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# Time to Event Principles for Pharmacometricians

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Holford N. A Time to Event Tutorial for Pharmacometricians. *CPT: pharmacomet syst pharmacol.* 2013;2:e43 doi:10.1038/psp.2013.18.

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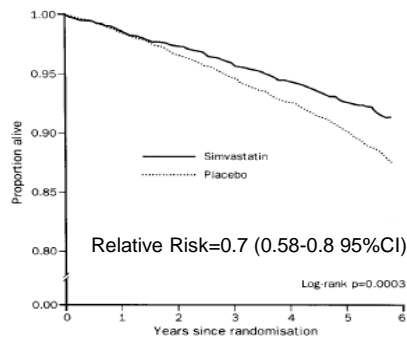
## Outline

- The Hazard: Biological basis for survival
- Types of Event and their Likelihood
  - Exact time
  - Interval censored
  - Right censored
- Joint Modelling of Continuous and Event Data

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## How Not to Understand Time to Event



Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994;344:1383-89.

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This landmark study led to the introduction of statins with a major impact on cardiovascular morbidity and mortality worldwide. However, this Kaplan-Meier plot shows that statins don't seem to have any effect on survival until at least a year after starting treatment. As far as I know there has never been any good explanation of why the benefits of statins are so delayed but when properly analysed this kind of survival data can describe the time course of hazard and give a clearer picture of how long it takes for statins to be effective.

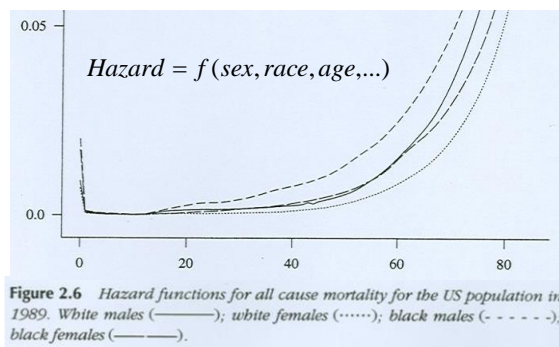
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## Why do women live longer than men?

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## Life is hazardous



"... a bathtub-shaped hazard is appropriate in populations followed from birth."  
Klein, J.P., and Moeschberger, M.L. 2003. *Survival analysis: techniques for censored and truncated data*. New York: Springer-Verlag.  
[http://en.wikipedia.org/wiki/Bathtub\\_curve](http://en.wikipedia.org/wiki/Bathtub_curve) "The bathtub curve"

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The hazard describes the death rate at each instant of time. The shape of the hazard function over the human life span has the shape of a bathtub.

US mortality data shows the hazard at birth falls quickly and eventually returns to around the same level by the age of 60. The hazard is approximately constant through childhood and early adolescence. The onset of puberty and subsequent life style changes (cars, drugs,...) adopted by men increases the hazard to a new plateau which lasts for 10 to 20 years.

It would require a time varying model to describe how development (children) and ageing (adults) are associated with changes in death rate.

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## Why Pharmacokineticists are Time to Event Experts

- What is an elimination rate constant?
  - Proportionality factor relating elimination to amount of drug

$$RateOut = k \cdot Amount$$

- What is a hazard?
  - » Proportionality factor relating death rate to number of people still alive

$$RateOut = h \cdot N_{ALIVE}$$

- Everything you know about elimination rate constants applies to hazards!

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The elimination rate constant is the hazard of a molecule 'dying'. Elimination rate constants and hazards always have units of 1/time

Unlike most drugs the hazard is not usually constant ('first-order elimination') but may change with time ('time dependent clearance') or with the number of people ('concentration dependent clearance')

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## PK and Survival

	Drug	Events
Rate of loss N=people alive A=molecules remaining	$\frac{dA}{dt} = -k_{el} \cdot A$	$\frac{dN}{dt} = -\lambda \cdot N$
Parameter 1/time	$k_{el}$	$\lambda$
Integral	AUC	Cumulative Hazard
Non-parametric	Non-compartmental	Kaplan-Meier
Time Course	$C(t) = \exp(-k_{el} \cdot t)$	$S(t) = \exp(-\lambda \cdot t)$

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The event rate is frequently scaled to a standard number of persons e.g. death rates per 100,000 people. Hazard models are more typically scaled to a single person. Pharmacokinetic models are scaled to the dose. In this example a unit dose is assumed for the time course of concentration.

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## Pharmacokinetic Survival

$$\text{hazard}(t) = \text{Rateconstant}(t) = CL/V$$

$$\text{Risk}(t) = \text{Cumhazard}(t) = \int_0^t \text{hazard}(t) dt$$

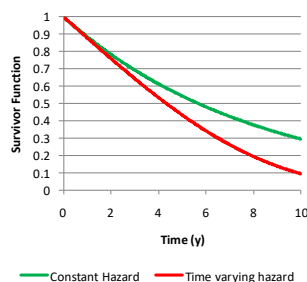
$$\text{Survival}(t) = C(t) = e^{-\text{Cumhazard}(t)}$$

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If the hazard varies with time (or a function of time, such as concentration) then exactly the same relationships between hazard, risk and survival exist as for the constant hazard case. It is possible to make non-linear pharmacokinetic model predictions of the amount eliminated and the time course of concentration using survival analysis functions.

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## Survivor Function



$$h(\text{const}) = \beta_0 \cdot \exp(\beta_1 \cdot \text{Status} \cdot S_0)$$

$$\text{Status} = S_0 + \text{slope} \cdot \text{time}$$

$$h(\text{varying}) = \beta_0 \cdot \exp(\beta_1 \cdot \text{Status} \cdot \text{Status})$$

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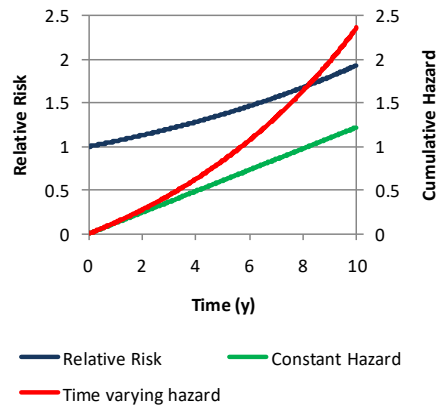
```

;Berkeley Madonna Simulation
Code
METHOD RK4
STARTTIME = 0
STOPTIME=10 ; y
DT = 0.02 ; y
beta0=0.1 ; 1/y
betaStatus=0.01 ; 1/(status units)
S0=20 ; status units
status=S0+12*time
hazconstant=beta0*exp(betaStatus*s*S0) ; status remains constant
hazvarying=beta0*exp(betaStatus*status*status) ; status increases with time (e.g. worsening disease state)
init(cumconstant)=0
d/dt(cumconstant)=hazconstant
survconstant=exp(-cumconstant)
init(cumvarying)=0
d/dt(cumvarying)=hazvarying
survvarying=exp(-cumvarying)
pdfconstant=survconstant*hazconstant
pdfvarying=survvarying*hazvarying
relative_risk=if (cumconstant<=0) then 1 else cumvarying/cumconstant

```

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## Cumulative Hazard and Relative Risk



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## Explanatory Variable Functions

$$h(t) = \beta_0 \cdot e^{\beta_1 \cdot x_1 + \beta_2 \cdot x_2 \dots + \beta_n \cdot x_n}$$

Includes exponential, Weibull, Gompertz as special cases

$$h(t) = \beta_0 \cdot e^{f(B, X)}$$

Linear and non-linear functions of explanatory variables

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The explanatory variable function is quite empirical. This form is used because there are some simple solutions for integrating the hazard and the exponential form ensures that the hazard is always non-negative.

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## Exponential Coefficients and the Hazard Ratio

$$h(t) = \beta_0 \cdot e^{\beta_1 \cdot x_1 + \beta_{SEX} \cdot SEX \dots + \beta_n \cdot x_n}$$

If the explanatory variable is 0 for females and 1 for males and the value of  $\beta_{SEX}$  is 0.693 then the hazard ratio for men is 2 (compared to women).

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The coefficients of the exponential function are convenient for describing how the hazard varies with the explanatory variable. Exponentiation of the coefficient gives the hazard ratio for the effect of the explanatory variable.

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## Pharmacokinetic Survival Non-Linear

$$\text{hazard}(t) = \text{Rateconstant}(t) = (V_{\max}/V)/(K_m + C(t))$$

$$\text{Risk}(t) = \text{CumConstant}(t) = \int_0^t \text{Rateconstant}(t) dt$$

$$\text{Survival}(t) = C(t) = e^{-\text{CumConstant}(t)}$$

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If the hazard varies with time (or a function of time, such as concentration) then exactly the same relationships between hazard, risk and survival exist as for the constant hazard case. It is possible to make non-linear pharmacokinetic model predictions of the amount eliminated and the time course of concentration using survival analysis functions.

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## Non-linear PK and Survival

dose=100  
v=1  
vmax=100  
km=50

```
rateconstant=(vmax/v)/(km+conc)
init(conc)=dose/v
d/dt(conc)=-rateconstant*conc

init(cumconstant)=0
d/dt(cumconstant)=rateconstant
survival=dose*exp(-cumconstant)
```

Time	Conc	Survival
0	100	100
1	42.6303	42.6303
2	10.8858	10.8858
3	1.76793	1.76793
4	0.246655	0.246655
5	0.033524	0.033524
6	0.00454	0.00454
7	6.14E-04	6.14E-04
8	8.32E-05	8.32E-05
9	1.13E-05	1.13E-05
10	1.52E-06	1.52E-06

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## Baseline Hazard Functions

$h(t) = \lambda$  Exponential

$h(t) = \lambda \cdot \gamma \cdot t^{\gamma-1}$  Weibull  
 $h(t) = \lambda \cdot \gamma \cdot e^{(\gamma-1) \cdot \ln(t)}$   
 $h(t) = \beta_0 \cdot e^{\beta_1 \cdot \ln(t)}$

$h(t) = \lambda \cdot e^{\beta_1 \cdot t}$  Gompertz

$h(t) = \lambda \cdot \frac{\left(\frac{\lambda-t}{\beta}\right)^{\beta-1}}{\left(1+\frac{\lambda-t}{\beta}\right)^\beta}$  Log-logistic

Cox Proportional: Baseline hazard undefined but the same for everyone

Non-Parametric: No good for simulation. Tricky with time varying hazards.

Parametric: Can be used for simulation and time varying hazards

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The hazard function is associated with a distribution of event times. Some common distributions have names e.g. Gompertz (one of the first mathematicians to explore survival analysis). Standard baseline hazard functions used by statisticians are chosen for their mathematical simplicity rather than any biological reason. The biology of event time distributions is largely based on descriptive and empirical approaches. However, the hazard is the way to introduce biological mechanism and understanding the variability of time to event distributions.  
[https://en.wikipedia.org/wiki/Log-logistic\\_distribution](https://en.wikipedia.org/wiki/Log-logistic_distribution)

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## Likelihoods for Survival

For an uncensored datum, with  $T_i$  equal to the age at death, we have

$$\Pr(T = T_i|\theta) = f(T_i|\theta) = S(T_i|\theta) * h(T_i)$$

For a left censored datum, such that the age at death is known to be less than  $T_i$ , we have

$$\Pr(T < T_i|\theta) = F(T_i|\theta) = 1 - S(T_i|\theta)$$

For a right censored datum, such that the age at death is known to be greater than  $T_i$ , we have

$$\Pr(T > T_i|\theta) = 1 - F(T_i|\theta) = S(T_i|\theta)$$

For an interval censored datum, such that the age at death is known to be greater than  $T_{i,r}$  and less than  $T_{i,l}$ , we have

$$\Pr(T_{i,l} < T < T_{i,r}|\theta) = S(T_{i,l}|\theta) - S(T_{i,r}|\theta)$$

[http://en.wikipedia.org/wiki/Survival\\_analysis](http://en.wikipedia.org/wiki/Survival_analysis)

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An alternative way of describing the likelihoods in terms of the survivor function and hazard function alone.

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## Applications

- Continuous Response
  - Standard PKPD
- Non-continuous Response
  - Binary Response
    - Awake or Asleep
  - Ordered Categorical Response
    - Neutropenic adverse event type
  - Count Response
    - Frequency of epileptic seizures
  - Time to Event
    - Death
    - Dropout
- Joint Response
  - Continuous plus non-continuous

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NONMEM (and many other parameter estimation procedures) uses the likelihood to guide the parameter search. The likelihood is the fundamental way to describe the probability of any observation given a model for predicting the observation. NONMEM shields us from the details for common PKPD models that use continuous response scales for the observation (e.g. drug concentration, effect on blood pressure).

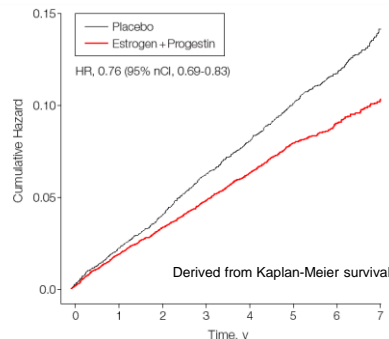
A variety of non-continuous responses are widely used to describe drug effects – especially clinical outcomes. By computing the likelihood directly for each of these kinds of response we can ask NONMEM to estimate parameters for any mixture of response types.

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## Effects of Estrogen Plus Progestin on Risk of Fracture and Bone Mineral Density

The Women's Health Initiative Randomized Trial

Jane A. Cauley, DrPH  
 John Robbins, MD  
 Zhao Chen, PhD  
 Steven R. Cummings, MD  
 Rebecca D. Jackson, MD  
 Andrea Z. LaCroix, PhD, MPH  
 Meryl LeBoff, MD  
 Cora E. Lewis, MD, MSPH  
 Joan McGowan, PhD  
 Joan Neuner, MD, MPH  
 Mary Pettinger, MS  
 Marcia L. Stefanick, PhD  
 Jean Wactawski-Wende, PhD  
 Nelson B. Watts, MD  
 for the Women's Health Initiative Investigators



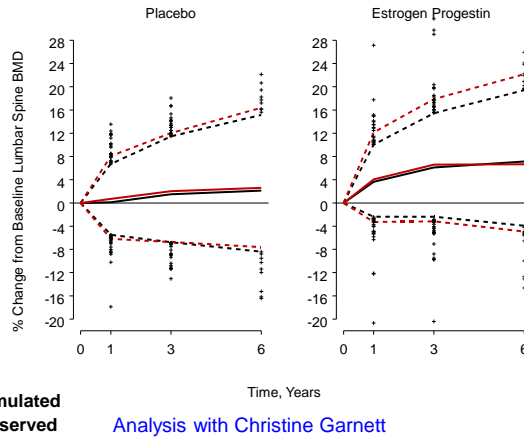
JAMA, 2003;290:1729-1738

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NOTE: Calcium + vitamin D at doses administered in the WHI trial show increases in BMD without added reduction in fracture (hip and total fracture) Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Calcium plus Vitamin D Supplementation and the Risk of Fractures. N Engl J Med. 2006 February 16, 2006;354(7):669-83.

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### Bone Mineral Density – Slow Biomarker Women’s Health Initiative Randomized Trial

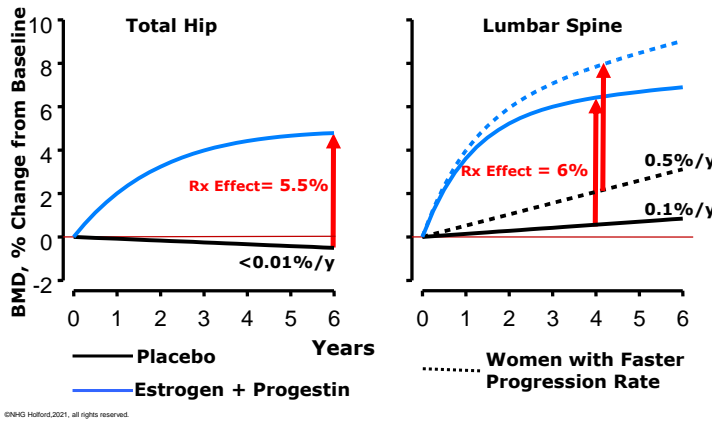


The Women’s Health Initiative trial observed the time course of changes in bone mineral density in 1000 women who were treated with placebo or with active hormone replacement therapy. Both groups were treated with active calcium + vitamin D. Half of the placebo patients were given placebo calcium + vitamin D. This plot is a visual predictive check showing the median and 90% interval for the observed (black) and predicted (red) BMD changes. The increase in BMD in the placebo group (and some of the change in the HRT group) is attributable to treatment with calcium + vitamin D.

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### BMD Time Course

70 kg woman 13 years post menopause



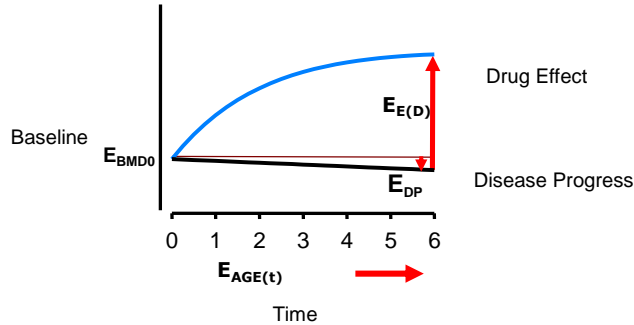
These figures shows some key results for the Hip and Spine models which represent the two different types of bone.  
**Teq for lumbar spine 0.81 y.**  
**Teq for hip 1.53 y.**  
 For the hip bone, there was a trend for bone loss with a progression rate of less than 0.01% per year. Maximum treatment effect was estimated to be 6% of baseline. But by year 6, 94% of treatment effect was observed.

For spine, women gained bone mass during the trial. Approximately 52% of the women’s progression rate was 0.1% per year and the remaining women gained bone with a rate of 0.5% per year. Maximum treatment effect from hormones was approximately 6% of baseline. Due to the shorter equilibration T1/2, maximum treatment effect was observed by year 4.

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## Hazard Model for Fractures Constant and Time Varying Explanatory Factors

$$h(t) = \beta_0 \cdot \exp(E_{BMD_0} + E_{AGE(t)} + E_{DP} + E_{E(D)}) + \eta$$

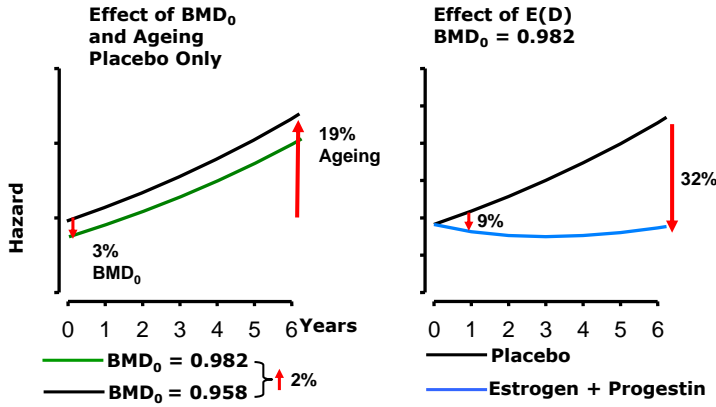


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Hazard model for fractures is a function of Bone Mineral Density. Instead of using the predicted BMD as a single time-varying covariate in the hazard, we chose to parameterize the hazard function by including each component of the disease status model as a covariate. This allowed us to assess the relative contributions of each component to the risk of fracture. Some women had more than one fracture which allowed the between subject difference in hazard to be estimated ( $\eta$ ). This kind of random effects model is called a 'frailty model' in the statistical survival analysis literature.

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## Baseline BMD, Age and Treatment Effect are Predictors of Fracture

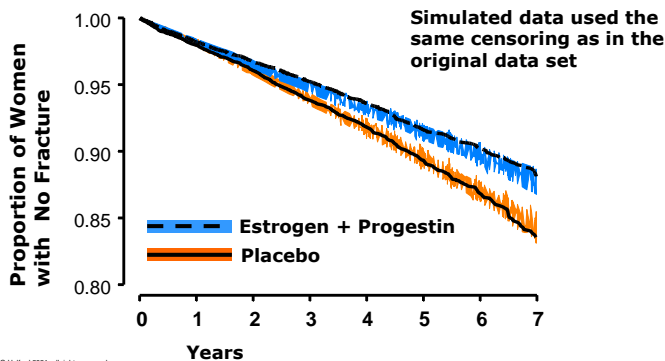


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This is a deterministic simulation of the final fracture model using total body BMD

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## A Visual Predictive Check for Time to Event Based on Kaplan-Meier Estimates of S(t)



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A visual predictive check using the Kaplan-Meier method was used to generate the predicted uncertainty in the survivor function (based on 500 replications of the WHI data set). The 90% predictive interval for placebo is shaded in orange and the blue represents the predictive interval for E+P. The black lines represent the observed probability of no fracture. Overall, the BMD model describes the observed data well.



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## Disease Progression

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2012.04192.x

### Progression of motor and nonmotor features of Parkinson's disease and their response to treatment

Thuy C. Vu,<sup>1</sup> John G. Nutt<sup>2</sup> & Nicholas H. G. Holford<sup>1</sup>

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

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#### Keywords

disease progression, levodopa, motor subscales, Parkinson's disease, pharmacodynamics, selegiline

#### Received

21 January 2011

#### Accepted

15 January 2012

#### Accepted Article

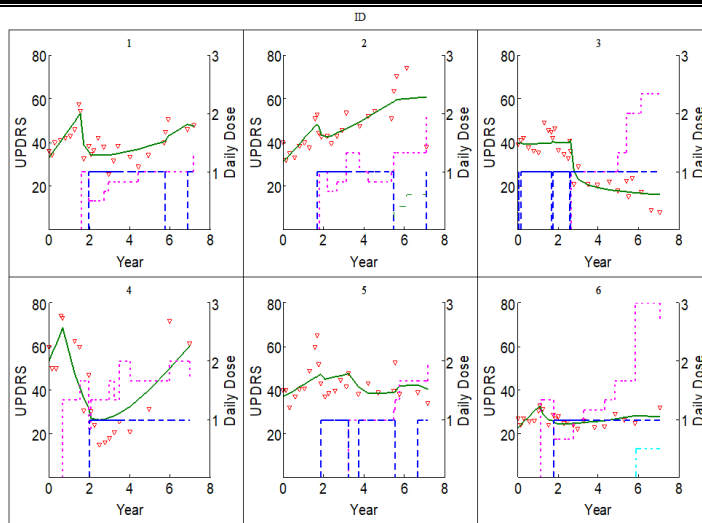
Published Online

29 January 2012

Vu TC, Nutt JG, Holford NHG. Progression of motor and nonmotor features of Parkinson's disease and their response to treatment. Br J Clin Pharmacol 2012; 74: 267-83.

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Disease status was followed with the Unified Parkinson's Disease Response Scale (UPDRS). The UPDRS patterns were quite variable from patient to patient. A major source of variability was the response to individual drug treatments.

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## Joint Time to Event Model

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2012.04208.x

### Disease progress and response to treatment as predictors of survival, disability, cognitive impairment and depression in Parkinson's disease

Thuy C. Vu,<sup>1</sup> John G. Nutt<sup>2</sup> & Nicholas H. G. Holford<sup>1</sup>

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

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#### Keywords

disease progress, levodopa, Parkinson's disease, selegiline, time-dependent covariate, time to event

#### Received

21 January 2011

#### Accepted

25 January 2012

#### Accepted Article

Published Online

2 February 2012

Vu TC, Nutt JG, Holford NHG. Disease progress and response to treatment as predictors of survival, disability, cognitive impairment and depression in Parkinson's disease. Br J Clin Pharmacol 2012; 74: 284-95.

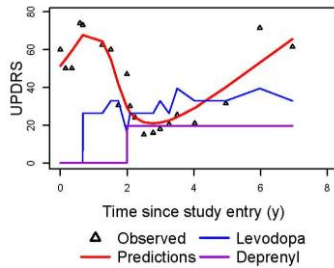
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## Outcome Event Hazard in Parkinson's Disease

### Hazard Model with Explanatory Variables

$$h(t) = h_0(t) \cdot \exp(\beta_{deprenyl} \cdot deprenyl(t) + \beta_{status} \cdot status(t) + \dots + \beta_n X_n)$$



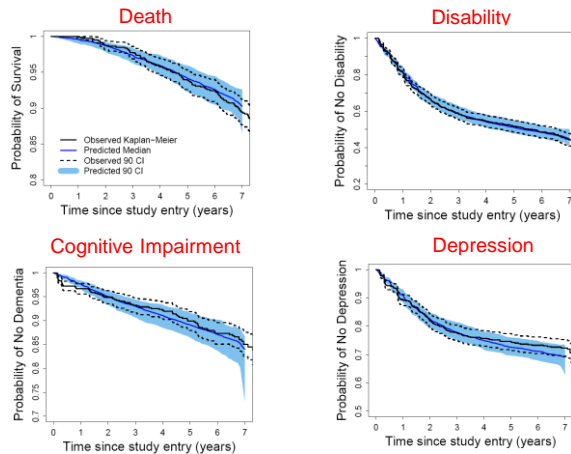
- $deprenyl(t)$  = 1 for on periods, 0 for off periods
- $status(t)$  = predicted disease status as measured by UPDRS or its subscales at time  $t$
- Other Explanatory Factors: ( $X_n$ )
  - Levodopa(t), baseline motor subtypes status
  - Age, sex, smoking status at study entry

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The severity of Parkinson's disease is usually assessed by the Unified Parkinson's disease response scale (UPDRS). The UPDRS score increases with time as the disease progresses. The disease status can be described by a model for disease progression (natural history) and the effects of treatment e.g. the use of levodopa (the mainstay of treatment) with or without deprenyl (a mono-amine oxidase inhibitor commonly used as an adjunctive treatment). The hazard of a clinical outcome event e.g. death, can be described by a baseline hazard,  $h_0(t)$ , and explanatory factors such as drug treatment and the time course of disease status. Other factors (age, sex, smoking, etc) are easily included in this kind of model.

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## Evaluation of Hazard Models visual predictive check



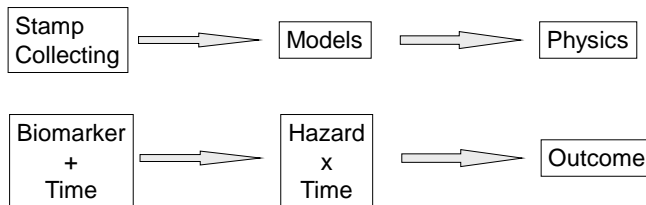
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The change of disease status, reflected by the time course of UPDRS, is the most important factor determining the hazard of clinical outcome events in Parkinson's disease. The different shapes of the survival function for death, disability, cognitive impairment and depression reflect different contributions of disease status to the probability of not having had the event as time passes.

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## Putting Time Back into The Picture

*"Science is either stamp collecting or physics"*  
Ernest Rutherford



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