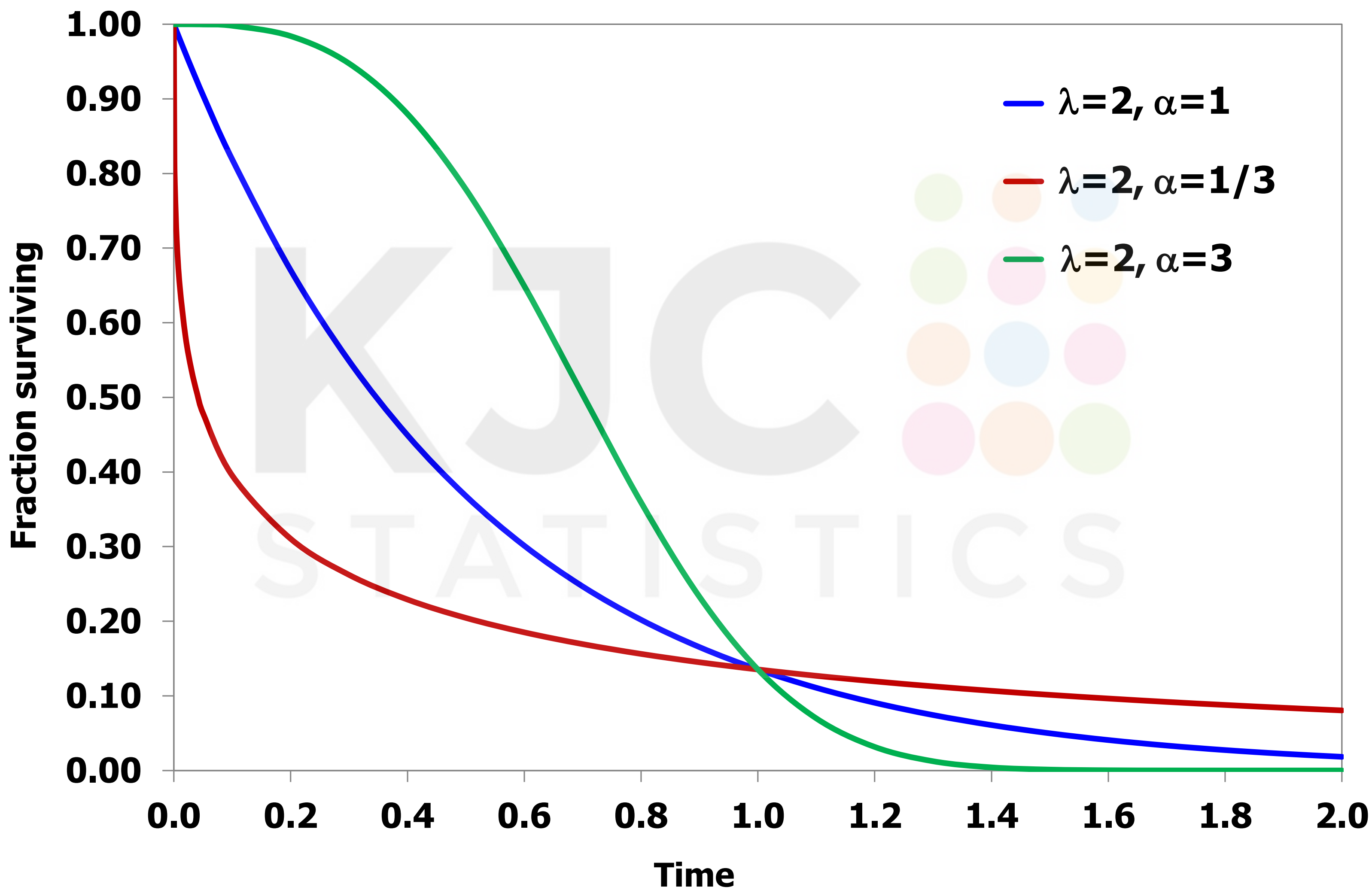
PARAMETRIC APPROACHES TO THE ANALYSIS OF TIME TO EVENT DATA:

WHY NOT?

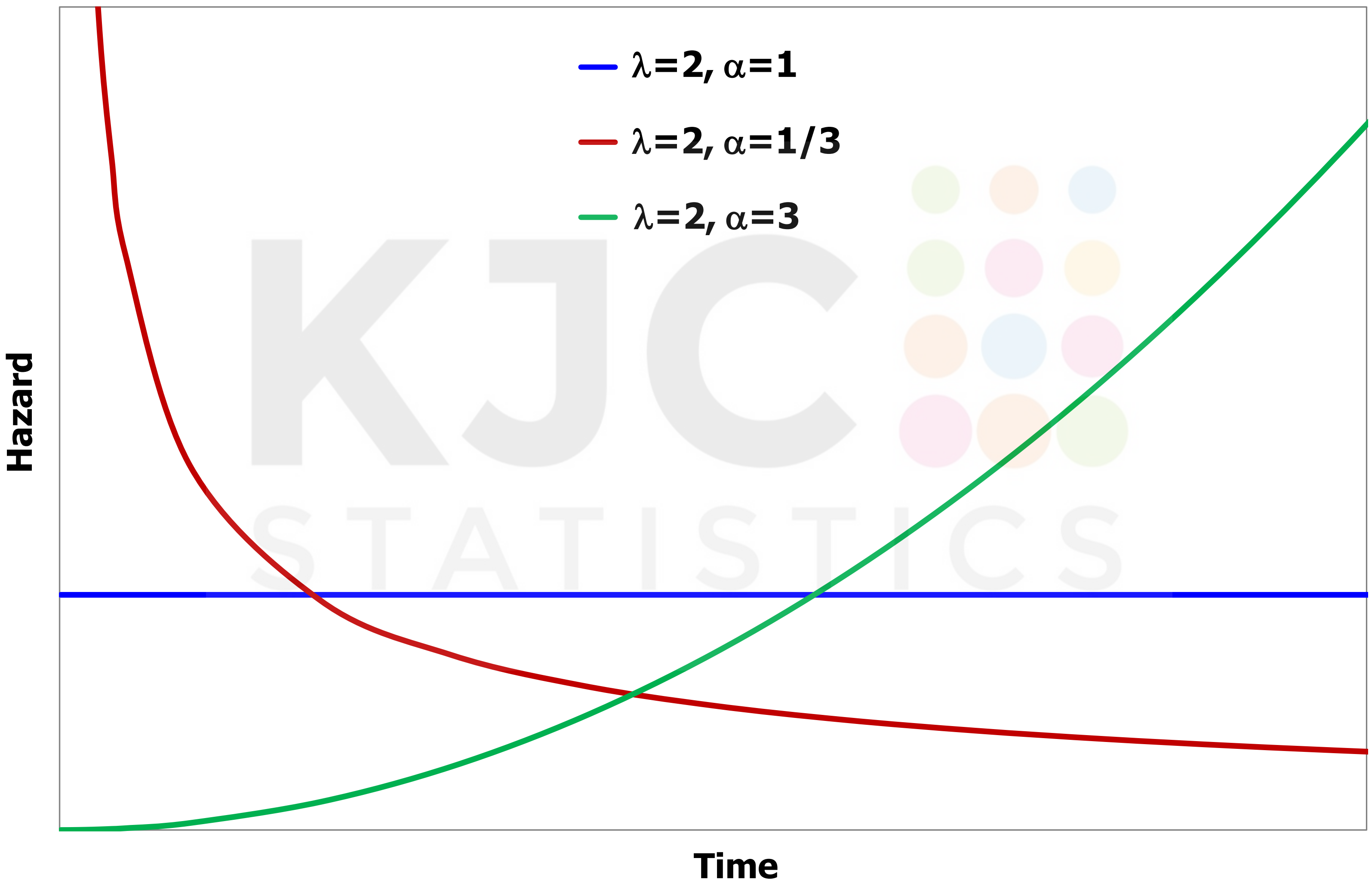
ACCELERATED FAILURE TIME AND THE WEIBULL

- **AFT analysis represents a powerful and versatile alternative to traditional Cox PH approach**
- **Let *T* represent log failure time, then an AFT model is simply**
  $\boldsymbol{t = \mu + \underline{\beta}' \underline{x} + \epsilon}$
- **Examples include Exponential, Log Normal and Weibull**
- **Weibull is the only AFT member that is simultaneously proportional:**
  - $f(t) = \alpha\lambda t^{\alpha-1} e^{-\lambda t^{\alpha}}$ with $t > 0$, $\alpha > 0$, $\lambda > 0$
  - $S(t) = e^{-\lambda t^{\alpha}}$, $h(t) = \alpha\lambda t^{\alpha-1}$
  - $HR(t) = \frac{\alpha_E \lambda_E}{\alpha_C \lambda_C} t^{\alpha_E - \alpha_C}$ so that $HR(t) = \frac{\lambda_E}{\lambda_C}$ if $\alpha_E = \alpha_C$

WEIBULL SURVIVOR FUNCTION



WEIBULL HAZARD FUNCTION



Some Properties and Features of the Weibull

- **AFTs easily fit in SAS via PROC LIFEREG**
  - Supports regular time to event and interval censored analysis
  - $\alpha = 1/\sigma$ and $\log(\lambda) = -\left(\mu + \underline{\beta}'\underline{x}\right)/\sigma$
  - If $x = 0, 1$ denotes control and experimental, $\log(HR) = -\beta/\sigma$ with variance $\widehat{var}\left[\log(\widehat{HR})\right] = (\hat{\beta}/\hat{\sigma})^2\left(\hat{\beta}^{-2}\widehat{var}\left(\hat{\beta}\right) + \hat{\sigma}^{-2}\widehat{var}(\hat{\sigma}) - 2\hat{\beta}^{-1}\hat{\sigma}^{-1}\widehat{cov}\left(\hat{\beta}, \hat{\sigma}\right)\right)$
- **Event Time Ratio**

- ○ Percentile: $\boldsymbol{t_p = \{\lambda^{-1} log(p^{-1})\}^{\alpha^{-1}}}$
- ○ $\boldsymbol{t_{Ep}/t_{Cp} = HR^{-\alpha^{-1}}}$
- ○ Allows quantification of treatment effect in terms of added time

SOME PROPERTIES AND FEATURES OF THE WEIBULL

- **Estimated survivor function $\boldsymbol{\widehat{S}(t) = e^{-\hat{\lambda} t^{\hat{\alpha}}}}$**
  - ○ $\widehat{var}\left[log\left(-log\hat{S}(t)\right)\right] = \frac{1}{\hat{\sigma}^2}\left(\widehat{var}(\hat{\mu}) + \widehat{var}\left(\underline{\hat{\beta}}'\right)\right) + \left\{\frac{\left(\hat{\mu}+\underline{\hat{\beta}}'\underline{x}-\log(t)\right)}{\hat{\sigma}^2}\right\}^2 \widehat{var}(\hat{\sigma})$

    $+\frac{2}{\hat{\sigma}^2} cov\left(\hat{\mu}, \underline{\hat{\beta}}'\right) - \frac{2}{\hat{\sigma}^3}\left(\hat{\mu} + \underline{\hat{\beta}}'\underline{x} - \log(t)\right)\left(cov(\hat{\mu}, \hat{\sigma}) + cov\left(\underline{\hat{\beta}}', \hat{\sigma}\right)\right)$
  - ○ Allows CI envelope for $\hat{S}(t)$ to be estimated
- **Direct test of proportionality**

- $\frac{\{log(\widehat{\alpha}_E/\widehat{\alpha}_C)\}^2}{\widehat{\alpha}_E^{-2}Var(\widehat{\alpha}_E)+\widehat{\alpha}_C^{-2}Var(\widehat{\alpha}_C)} \sim \chi_1^2$

- **Asymptotically equally efficient to Cox regression**
  - $\widehat{var}\left[\log(\widehat{HR}_{Cox})\right] \cong 1/d_E + 1/d_C$ (Sellke and Siegmund 1983)
  - $\widehat{var}\left[\log(\widehat{HR}_{AFT})\right] \cong 1/d_E + 1/d_C$ (Carroll 2003)

Some Properties and Features of the Weibull

- **Average event rate over (0,T]**
  - Integrated hazard over (0,T] = λT^{α} so the average hazard, H, = $\lambda T^{\alpha-1}$
  - $\widehat{var}[log(\lambda T^{\alpha-1})]$ easily attained via delta method as for $\widehat{var}\left[log\left(-log\hat{S}(t)\right)\right]$
  - H_E/H_C = ratio of average hazards over (0,T] even if data non-proportional
- **Predicting data maturation**

- Assume an analysis has been performed with a mean follow-up time F, at which time d patients have died and $c = n - d$ are censored.
- Consider the individual i with covariates $\underline{x}_i$, censored at time F. The probability that this individual survives to time $F + S$ is $e^{-\lambda_i\{(F+S)^\alpha + F^\alpha\}}$ so that $F + S = \left(-\lambda_i^{-1}\ln(u) + F^\alpha\right)^{-\alpha}$ where $u \sim U(0,1)$

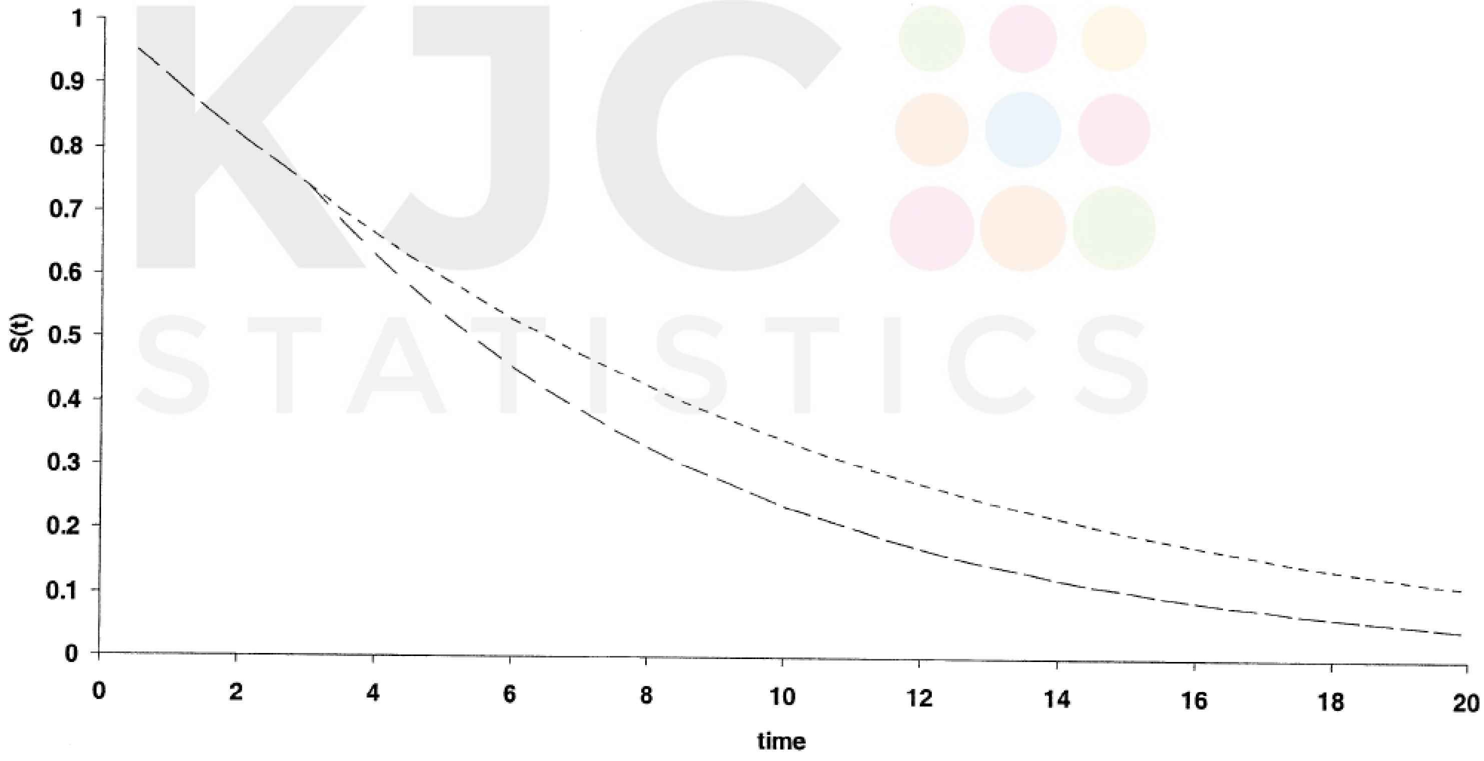
SOME PROPERTIES AND FEATURES OF THE WEIBULL

- **Predicting data maturation (contd.)**
  - Survival times for the c censored individuals can be predicted if c deviates are randomly sampled from a $U(0,1)$ distribution, and substituted into $\left(-\lambda_i^{-1}\ln(u) + F^\alpha\right)^{-\alpha}$.

- If, for the i^{th} patient, predicted survival exceeds $F + S$, then the patient remains censored; otherwise the patient is predicted to have died in the interval $(F, F + S]$.
- Repeating this process and averaging over repeats provides an estimate of the number of additional deaths expected in the interval $(F, F + S]$.

SOME PROPERTIES AND FEATURES OF THE WEIBULL

- **Impact of departures from the Weibull**
  - Simulation studies show similar results via Cox and Weibull modelling irrespective of true underlying distribution of the time to event (Carroll 2003)



SOME PROPERTIES AND FEATURES OF THE WEIBULL

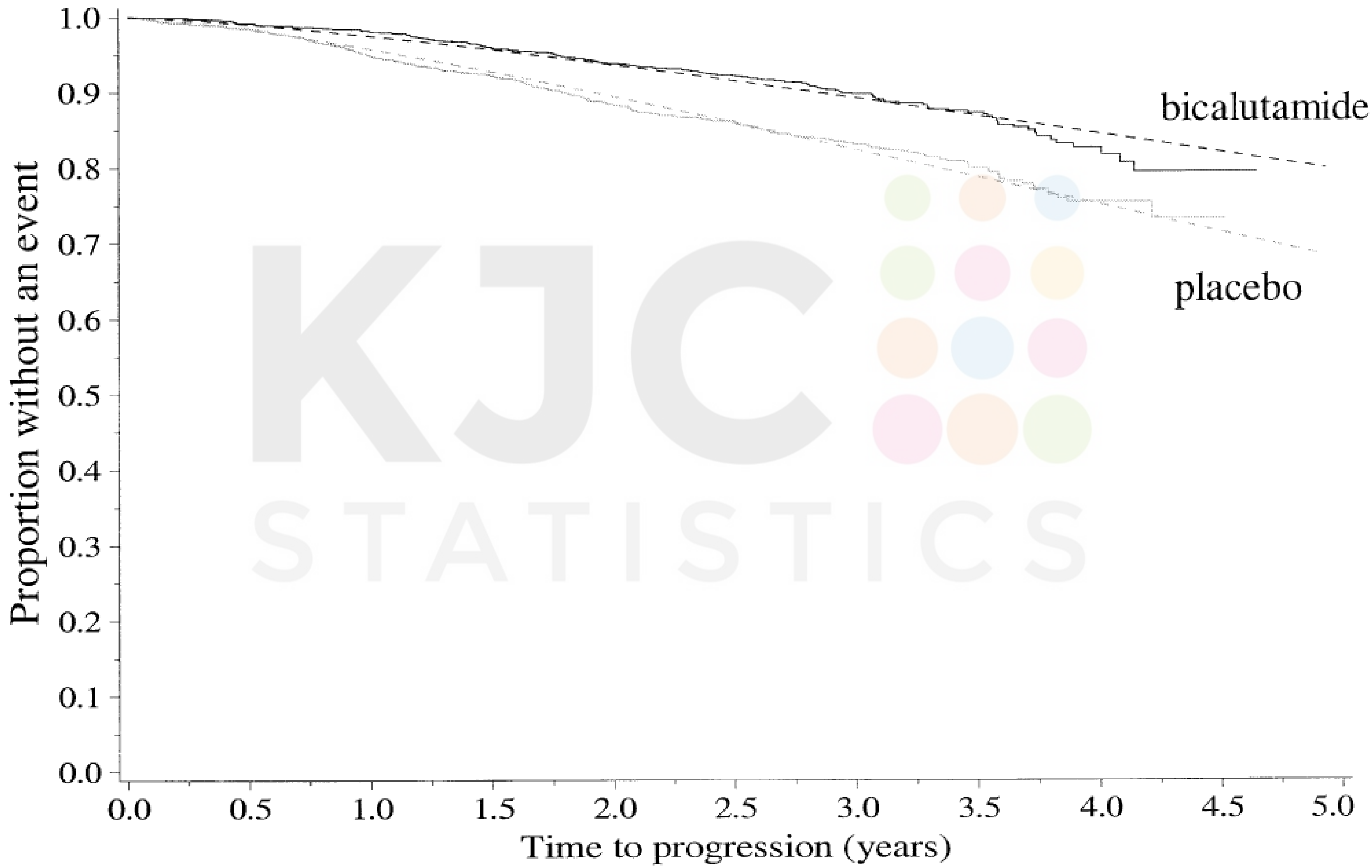
- **Impact of departures from the Weibull**

Table 4. Simulation of piecewise exponential: analysis by Cox and by Weibull

			Cox analysis			Weibull analysis					
λ_1[a]	μ_A/μ_B[b]	$\tilde{\mu}_A/\tilde{\mu}_B$[c]	*HR*[d]	*SE*[e] *ln HR*	*t*	HR	SE ln HR	*t*	ETR[f]	SE ln ETR	*t*
0.01	1.25	1.13	0.834	0.1199	−1.51	0.826	0.1185	−1.62	1.099	0.0585	1.62
0.01	1.50	1.26	0.716	0.1270	−2.64	0.702	0.1251	−2.83	1.191	0.0612	2.86
0.10	1.25	1.10	0.872	0.1142	−1.19	0.874	0.1073	−1.25	1.115	0.0868	1.25
0.10	1.50	1.21	0.783	0.1195	−2.05	0.784	0.1123	−2.16	1.221	0.0920	2.17
1	1.25	1.00	0.995	0.1096	−0.05	0.982	0.1341	−0.33	1.033	0.1568	0.14
1	1.50	1.00	0.987	0.1127	−0.12	0.967	0.1407	−0.25	1.043	0.1658	0.25

[a] Common event rate over first 3 months.
[b] Ratio of mean times to event; $\mu_A = 6$ *months throughout.*
[c] Ratio of median times to event.
[d] Hazard ratio.
[e] Standard error.
[f] Event time ratio.

EXAMPLE #1



1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Proportion without an event
bicalutamide
placebo
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
Time to progression (years)
KJC STATISTICS

EXAMPLE #1

Table 3. Estimated hazard (HR) and event time ratios (ETR) for active relative to placebo

Cox			Weibull					
HR	SE[a]	95% CI[b]	HR	SE	95% CI	ETR	SE	95% CI
0.574	0.0947	0.477, 0.692	0.575	0.0947	0.477, 0.693	1.495	0.0706	1.302, 1.717

[a] Standard error.
[b] Confidence interval.

Additional follow-up:	**Expected maturity:**
1 year	**21%**
2 years	**28%**
3 years	**35%**

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EXAMPLE #2

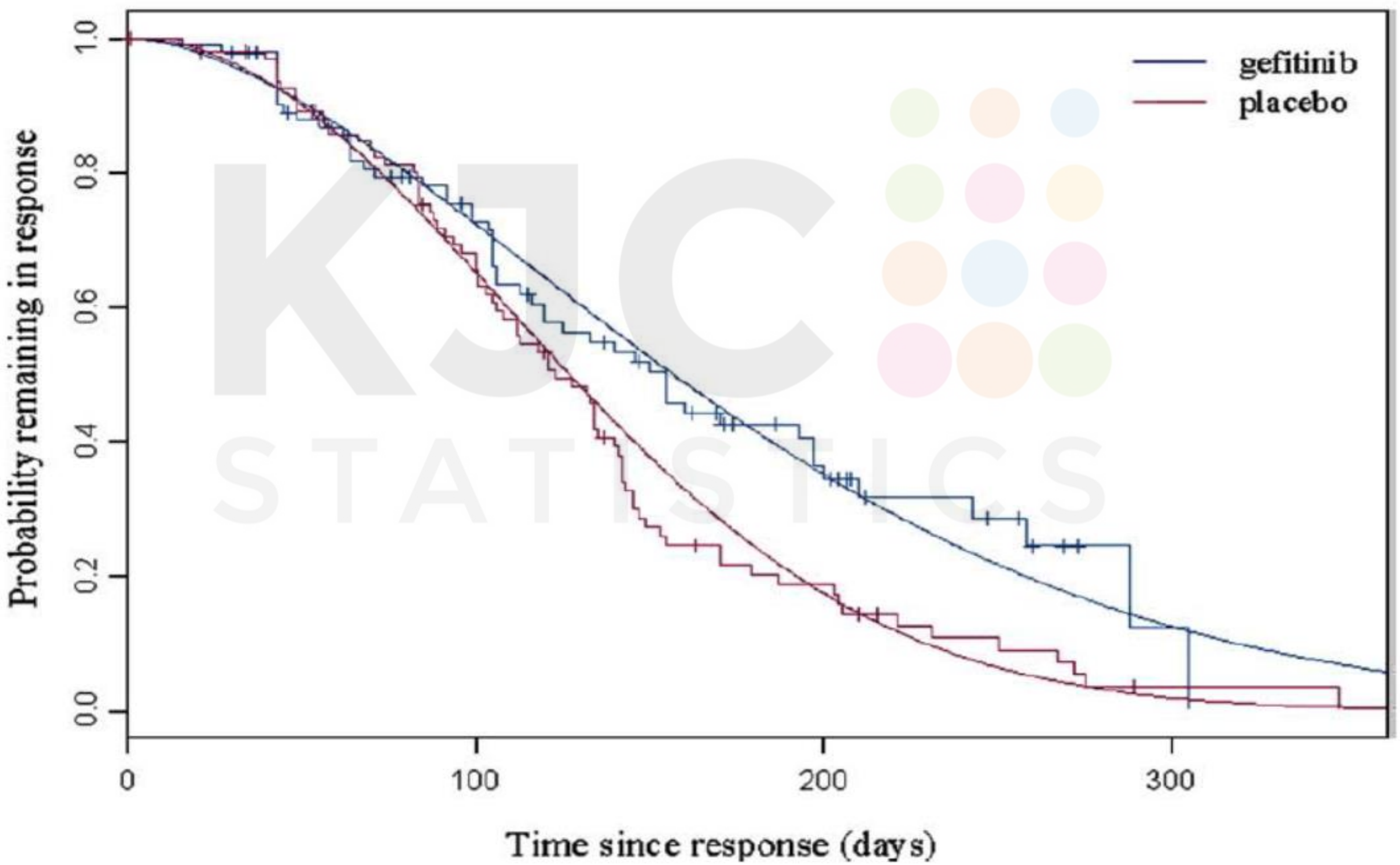
- **PLATO trial: ticagrelor vs clopidogrel in acute coronary syndromes**
- **18,642 patients**
- **Primary endpoint time to first of non-fatal stroke, non-fatal myocardial infarction or CV death**
- **Highly significant interaction between treatment effect (HR) and aspirin dose ($p<0.00001$)**
- **Aim : to describe and characterise the relationship between the HR and aspirin dose**

Example #3

- **Determination of sample size**
  - d events required for $1-\beta$ power, 1-sided α level
  - $n = d\tilde{\pi}^{-1}$ where $\tilde{\pi} = 2/(\pi_E^{-1} + \pi_C^{-1})$ is the average probability of an event over the trial follow-up period $R + F$.
  - If patient entry times r, over accrual period of length R has pdf $f(r)$ then $\pi = \int_{r=0}^{R}\int_{t=r}^{R+F} f(t|r)f(r)dtdr = 1 - E_r\left[e^{-\lambda(R+F-r)^\alpha}\right] \approx 1 - e^{-\lambda(R+F-E[r])^\alpha}$
  - If $r \sim U(0,R)$, $\pi \approx 1 - e^{-\lambda(R+F-R/2)^\alpha}$
  - E.g. 508 events to test hypothesis true HR is 0.75.
  - R=12, F=6, $\alpha = 0.33$, $\lambda_C = 0.385$ then $\pi_C = 0.586$ and $\pi_E = 0.551$ so that $\tilde{\pi} = 0.568$, hence $n = 508/0.568 = 895$

EXAMPLE #4

- **Expected duration of response**



EXAMPLE #4

- **Expected duration of response**

Table 3

Gefitinib vs. placebo, INTACT 2. Comparison of treatments for Expected Duration of Response using exponential, Weibull and log Normal densities

	Exponential		Weibull		Log Normal	
	Gefitinib $N=347$	Placebo $N=345$	Gefitinib $N=347$	Placebo $N=345$	Gefitinib $N=347$	Placebo $N=345$
Response rate, % [1]	30.6%	29.9%	30.6%	29.9%	30.6%	29.9%
Mean DoR[a] [2]	221.6	148.8	173.7	134.7	202.6	139.5
SE[b] DoR	0.137	0.115	0.083	0.057	0.131	0.074
EDoR[c] [1]x[2]	67.7	44.4	53.1	40.2	61.9	41.7
Ratio of EDoR and 95% CI[d]	1.524 (1.003 to 2.313) $P=0.048$		1.320 (0.977 to 1.783) $P=0.07$		1.486 (1.025 to 2.155) $P=0.04$	

[a]DoR = Duration of response in responding patients, days.
[b]SE = standard error.
[c]EDoR = Expected duration of response, days.
[d]CI = Confidence interval.