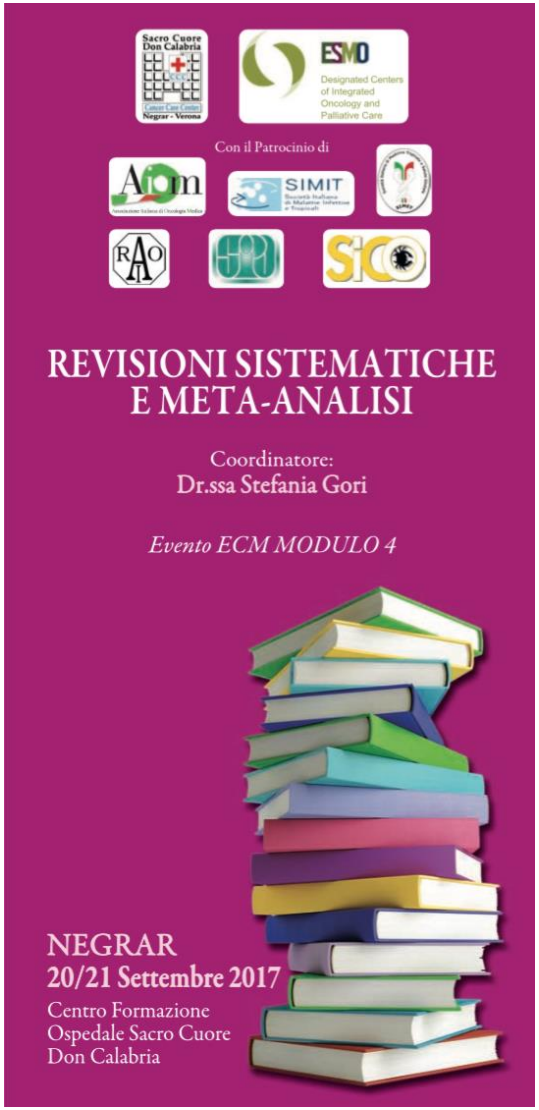

Misure riassuntive di effetto per varie tipologie di variabili statistiche

VARIABILE DI RISPOSTA

- di tipo **qualitativo**
  - esprime categorie di risposta del tipo successo / insuccesso (di un trattamento somministrato).
- di tipo **quantitativo**
  - assume uno spettro continuo di valori e viene misurata in riferimento a una scala a intervalli costanti.
- del tipo **“tempo a evento”**
  - rappresenta il tempo trascorso fino al verificarsi (o meno) di un evento.

VARIABILE DI RISPOSTA

- di tipo **qualitativo**
  - esprime categorie di risposta del tipo successo / insuccesso (di un trattamento somministrato).
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- del tipo “tempo a evento”
  - rappresenta il tempo trascorso fino al verificarsi (o meno) di un evento.

Calcolo delle Incidenze (Rischi)
(a partire da una tabella 2x2)

	Evento	NON Evento
Trattamento sperimentale	**a**	**b**
Gruppo di controllo	**c**	**d**

- **(a/a+b) = incidenza dell'evento nel gruppo sperimentale**
- **(c/c+d) = incidenza dell'evento nel gruppo di controllo**

*** rischi**

Risks, Rates and Odds

- ***Risk*** **(proportion of persons with disease =** ***cumulative incidence*****)**
  - **Risk Ratio = ratio of 2 cumulative incidence estimates =** ***Relative Risk***
- ***Rate*** **(based on events per person-time =** ***incidence rate*****)**
  - **Rate Ratio = ratio of 2 incidence rates =** ***Relative Rate***
- ***Odds*** **(the number of events divided by the number of non events)**
  - **Odds Ratio = ratio of 2 odds**

Rischio Relativo

$$\frac{\text{incidenza}^{\text{sperim}}}{\text{incidenza}^{\text{contr}}}$$

RRR (RRI) e RR sono misure complementari:

RR 0.40 → RRR 60%

RR 1.20 → RRI 20%

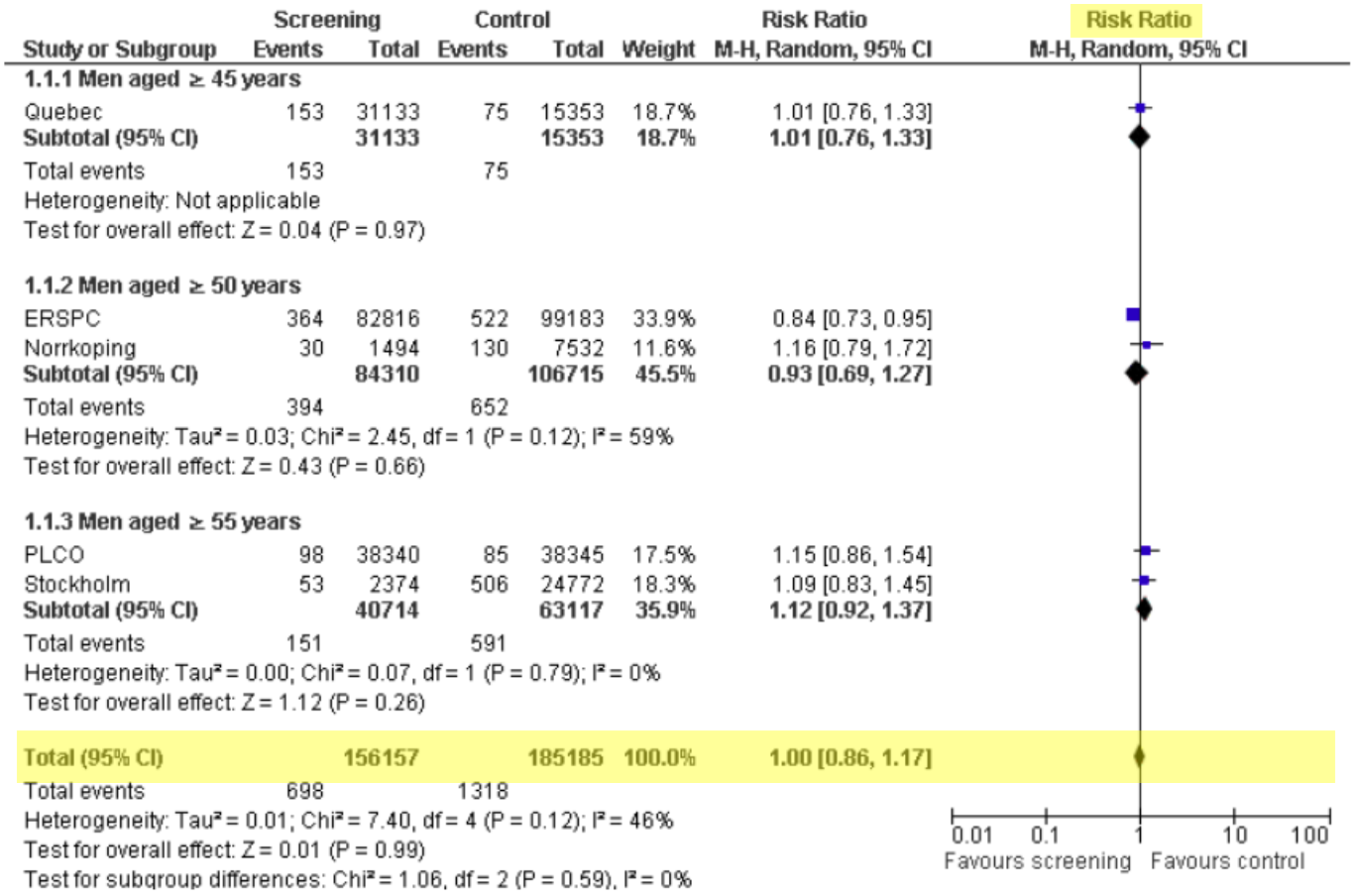
THE COCHRANE COLLABORATION®

Screening for prostate cancer (Review)

Ilic D, Neuberger MM, Djulbegovic M, Dahm P

Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD004720.

Figure 2. Forest plot of comparison: 1 Screening versus control, outcome: 1.3 Prostate cancer-specific mortality (subgroup analysis age)



MISURE ASSOLUTE DI RISCHIO e BENEFICIO (1)

- **Riduzione Assoluta del Rischio (ARR)**
- **Incremento Assoluto del Rischio (ARI)**
  - Differenza aritmetica tra $incid^{sperim}$ e $incid^{control}$ ("Risk Difference")
  - Riduzione / Incremento assoluto di evento nel gruppo dei pazienti
    - nei quali è presente il fattore di rischio
    - trattati con il trattamento sperimentale

Association of Androgen Deprivation Therapy With Cardiovascular Death in Patients With Prostate Cancer

A Meta-analysis of Randomized Trials

Paul L. Nguyen, MD | Jim C. Hu, MD, MPH
Youjin Je, MS | Arti Parekh, BA
Fabio A. B. Schutz, MD | Joshua A. Beckman, MD, MSc
Karen E. Hoffman, MD, MPH, MHSc | Toni K. Choueiri, MD

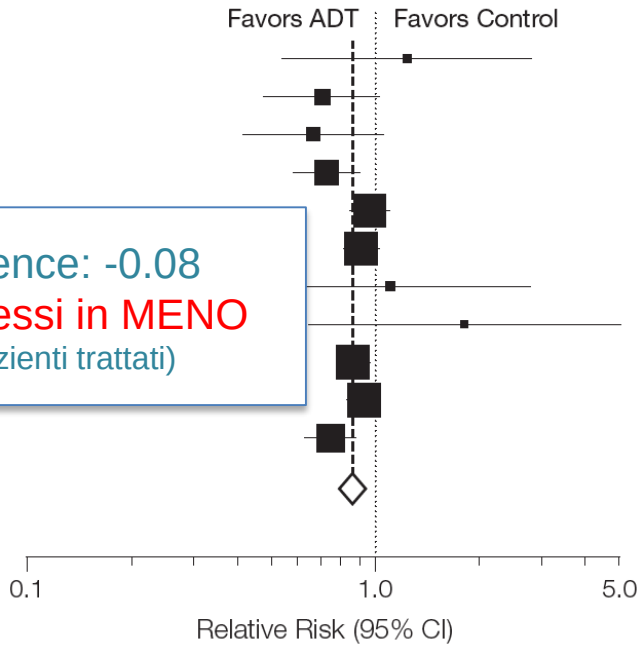
JAMA. 2011;306(21):2359-2366

Relative Risk of All-Cause Mortality Associated With ADT Among Patients With Prostate Cancer

Source	No./Total No. of Events: ADT	No./Total No. of Events: Control	Relative Risk (95% CI)
Aus et al,[17] 2002 (Aus)	11/63	9/63	1.22 (0.54-2.74)
D'Amico et al,[3] 2008 (DFCI 95-096)	30/102	44/104	0.70 (0.48-1.01)
Messing et al,[12] 2006 (ECOG/EST 3886)	17/47	28/51	0.66 (0.42-1.04)
Bolla et al,[13] 2010 (EORTC 22863)	80/207	112/208	0.72 (0.58-0.89)
Schröder et al,[14] 2009 (EORTC 30846)	96/119	97/115	
Studer et al,[15] 2006 (EORTC 30891)	257/492	284/493	
Schulman et al,[18] 2000 (ESGNTPC)	8/192	8/210	
Yee et al,[19] 2010 (MSKCC)	10/72	5/64	
Efstathiou et al,[8] 2009 (RTOG 85-31)	269/477	306/468	
Roach et al,[9] 2008 (RTOG 86-10)	164/224	184/232	
Denham et al,[16] 2011 (TROG 96.01)	198/532	136/270	0.1 -0.87)
Overall	1140/2527	1213/2278	0.86 (0.80-0.93)

Test for heterogeneity: Q = 16.86; $P = .08$; $I^2 = 40.7\%$

Risk Difference: -0.08
ovvero 8 decessi in MENO
(ogni 100 pazienti trattati)



MISURE ASSOLUTE DI RISCHIO e BENEFICIO (1)

- **Riduzione Assoluta del Rischio (ARR)**
- **Incremento Assoluto del Rischio (ARI)**
  - Differenza aritmetica tra $incid^{sperim}$ e $incid^{control}$ ("Risk Difference")
  - Riduzione / Incremento assoluto di evento nel gruppo dei pazienti
    - nei quali è presente il fattore di rischio
    - trattati con il trattamento sperimentale
  - **Tendono a sottostimare l'entità del rischio o del beneficio (in caso di bassa $incid^{control}$)**

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D., Jean Bergeron, M.D., Gérald Luc, M.D., Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langslet, M.D., Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pordy, M.D., Umesh Chaudhari, M.D., and John J.P. Kastelein, M.D., Ph.D., for the ODYSSEY LONG TERM Investigators*

N Engl J Med 2015;372:1489-99.

Table 3. Adverse Events of Interest: Safety Analysis.

Event	Alirocumab (N=1550)	Placebo (N=788)	P Value†
Adjudicated major adverse cardiovascular events in post hoc analysis‡	27 (1.7)	26 (3.3)	0.02
Myalgia — no. of patients (%)	84 (5.4)	23 (2.9)	0.006
Neurocognitive disorder — no. of patients (%)¶		4 (0.5)	0.17
Ophthalmol			0.65

Relative effect:
RR 1.86 (95%CI, 1.18 to 2.92)

Absolute effect:
2 higher / 100 treated (95%CI, 1 to 6 higher)

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D., Jean Bergeron, M.D., Gérald Luc, M.D., Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langslet, M.D., Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pordy, M.D., Umesh Chaudhari, M.D., and John J.P. Kastelein, M.D., Ph.D., for the ODYSSEY LONG TERM Investigators*

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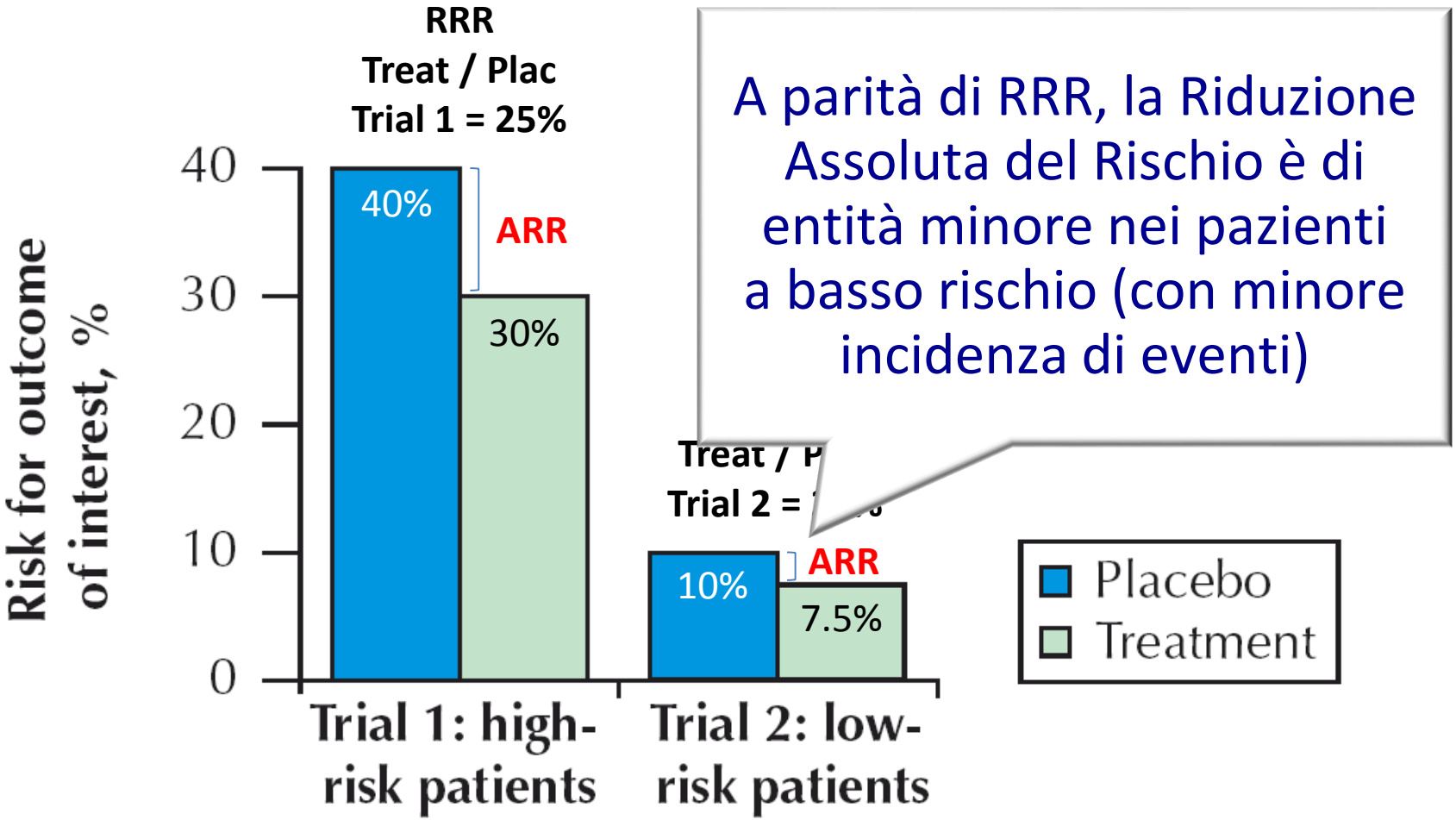
Myalgia — no. of patients (%)	84 (5.4)	23 (2.9)	0.006
Neurocognitive disorder — no. of patients (%)¶	18 (1.2)	4 (0.5)	0.17
Ophthalmologic event — no. of patients (%)‖		15 (1.9)	0.65

Relative effect:
RR 2.29 (95%CI, 0.78 to 6.74)

Absolute effect:
1 higher / 100 treated (95%CI, 0 lower to 3 higher)

Riduzione Relativa del Rischio (RRR) *Vs* Riduzione Assoluta del Rischio (ARR)

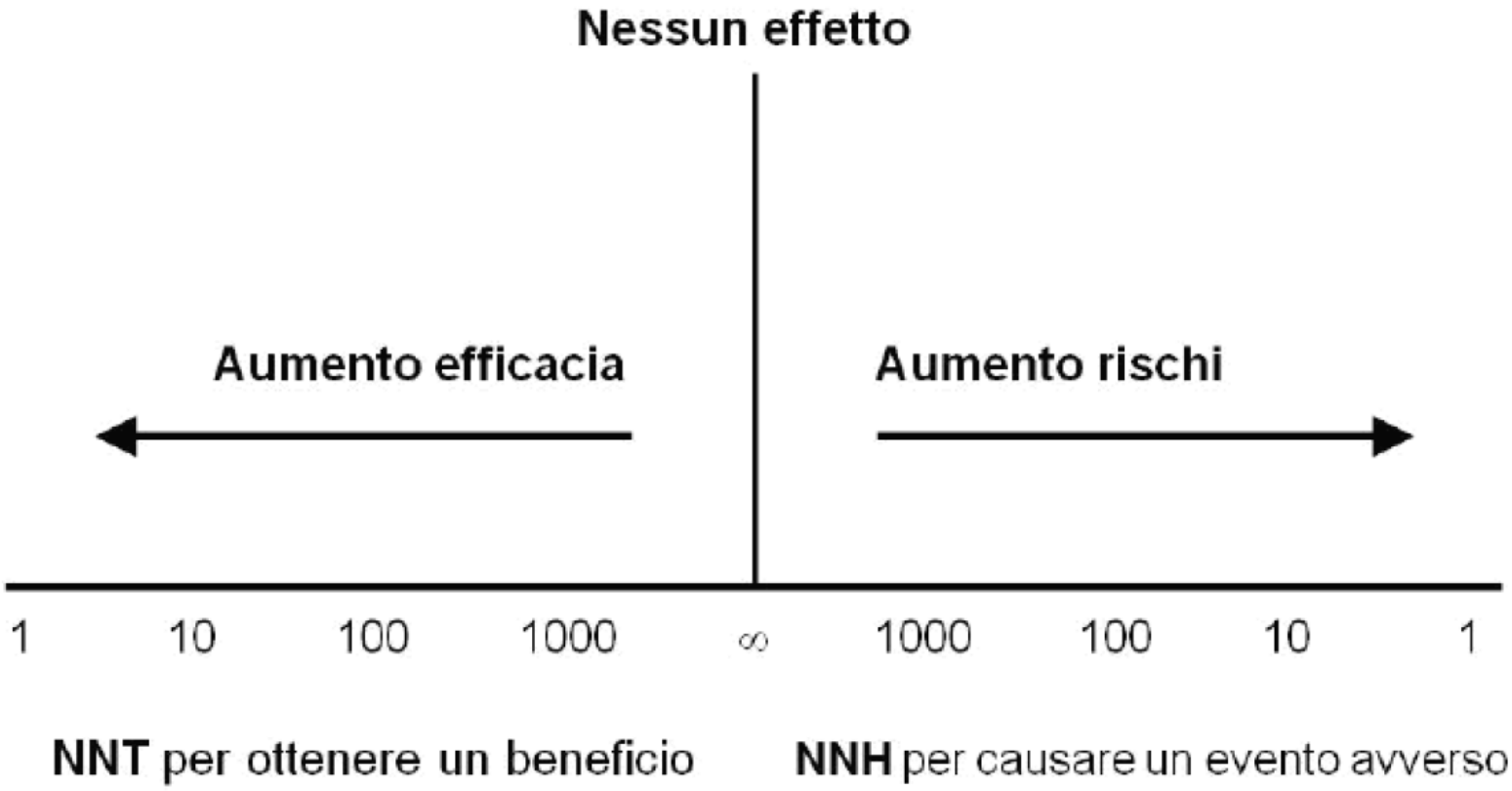


MISURE ASSOLUTE DI RISCHIO e BENEFICIO (2)

- **Number Needed to Treat (NNT) = 1/ARR**
  - Numero di pazienti da trattare per ottenere 1 beneficio terapeutico*
    - Al diminuire del NNT aumenta l'efficacia del trattamento
- **Number Needed to Harm (NNH) = 1/ARI**
  - Numero di pazienti da trattare per osservare 1 effetto avverso del trattamento*
    - All'aumentare del NNH e aumenta la sicurezza del trattamento

** rispetto al braccio di controllo*

- **L'NNT ideale è 1, ovvero il riscontro di un successo per ogni paziente trattato**
- **Il NNH ideale tende all'infinito (assenza di eventi avversi)**



Risks, Rates and Odds

- *Risk* (proportion of persons with disease = *cumulative incidence*)
  - Risk Ratio = ratio of 2 cumulative incidence estimates = *Relative Risk*
- *Rate* (based on events per person-time = *incidence rate*)
  - Rate Ratio = ratio of 2 incidence rates = *Relative Rate*
- *Odds* (the number of events divided by the number of non events)
  - Odds Ratio = ratio of 2 odds

Incidence Rate

Incidence rate or person-time rate:

- is a measure of incidence that incorporates time directly into the denominator;
- describes how quickly disease occurs in a population

$$\frac{\textit{Number of new cases of disease or injury during specified period}}{\textit{Time each person was observed, totaled for all persons}}$$

Incidence Rate

Incidence rate or person-time rate:

- is a measure of incidence that incorporates time directly into the denominator;
- describes how quickly disease occurs in a population

Annualized relapse rate is often included as an outcome measure for clinical trials because it is easy to quantify, and prevention of relapses benefits patients immediately

Multiple Sclerosis International
Volume 2014, Article ID 262350,

Pre-specified subgroup analyses of a placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis

Aaron E Miller[1], Paul O'Connor[2], Jerry S Wolinsky[3], Christian Confavreux[4], Ludwig Kappos[5], Tomas P Olsson[6], Philippe Truffinet[7], Lin Wang[8], Laura D'Castro[9], Giancarlo Comi[10] and Mark S Freedman[11] for the Teriflunomide Multiple Sclerosis Trial Group

Multiple Sclerosis Journal 18(11) 1625–1632 © The Author(s) 2012

Study evaluations

The primary objective of TEMSO was to determine the effect of teriflunomide on ARR, defined as the number of confirmed relapses per patient-year

Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes

R. Ritzel[1], R. Roussel[2,3,4], G. B. Bolli[5], L. Vinet[6], C. Brulle-Wohlhueter[7], S. Glezer[7] & H. Yki-Järvinen[8]

Diabetes, Obesity and Metabolism 2015.

Aims: To conduct a patient-level meta-analysis of the EDITION 1, 2 and 3 studies, which compared the efficacy and safety of new insulin glargine 300 U/ml (Gla-300) with insulin glargine 100 U/ml (Gla-100) in people with type 2 diabetes (T2DM) on basal and mealtime insulin, basal insulin and oral antihyperglycaemic drugs, or no prior insulin, respectively.

Methods: The EDITION studies were multicentre, randomized, open-label, parallel-group, phase IIIa studies, with similar designs and endpoints. A patient-level meta-analysis of the studies enabled these endpoints to be examined over 6 months in a large population with T2DM (Gla-300, n = 1247; Gla-100, n = 1249).

Results: No significant study-by-treatment interactions across studies were found, enabling them to be pooled. The mean change in glycated haemoglobin was comparable for Gla-300 and Gla-100 [each −1.02 (standard error 0.03)%; least squares (LS) mean difference 0.00 (95% confidence interval (CI) −0.08 to 0.07)%]. Annualized rates of confirmed (≤3.9 mmol/l) or severe hypoglycaemia were lower with Gla-300 than with Gla-100 during the night (31% difference in rate ratio over 6 months) and at any time (24 h, 14% difference). Consistent reductions were observed in percentage of participants with ≥1 hypoglycaemic event. Severe hypoglycaemia at any time (24 h) was rare (Gla-300: 2.3%; Gla-100: 2.6%). Weight gain was low (<1 kg) in both groups, with less gain with Gla-300 [LS mean difference −0.28 kg (95% CI −0.55 to −0.01); p = 0.039]. Both treatments were well tolerated, with similar rates of adverse events.

Conclusion: Gla-300 provides comparable glycaemic control to Gla-100 in a large population with a broad clinical spectrum of T2DM, with consistently less hypoglycaemia at any time of day and less nocturnal hypoglycaemia.

Keywords: basal insulin, insulin glargine, insulin therapy

Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes

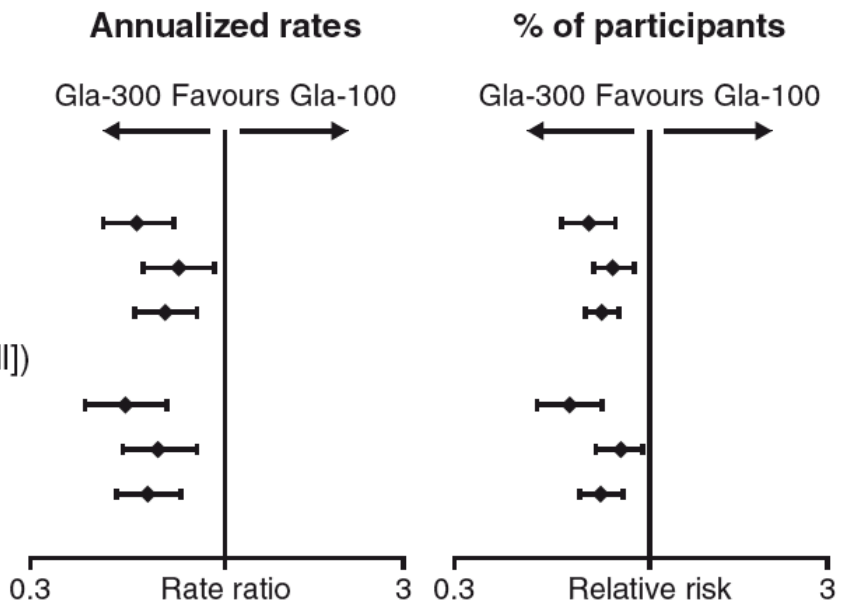
R. Ritzel[1], R. Roussel[2,3,4], G. B. Bolli[5], L. Vinet[6], C. Brulle-Wohlhueter[7], S. Glezer[7] & H. Yki-Järvinen[8]

Diabetes, Obesity and Metabolism 2015.

Annualized rates and percentage of participants with ≥1 hypoglycaemic event during the night

B

	Annualized rates		% of participants	
	Rate ratio	95% CI	Relative risk	95% CI
Confirmed (≤3.9 mmol/l [≤70 mg/dl]) or severe hypoglycaemia				
BL to W8	0.58	0.47 to 0.73	0.69	0.58 to 0.81
W9 to M6	0.75	0.60 to 0.94	0.80	0.71 to 0.91
BL to M6	0.69	0.57 to 0.84	0.75	0.68 to 0.83
Documented symptomatic hypoglycaemia (≤3.9 mmol/l [≤70 mg/dl])				
BL to W8	0.54	0.42 to 0.70	0.61	0.50 to 0.75
W9 to M6	0.66	0.53 to 0.84	0.84	0.72 to 0.97
BL to M6	0.62	0.51 to 0.76	0.75	0.66 to 0.85



Risks, Rates and Odds

- *Risk* (proportion of persons with disease = *cumulative incidence*)
  - Risk Ratio = ratio of 2 cumulative incidence estim[illegible] = *Relative Risk*
- *Rat*[illegible] [illegible]er person-time = *inci*[illegible]
  - Rate Ratio = ratio of 2 incidence rates = *Rela*[illegible] *Rate*
- *Odd*[illegible] [illegible]nts divided by the nu[illegible]
  - Odds Ratio = ratio of 2 odds

How different the long term probability of the event is…

The more reliable measure of event occurrence (by time)…

Calcolo degli Odds
(a partire da una tabella 2x2)

	Evento	NON Evento
Trattamento sperimentale	**a**	**b**
Gruppo di controllo	**c**	**d**

- **(a/b) = odds dell'evento nel gruppo sperimentale**
- **(c/d) = odds dell'evento nel gruppo di controllo**

*** rischi**

Risks, Rates and Odds

- *Risk* (proportion of persons with disease =

Odds Ratios are used to compare the occurrence of the outcome of interest (e.g. disease or unfavourable event), given exposure to the variable of interest (e.g. health characteristic, or intervention).

Most commonly used in **case-control studies**

- *Odds* (the number of events divided by the number of non events)
  - Odds Ratio = ratio of 2 odds

Rischio Relativo

$$\frac{\text{incidenza}^{\text{sperim}}}{\text{incidenza}^{\text{contr}}}$$

Odds Ratio

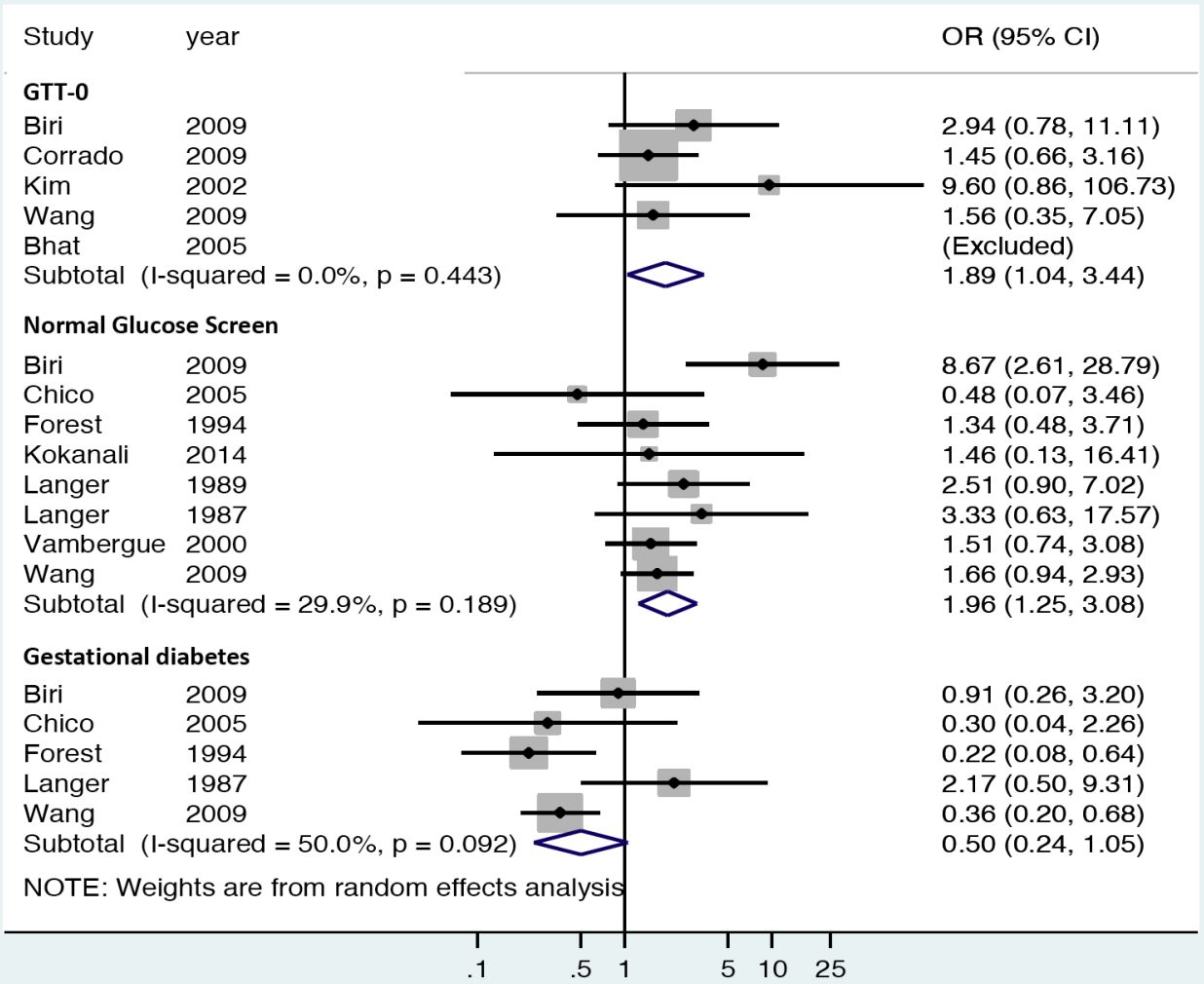
$$\frac{\text{odds}^{\text{sperim}}}{\text{odds}^{\text{contr}}}$$

Accepted Manuscript

Single abnormal value on 3 hour oral glucose tolerance test during pregnancy is associated with adverse maternal and neonatal outcomes: A systematic review and meta-analysis

Jared T. Roeckner, MD, Luis Sanchez-Ramos, MD, Rubymel Jijon-Knupp, MD, Andrew M. Kaunitz, MD

Neonatal Hypoglycemia

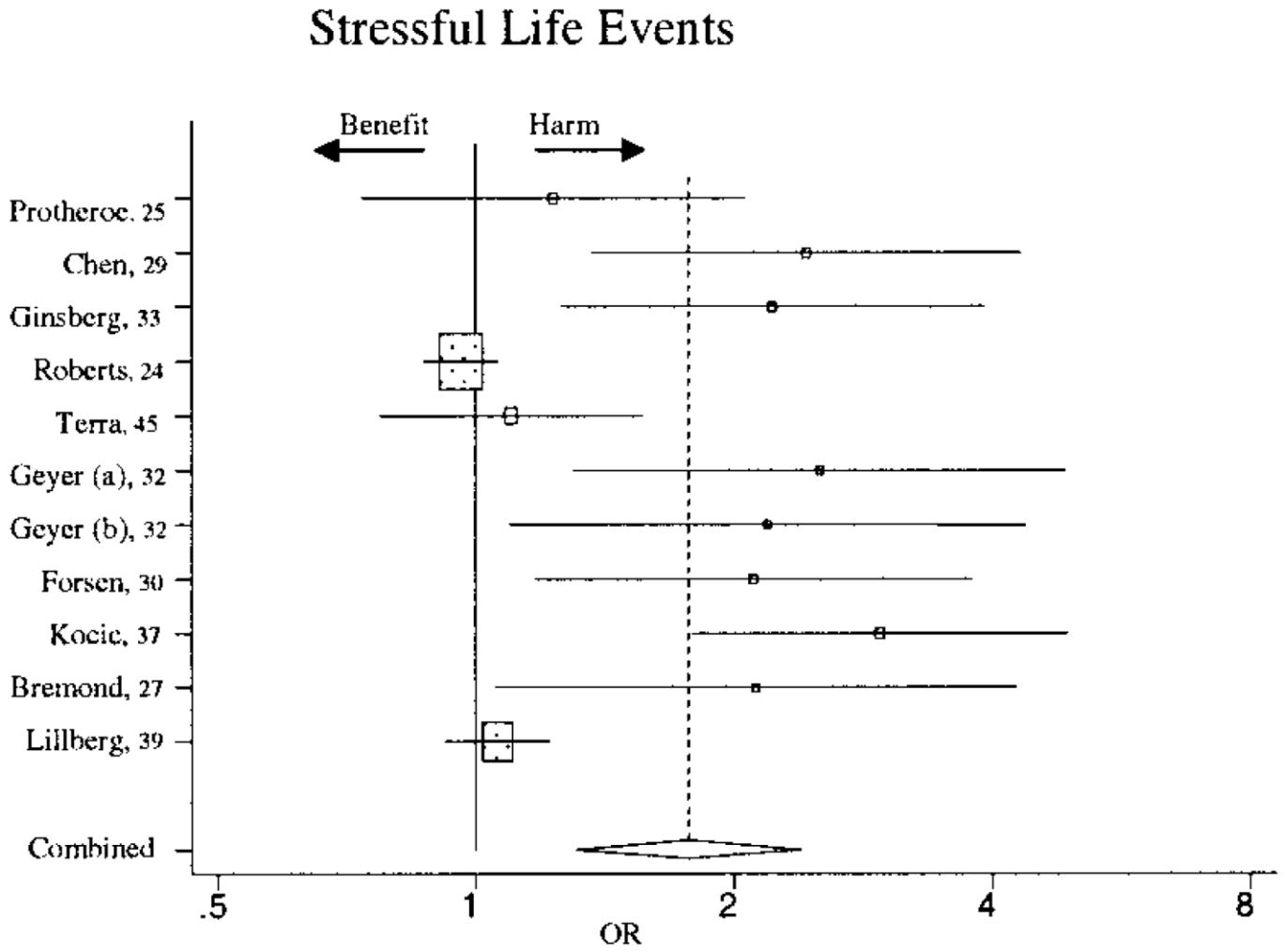


Int. J. Cancer: **107,** 1023–1029 (2003)
© 2003 Wiley-Liss, Inc.

Publication of the International Union Against Cancer

THE ASSOCIATION BETWEEN STRESSFUL LIFE EVENTS AND BREAST CANCER RISK: A META-ANALYSIS

Saskia F.A. DUIJTS[1]*, Maurice P.A. ZEEGERS[1] and Bart Vd BORNE[2]



VARIABILE DI RISPOSTA

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- di tipo **quantitativo**
  - assume uno spettro continuo di valori e viene misurata in riferimento a una scala a intervalli costanti.
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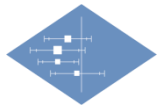


Effect measures for continuous outcomes

The **mean difference** (more correctly, 'difference in means') measures the absolute difference between the mean value in two groups in a clinical trial.

- ✓ It estimates the amount by which the experimental intervention changes the outcome on average compared with the control.

The **standardized mean difference** is used as a summary statistic in meta-analysis when the studies all assess the same outcome but measure it in a variety of ways.

- ✓ The standardized mean difference expresses the size of the intervention effect in each study relative to the variability observed in that study.

Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: Results of a 24 week, double-blind, randomized Phase 3 trial

Eli M. Roth [a,*], Marja-Riitta Taskinen [b], Henry N. Ginsberg [c], John J.P. Kastelein [d], Helen M. Colhoun [e], Jennifer G. Robinson [f], Laurence Merlet [g], Robert Pordy [h], Marie T. Baccara-Dinet [i]

International Journal of Cardiology 176 (2014) 55–61

2.3. Endpoints and assessments

The primary endpoint was the percent change from baseline in calculated LDL-C at 24 weeks with alirocumab compared with ezetimibe.

2.4. Statistical analyses

A sample size of 45 patients per treatment arm was calculated to have 95% power to detect a mean difference between alirocumab and ezetimibe of 20% in LDL-C percent change from baseline to week 24 using a 2-sided *t*-test with 5% significance, assuming a common standard deviation (SD) of 25% based on a previous alirocumab trial [1] and with an expected rate of exclusion of 5%.

Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: Results of a 24 week, double-blind, randomized Phase 3 trial

Eli M. Roth [a,*], Marja-Riitta Taskinen [b], Henry N. Ginsberg [c], John J.P. Kastelein [d], Helen M. Colhoun [e], Jennifer G. Robinson [f], Laurence Merlet [g], Robert Pordy [h], Marie T. Baccara-Dinet [i]

International Journal of Cardiology 176 (2014) 55–61

Table 2
Percent change in LDL-C from baseline to week 24 (ITT and on-treatment analysis).

LDL-C	Alirocumab 75 mg Q2W	Ezetimibe 10 mg	Alirocumab versus ezetimibe		
			LS mean difference (SE) %	95% CI	*p*-Value
ITT	$N = 52$	$N = 51$			
LS mean (SE) change from baseline (%)	−47.2 (3.0)	−15.6 (3.1)	−31.6 (4.3)	−40.2 to −23.0	<0.0001[a]
On-treatment[b]	$N = 51$	$N = 50$			
Baseline LDL-C, mean (SD), mg/dL	141.1 (27.4)	137.5 (24.1)			
Min:max	77:207	73:186			
LS mean (SE) change from baseline (%)	−54.1 (2.0)	−17.2 (2.0)	−36.9 (2.9)	−42.7 to −31.2	<0.0001[c]

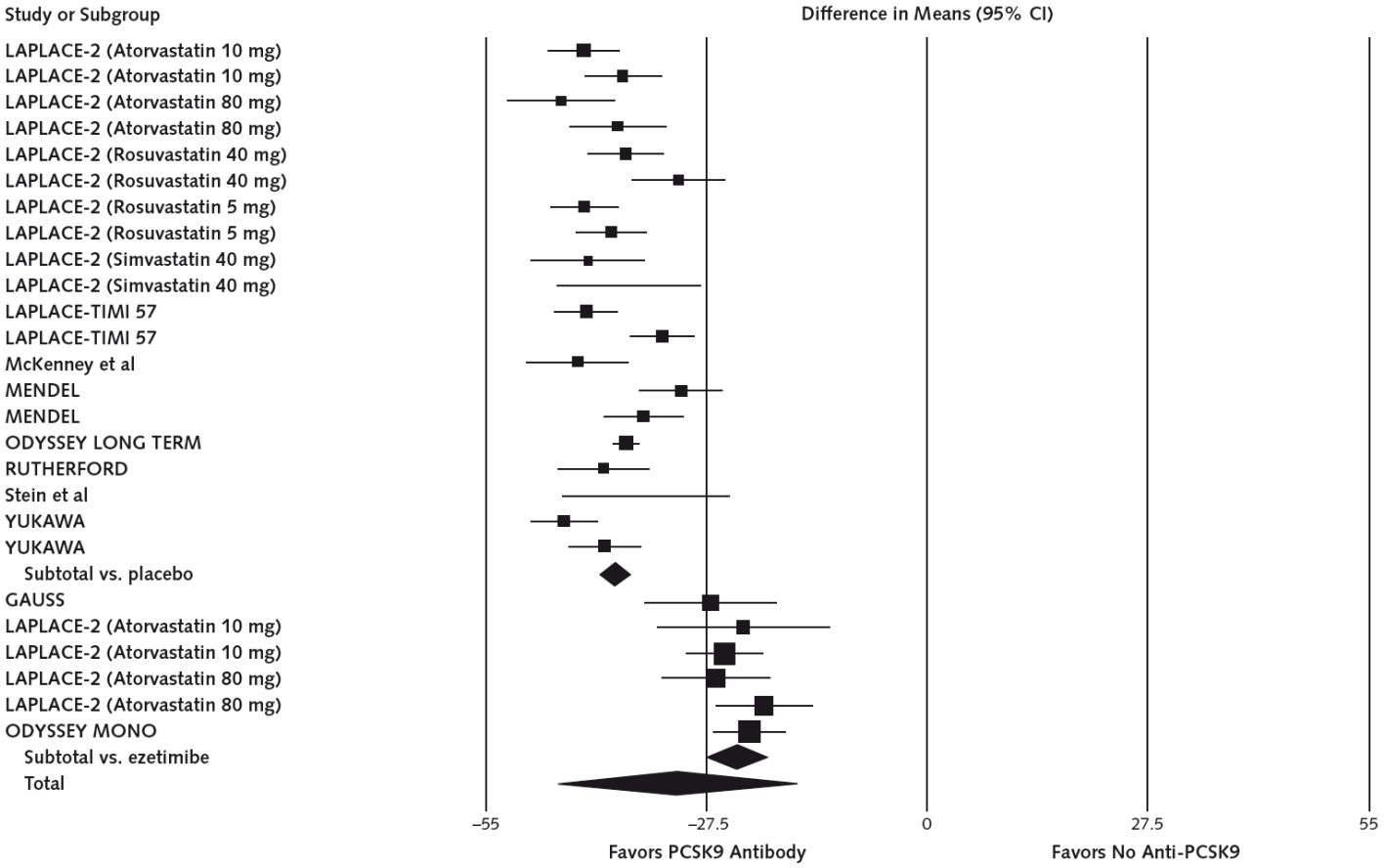
CI = confidence intervals; ITT = intent-to-treat; LDL-C = low-density lipoprotein cholesterol; LS = least squares; Q2W = every 2 weeks; SD = standard deviation; and SE = standard error.

Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia

A Systematic Review and Meta-analysis

Eliano Pio Navarese, MD, PhD; Michalina Kołodziejczak, MD; Volker Schulze, MD; Paul A. Gurbel, MD; Udaya Tantry, PhD; Yingfeng Lin, MD; Maximilian Brockmeyer, MD; David E. Kandzari, MD; Julia M. Kubica, MD; Ralph B. D'Agostino Sr., PhD; Jacek Kubica, MD, PhD; Massimo Volpe, MD; Stefan Agewall, MD; Dean J. Kereiakes, MD; and Malte Kelm, MD

Ann Intern Med. 2015;163:40-51.



Group	Effect Size (95% CI)						Test of Null (2-Tail)		Heterogeneity		
	Number of Studies	Point Estimate	SE	Variance	Lower Limit	Upper Limit	*Z* Value	*P* Value	*Q* Value	*P* Value	I^2
Random-effects analysis											
Overall	26	−31.492	7.580	57.455	−46.348	−16.635	−4.155	0.000	187.788	0.000	86.687

Serum lipids and lipoproteins in malaria - a systematic review and meta-analysis

Benjamin J Visser[1,2,4], Rosanne W Wieten[1,2], Ingeborg M Nagel[3] and Martin P Grobusch[1,2,4*]

Malaria Journal 2013, **12**:442

Study or Subgroup	Malaria cases Mean	SD	Total	Healthy controls Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Seshadri 1981	2.82	0.09	30	4.4	0.11	39	7.1%	-1.58 [-1.63, -1.53]	1981
Djoumessi 1989	3.18	0.96	37	4.16	1.55	37	5.9%	-0.98 [-1.57, -0.39]	1989
Cuisinier-Raynal 1990	4.8	1.04	67	5	0.89	51	6.6%	-0.20 [-0.55, 0.15]	1990
Agbedana 1990	2.56	0.7	15	3.54	0.77	11	5.9%	-0.98 [-1.56, -0.40]	1990
Mohanty 1992	2.7	0.87	60	4.77	0.91	83	6.7%	-2.07 [-2.36, -1.78]	1992
Selvam 1992	3.9	1.04	98	5.18	0.83	174	6.9%	-1.28 [-1.52, -1.04]	1992
Sumitha 1996	5.46	0.5	20	6.09	0.68	20	6.6%	-0.63 [-1.00, -0.26]	1996
Das 1996	2.23	0.62	100	3.47	0.59	50	6.9%	-1.24 [-1.44, -1.04]	1996
Erel 1998	2.96	0.8	60	3.4	1.12	50	6.6%	-0.44 [-0.81, -0.07]	1998
Njoku 2001	2.95	0.35	33	4.2	0.49	22	6.9%	-1.25 [-1.49, -1.01]	2001
Faucher 2002	3.49	0.88	47	3.87	0.66	47	6.7%	-0.38 [-0.69, -0.07]	2002
Parola 2004	0	0	0	0	0	0		Not estimable	2004
Kim 2008	1.97	0.7	55	4.38	0.67	52	6.8%	-2.41 [-2.67, -2.15]	2008
Ogbodo 2008	2.27	0.43	20	2.88	0.58	15	6.6%	-0.61 [-0.96, -0.26]	2008
Al Omar 2010	1.93	1.59	200	3.6	0.99	200	6.8%	-1.67 [-1.93, -1.41]	2010
Mfonkeu 2010	2.57	0.14	139	3.08	0.21	45	7.1%	-0.51 [-0.58, -0.44]	2010
Eteng 2010	4.28	1.16	17	2.95	0.71	20		Not estimable	2010
Total (95% CI)			**981**			**896**	**100.0%**	**-1.09 [-1.44, -0.74]**	

Heterogeneity: Tau² = 0.44; Chi² = 897.72, df = 14 (P < 0.00001); I² = 98%

Test for overall effect: Z = 6.14 (P < 0.00001)

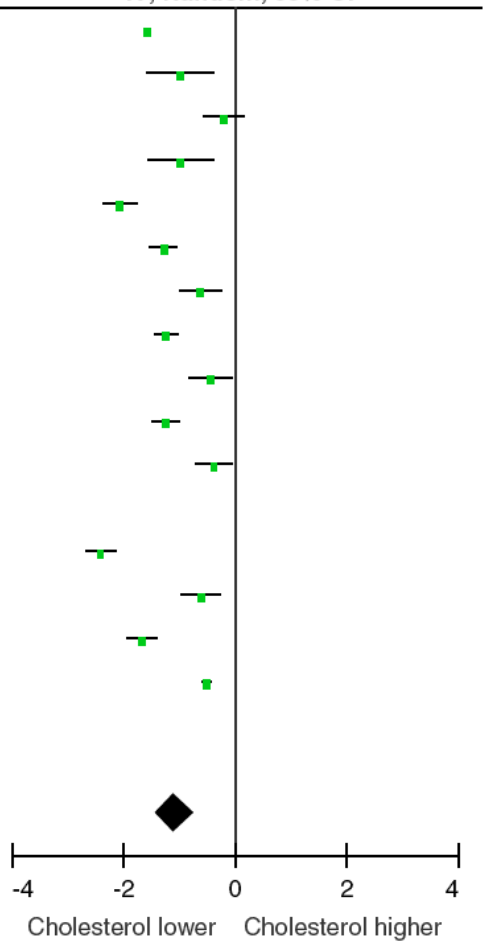


Figure 2 Forest plot Mean difference for cholesterol (mmol/l) between malaria patients and healthy controls. Random-effect model.

Effect measures for continuous outcomes

The **mean difference** (more correctly, 'difference in means') measures the absolute difference between the mean value in two groups in a clinical trial.

- ✓ It estimates the amount by which the experimental intervention changes the outcome on average compared with the control.

The **standardized mean difference** is used as a summary statistic in meta-analysis when the studies all assess the same outcome but measure it in a variety of ways.

- ✓ The standardized mean difference expresses the size of the intervention effect in each study relative to the variability observed in that study.

Selection of summary statistics for continuous data is principally determined by whether studies all report the outcome using the same scale (when the mean difference can be used) or using different scales (when the standardized mean difference has to be used)

VARIABILE DI RISPOSTA

- di tipo quantitativo
  - assume uno spettro continuo di valori e viene misurata in riferimento a una scala a intervalli costanti.
- di tipo qualitativo
  - esprime categorie di risposta del tipo successo / insuccesso (di un trattamento somministrato).
- del tipo "**tempo a evento**"
  - rappresenta il tempo trascorso fino al verificarsi (o meno) di un evento.

Indicatori riassuntivi di effetto di variabili tempo-a-evento

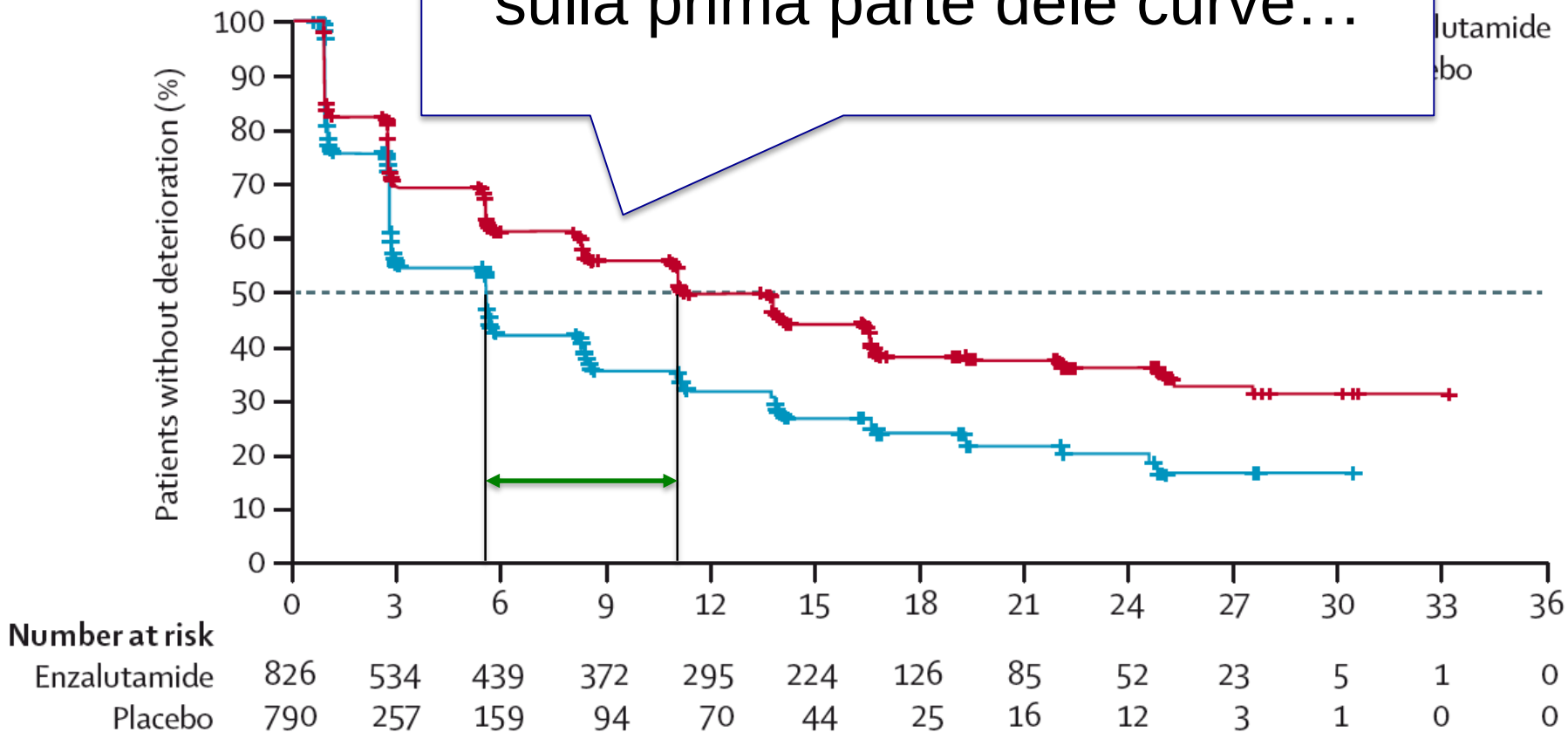
- Differenza tra stime della mediana di sopravvivenza (KM)
- Differenza media di sopravvivenza (*restricted means*) al tempo *t*
- Differenza tra stime di sopravvivenza (KM) al tempo *t*
- Hazard Ratio (KM+Cox)

Indicatori riassuntivi di effetto di variabili tempo-a-evento

- **Differenza tra stime della mediana di sopravvivenza (KM)**
- Differenza media di sopravvivenza (*restricted means*) al tempo *t*
- Differenza tra stime di sopravvivenza (KM) al tempo *t*
- Hazard Ratio (KM+Cox)

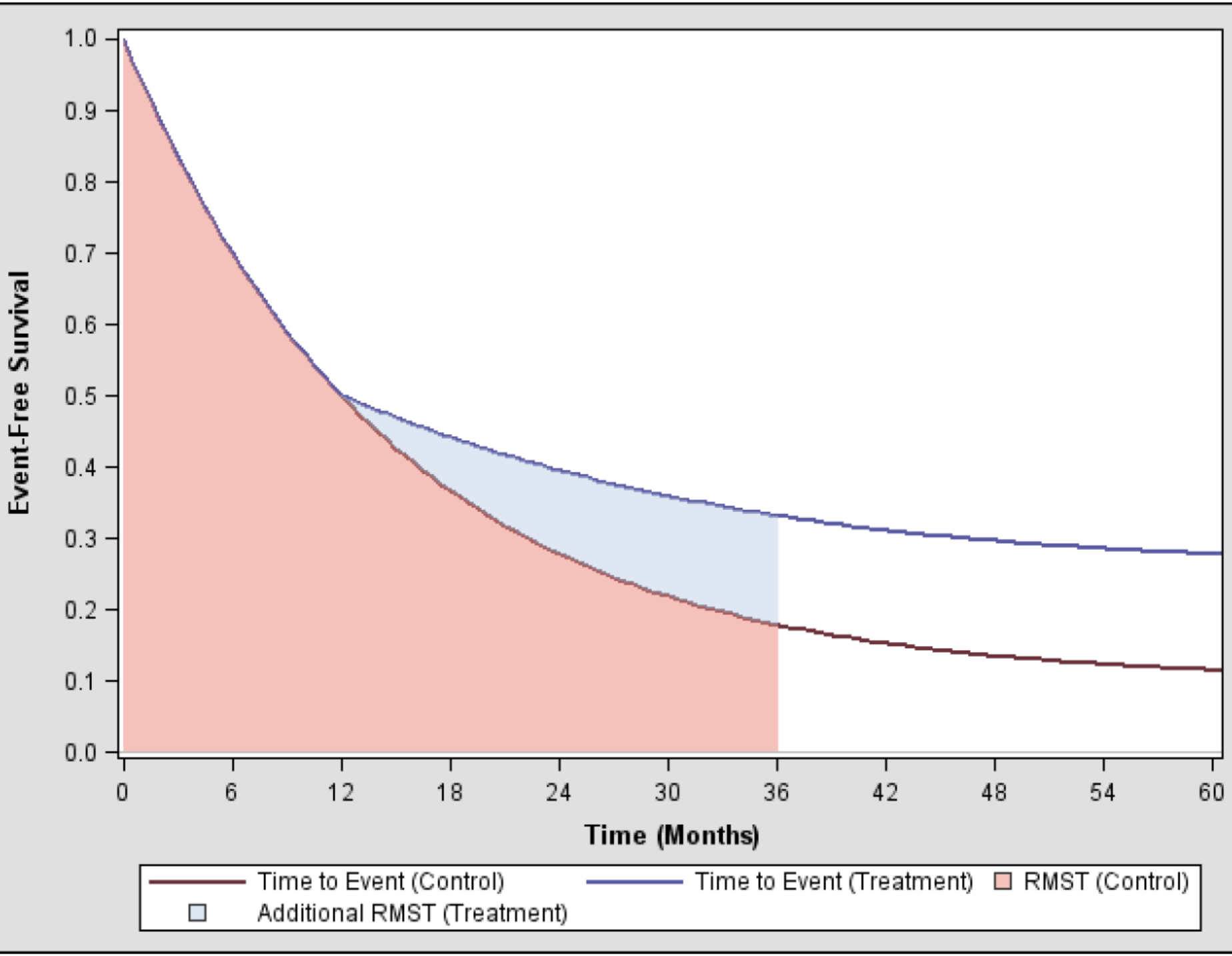
Differenza tra stime dell

Fornisce informazione solo sulla prima parte dele curve…



Indicatori riassuntivi di effetto di variabili tempo-a-evento

- Differenza tra stime della mediana di sopravvivenza (KM)
- **Differenza media di sopravvivenza (*restricted means*) al tempo *t***
- Differenza tra stime di sopravvivenza (KM) al tempo *t*
- Hazard Ratio (KM+Cox)


Event-Free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
6
12
18
24
30
36
42
48
54
60
Time (Months)
Time to Event (Control)
Time to Event (Treatment)
RMST (Control)
Additional RMST (Treatment)

MRC Clinical Trials Unit

Restricted mean survival time

Patrick Royston

- RMST = area under the survival curve up to t^*

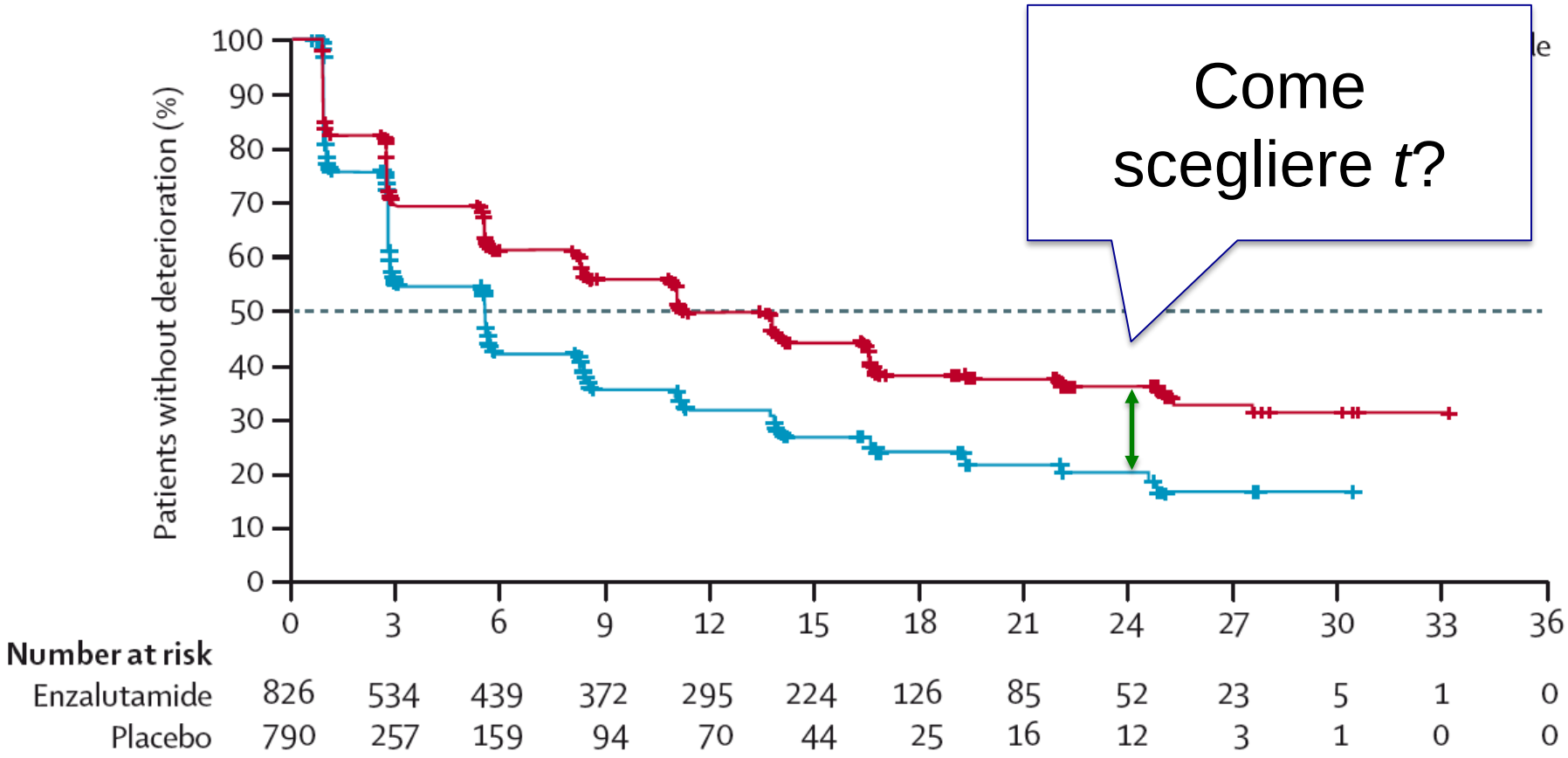
Choice of t^*

- t^* should be chosen to cover the follow-up period of clinical interest
- Usually take t^* close to the last observed event time
- In a randomized trial, t^* needs to be pre-specified in the statistical analysis plan

Indicatori riassuntivi di effetto di variabili tempo-a-evento

- Differenza tra stime della mediana di sopravvivenza (KM)
- Differenza media di sopravvivenza (*restricted means*) al tempo *t*
- **Differenza tra stime di sopravvivenza (KM) al tempo *t***
- Hazard Ratio (KM+Cox)

Differenza tra stime di sopravvivenza (KM) al tempo x



Indicatori riassuntivi di effetto di variabili tempo-a-evento

- Differenza tra stime della mediana di sopravvivenza (KM)
- za (*restricted*
- venza (KM) al tempo
- **Hazard Ratio** (KM+Cox)

Rapporto tra *hazard rate* dei trattamenti a confronto

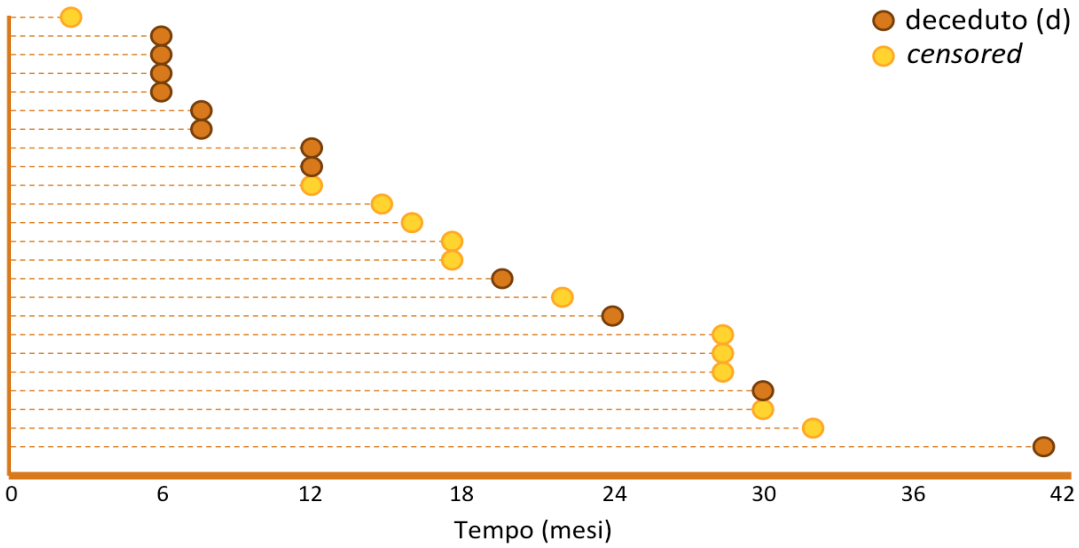
HAZARD

- **Hazard rate (number of failures per time units in the respective interval, divided by the average number of surviving cases at the mid-point of the interval)**

Hazard Rate = probabilità di evento nell'unità di tempo considerata

$$\lambda = \frac{d}{f + F}$$

dove:
d = numero di eventi
f = somma della lunghezza dei follow-up nei pazienti con l'evento
F = somma della lunghezza dei follow-up nei pazienti censored



d = 12
f = 6+6+6+6+8+8+12+12+20+24+30+42 = 180
F = 3+12+15+16+18+18+22+28+28+28+30+33 = 251

$$\lambda = \frac{12}{431} = 0.0278$$

Riferimenti bibliografici:

- Presentazione di R. D'Amico, UniMoRe, 2009, modificata da GL Pappagallo, 2013

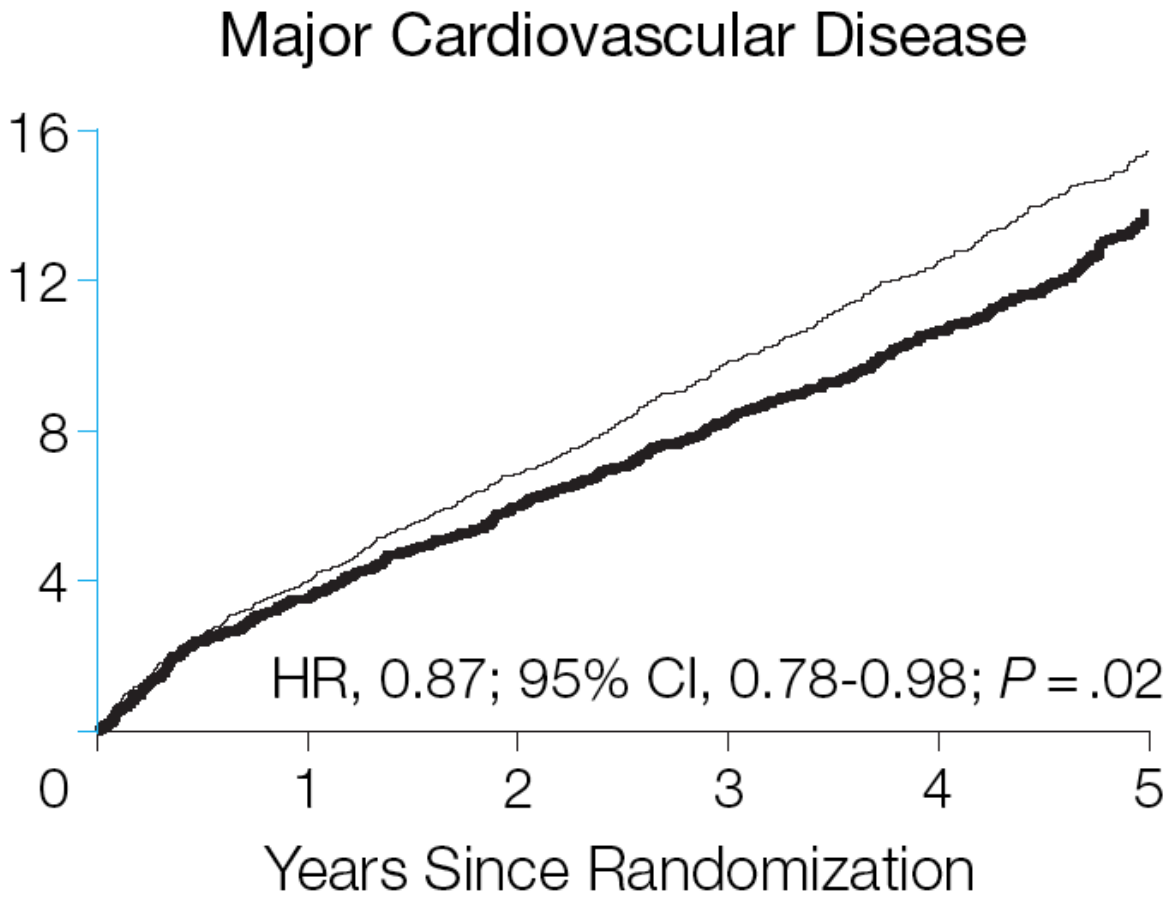
- ✓ La stima dell'hazard rate □ è data dal rapporto tra il numero di eventi e la lunghezza del follow-up nell'intervallo di tempo considerato
- ✓ L'hazard rate non viene di norma utilizzato per riassumere una curva di sopravvivenza, ma rappresenta il parametro che ne descrive la pendenza…
- ✓ …e rappresenta la base per il calcolo dell'hazard ratio.

Indicatori riassuntivi di variabili tempo-a-evento

- ... *icted*
- Differe... ime di sopravvivenza (KM) al tempo
- **Hazard Ratio** (KM+Cox)

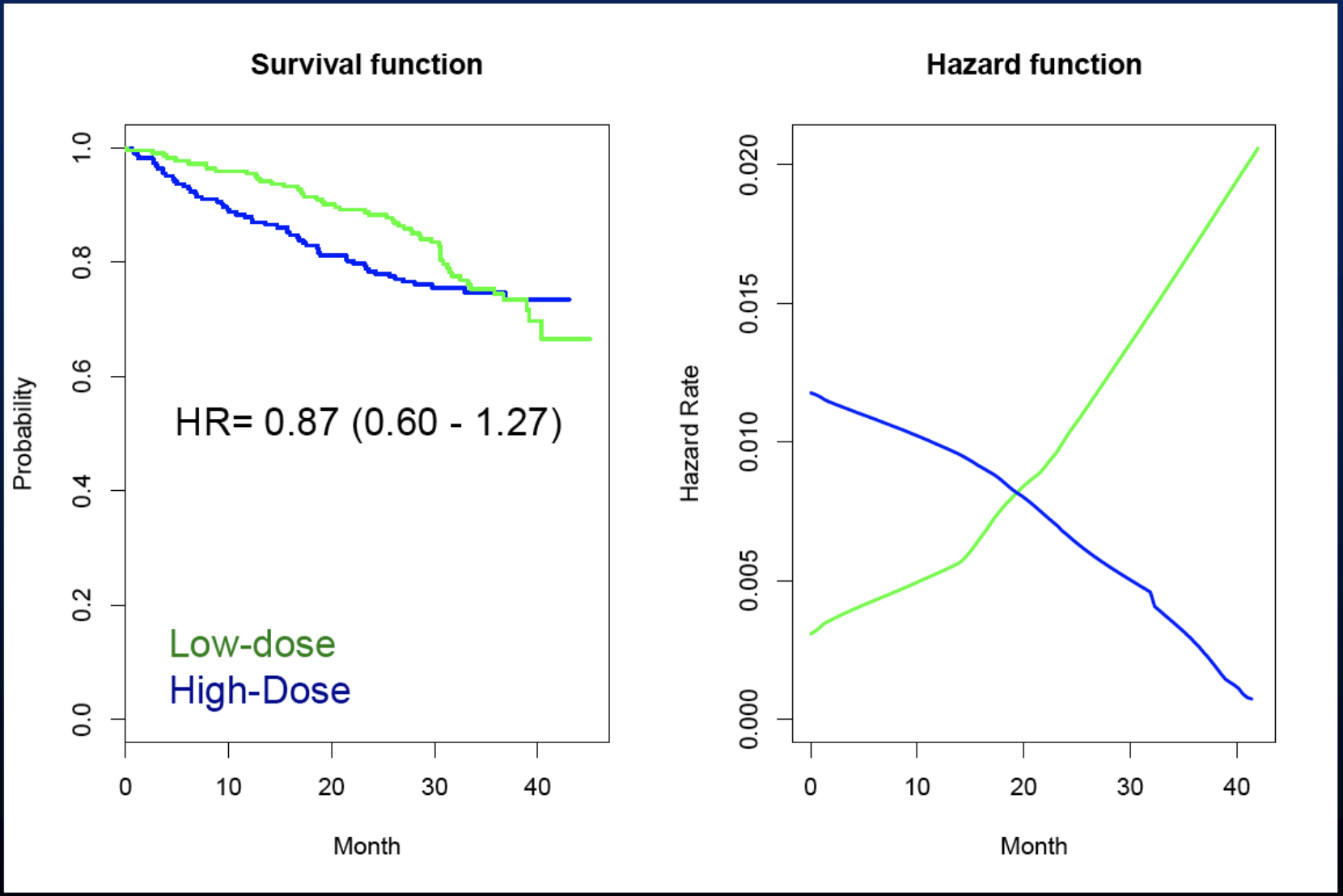
Appropriato quando il rapporto tra gli *hazard* dei due gruppi si mantiene (relativamente) costante

Rapporto tra gli *hazard* dei due gruppi costante nel tempo



Hazard Ratio è la misura di effetto più appropriata

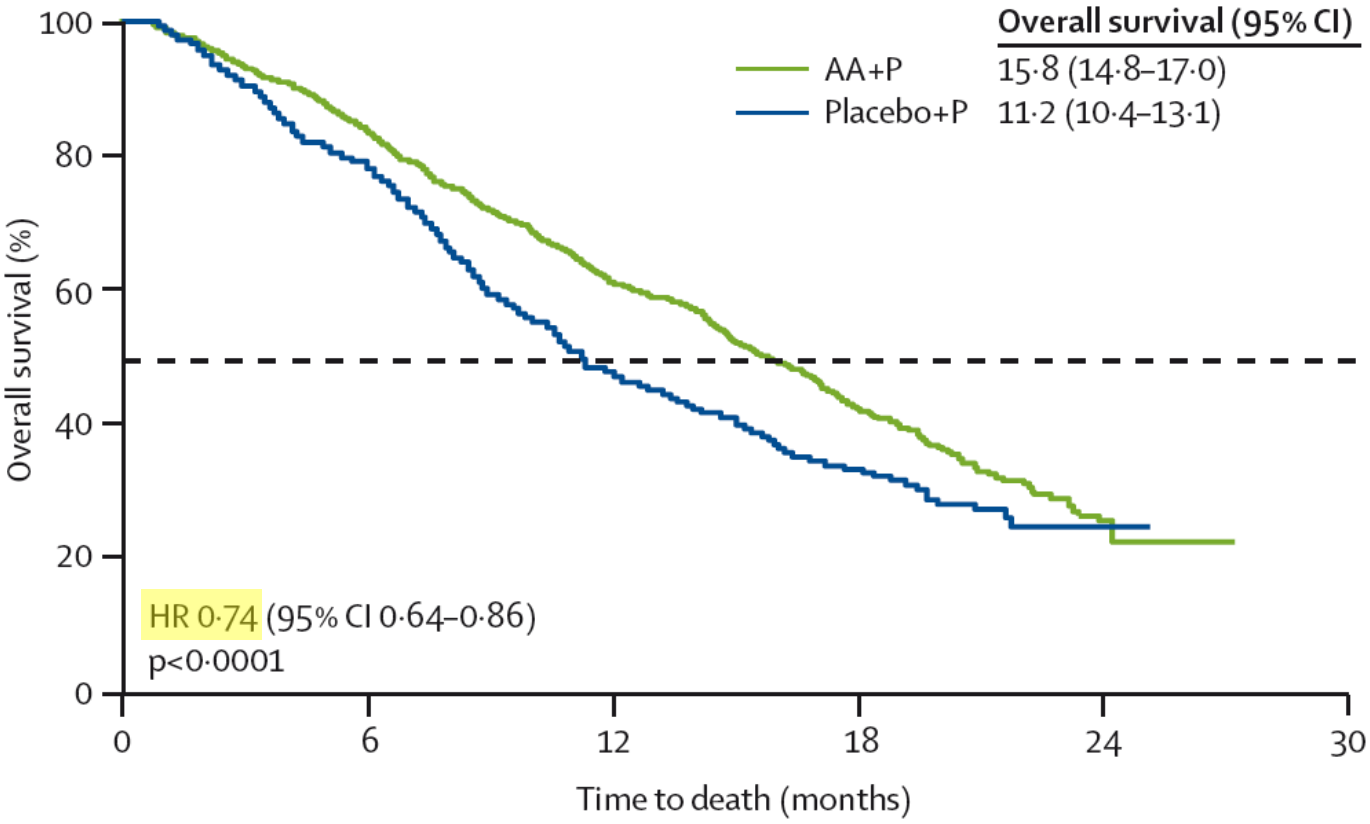
How hazard functions looked like?

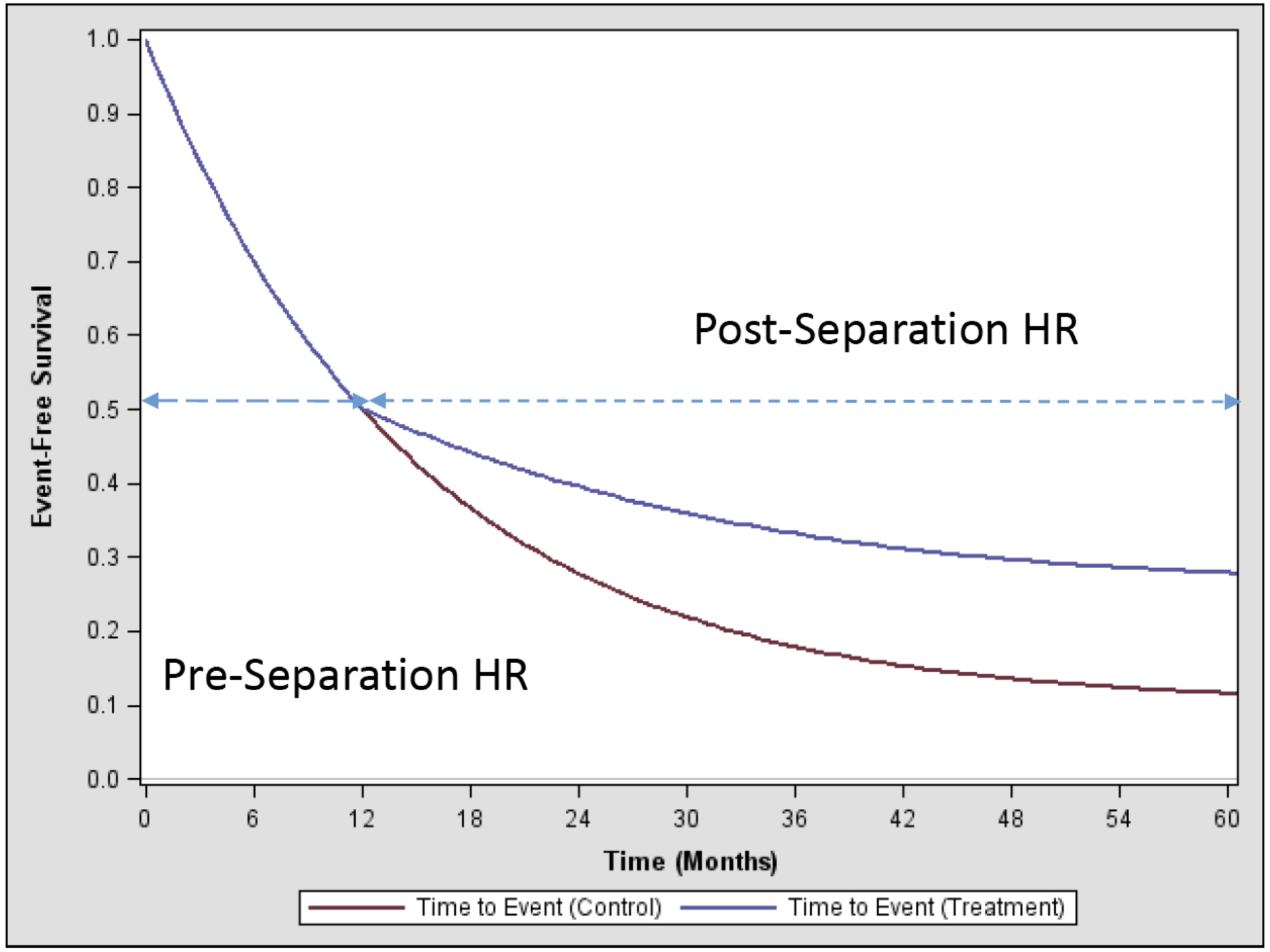


Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study

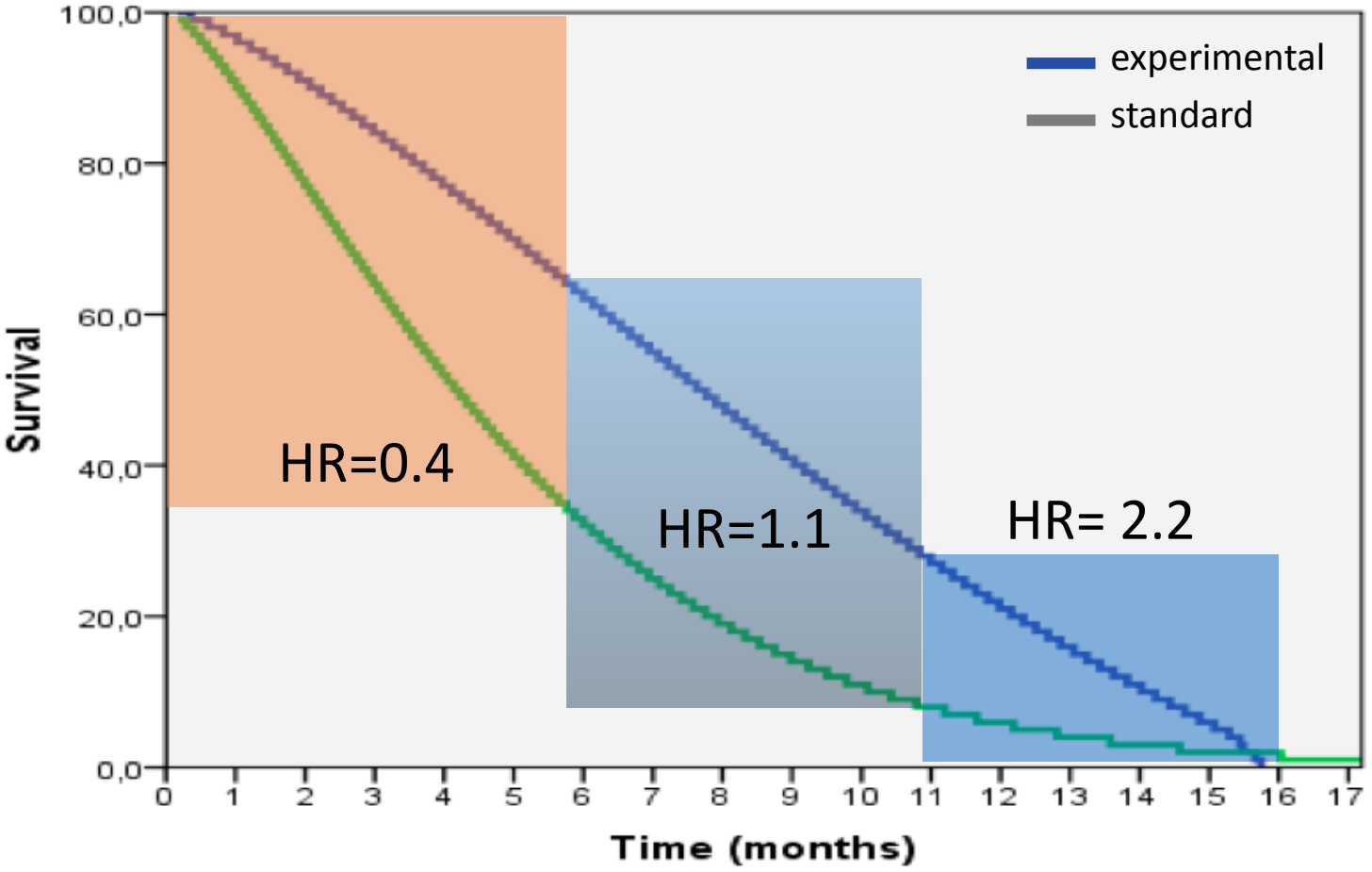
*Karim Fizazi, Howard I Scher, Arturo Molina, Christopher J Logothetis, Kim N Chi, Robert J Jones, John N Staffurth, Scott North, Nicholas J Vogelzang, Fred Saad, Paul Mainwaring, Stephen Harland, Oscar B Goodman Jr, Cora N Sternberg, Jin Hui Li, Thian Kheoh, Christopher M Haqq, Johann S de Bono, for the COU-AA-301 Investigators**

Lancet Oncol **2012; 13: 983–92**




Event-Free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Post-Separation HR
Pre-Separation HR
0
6
12
18
24
30
36
42
48
54
60
Time (Months)
Time to Event (Control)
Time to Event (Treatment)

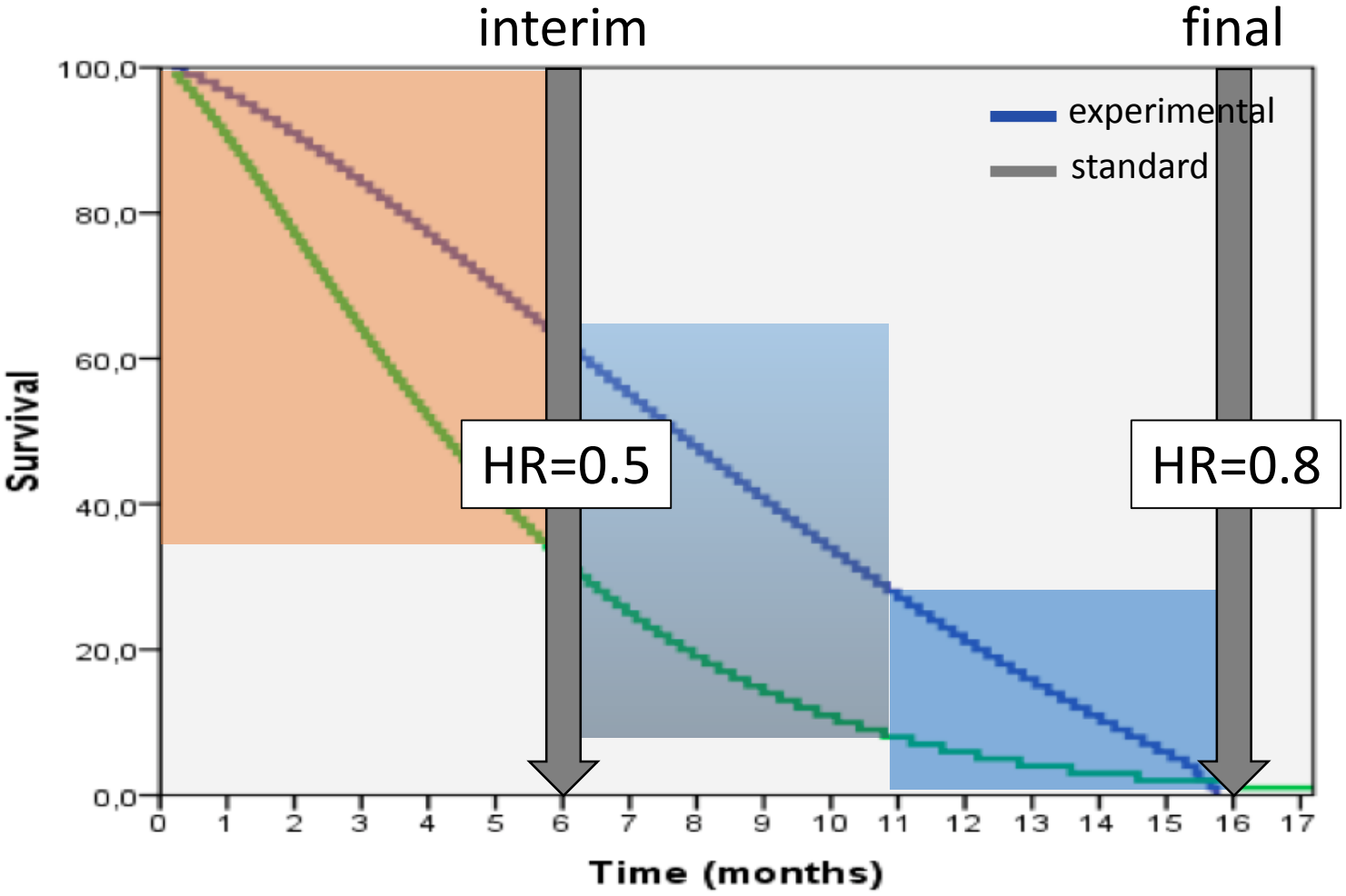
Rapporto tra gli *hazard* dei due gruppi non costante nel tempo – non (pochi) lungo-sopravviventi



Hazard Ratio "globale" =

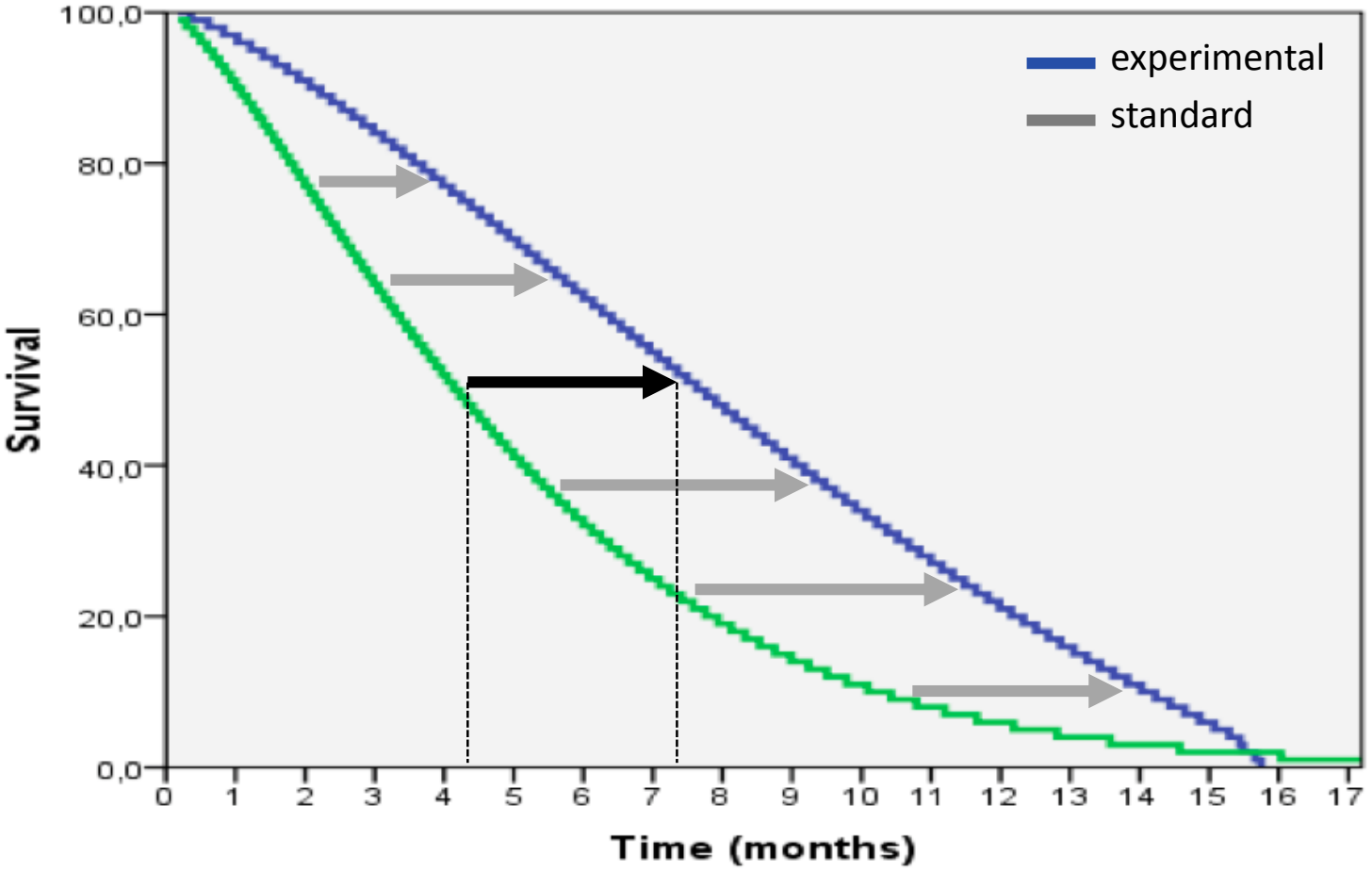
media *pesata* degli HR 'tempo-specifici' (*pesi* = eventi)

Rapporto tra gli *hazard* dei due gruppi non costante nel tempo – non (pochi) lungo-sopravviventi



Se analisi precoce, i pazienti sono troncati (*censored*) nel periodo di inversione del HR, che così va a pesare di meno: HR sovrastimato

Rapporto tra gli *hazard* dei due gruppi non costante nel tempo – non (pochi) lungo-sopravviventi

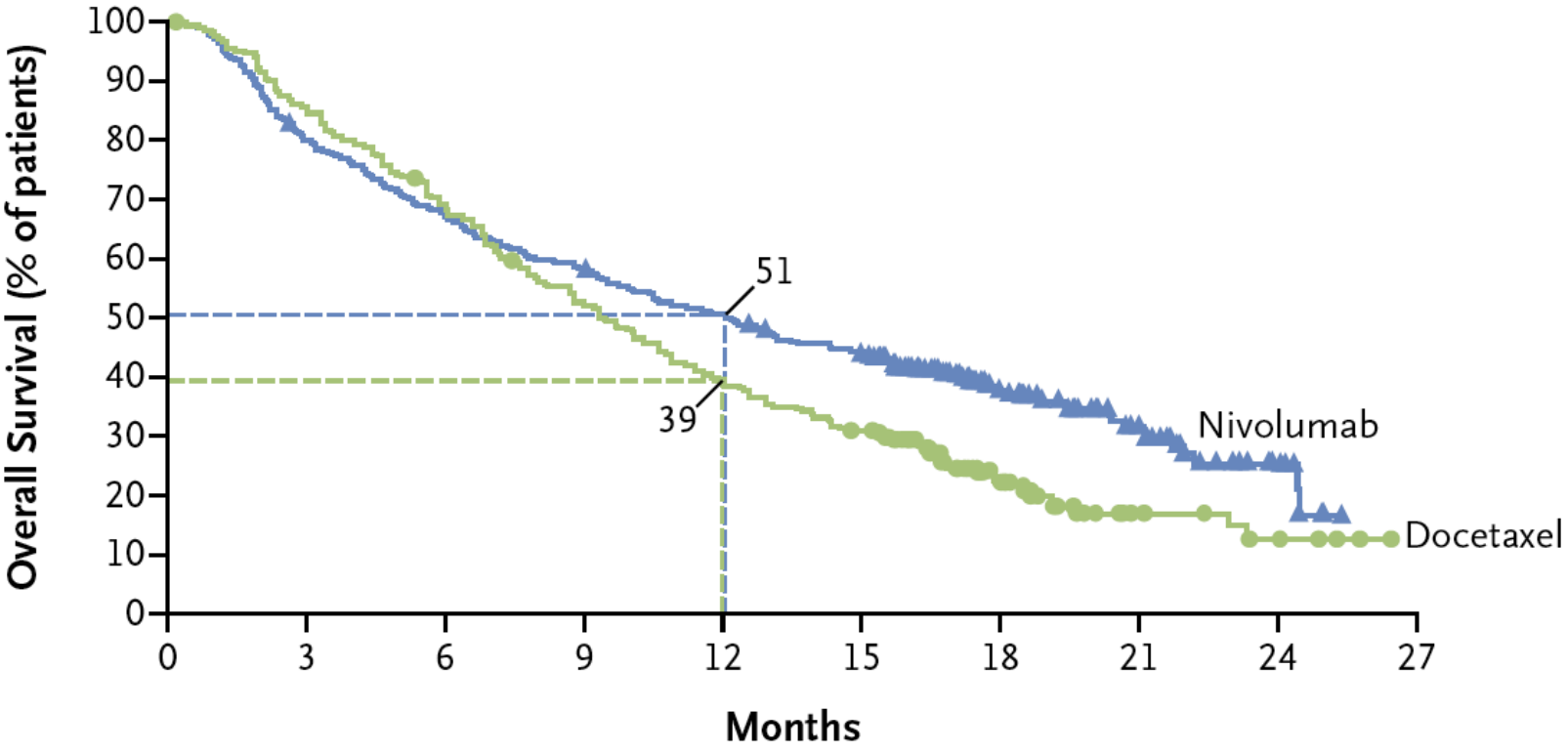


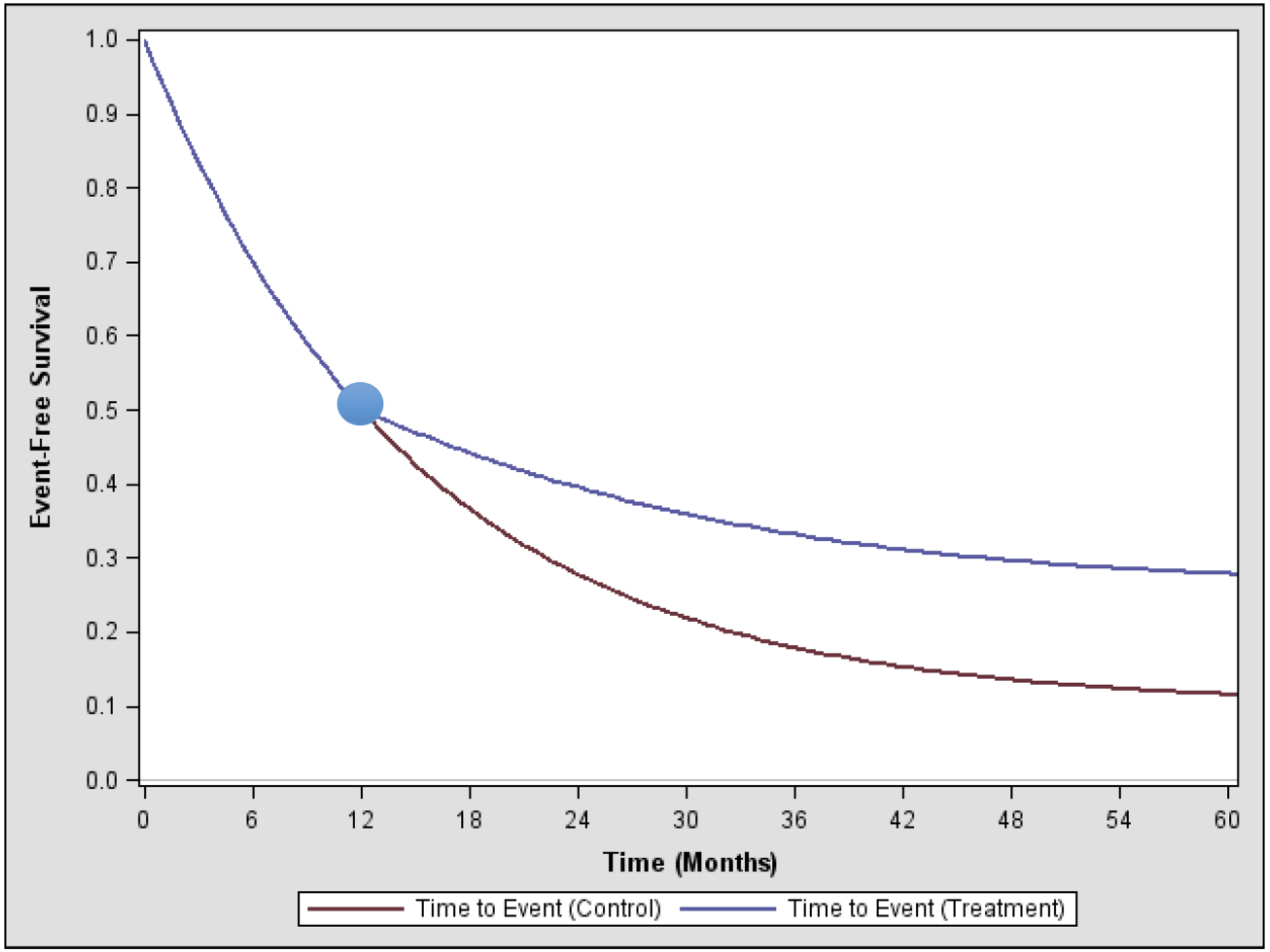
Differenza tra mediane: spesso interpretata come beneficio medio per ogni paziente (di solito questo è minore del 20-30%)

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, Jr., S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, and J.R. Brahmer

N Engl J Med 2015;373:1627-39




Event-Free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
6
12
18
24
30
36
42
48
54
60
Time (Months)
Time to Event (Control)
Time to Event (Treatment)

Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome

Patrick Royston* and Mahesh KB Parmar

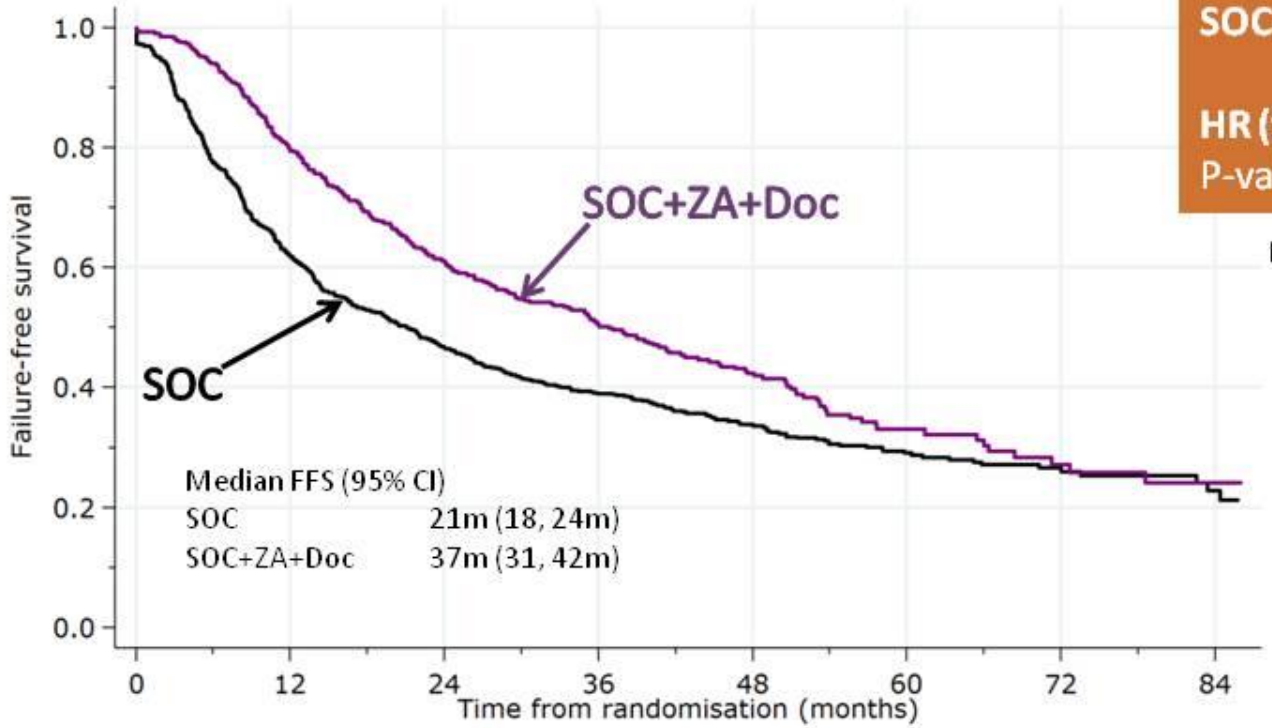
BMC Medical Research Methodology 2013, **13**:152

The restricted mean is a measure of average survival from time 0 to a specified time point, and may be estimated as the area under the survival curve up to that point.

Criterion	Measure		
	log HR	Median[a]	RMST[a]
1. Is easily interpreted	no	yes	yes
2. Does not assume proportional hazards	no	yes	yes
3. Reflects entire survival history	yes	no	yes
4. Is a measure of survival time	no	yes	yes
5. Can be used with all models	no	yes	yes
6. Can be calculated in any dataset	yes	no	yes
7. Does not require a time point to be specified	yes	yes	no
8. Does not change with extended follow-up	no	yes	yes
9. Is routinely associated with a clinically meaningful time point	no	no	yes

[a]The measure is the difference in the given statistic between trial arms.

Zoledronic acid + docetaxel: Failure-free survival



SOC	750 FFS events
SOC+ZA+Doc	371 FFS events
HR (95%CI)	0.62 (0.54, 0.71)
P-value	<0.0000000001*a

Non-PH p-value <0.0000000001*b

Restricted mean FFS time

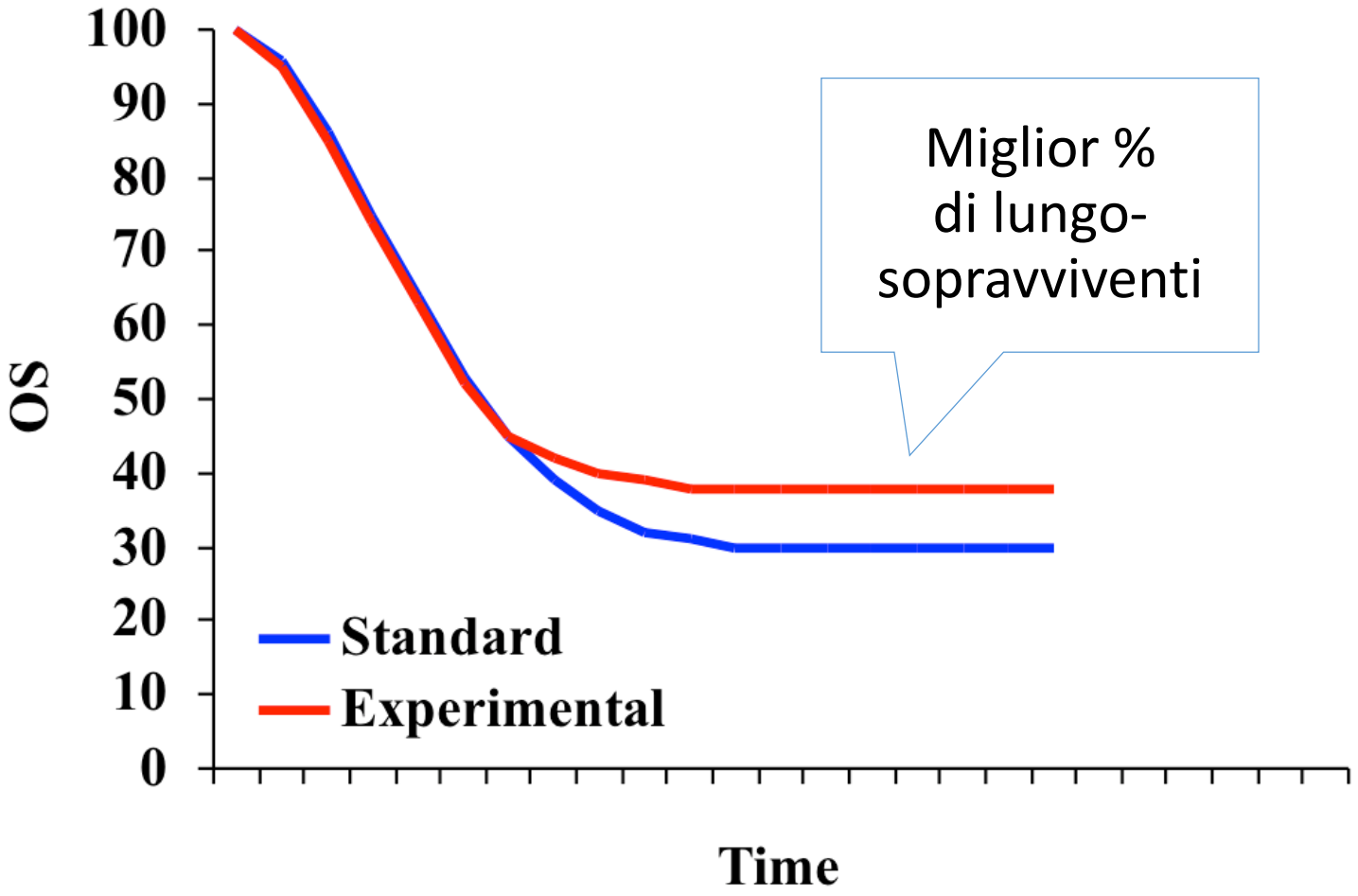
SOC	35.3m
SOC+ZA+Doc	43.5m
Diff (95%CI)	8.2m (5.5, 11.1m)

Group
At risk (events)

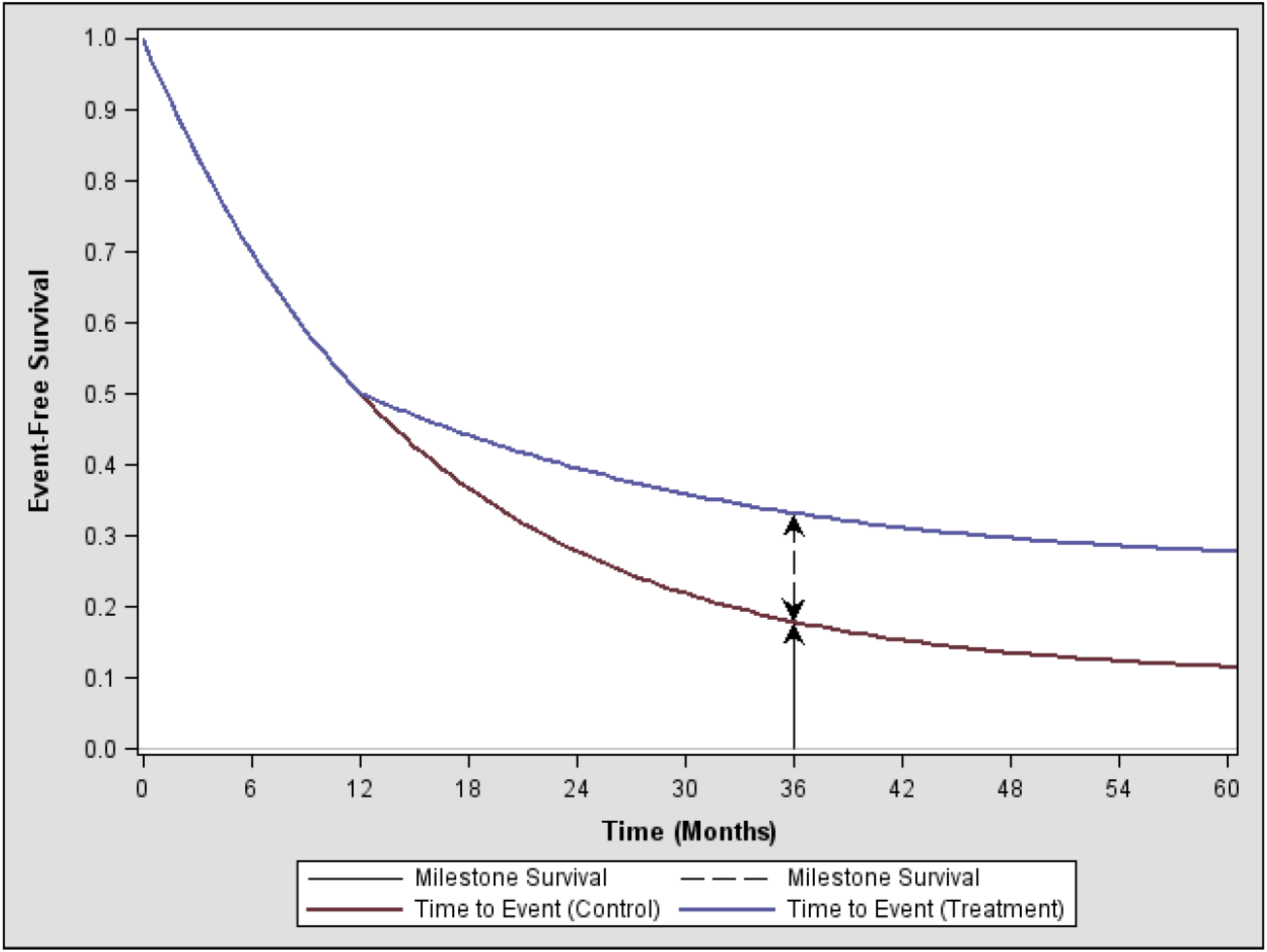
SOC	1184	(446)	713	(173)	488	(70)	287	(31)	161	(19)	84	(6)	45	(4)	17
SOC+ZA+Doc	593	(116)	448	(102)	303	(45)	180	(24)	103	(19)	42	(6)	20	(2)	13

*[a]exact HR p-value 0.0000000000005038
*[b]exact non-PH p-value 0.000000010376

Rapporto tra gli *hazard* dei due gruppi non costante nel tempo – presenza di lungo-sopravviventi



Hazard Ratio "globale" = 0.9 (NS)


Event-Free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
6
12
18
24
30
36
42
48
54
60
Time (Months)
Milestone Survival
Time to Event (Control)
Milestone Survival
Time to Event (Treatment)

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

Caroline Robert, M.D., Ph.D., Luc Thomas, M.D., Ph.D., Igor Bondarenko, M.D., Ph.D., Steven O'Day, M.D., Jeffrey Weber M.D., Ph.D., Claus Garbe, M.D., Celeste Lebbe, M.D., Ph.D., Jean-François Baurain, M.D., Ph.D., Alessandro Testori, M.D., Jean-Jacques Grob, M.D., Neville Davidson, M.D., Jon Richards, M.D., Ph.D., Michele Maio, M.D., Ph.D., Axel Hauschild, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Pere Gascon, M.D., Ph.D., Michal Lotem, M.D., Kaan Harmankaya, M.D., Ramy Ibrahim, M.D., Stephen Francis, M.Sc., Tai-Tsang Chen, Ph.D., Rachel Humphrey, M.D., Axel Hoos, M.D., Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

N ENGL J MED 364;26 JUNE 30, 2011