Univerza v Ljubljani
Fakulteta za farmacijo

Analiza preživetja in primerjava učinkovitosti

Farmakoekonomika 2010/2011, 9. semester

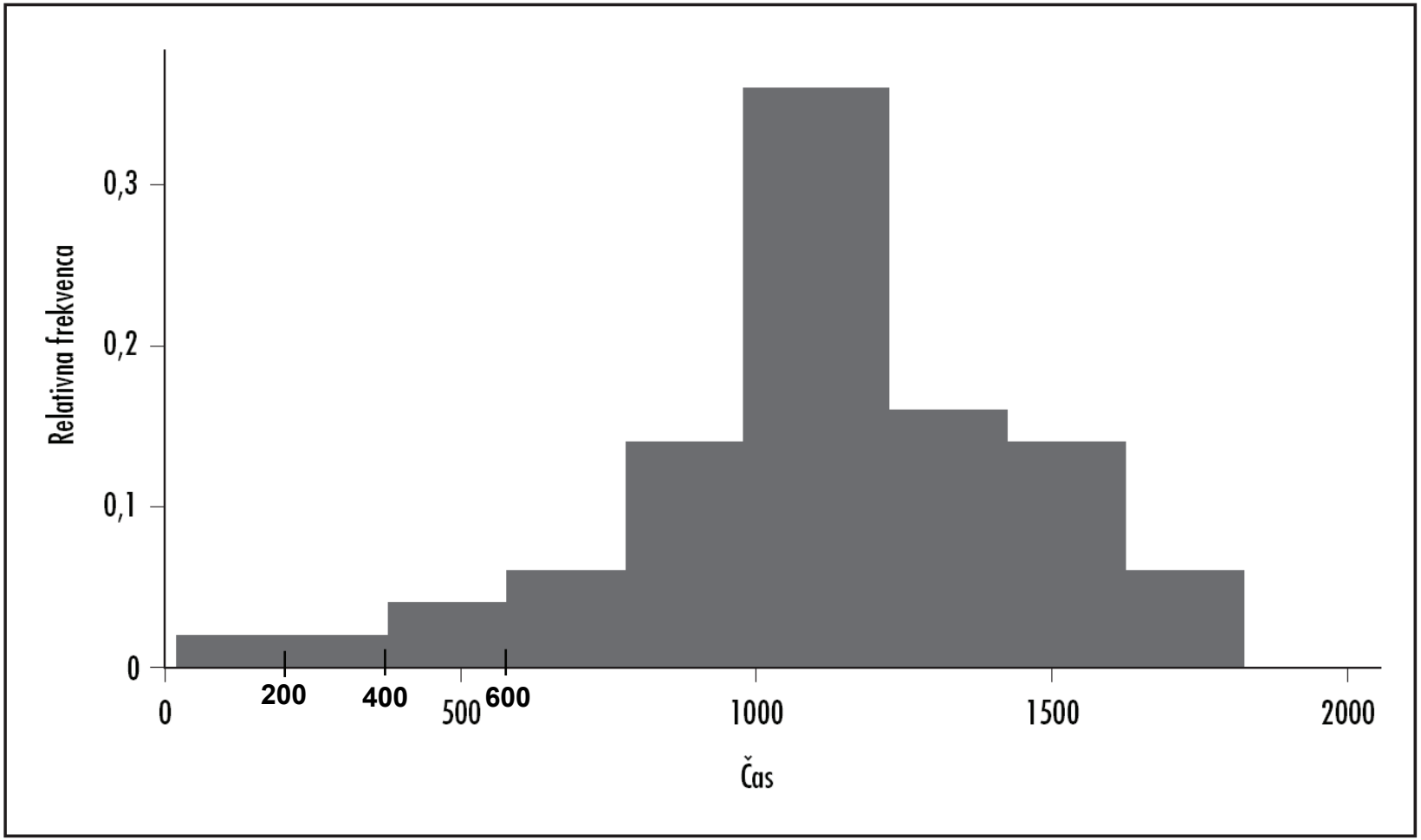
Asist. dr. Igor Locatelli, *mag. farm.*

Ljubljana, 10. 11. 2010

Analiza preživetja
Survival analysis

- Proučevanje (modeliranje) časa do nekega dogodka (time to event data)
- Začetek?
  - Postavitev diagnoze, začetek zdravljenja z določenim zdravilom
- Dogodek?
  - Pojav smrti zaradi bolezni
  - Progresija bolezni (npr. večanje tumorja) - time to progression (TTP)
  - Trajanje remisije bolezni (delna in popolna remisija) - čas do relapsa
  - Pojav infekcij pri opečenih bolnikih
  - …

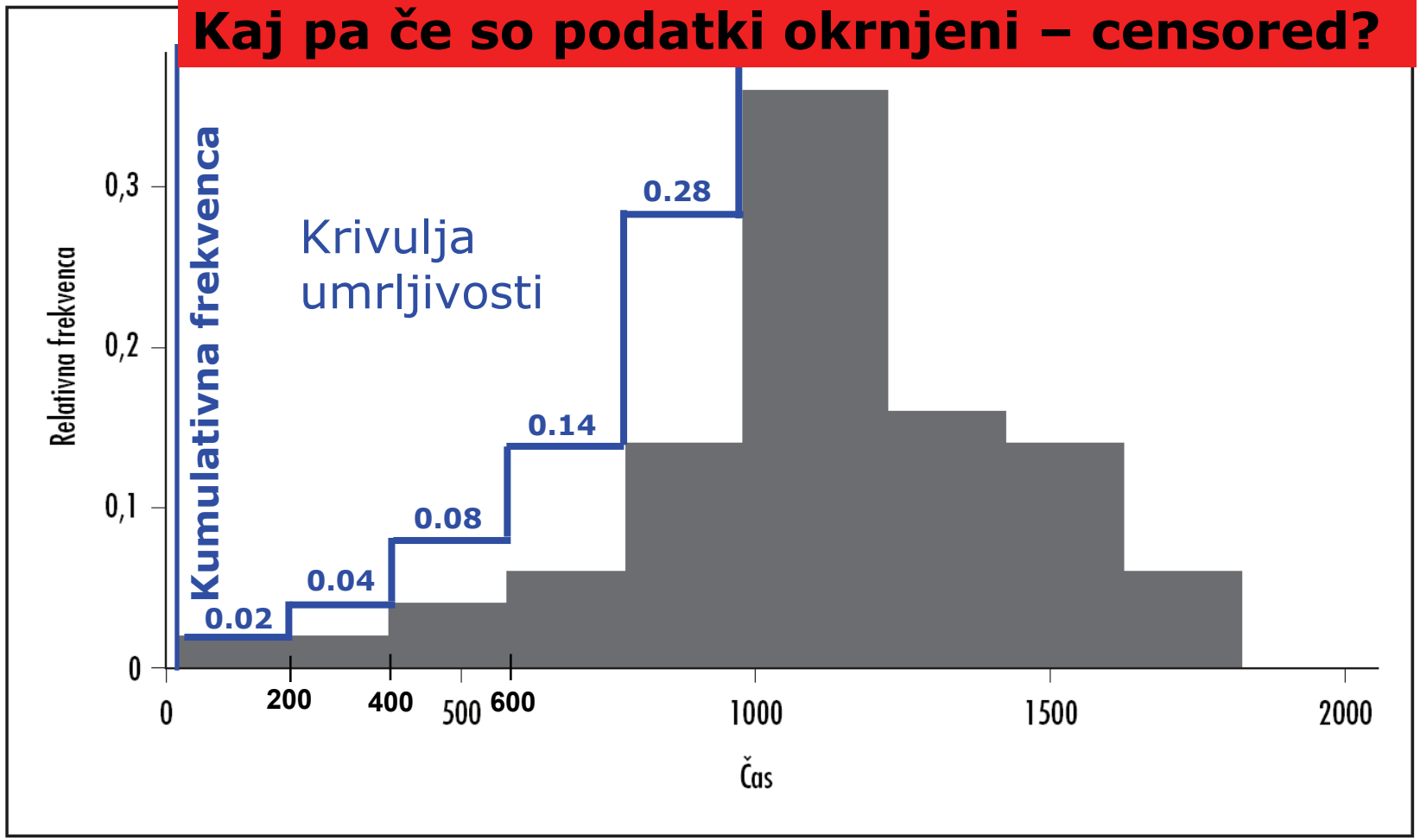
Čas preživetja



Slika 1. *Histogram časov preživetja iz primera 1.* n=50

Čas preživetja

Kaj pa če so podatki okrnjeni – censored?



Slika 1. *Histogram časov preživetja iz primera 1.* n=50

Krnjenje podatkov

Desno krnjenje:

- prekinitev študije in dogodek se še ni zgodil
- smrt zaradi drugih razlogov
- izgubljeno spremljanje bolnikov – lost to follow up
- prekinitev terapije zaradi neželenih učinkov - withdraws

Desno krnenje tipa I

- Raziskava se zaključi po poprej določenem času

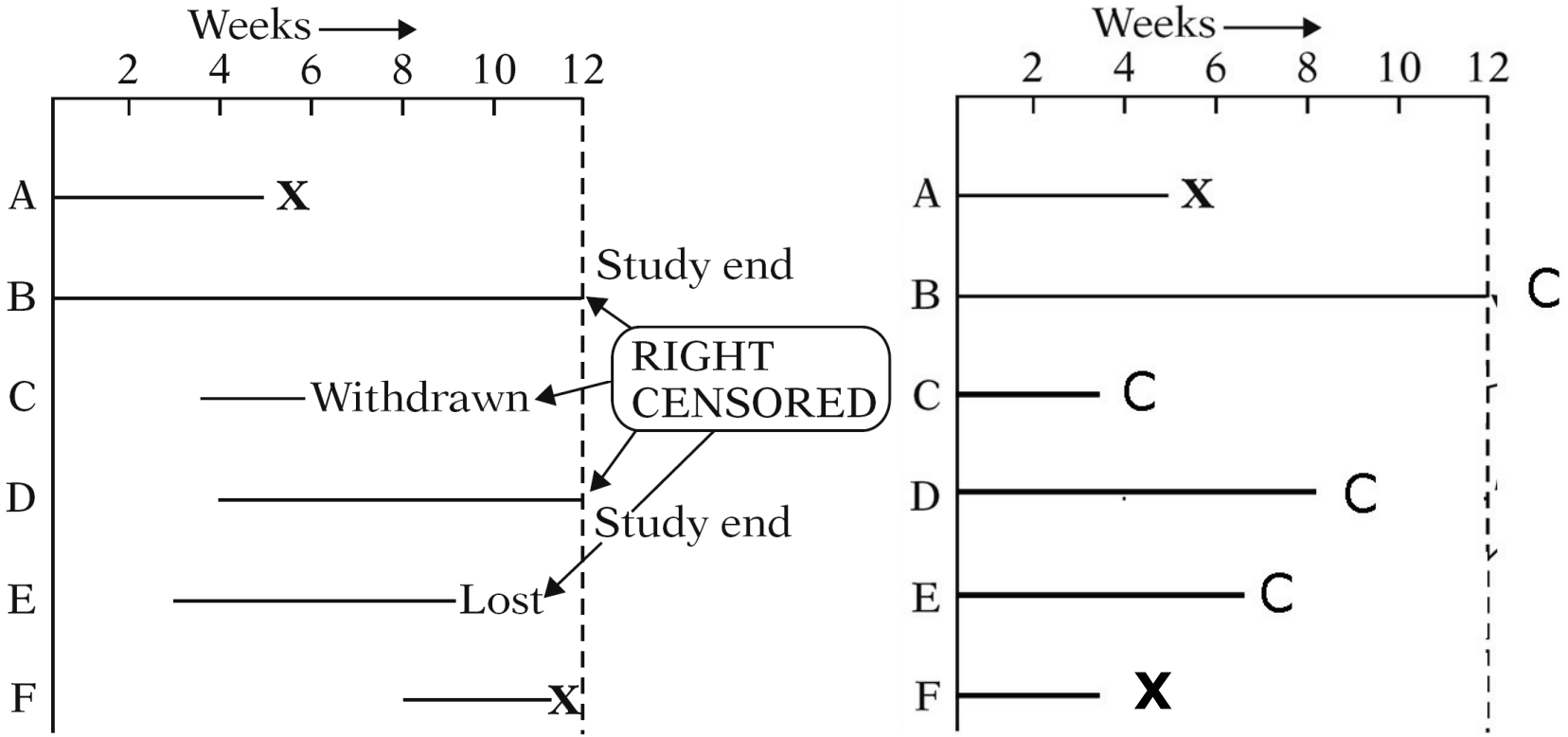
Desno krnjenje tipa II

- Raziskava se zaključi, ko poprej določen delež bolnikov doživi dogodek

Intervalno krnjenje (periodično spremljanje bolnika)

Krnjenje naj bo slučajno!

Desno krnjenje tipa I



A, B, C, D, E, F → 5, 12+, 3.5+, 8+, 6+, 3.5

Kaj pa grafični/tabelarični prikaz preživetja v odvisnosti od časa?

Izračun preživetja po Kaplan-Meierju $S_{KM}(t)$

$$S_{KM}(t) = \begin{cases} 1 & if\ t \le t_1 \\ \prod_{t_i \le t}\left[1 - \frac{d_i}{Y_i}\right] & if\ t_1 \le t \end{cases}$$

123,144+, 238+, 310, 346+, 357+, 532+, 550+, 554+, 681, 753, 766, 828+, 852, 873+, 882, 920, 921, 940, 951+, 957, 964+, 973, 993+, 1021, 1028+ 1037, 1039+ 1053, 1065, 1077, 1107, 1147, 1148, 1167, 1172, 1192, 1196, 1198, 1254, 1301+ 1348, 1494, 1495, 1537, 1541, 1563, 1603, 1646, 1667.

	Y_i	S_{KM}
Čas v dnevih	Izpostavljeni h tveganju	Preživetje
123	50	0,9800
310	47	0,9591
681	41	0,9358
753	40	0,9124
766	39	0,8890
852	37	0,8649
882	35	0,8402
920	34	0,8155
921	33	0,7908
940	32	0,7661
957	30	0,7406

$$S_{KM}(123) = 1 - \frac{1}{50} = 0.9800$$

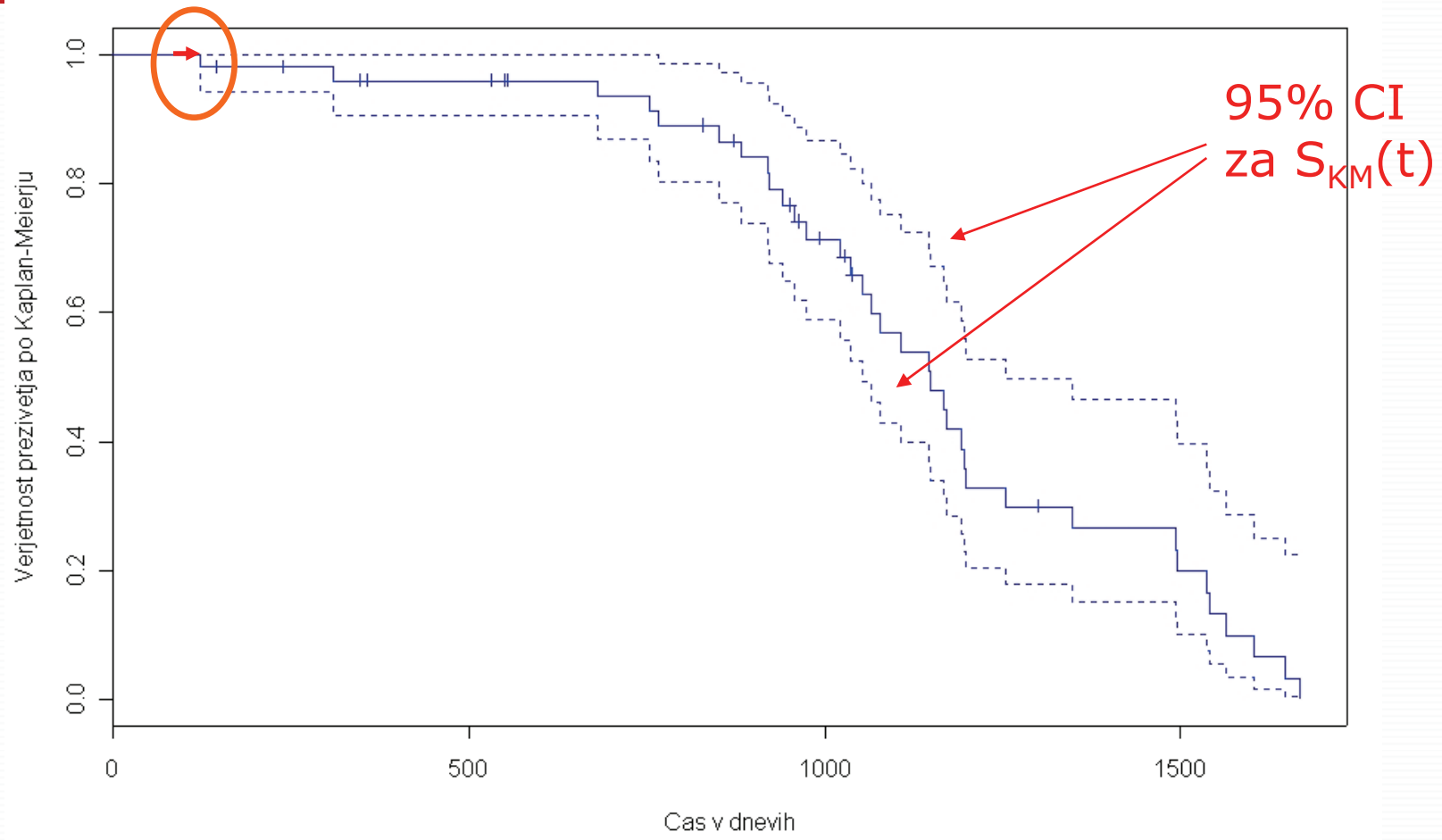
$$S_{KM}(310) = \left(1 - \frac{1}{50}\right) \cdot \left(1 - \frac{1}{47}\right)$$

$$S_{KM}(310) = 0.98 \cdot 0.9787 = 0.9591$$

$$S_{KM}(681) = 0.9591 \cdot \left(1 - \frac{1}{41}\right) = 0.9358$$

Stare J. Krivulje preživetja. Med Mes 1(12): 10-15. (2005)

Izračun preživetja po Kaplan-Meierju $S_{KM}(t)$



Stare J. Krivulje preživetja. Med Mes 1(12): 10-15. (2005)

Izračun standardne napake ocen preživetja po Kaplan-Meierju

$$S_{KM}(t) = \begin{cases} 1 & if\ t \le t_1 \\ \prod_{t_i \le t}\left[1 - \frac{d_i}{Y_i}\right] & if\ t_1 \le t \end{cases}$$

Greenwoodova fromula:

$$SE(S_{KM}(t)) = S_{KM}(t) \cdot \sqrt{\sum_{t_1 \le t} \frac{d_i}{Y_i\left(Y_i - d_i\right)}}$$

$$95\%\ CI\ za\ S_{KM}(t) = S_{KM}(t) \pm 1.96 \cdot SE(S_{KM}(t))$$

Čas	Y_i	d_i	$S_{KM}(t)$	$\sum d_i/Y_i(Y_i-d_i)$	SE ($S_{KM}(t)$)	95% CI $S_{KM}(t)$
123	50	1	0.9800	0.000408	0.01980	0.941 - 1
310	47	1	0.9591	0.000871	0.02830	0.904 - 1
681	41	1	0.9358	0.001480	0.03601	0.865 - 1
753	40	1	0.9124	0.002121	0.04202	0.830 - 0.995
766	39	1	0.8890	0.002796	0.04701	0.797 - 0.981
852	37	1	0.8649	0.003547	0.05151	0.764 - 0.966
882	35	1	0.8402	0.004387	0.05565	0.731 - 0.949
920	34	1	0.8155	0.005279	0.05925	0.699 - 0.932

1/50*49

0.000408+1/47*46

Opredelitev časa preživetja s parametri

- Povprečni čas preživetja (*mean life*)

$$\mu = \int_0^\infty S(t)\,dt$$

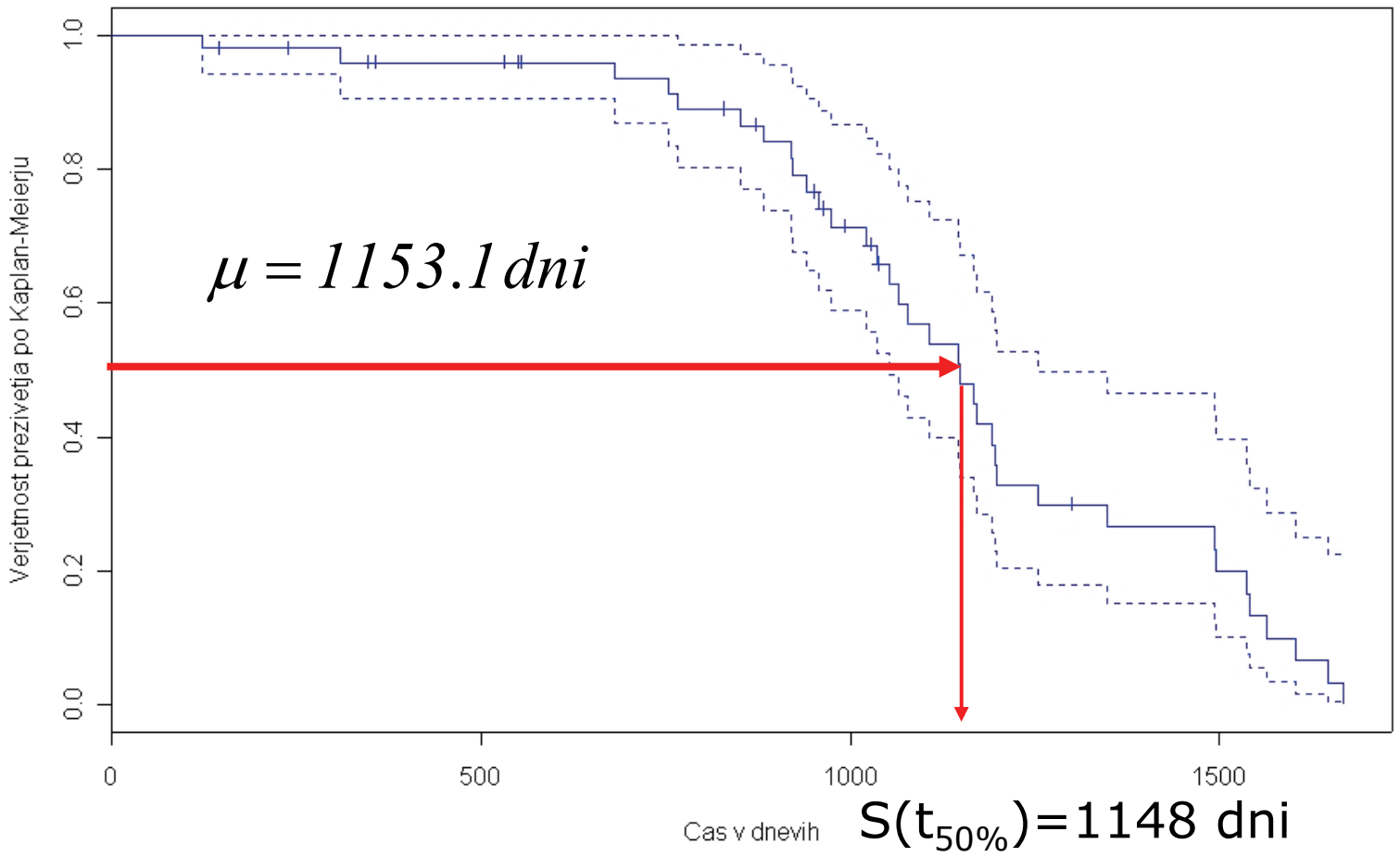
- *Mean residual lifetime at time t*
  pričakovani srednji čas preživetja po določenem že preživetem času

$$mrl(t) = \frac{\int_t^\infty S(t)\,dt}{S(t)}$$

- Mediana časa preživetja (median lifetime)

  $S(t_{50\%})=0.5$

Opredelitev čas preživetja s parametri



Primerjava dveh krivulj preživetja Log-rank test ali Mantel-Cox test

Chi^2 test (d.f.=1)

Primerjava skupnega opazovanega in skupnega pričakovanega števila dogodkov.

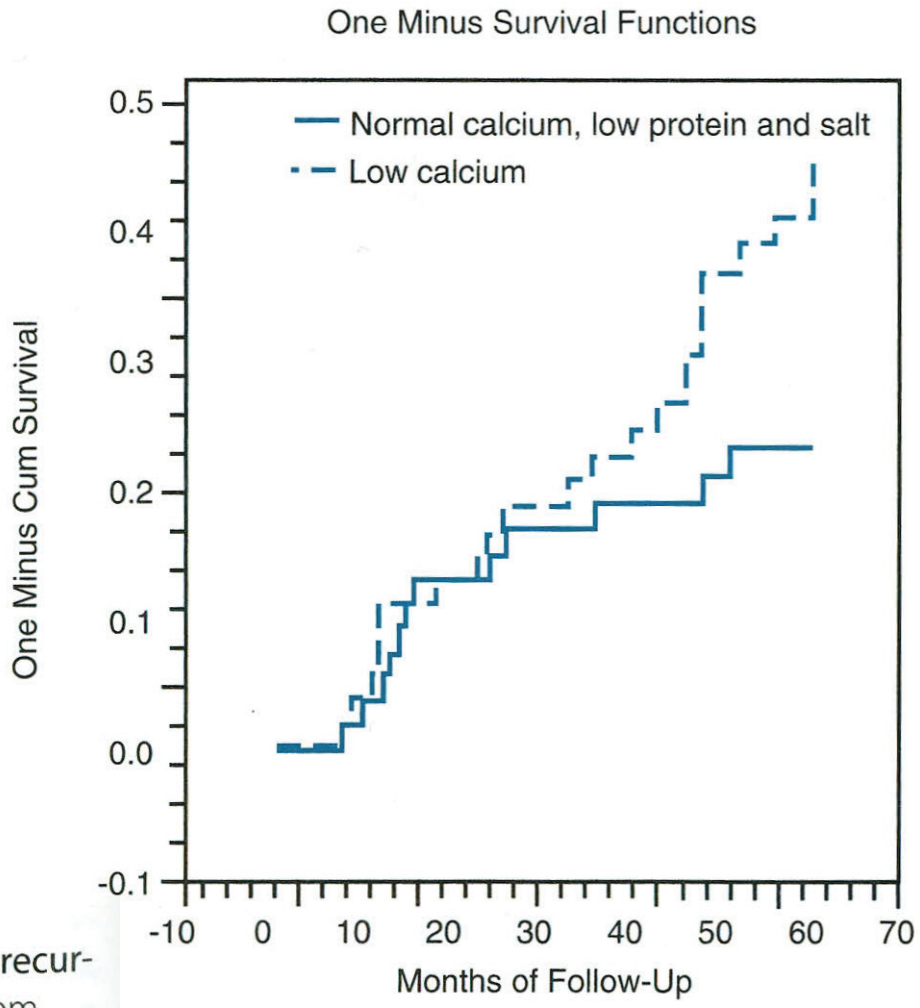


Figure 9–6. Kaplan–Meier survival curve for recurrence of stones. (Data, used with permission, from

Primerjava dveh krivulj preživetja Log-rank test ali Mantel-Cox test

Table 9–8. Logrank statistic for survival.

	Number of Patients at Risk			Number of Observed Occurrences			Number of Expected Occurrences		
Time Period	**Group 1**	**Group 2**	**Total**	**Group 1**	**Group 2**	**Total**	**Group 1**	**Group 2**	**Total**
0–10	60	60	120	2	2	4	2	2	4
11–20	55	54	109	5	5	10	5.045872	4.954128	10
21–30	49	47	96	3	2	5	2.552083	2.447917	5
31–40	44	46	90	3	1	4	1.955556	2.044444	4
41–50	39	43	82	6	1	7	3.329268	3.670732	7
51–60	32	41	73	4	1	5	2.191781	2.808219	5
Totals				23	12	35	17.07456	17.92544	35

Calculations of the logrank statistic

$O-E$	$(O-E)^2$	$(O-E)^2/E$	Sum
5.925440437	35.11084	2.056325	4.015041
−5.925440437	35.11084	1.958716	

$$\text{HR (1vs.2)} = \frac{23/17.07}{12/17.92} = \frac{1.35}{0.67} = 2.01$$

Group 1: Low-calcium diet
Group 2: Normal-calcium, low-protein & salt diet

Source: Data, used with permission, from Borghi L, Schianchi T, Meschi T, Guerra A, Allergri F, Maggiore U, et al: Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med* 2002;**346:**77–88. Table produced with Microsoft Excel.

Primerjava dveh krivulj preživetja Log-rank test ali Mantel-Cox test (2)

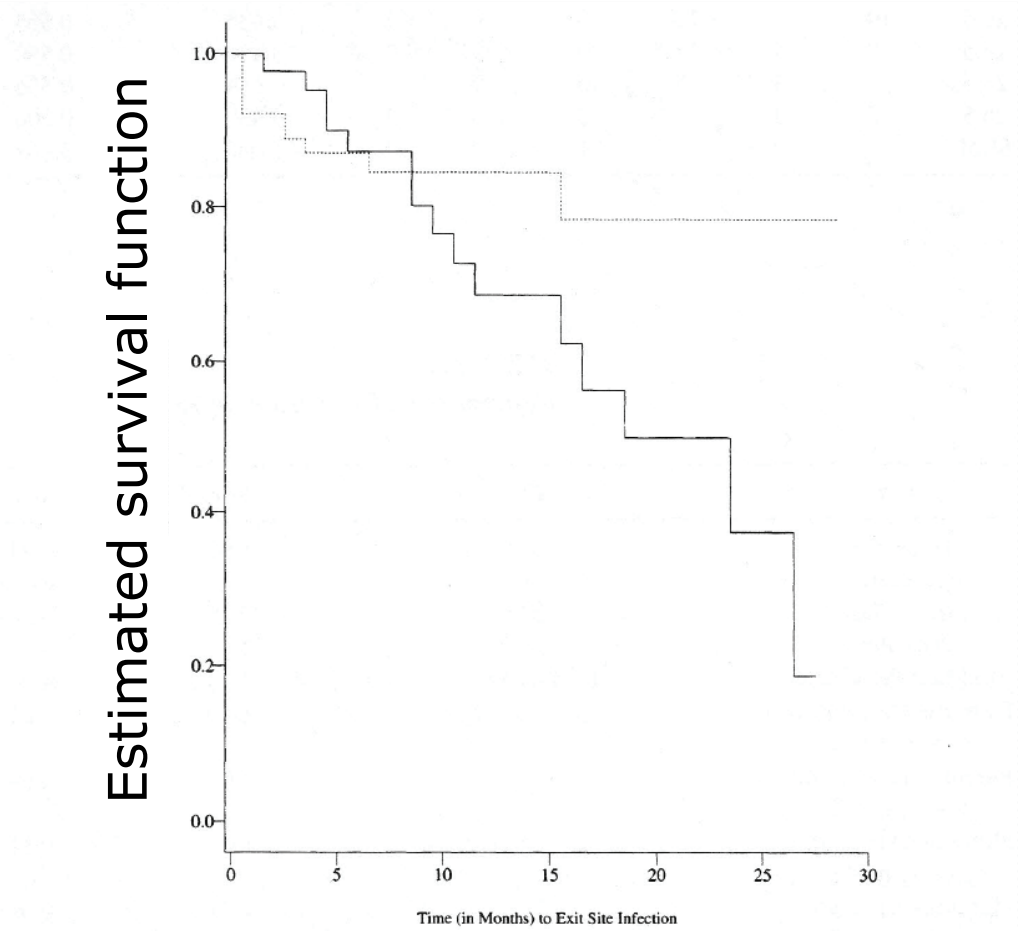


Figure 7.1 *Estimated (Infection-free) survival function for kidney dialysis patients with percutaneous (------) and surgical (———) placements of catheters.*

Primerjava dveh krivulj preživetja Log-rank test ali Mantel-Cox test (2)

Construction of Two-Sample, Log-Rank Test

t_i	Y_{i1}	d_{i1}	Y_{i2}	d_{i2}	Y_i	d_i	$Y_{i1}\left(\frac{d_i}{Y_i}\right)$	$d_{i1} - Y_{i1}\left(\frac{d_i}{Y_i}\right)$	$\frac{Y_{i1}}{Y_i}\left(1-\frac{Y_{i1}}{Y_i}\right)\left(\frac{Y_i-d_i}{Y_i-1}\right)d_i$
0.5	43	0	76	6	119	6	2.168	−2.168	1.326
1.5	43	1	60	0	103	1	0.417	0.583	0.243
2.5	42	0	56	2	98	2	0.857	−0.857	0.485
3.5	40	1	49	1	89	2	0.899	0.101	0.489
4.5	36	2	43	0	79	2	0.911	1.089	0.490
5.5	33	1	40	0	73	1	0.452	0.548	0.248
6.5	31	0	35	1	66	1	0.470	−0.470	0.249
8.5	25	2	30	0	55	2	0.909	1.091	0.487
9.5	22	1	27	0	49	1	0.449	0.551	0.247
10.5	20	1	25	0	45	1	0.444	0.556	0.247
11.5	18	1	22	0	40	1	0.450	0.550	0.248
15.5	11	1	14	1	25	2	0.880	0.120	0.472
16.5	10	1	13	0	23	1	0.435	0.565	0.246
18.5	9	1	11	0	20	1	0.450	0.550	0.248
23.5	4	1	5	0	9	1	0.444	0.556	0.247
26.5	2	1	3	0	5	1	0.400	0.600	0.240
SUM		15		11		26	11.036	3.964	6.211

$$Z = 3.964 \Big/ \sqrt{6.211} = 1.59 \rightarrow p = 0.1117\ NS$$

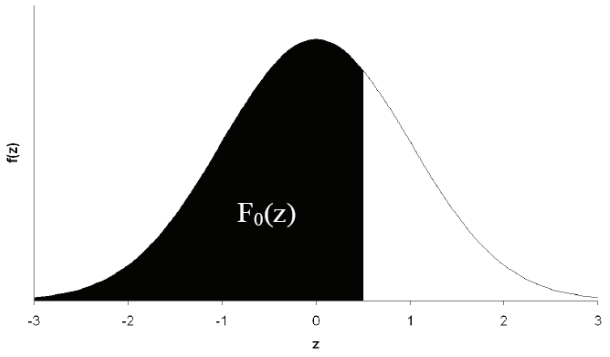
$$\text{HR (1vs.2)} = \frac{15/11.04}{11/(26-11.04)} = \frac{1.359}{0.735} = 1.84$$

Funkcija preživetja - $S(t)$ in funkcija ogroženosti ali hazard rate – $h(t)$

Funkcija preživetja:

$S(t)=P(T>t)=1-F(t)$

$$F(t)=\int_0^t f(t)\,dt \rightarrow S(t)=\int_t^\infty f(t)\,dt$$



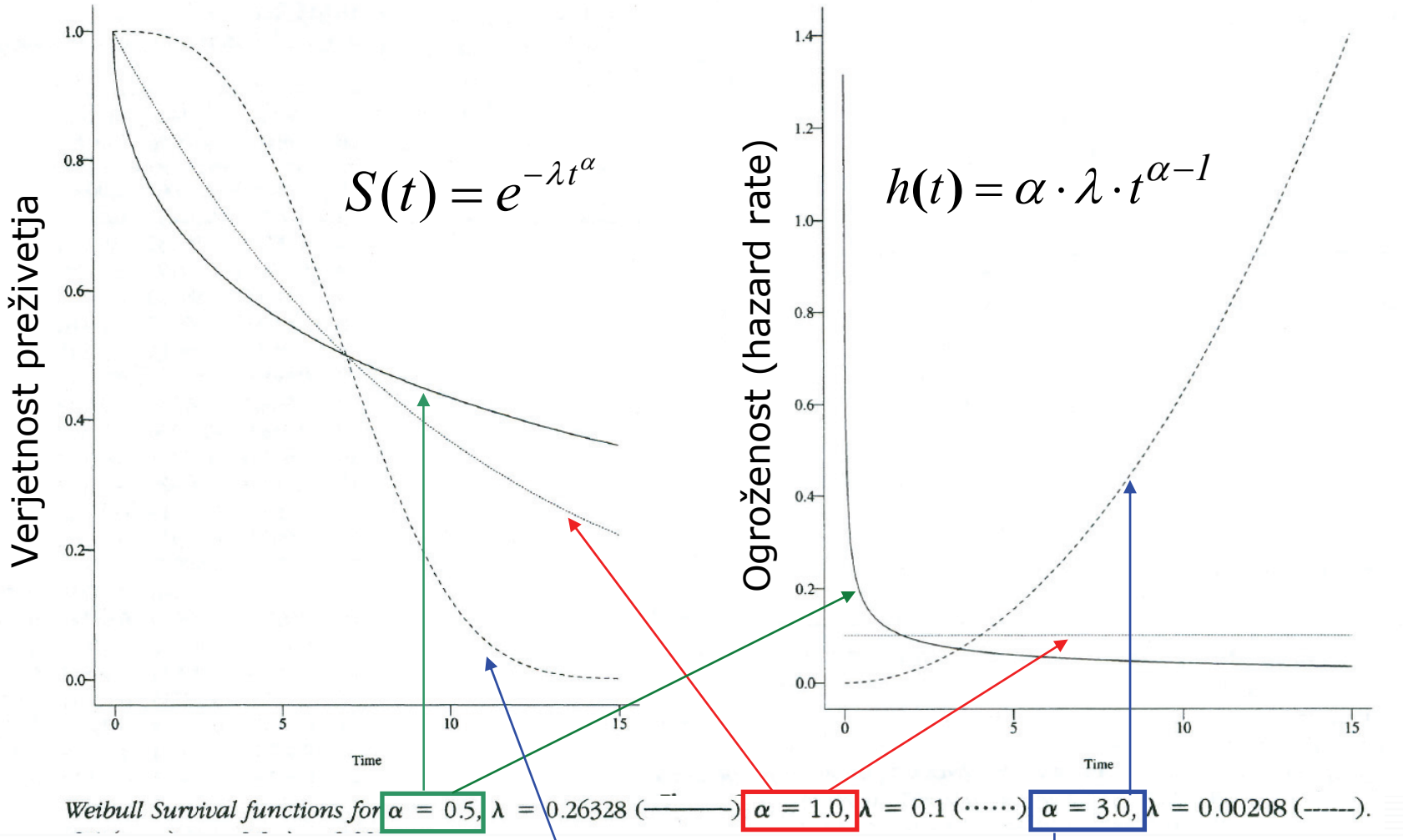
Funkcija ogroženosti – *h(t)*:

$$h(t)=\lim_{\Delta t\to 0}\frac{P(t\le T<t+\Delta t\,|\,T\ge t)}{\Delta t}$$

$$h(t)=\frac{f(t)}{S(t)}$$

h(t) opisuje verjetnost, da bo smrt nastopila v naslednjem trenutku, če je oseba že preživela nek čas t.

Weibulove krivulje preživetja in ogroženost



Coxov regresijski model
Model sorazmernega tveganja

Cox proportional hazards model

Testiranje vpliva dejavnikov:

Spol: ženski spol (Sp=1), moški spol (Sp=0)

Starost: zvezna spremenljivka

$$h(t \mid Sp = \check{z}, St = 70) = h_0(t) \cdot e^{\beta_1 \times Sp + \beta_2 \times St}$$

$$\frac{h(t \mid spol = \check{z};1)}{h(t \mid spol = m;0)} = \frac{h_0(t) \cdot e^{\beta_1 \times Sp=1} \cdot e^{\beta_2 \times Star=70}}{h_0(t) \cdot e^{\beta_1 \times Sp=0} \cdot e^{\beta_2 \times Star=70}} = e^{\beta_1} = HR$$

Although the hazard may vary with time, the assumption in proportional hazard models for survival analysis is that the hazard in one group is a constant proportion of the hazard in the other group. This proportion is the hazard ratio.

Primer: gefitinib vs. docetaksel

- Zdravljenje pljučnega raka (NSCLC)
- 3. faza kliničnih raziskav
- Vključeni raziskavi:
  - V-15-32 (n=489, napredujoča stopnja NSCLC z eno ali dvema neuspelima kemoterapijama)
  - INTEREST (n=1466, že zdravljena napredujoča stopnja NSCLC)
- Namen: potrditi neinferiornost gefitiniba

Kim ES, Hirsh V, Mok T, *et. al.*
Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial.
Lancet 372 (9652): 1809-18 (2008)

Maruyama R, Nishiwaki Y, Tamura T, *et. al.*
Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer.
J Clin Oncol 26 (26): 4244-52 (2008)

NSCLC = non-small-cell lung cancer, nedrobnocelični rak pljuč

Različni načini opredeljevanja preživetja v onkologiji (I)

Overall Survival (OS)

Overall survival is an indication of the proportion of people within a group who are expected to be alive after a specified time. It takes into account death due to any cause - both related and unrelated to the cancer.

Progression-Free Survival (PFS)

verjetnost, da se progresija bolezni ne zgodi

Progression-free survival measures the proportion of people among those treated for a cancer whose disease will remain stable (without signs of progression) at a specified time after treatment.

Različni načini opredeljevanja preživetja v onkologiji (II)

Cause-Specific Survival (CSS)

Cause-specific survival is a term similar to overall survival. It measures the proportion of people who are expected to die due to the cancer at a specified time. Unlike overall survival, it excludes death due to causes unrelated to the cancer.

Disease-Free Survival (DFS)

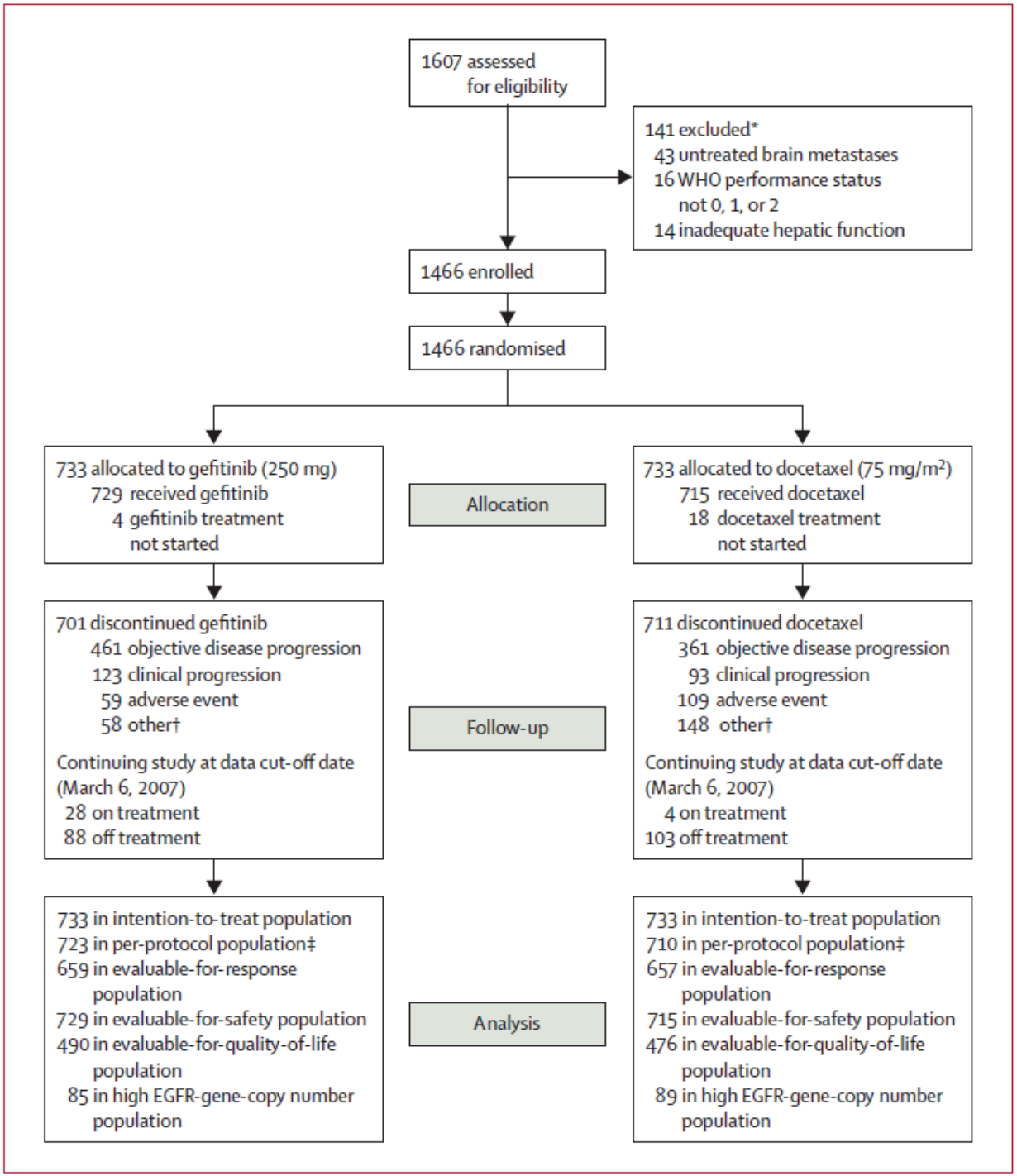
Disease-free survival measures the proportion of people among those treated for a cancer who will remain free of disease at a specified time after treatment.

Event-Free Survival (EFS)

Event-free survival is a measure of the proportion of people who remain free of a particular complication of disease (called an event) after treatment that is designed to prevent or delay that particular complication.

Profil raziskave

Raziskava INTEREST



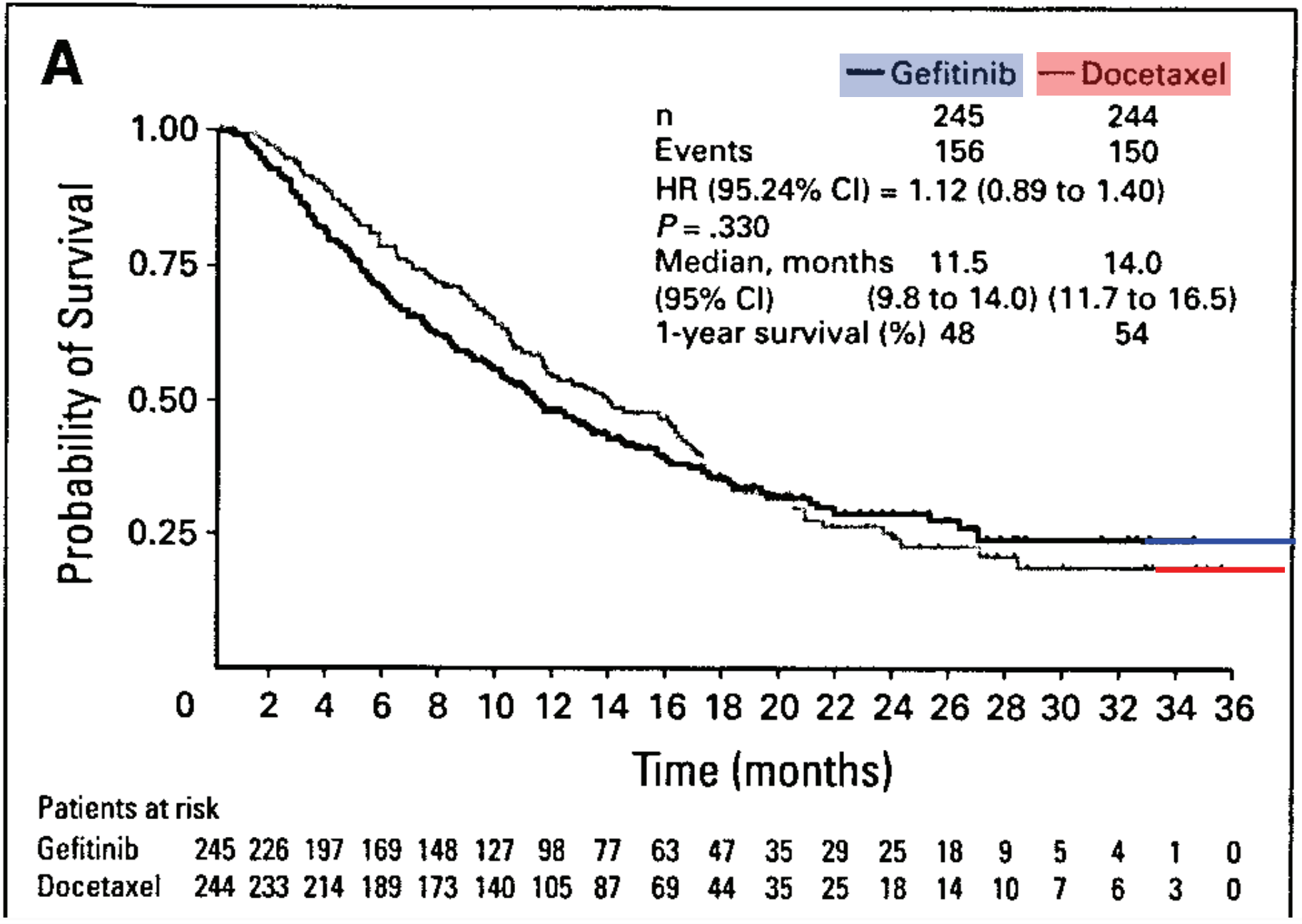
Raziskava V-15-32

- Intention to treat population (vključimo vse bolnike, ki so vstopili v raziskavo)
- Interim analysis
- Primarni cilj: celotno preživetje
  - Neinferiornost: zgornja meja interval zaupanja za HR <= 1.25 za gefitinib vs. docetaksel (superiornost?)
- Sekundarni cilj: progression-free survival, time to treatment failure

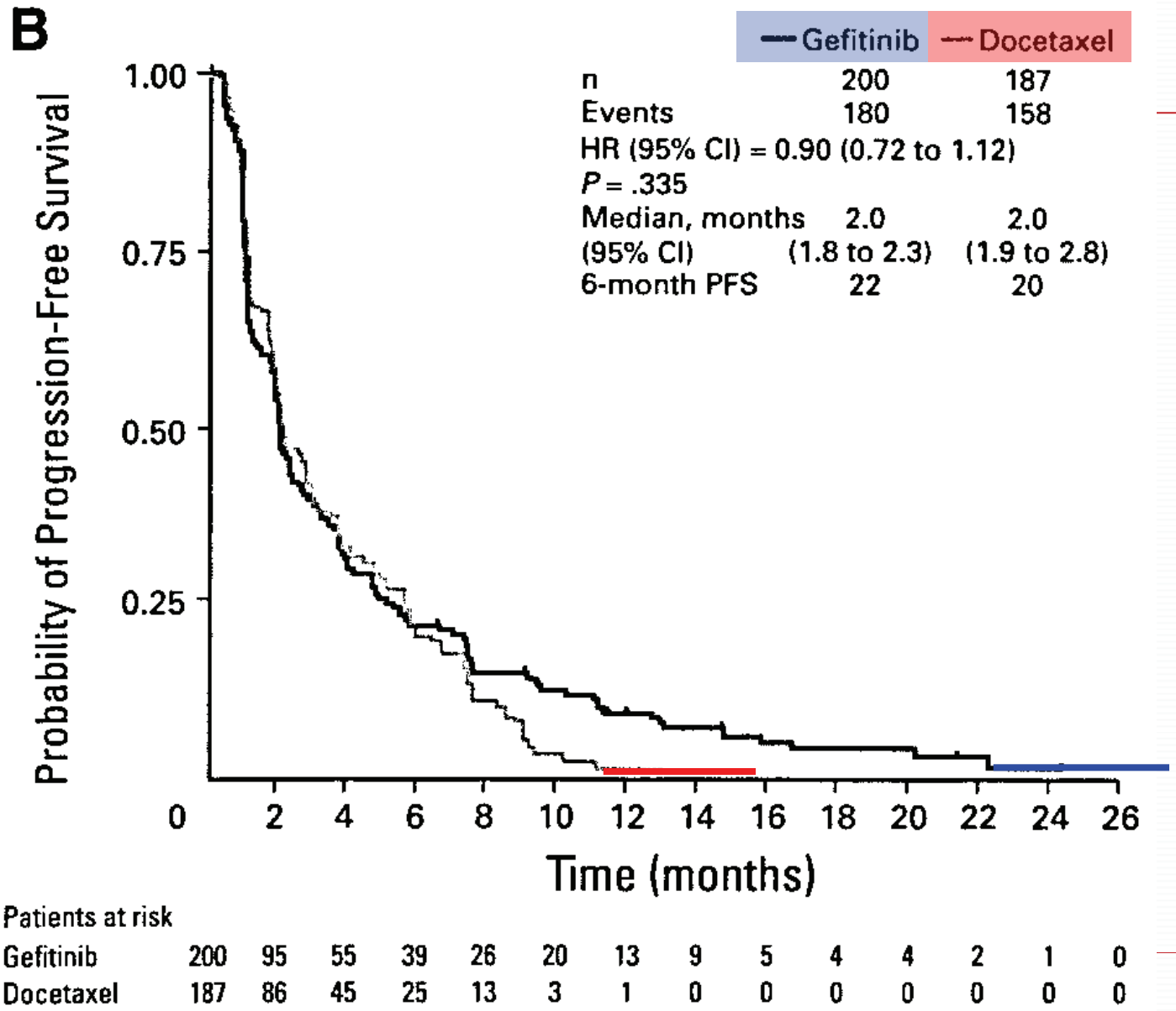
Raziskava INTEREST

- Per-protocol vs. Intention-to-treat population
- Primarni cilj: celotno preživetje
  - Neinferiornost za celotno populacijo (α=0.04)
    - Zgornja meja za HR <= 1.154
  - Superiornost pri bolnikih z veliko kopijami gena EGFR (α = 0.05)
- Sekundarni cilj: progression-free survival, time to treatment failure

Raziskava V-15-32

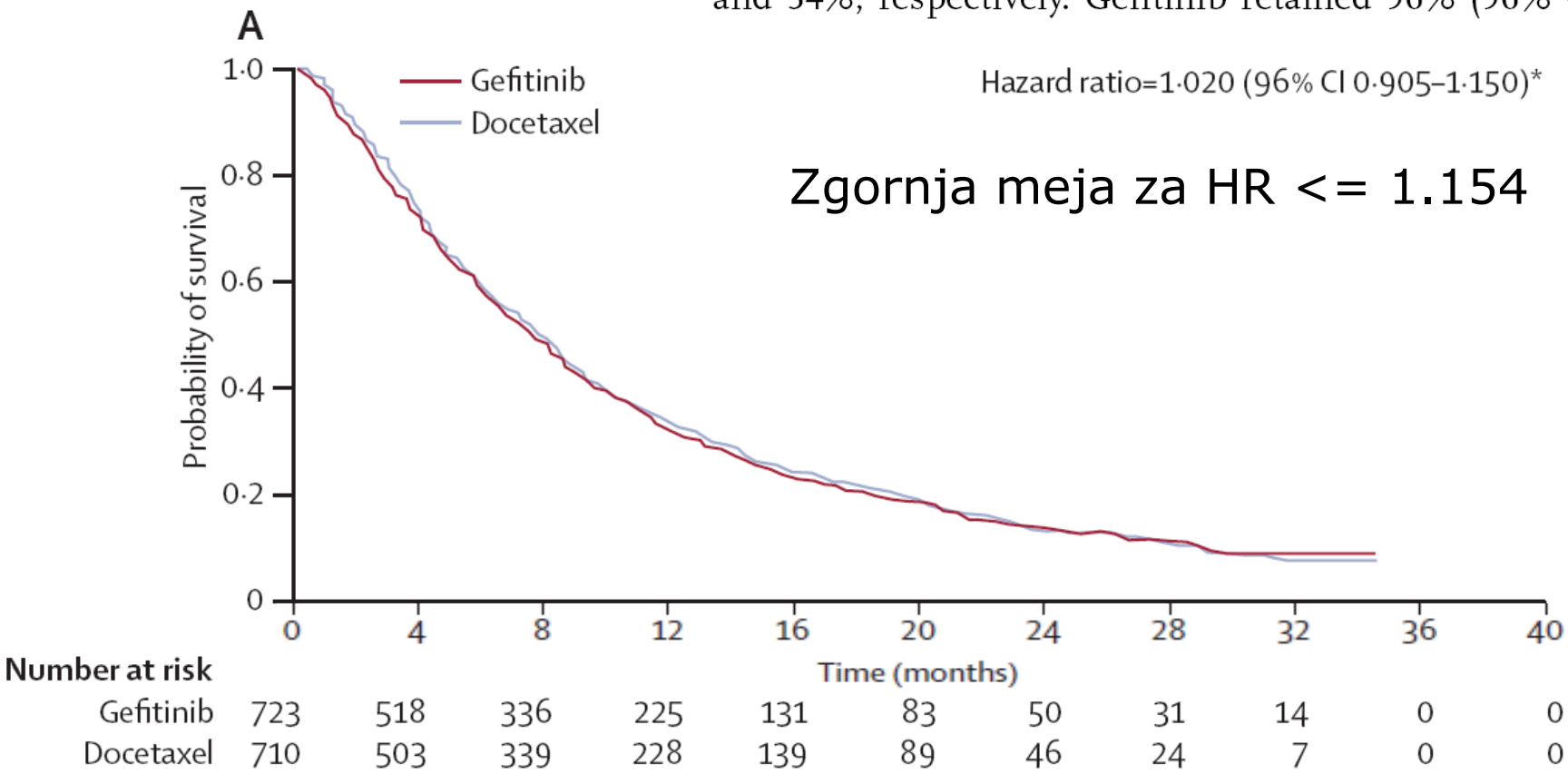


Raziskava V-15-32



Raziskava INTEREST

Figure 2 shows the non-inferiority of gefitinib in terms of overall survival in the per-protocol population. The overall survival HR (gefitinib *vs* docetaxel) was 1·020 (96% CI 0·905–1·150), with the upper confidence limit less than the non-inferiority limit of 1·154 (593 [82·0%] *vs* 576 [81·1%] death events). Median overall survival was 7·6 months in the gefitinib group and 8·0 months in the docetaxel group, and 1-year survival was 32% and 34%, respectively. Gefitinib retained 96% (96% CI



Zgornja meja za HR <= 1.154

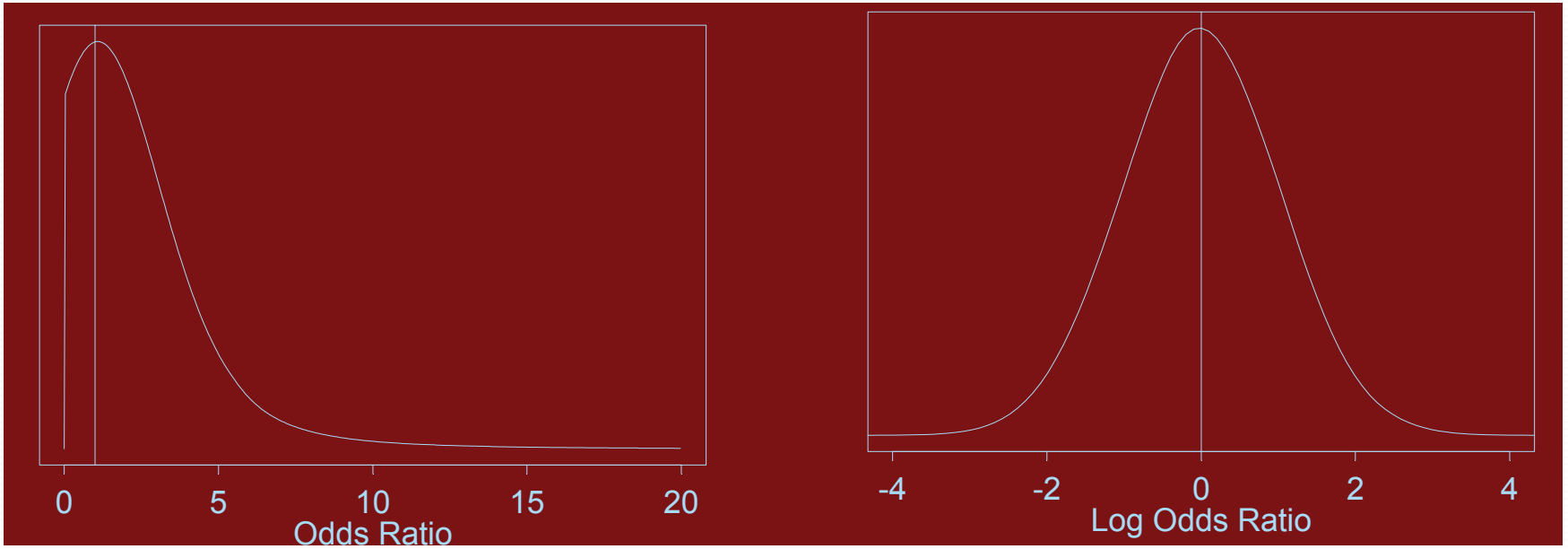
Odds Ratio from a 2x2 table

	SAT	No SAT	
Women	a = 298	b = 252	550
Men	c = 202	d = 248	450
	500	500	1000

$$\mathbf{OR} = \frac{p_1 / (1 - p_1)}{p_2 / (1 - p_2)} = \frac{(298 / 550) / (252 / 550)}{(202 / 450) / (248 / 450)}$$

$$= \frac{298 / 252}{202 / 248} = \frac{298 * 248}{252 * 202} = \frac{ad}{bc}$$

log odds ratio in odds ratio.



- The log OR comparing women to men is log(1.44) = 0.36
- The log OR comparing men to women is log(0.69) = -0.36

log OR > 0: increased risk
log OR = 0: no difference in risk
log OR < 0: decreased risk

Why do we so often see OR and not others?

(1) Logistic regression:

- Allows us to look at association between two variables, adjusted for other variables.
- "Output" is a log odds ratio.
- Example: In the gender ~ SAT example, the odds ratios were evaluated using logistic regression. In reality, the gender ~ SAT odds ratio is adjusted for age, race, year of dx, region, marital status,…..

(2) Can be more globally applied. Design of study does not restrict usage.