Time-to-Event Data: A Different Angle by Population Evolution Charts And New Statistical Tests

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the idea for population evolution charts came from…..

- A practical question: in a pool of studies with differing observation length, we observed a decrease in estimated hazard for CV disease in the later stage.
- Initially we had about 35% who reported preexisting heart disease at baseline – can we still compare this population with the one selected out by death after 3 years?
- After 3 years the hazard for CV disease seemed to be lower – may be all problematic patients already died?
- Finally we found that the proportion of patients reporting heart disease at baseline even slightly increased for the pool population after 3 years.

This was the beginning !

A slightly more formal setup …

- Consider a random variable T for the event time
- Allow for censoring: a second rv C for time-to-censoring
- Assume covariates, known at baseline, either metric or categorial (binary)

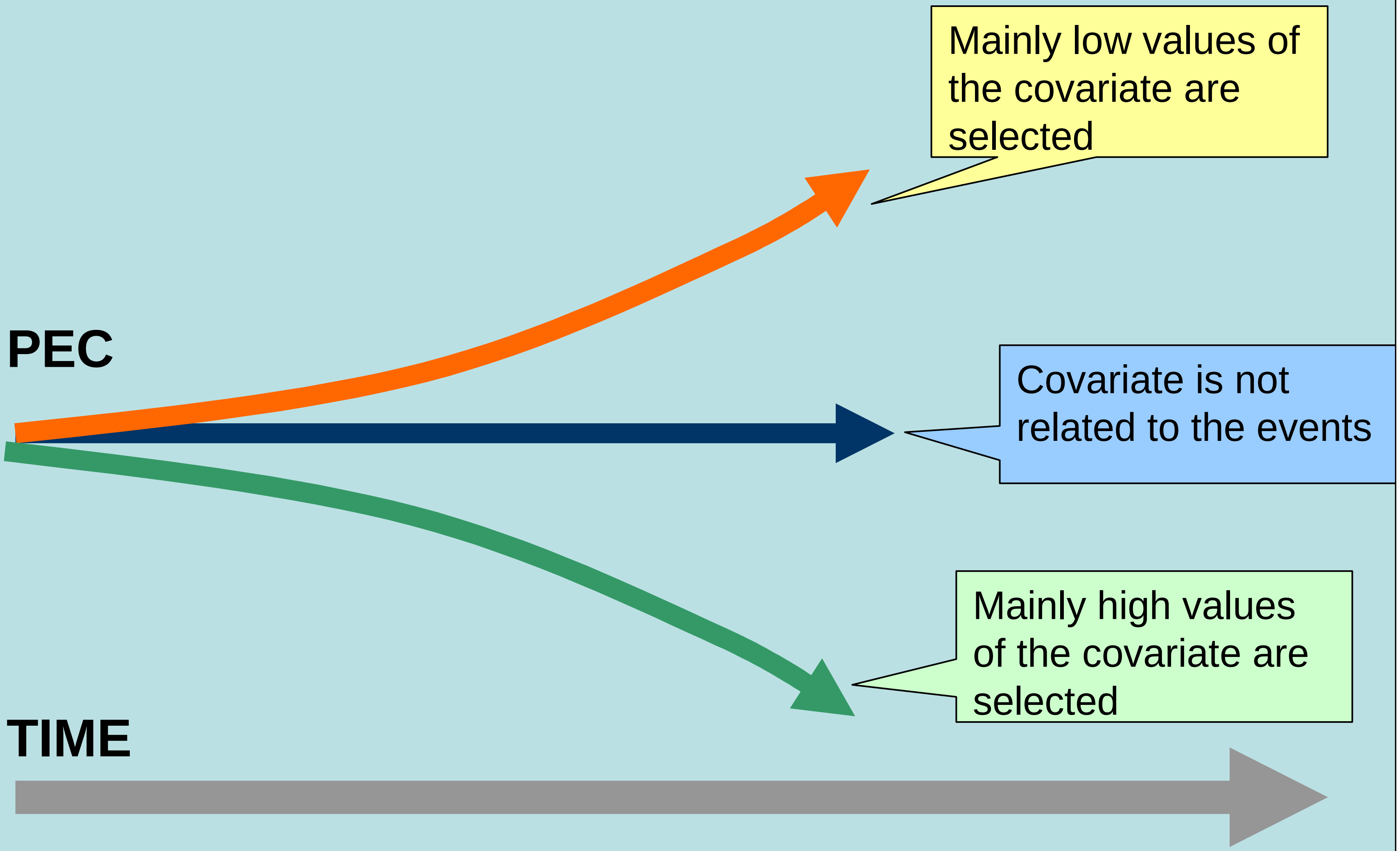
Selection Processes

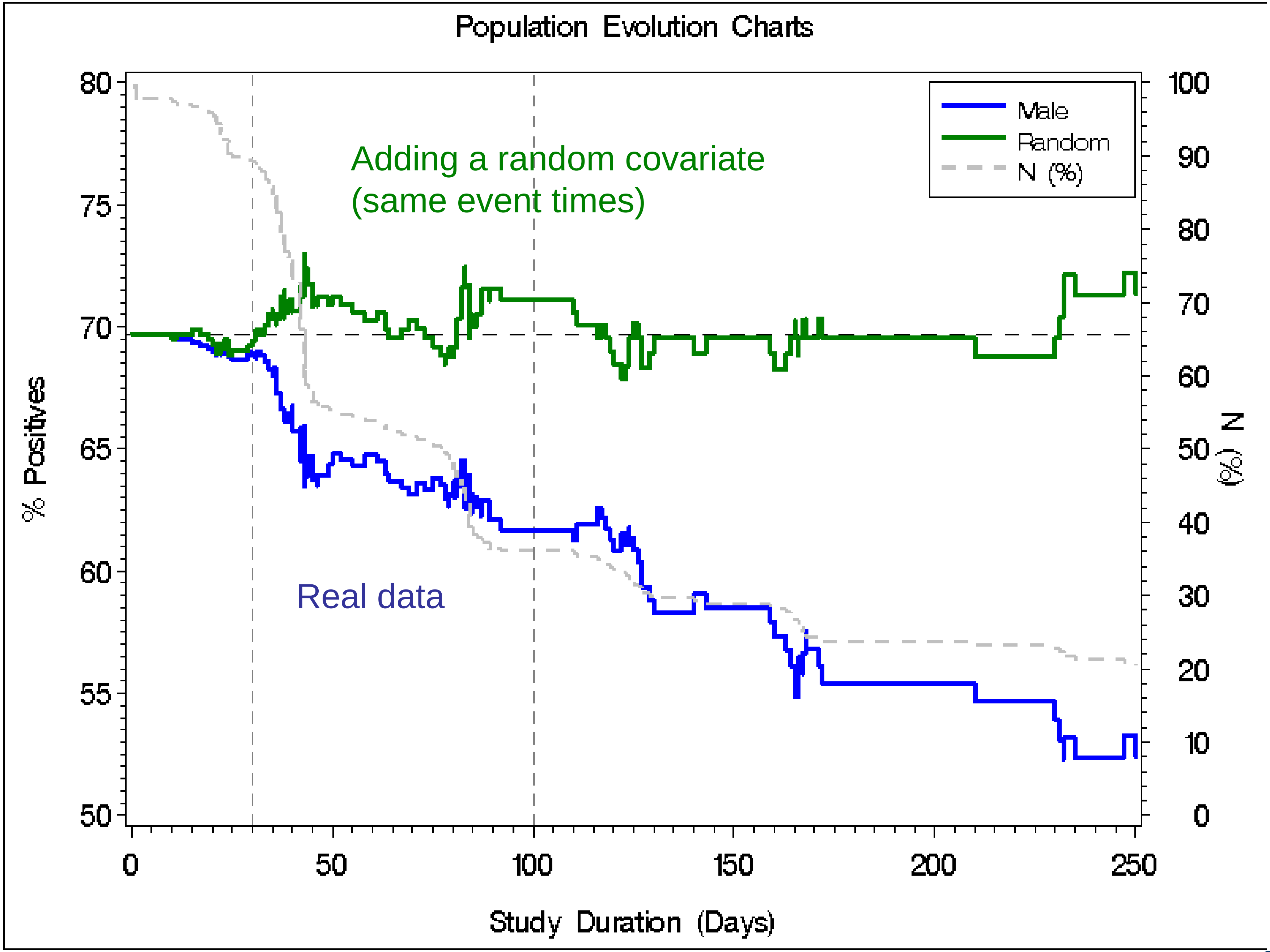
- The following groups/cohorts are considered:
  - $G(0)$ the initial group at time zero; the full group
  - $E(t)$ the group of patients with an event $\leq$ t
  - $Z(t)$ the group of patients with censoring $\leq$ t
- Thus the available group $G(t)$ at time t can be written:
  - $G(t) = G(0) \div E(t) \div Z(t)$, where $\div$ denotes set subtraction.
- $G(t)$ can be conceived to arise from $G(0)$ by two selection processes, namely events and censoring.

Selection Processes: binary

Simple idea behind Population Evolution Charts (PEC)	
Cohort at baseline: $G(0)$	This cohort is reduced through events/censoring in the course of the study
Cohort at time t: $G(t)$	This cohort is at risk after the time t has elapsed
Binary covariate X e.g. sex	$P(X=1)=\pi_1(0)$ the expectation at $t=0$
Suppose ***X* not related** to events/censoring	Expect $P(X=1)=\pi_1(t)=\pi_1(0)$
Suppose ***X* is related** to events/censoring	Expect $\pi_1(t)<\pi_1(0)$ or $\pi_1(t)>\pi_1(0)$
Define a simple PEC	Course of $\hat{\pi}_1(t)$, i.e. the proportion of $X=1$ for the cohorts $G(t)$.
PECs come as graphics	**PECs do not need difficult assumptions**

Selection Processes Interpretation





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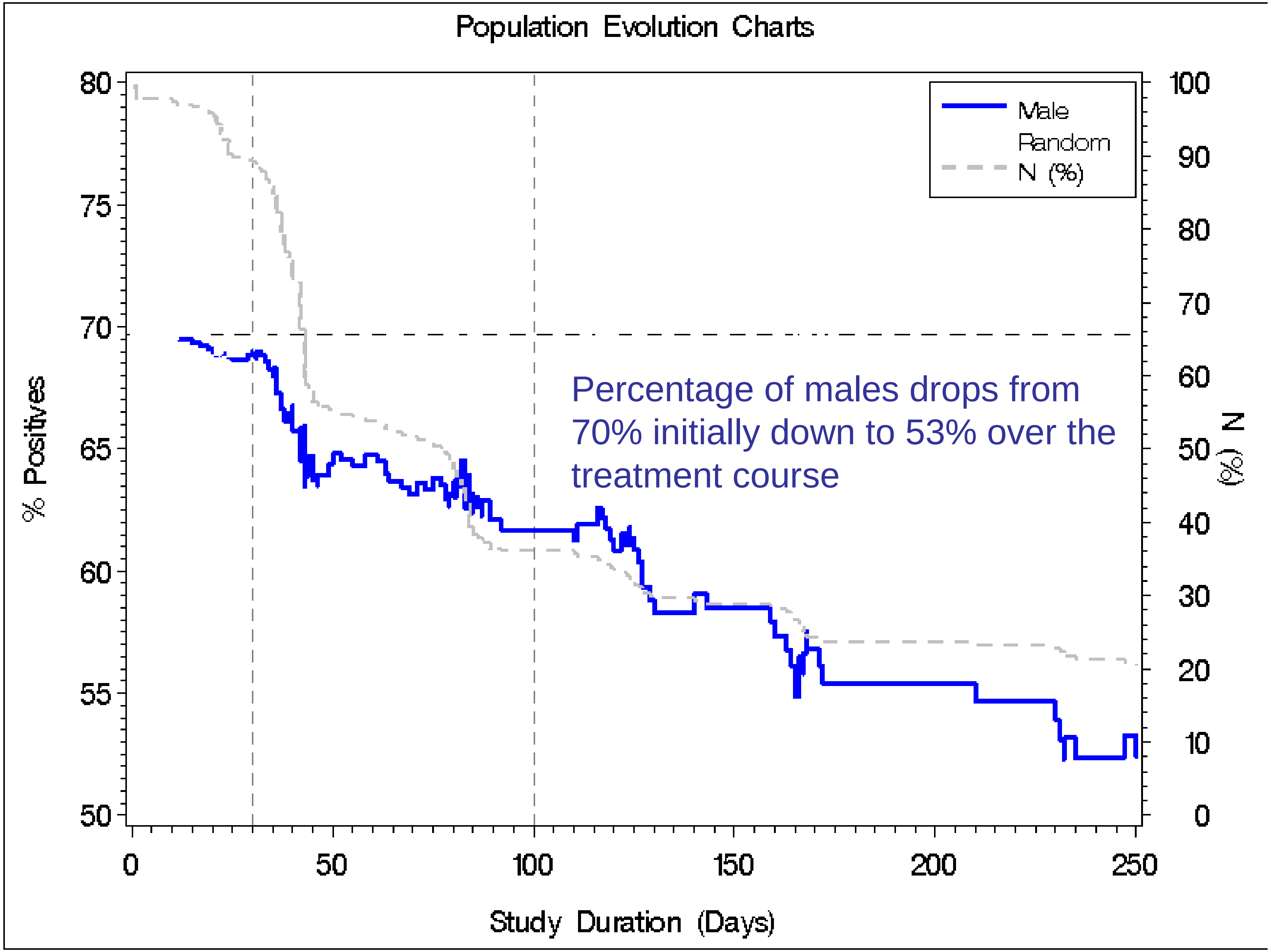

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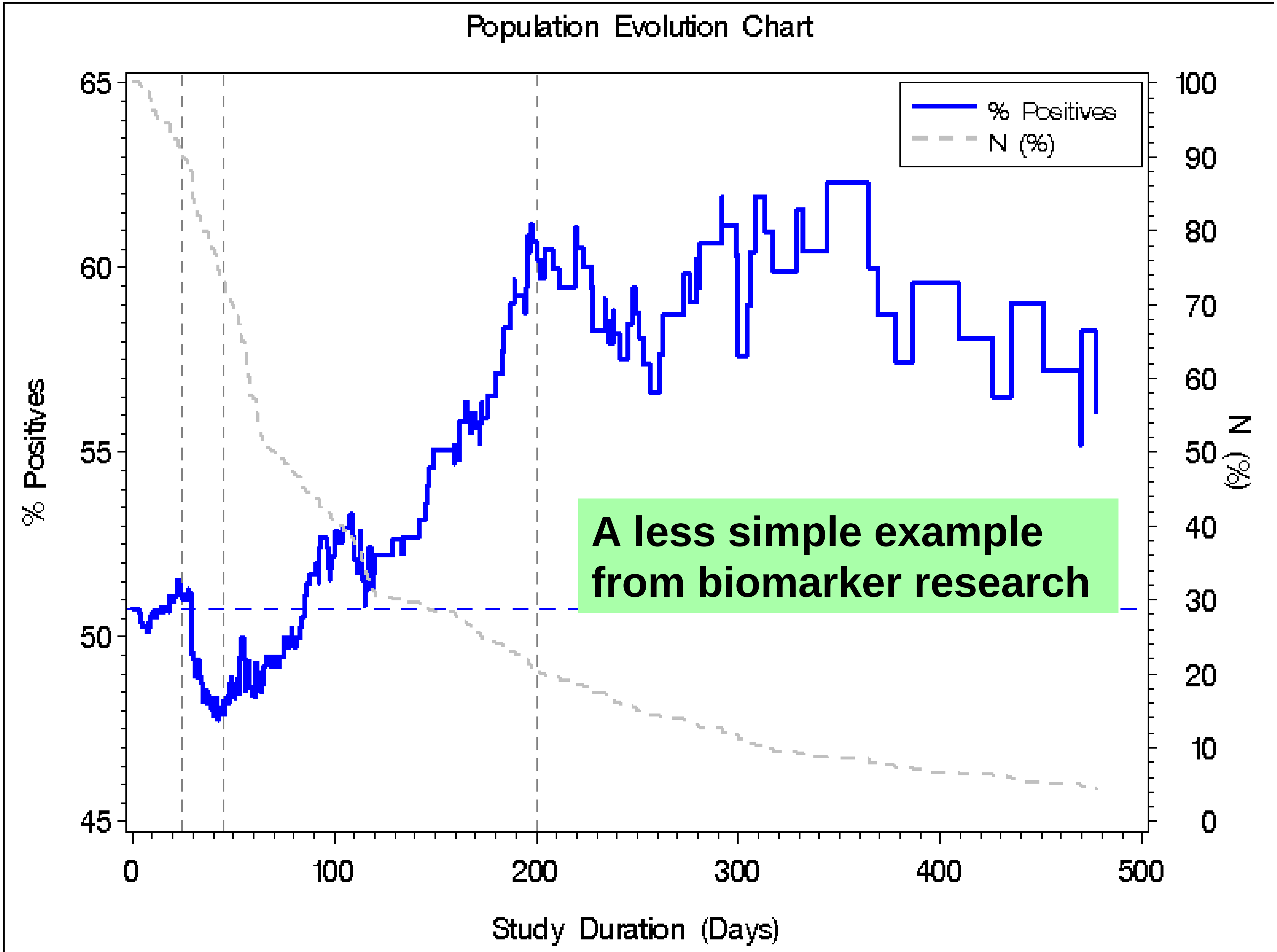

A less simple example from biomarker research

Set up of the terminology for the case of binary covariates ….

Basic Notation

Basic Definitions	**Random Variable T**
Survivor Function $S(t)$	$S(t)=1-F(t)=P(T>t)$
Integrated Hazard $H(t)$	$H(t)=-\log(S(t))$
Density $f(t)$	$f(t)={}^{d}\!/_{dt}F(t)$
Hazard $h(t)$	$h(t)={}^{d}\!/_{dt}H(t)=-{}^{d}\!/_{dt}\log(S(t))=\dfrac{f(t)}{S(t)}$

Define
Population Evolution Chart (PEC)

PEC Base Definition	$P(X = 1 \mid T > t)$
Usual regression considers	$P(T > t \mid X)$

Define
Population Evolution Chart (PEC)

Equivalent Definitions of Population Evolution Charts (PEC) $\Psi_X(t)$	
I. Base Definition	$P(X=1 \mid T>t)$
II. PEC as selection process	$\frac{1}{S(t)}\left[P(X=1)-(1-S(t))\cdot P(X=1 \mid T\leq t)\right]$
III. PEC in terms of subgroup survivor function	$\frac{S_1(t)}{S(t)}P(X=1)$
PECs come as graphics	**PECs do not need difficult assumptions**

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Wait a moment ….

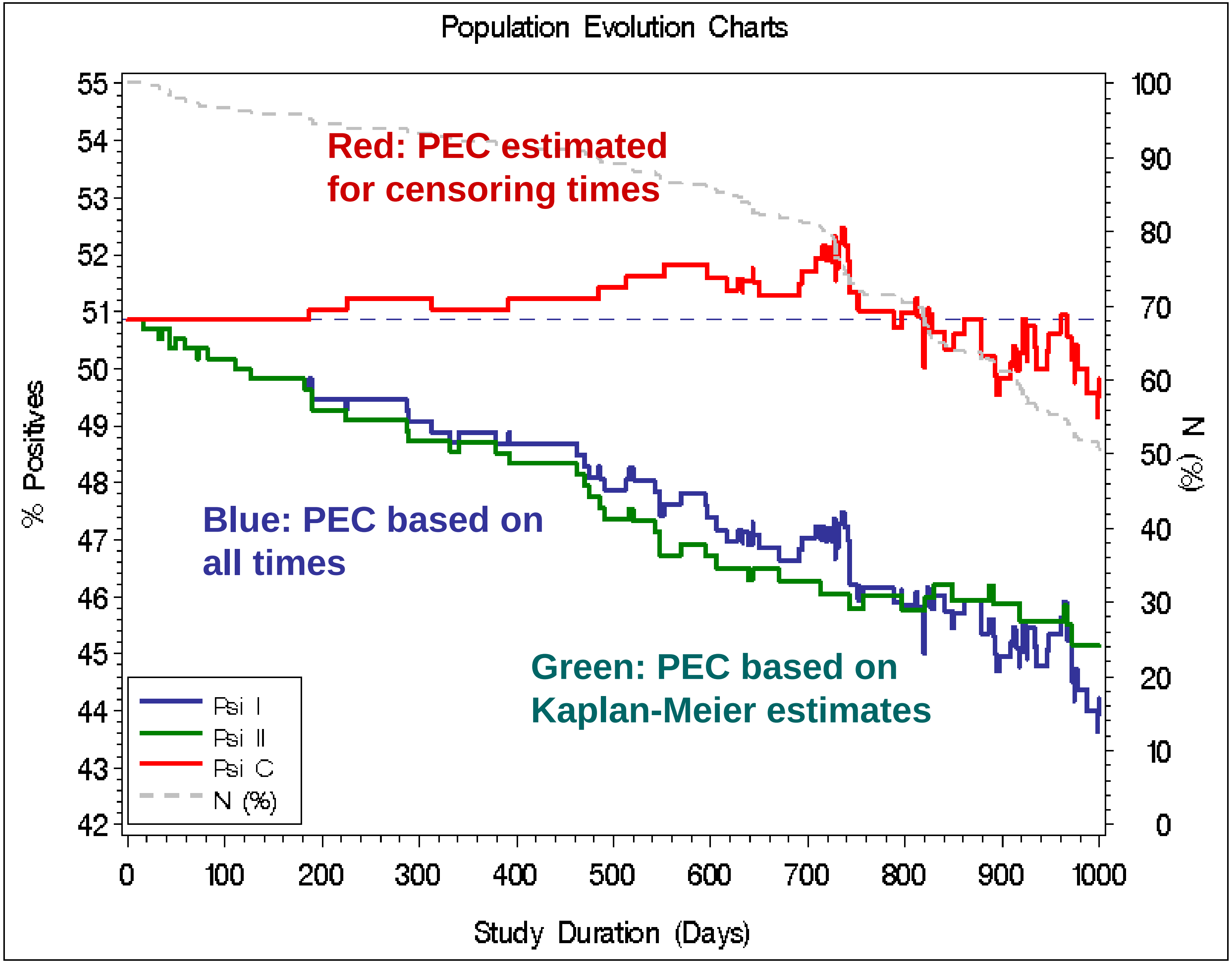
- What about censoring?

- How to deal with it in the estimation of a PEC?

Estimate Population Evolution Chart

Estimation of Population Evolution Charts (PEC) The Censoring Problem	
Censoring C independent of T Consider all observed times $A = \min(T, C)$	$P(A > t) = P(T > t) \cdot P(C > t)$ KM-estimates $\hat{P}(A > t) = \hat{P}(T > t) \cdot \hat{P}(C > t)$
Assumption: Covariate not related to censoring	Since $P(X = 1 \mid A > t) = P(X = 1 \mid T > t)$ Estimate $\hat{\Psi}_{\mathrm{I}}(t) = \frac{1}{\lvert G(t) \rvert} \sum_{j \in G(t)} x_j$ from all times
Using only assumptions for Kaplan-Meier estimates	$\hat{\Psi}_{\mathrm{II}}(t) = \frac{\hat{S}_1(t)}{\hat{S}(t)} \cdot \overline{x}(0)$ Provides proper dealing with censoring times
Define a PEC for the censoring process – to check for selective censoring	$\hat{\Psi}_{\mathrm{C}}(t) = \frac{\hat{P}(C > t \mid X = 1)}{\hat{P}(C > t)} \cdot \overline{x}(0)$
PECs come as graphics	**PECs do not need difficult assumptions**

All Estimates



For binary covariates Evolution Charts offer ….

- A simple graphical representation of dependencies
- Depicts time dynamics in an easy way
- Could also serve to check for selective censoring

Population Evolution Charts
and
Cox proportional hazard model

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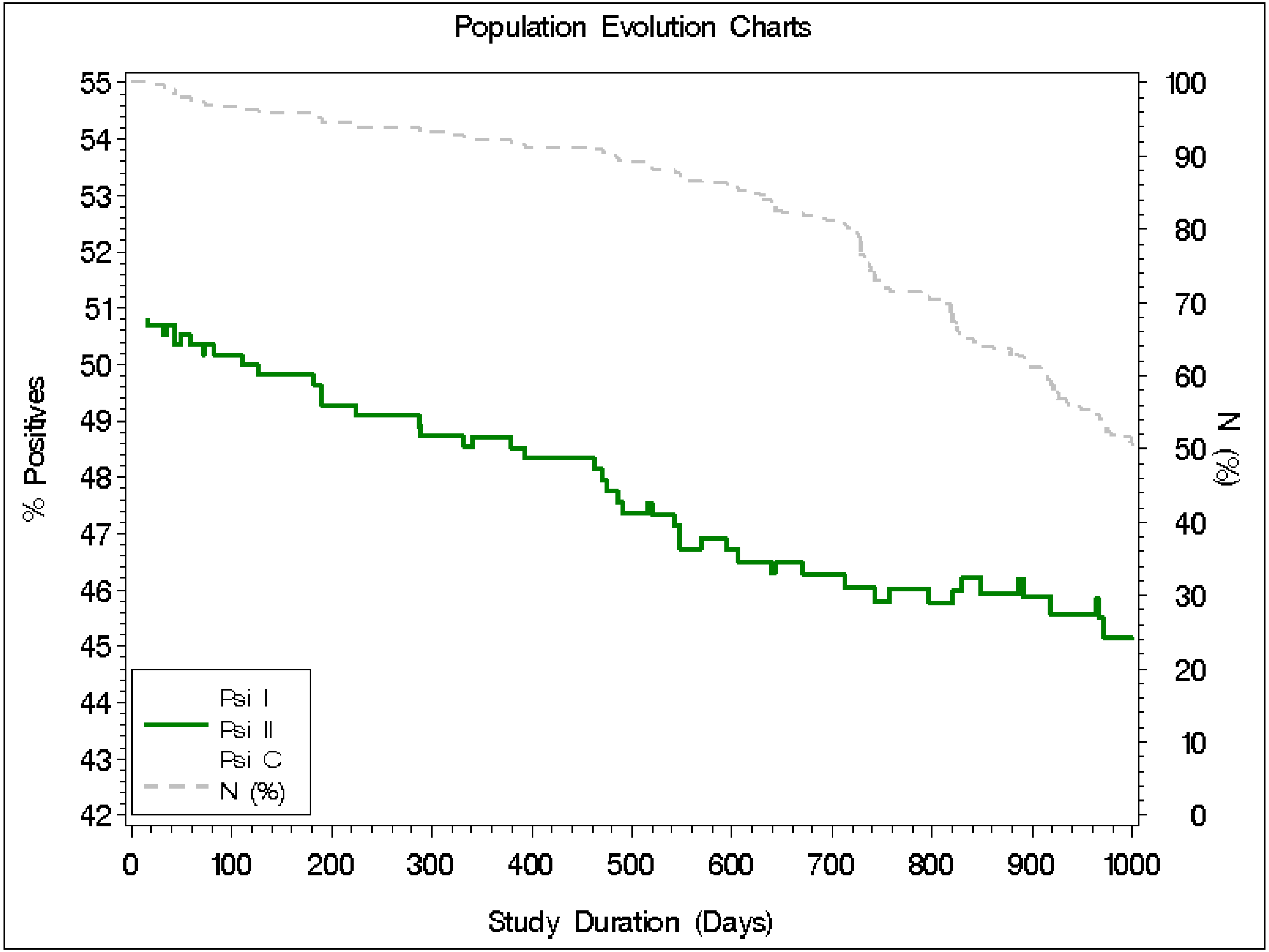
PEC & Cox

Studying Relation of a Binary Covariate with Event Times	
Standard Approach $P(T > t \mid X)$	Cox model $S(t \mid X = 1) = S(t \mid X = 0)^{\lambda}$ Crucial proportionality $h_1(t) = \lambda h_0(t)$
Population Evolution Chart $P(X = 1 \mid T > t)$	No assumptions regarding the hazards
PECs come as graphics	**PECs do not need difficult assumptions**

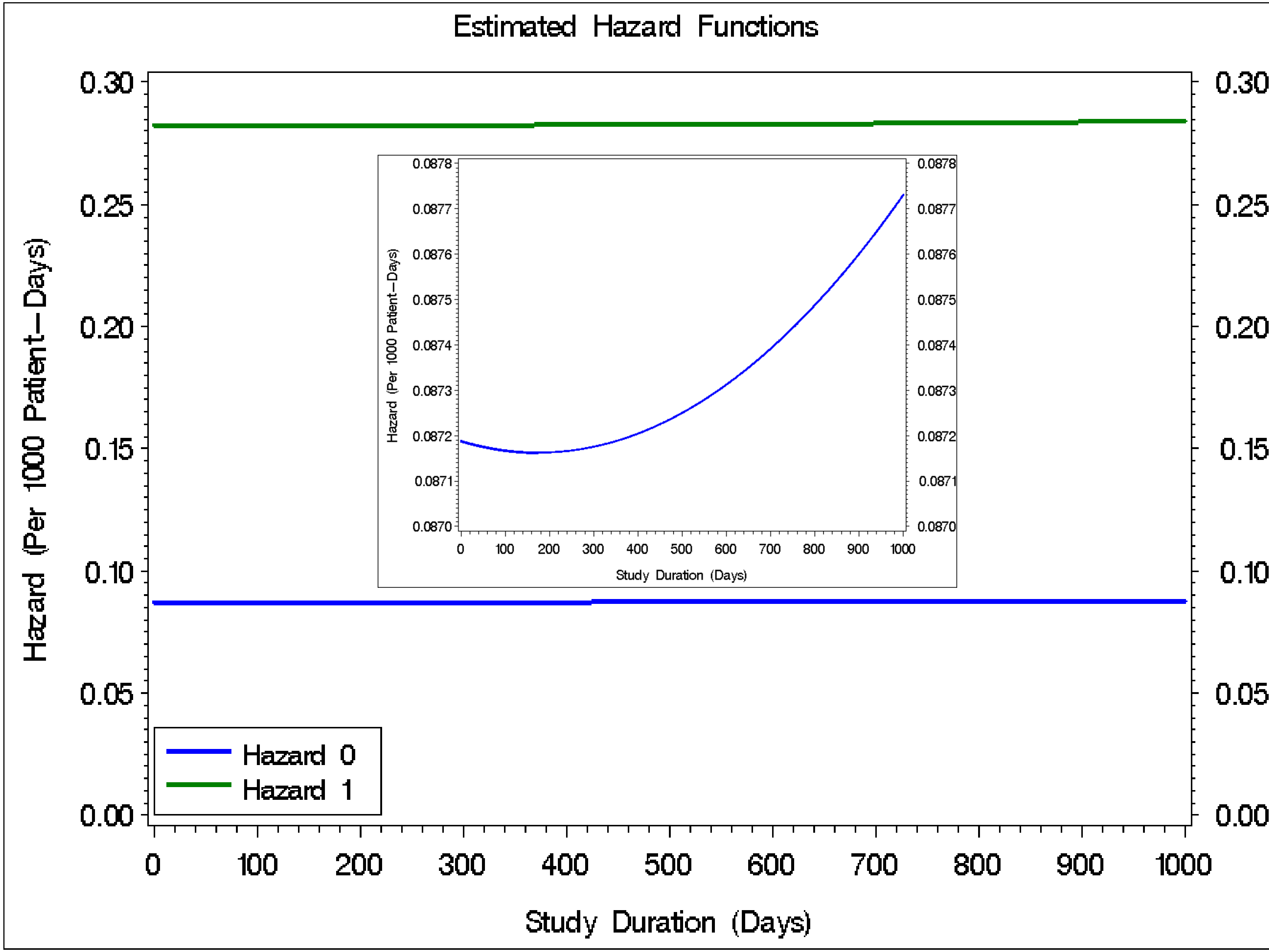
PEC & Cox

PEC monotonic	A necessary condition for validity of the Cox model $\Psi'_X(t) = (1-\lambda)\cdot h_0(t)\cdot \Psi_X(t)\cdot(1-\Psi_X(t))$
PEC monotonic & Cox Model holds	Explicit hazard estimate is possible
PEC linear & Cox Model holds $\Psi_X(t) = \alpha \cdot t + \pi_1$	$h_0(t) = \frac{1}{1-\lambda}\cdot\frac{\alpha}{(\alpha\cdot t+\pi_1)\cdot(-\alpha\cdot t+\pi_0)}$
results: $\pi_1 = 50.86\%$ $\alpha = 4.88\frac{\%}{1000d}$ $\lambda = 3.24$	obtained from PEC obtained by linear regression PEC obtained from Cox regression

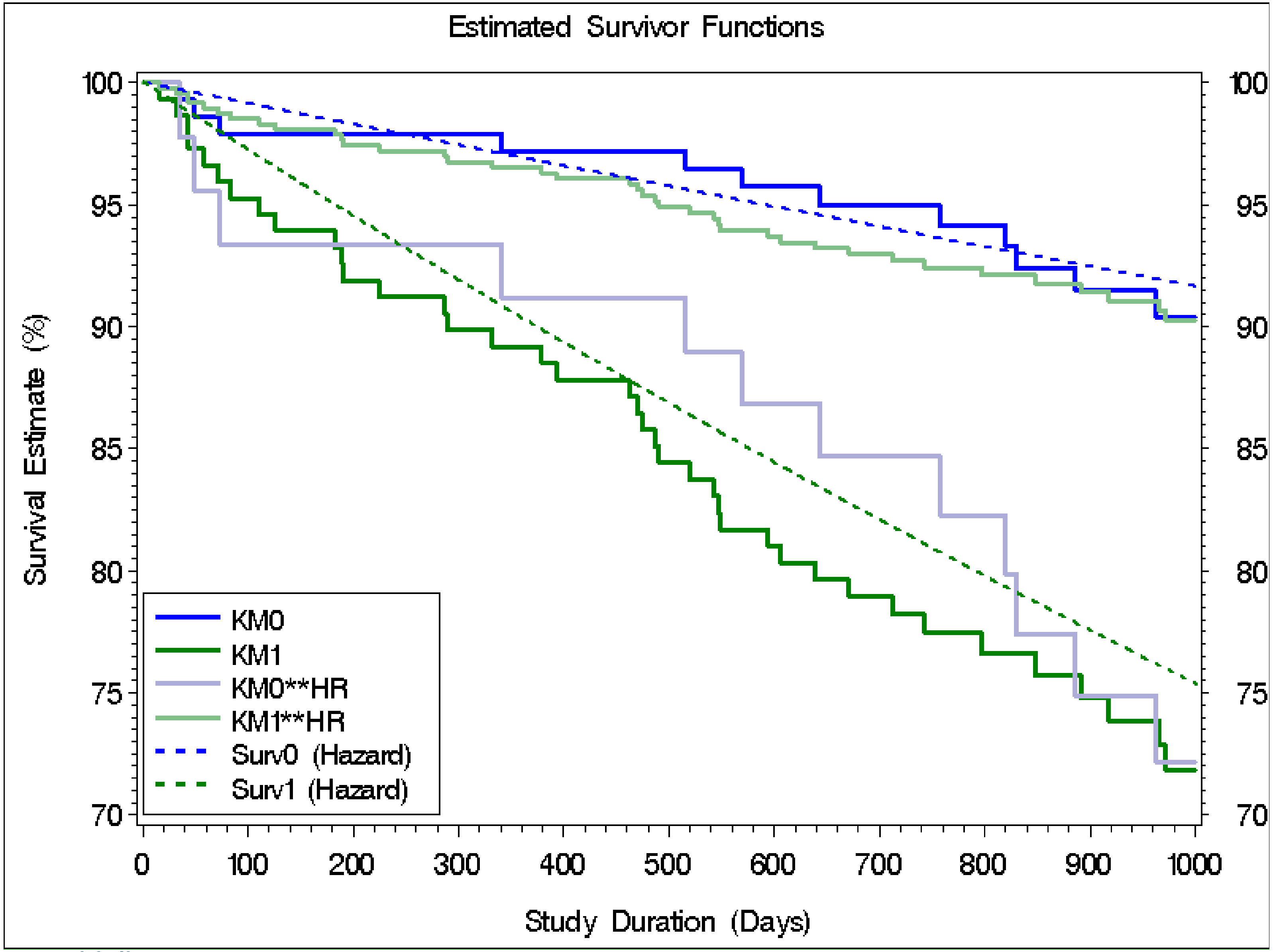
Estimate PEC by KM-method



Estimate explicit hazard



Survival Estimates



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For binary covariates Evolution Charts + Cox offer ….

- A simple check of the proportional hazard assumption (necessary condition: monotonic course of PEC)
- May be used to achieve explicit estimates of the hazard function

Testing options for Evolution Charts

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Global Tests

Testing on constancy of Population Evolution Charts (PEC) Binary covariate case : overall test	
H_0: PEC overall constant Test variant 1	H0: $\Psi_X(t) := P(X=1 \mid T>t) = \text{const.}$ Equivalent to H0: $S_1(t) = S_0(t)$ Testing as usual e.g. by logrank test
H_0: PEC overall constant Test variant 2	H0: $\Psi_X(t) := P(X=1 \mid T>t) = \text{const.}$ Can be tested by the Wald-Wolfowitz runs test Warning: doesn't work with ties in the time variable !!
PECs come as graphics	**PECs do not need difficult assumptions**

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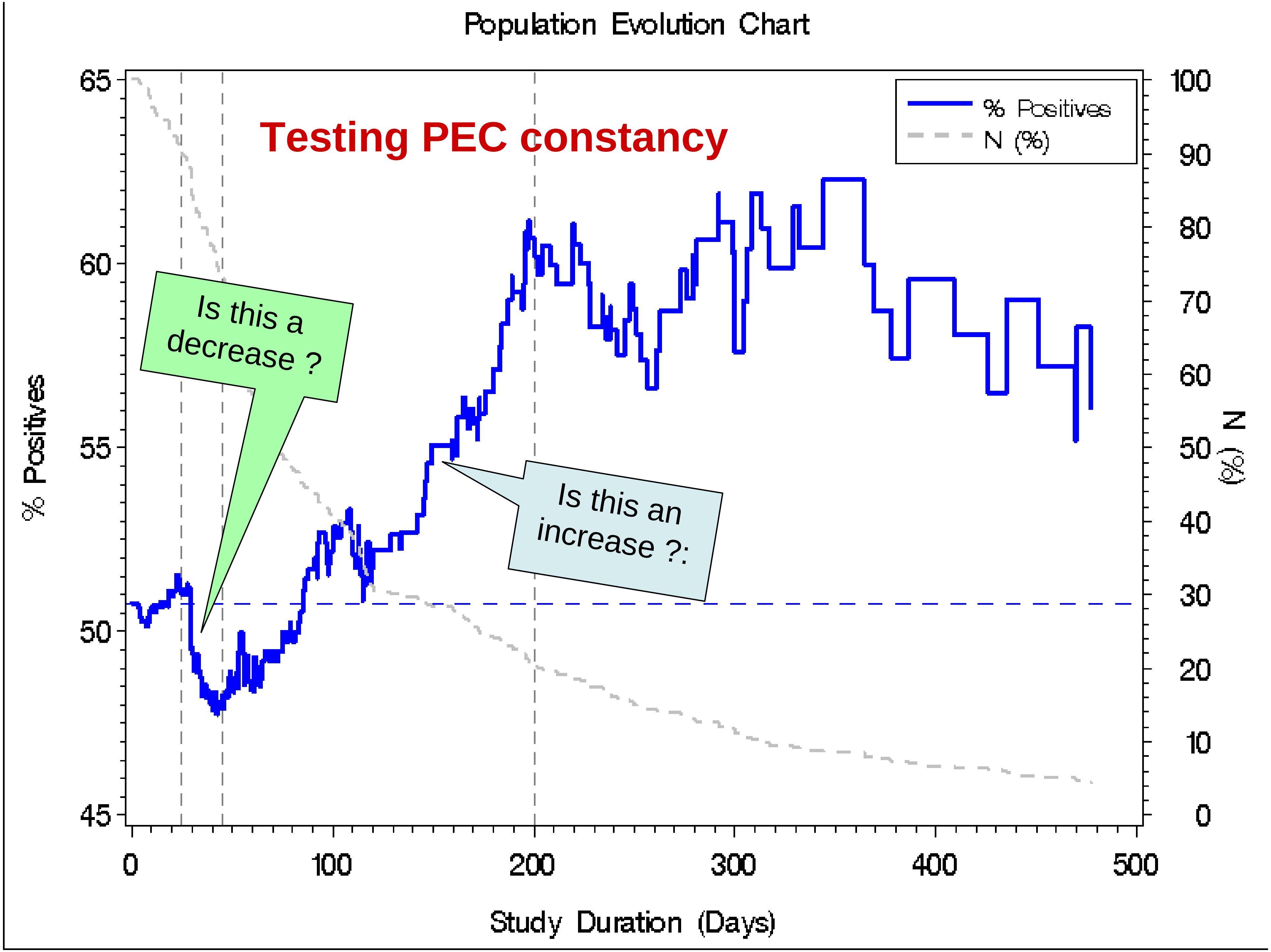
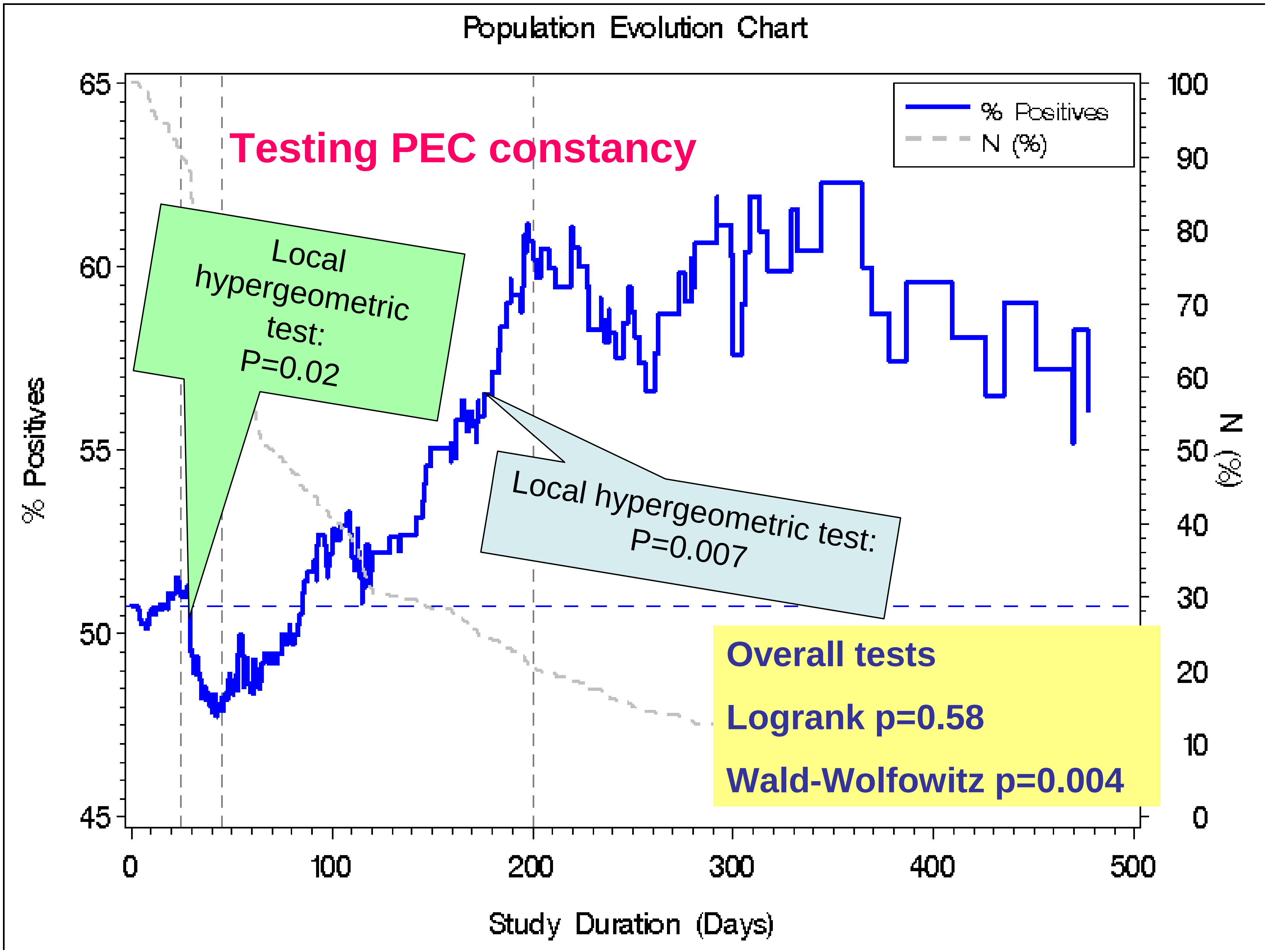


Population Evolution Chart
Testing PEC constancy
% Positives
N (%)
Is this a decrease ?
Is this an increase ?:
65
60
55
50
45
100
90
80
70
60
50
40
30
20
10
0
0
100
200
300
400
500
Study Duration (Days)
% Positives
N (%)

Local Tests

Testing on constancy of Population Evolution Charts (PEC) Binary covariate case: local hypotheses	
H_0: PEC constant between t_1 and t_2	$H0: \Psi_X(t_1) = \Psi_X(t_2) = \Psi_X(t) \quad t_1 < t < t_2$
H_0: local	**Testing:** may be based on hypergeometric probability
H_0: PEC regarding CENSORING	Interchange the roles of event times T and censoring times C


Population Evolution Chart
Testing PEC constancy
% Positives
N (%)
Local hypergeometric test: P=0.02
Local hypergeometric test: P=0.007
Overall tests
Logrank p=0.58
Wald-Wolfowitz p=0.004
% Positives
65
60
55
50
45
N (%)
100
90
80
70
60
50
40
30
20
10
0
0
100
200
300
400
500
Study Duration (Days)

Local Tests/Details

Testing on constancy of Population Evolution Charts (PEC) Binary covariate case: local hypotheses	
H_0: PEC constant between t_1 and t_2	$\text{H0}: \Psi_X(t_1) = \Psi_X(t_2) = \Psi_X(t) \quad t_1 < t < t_2$
Assume: censoring and covariate independent	**Testing**: may be based on all times **Use:** hypergeometric probability **But:** compromised power
Exact approach	**Testing:** based on event times conditioned on the censored times in the interval t1 to t2 **But:** complicated algorithm
Approximate: **Exact approach**	Hyp. Prob1: #censor shifted to t1. Hyp. Prob2: #censor shifted to t2. Geom. mean of Prob1 and Prob2

For binary covariates Evolution Charts offer….

- Global and local test opportunities to assess changes in the time dynamic

What to do with metric covariates ….

Define Evolution Chart for metric covariates

Definitions of Evolution Charts $\Psi_X(t)$	
I. Density Base	$f(x \mid T > t)$
II. Selection process	$\frac{1}{S(t)}\left[f(x \mid T = 0) - (1 - S(t)) \cdot f(x \mid T \le t)\right]$
PECs come as graphics	**PECs do not need difficult assumptions**

Difficulties ….

- How to follow up a conditional distribution over time graphically?

- Choose some property of the distribution and follow up over time - choices

Evolution Chart for Metric Covariates

Choices	
Take one or several **quantiles** of the distribution	Reduces the problem to the binary case **Quantile Evolution Chart (QuEC)**
Choose a **moment** of the distribution e.g. the **mean**	**Moment Evolution Chart (MEC)**
Estimate a MEC based on the selection process view	$\frac{1}{\hat{S}(t)}\left[\hat{\mu}(x \mid T=0)-(1-\hat{S}(t)) \cdot \hat{\mu}(x \mid T \leq t)\right]$
MECs come as graphics	**MECs do not need difficult assumptions**

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For metric covariates Evolution Charts offer ….

- Cutoff-free representation of dependencies
- Time-dynamic is made obvious
- Can suggest potential cutoffs

Published PEC

[1] Moecks J., Franke W., Ehmer B., Quarder O. (1997): Analysis of Safety Database for Long-Term Epoetin-β Treatment: A Meta-Analysis Covering 3697 Patients. *In: Koch & Stein (editors) "Pathogenetic and Therapeutic Aspects of Chronic Renal Failure"*. Marce Dekker: New York, 163-179.

[2] Moecks J., Köhler W., Scott M., Maurer J., Budde M., Givens S.(2002): Dealing with Selective Dropout in Clinical Trials. *Pharmaceutical Statistics, Vol 1: 119-130*

[3] Moecks J., Koehler W.(2007): Population Evolution Charts: A Fresh Look to Time-To-Event Data. *Statistical Computing and Graphics, Vol. 18, No 2, Dec 2007, p. 12-19*

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