (β)	SE	95% CI	dOFV	Delta	OR (95% CI)
Probability of grade ≥ 2 corneal event						
Intercept (β_0)	–1.56	0.57	(–2.71, –0.47)	NA	NA	NA
C_{TAUA}	1.18	0.22	(0.78, 1.65)	63.3	0.8	2.58 (1.87, 3.74)
HISTDRYEYE	2.20	0.62	(1.06, 3.53)	13.1	1	9.04 (2.88, 34)
BSBCMA	–0.004	0.001	(–0.007, –0.002)	19.7	20	0.92 (0.87, 0.96)
Logistic regression: $\text{Ln}(p/(1-p)) = \beta_0 + \beta_{C_{TAUA}} \cdot C_{TAUA} + \beta_{HISTDRYEYE} \cdot \text{HISTDRYEYE} + \beta_{BSBCMA} \cdot \text{BSBCMA}$						
Probability of grade ≥ 3 corneal event						
Intercept (β_0)	–0.81	0.48	(–1.77, 0.12)	NA	NA	NA
C_{TAUA}	0.55	0.14	(0.30, 0.83)	46.2	0.8	1.55 (1.27, 1.93)
BSBCMA	–0.005	0.001	(–0.008, –0.003)	21.1	20	0.9 (0.85, 0.95)
Logistic Regression: $\text{Ln}(p/(1-p)) = \beta_0 + \beta_{C_{TAUA}} \cdot C_{TAUA} + \beta_{BSBCMA} \cdot \text{BSBCMA}$						

Table 1 Probability of response using final logistics regression model

Covariate	Beta (β)	SE	95% CI	dOFV	Delta	OR (95% CI)
Model with all FL data (DREAMM-2 FL presentation)						
Intercept (β_0)	0.109	0.223	–0.325, 0.551	NA	NA	NA
BSBCMA	–0.00608	0.00153	–0.00937, 0.00335	26.7	20	0.886 (0.829, 0.935)

Ferron-Brady G, Rathi C, Collins J, et al. Exposure-Response Analyses for Therapeutic Dose Selection of Belantamab Mafodotin in Patients With Relapsed/Refractory Multiple Myeloma. *Clin Pharmacol Ther*. 2021;110(5):1282-1292. doi:10.1002/cpt.2409

Survival Analysis for Time-to-Event Data

What are time-to-event data?

This tutorial will cover time to a single event (not repeated events) with one observation per subject.

- Time-to-event variables measure how long it takes for an event to occur. Examples:
  - In oncology settings: time to disease progression or death (progression-free survival), time to death (overall survival)
  - Time to dropout from a study
  - Time to the first occurrence of an adverse event

- Although time-to-event data are continuous data, they are different from other continuous data (e.g., concentration and biomarker data) in the following ways:
  - The presence of right-censored data (when an event does not occur during the study) and/or interval-censored data (when an event occurred within a known interval but the exact time of event is not known).
  - There is no pre-specified time to observe the event – it happens when it happens.

Adapted from Metrum course MI255: https://www.metrumrg.com/course/mi255-exposure-response-modeling-categorical-count-time-event-data-using-bayesian-methods/

Survival Hazard

- With time-to-event models, we are concerned with the **hazard (or hazard rate)**: instantaneous probability per unit time of an event occurring if it has not yet occurred (conditional probability):

$$h(t) = \lim_{\Delta t \to 0} \frac{\Pr(t \leq T < t + \Delta t | T \geq t)}{\Delta t} = \lim_{\Delta t \to 0} \frac{S(t) - S(t + \Delta t)}{\Delta t \cdot S(t)} = -\frac{1}{S(t)} \frac{dS(t)}{dt}$$

where h(t) is the hazard rate at time *t*, T is the time to the event, and S(t) is the probability of survival up to time *t*.

Note that h(t) can exceed 1 as it is not a probability but the instantaneous event *rate*.

- Larger hazard means the event is more likely to occur sooner; smaller hazard means it is less likely

Adapted from Metrum course MI255: https://www.metrumrg.com/course/mi255-exposure-response-modeling-categorical-count-time-event-data-using-bayesian-methods/

Hazard and Survival functions

- Let T be a random variable representing the survival time (alternatively, event time)
- The survival function is the probability of surviving beyond time t, i.e., that the event has not happened by time t:
  - S(t) = Pr(T > t): this is a probability and can only take values from 0 – 1.
- F(t) is the cumulative *failure* distribution function representing the probability of the event having happened by time t:
  - F(t) = 1 – S(t)
- Previously we showed that $h(t) = -\frac{1}{S(t)}\frac{dS(t)}{dt}$
- Therefore, $S(t) = 1 - F(t) = e^{-\int_0^t h(u)du}$ and $F(t) = 1 - e^{-\int_0^t h(u)du}$
- And the corresponding probability density function f(t) representing the frequency of events per unit time is:
  - $f(t) = \frac{dF(t)}{dt} = -\frac{dS(t)}{dt} = h(t)\,S(t)$
- For a constant (time-independent hazard), h(t) = h, f(t) = h*S(t) = h*e^{-ht} → T follows an exponential distribution.

Likelihood for Time-to-event Data

- The likelihood for subjects who experienced the event at a known time t is based on the failure rate probability distribution function:

$$f(t) = \frac{dF(t)}{dt} = -\frac{dS(t)}{dt} = h(t)\,S(t)$$

$$p(t_i|\boldsymbol{\theta}, \boldsymbol{x}) = f(t_i|\,\boldsymbol{\theta}, \boldsymbol{x}_i) = h(t_i|\,\boldsymbol{\theta}, \boldsymbol{x}_i) \cdot S(t_i|\,\boldsymbol{\theta}, \boldsymbol{x}_i)$$

or: p = h * S

- Right-censored data: The likelihood for subjects who had not experienced the event up to the last time of observation t_i is the probability of surviving up to time t_i:

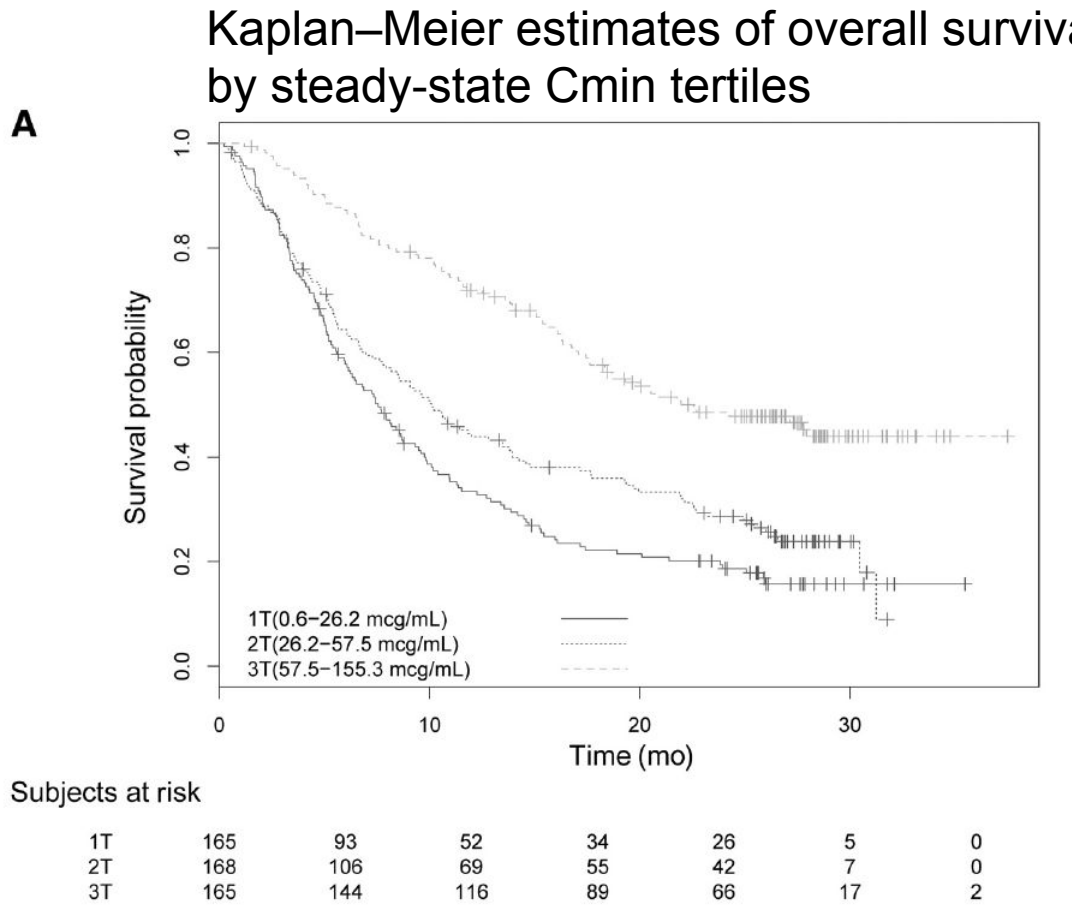
$$p(t_i|\boldsymbol{\theta}, \boldsymbol{x}) = Pr(T > t_i|\,\boldsymbol{\theta}, \boldsymbol{x}_i) = 1 - F(t_i|\,\boldsymbol{\theta}, \boldsymbol{x}_i) = S(t_i|\,\boldsymbol{\theta}, \boldsymbol{x}_i)$$

or: p = S

- Interval-censored data: The likelihood for subjects whose event happened between t_1 and t_2 but the exact time of the event is unknown is the probability of the event happening between t_1 and t_2:

Kaplan-Meier curves are used to visualize time-to-event data.

"The Kaplan Meier Curve is the visual representation of [the survival] function that shows the probability of an event at a respective time interval." https://www.mygreatlearning.com/blog/kaplan-meier-curve-explained/



- Each curve represents the proportion of subjects who have not yet had an event (i.e., proportion surviving) by time t.
  - Steeper curve more frequent events over time
  - Censored observations, represented by small vertical tick marks, are not counted as events.
- The number of subjects at risk (i.e., still remaining under observation) is often shown beneath KM plots.
- In this example, there appears to be a clear exposure-response relationship, with better/longer survival as exposures increase.

Feng, Y., Roy, A., Masson, E., Chen, T. T., Humphrey, R., & Weber, J. S. (2013). Exposure–response relationships of the efficacy and safety of ipilimumab in patients with advanced melanoma. *Clinical Cancer Research*, *19*(14), 3977-3986.

Cox proportional hazards Model is often used to analyze survival data

The Cox proportional hazards model is a semi-parametric model used to investigate covariate effects without requiring specification of the shape of the baseline hazard function.

- $$h(t|\,\boldsymbol{\theta}, \boldsymbol{x}_i) = h_0(t)\,\exp(\theta_1 X_1 + \theta_2 X_2 + \ \ldots + \theta_n X_n)$$

  where $h_0(t)$ is the baseline hazard, i.e., the hazard when all covariate values = 0.

- Proportional hazards assumption: relative hazard is constant over time with different predictor or covariate levels, i.e., ratio of the hazards for any two individuals/groups is constant over time.
  - This assumption can be tested using the *cox.zph* function of the *survival* package in R.
- The equation for the hazard ratio (HR) can be derived using similar calculations as those for the odds ratio:
- Categorical variable

  Model: $h(t) = h_0(t)\,\exp(\theta_1 X_1 + \ \ldots.)$; X_1 = 1 if patient is diabetic and X_1 = 0 if patient is non-diabetic

  HR for diabetic patient relative to non-diabetic patient = $\exp(\theta_1 + \ \ldots)/\exp(0 + \ \ldots) = \exp(\theta_1)$
- Continuous variable

  Model: $h(t) = h_0(t)\,\exp(\theta_1 X_1 \cdot AUC + \ \ldots)$

Implementation in R – Kaplan-Meier curves

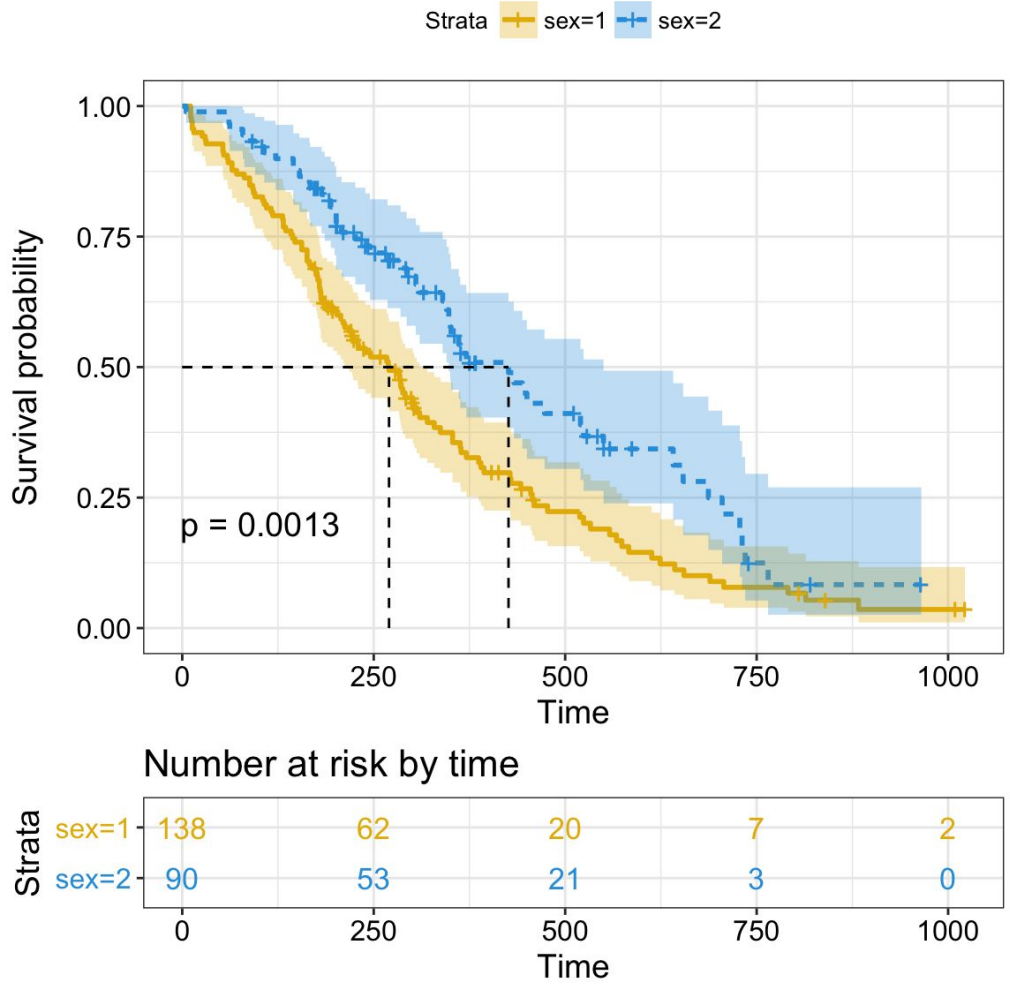
http://www.sthda.com/english/wiki/survival-analysis is a good resource.

- Packages:
  - survival: for survival analyses
  - survminer: for visualization using ggplot2 graphics

```
fit <- survfit(Surv(time, status) ~ sex, data = lung)
print(fit)
```

```
Call: survfit(formula = Surv(time, status) ~ sex, data = lung)
        n events median 0.95LCL 0.95UCL
sex=1 138    112    270     212     310
sex=2  90     53    426     348     550
```

```
ggsurvplot(fit,
          pval = TRUE, conf.int = TRUE,
          risk.table = TRUE, # Add risk table
          risk.table.col = "strata", # Change risk table color by groups
          linetype = "strata", # Change line type by groups
          surv.median.line = "hv", # Specify median survival
          ggtheme = theme_bw(), # Change ggplot2 theme
          palette = c("#E7B800", "#2E9FDF"))
```



http://www.sthda.com/english/wiki/survival-analysis-basics

Implementation in R – Cox PH model

```
res.cox <- coxph(Surv(time, status) ~ age + sex + ph.ecog, data =  lung)
summary(res.cox)
```

```
Call:
coxph(formula = Surv(time, status) ~ age + sex + ph.ecog, data = lung)
  n= 227, number of events= 164
   (1 observation deleted due to missingness)
             coef exp(coef)  se(coef)      z Pr(>|z|)
age      0.011067  1.011128  0.009267  1.194 0.232416
sex     -0.552612  0.575445  0.167739 -3.294 0.000986 ***
ph.ecog  0.463728  1.589991  0.113577  4.083 4.45e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
        exp(coef) exp(-coef) lower .95 upper .95
age        1.0111     0.9890    0.9929    1.0297
sex        0.5754     1.7378    0.4142    0.7994
ph.ecog    1.5900     0.6289    1.2727    1.9864
Concordance= 0.637  (se = 0.026 )
Rsquare= 0.126   (max possible= 0.999 )
Likelihood ratio test= 30.5  on 3 df,   p=1.083e-06
Wald test            = 29.93  on 3 df,   p=1.428e-06
Score (logrank) test = 30.5  on 3 df,   p=1.083e-06
```

This section provides the hazard ratios (exp(coef)) and 95% CI.

http://www.sthda.com/english/wiki/cox-proportional-hazards-model

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Implementation in R – Cox PH Model Diagnostics

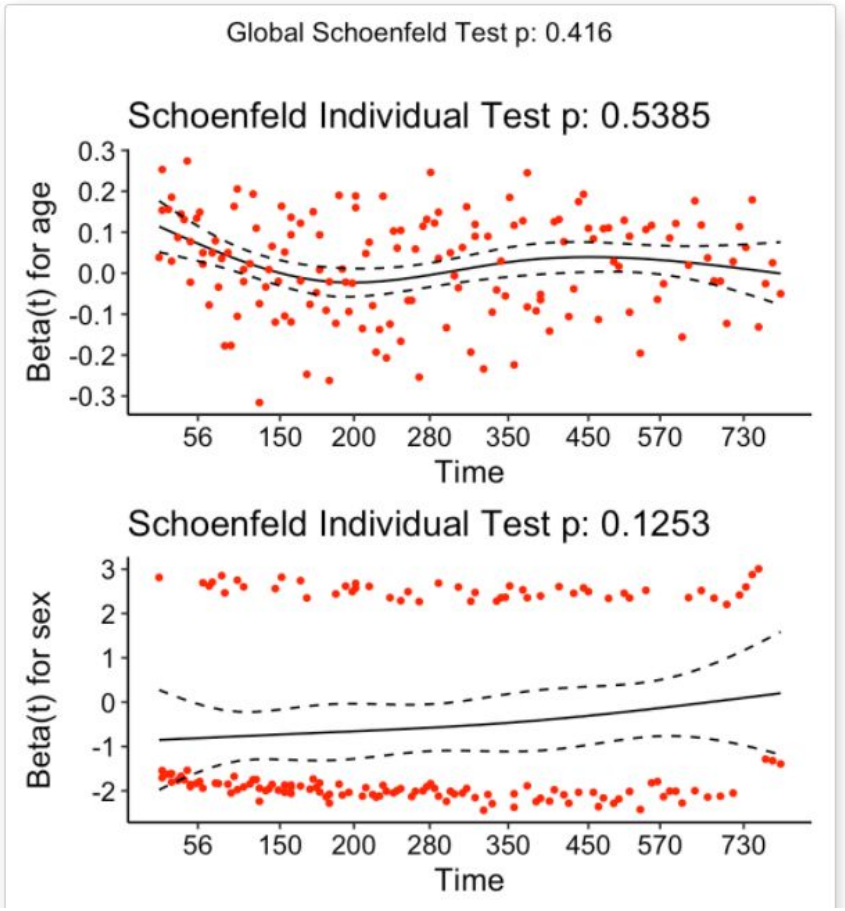
Testing proportional hazards assumption

```
test.ph <- cox.zph(res.cox)
test.ph
```

```
            rho chisq     p
age     -0.0483 0.378 0.538
sex      0.1265 2.349 0.125
wt.loss  0.0126 0.024 0.877
GLOBAL       NA 2.846 0.416
```

Here, the test for covariate and the global test are not statistically significant – assumption met.

```
ggcoxzph(test.ph)
```



Schoenfeld residuals should be flat with respect to time.

See the link below for more diagnostics.

http://www.sthda.com/english/wiki/cox-model-assumptions

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Questions?

Additional resources – Textbooks

- Introduction to pharmacokinetics and pharmacodynamics, Tozer and Rowland
- Pharmacokinetic and Pharmacodynamics data analysis, Gabrielson and Weiner

Additional Resources – Journal Articles

- Derendorf H, Meibohm B. Modeling of pharmacokinetic/pharmacodynamic (PK/PD) relationships: concepts and perspectives. Pharm Res. 1999;16(2):176-185. doi:10.1023/a:1011907920641
- Sharma A, Ebling WF, Jusko WJ. Precursor-dependent indirect pharmacodynamic response model for tolerance and rebound phenomena. J Pharm Sci. 1998;87(12):1577-1584. doi:10.1021/js980171q
- Gabrielsson J, Hjorth S. Pattern Recognition in Pharmacodynamic Data Analysis. AAPS J. 2016;18(1):64-91. doi:10.1208/s12248-015-9842-5
- Mould, D., Walz, A.-C., Lave, T., Gibbs, J. and Frame, B. (2015), Developing Exposure/Response Models for Anticancer Drug Treatment: Special Considerations. CPT Pharmacometrics Syst. Pharmacol., 4: 12-27. https://doi.org/10.1002/psp4.16
- Garnett, C., Bonate, P.L., Dang, Q. et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn 45, 383–397 (2018). https://doi.org/10.1007/s10928-017-9558-5 Zhang Z. Residuals and regression diagnostics: focusing on logistic regression. Ann Transl Med. 2016;4(10):195. doi:10.21037/atm.2016.03.36
- Holford N. A time to event tutorial for pharmacometricians. CPT Pharmacometrics Syst Pharmacol. 2013;2(5):e43. Published 2013 May 15. doi:10.1038/psp.2013.18

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Additional resources – links

- FDA Guidance. Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications (May 2003). https://www.fda.gov/media/71277/download
- MI210: Essentials of Population PK-PD Modeling and Simulation (https://www.metrumrg.com/course/mi210-essentials-population-pk-pd-modeling-simulation/)
- MI212: Advanced Topics in Population PK-PD Modeling & Simulation (https://www.metrumrg.com/course/mi212-advanced-topics-population-pk-pd-modeling-simulation/)
- https://www.page-meeting.org/pdf_assets/2573-time-to-event-tutorial.pdf