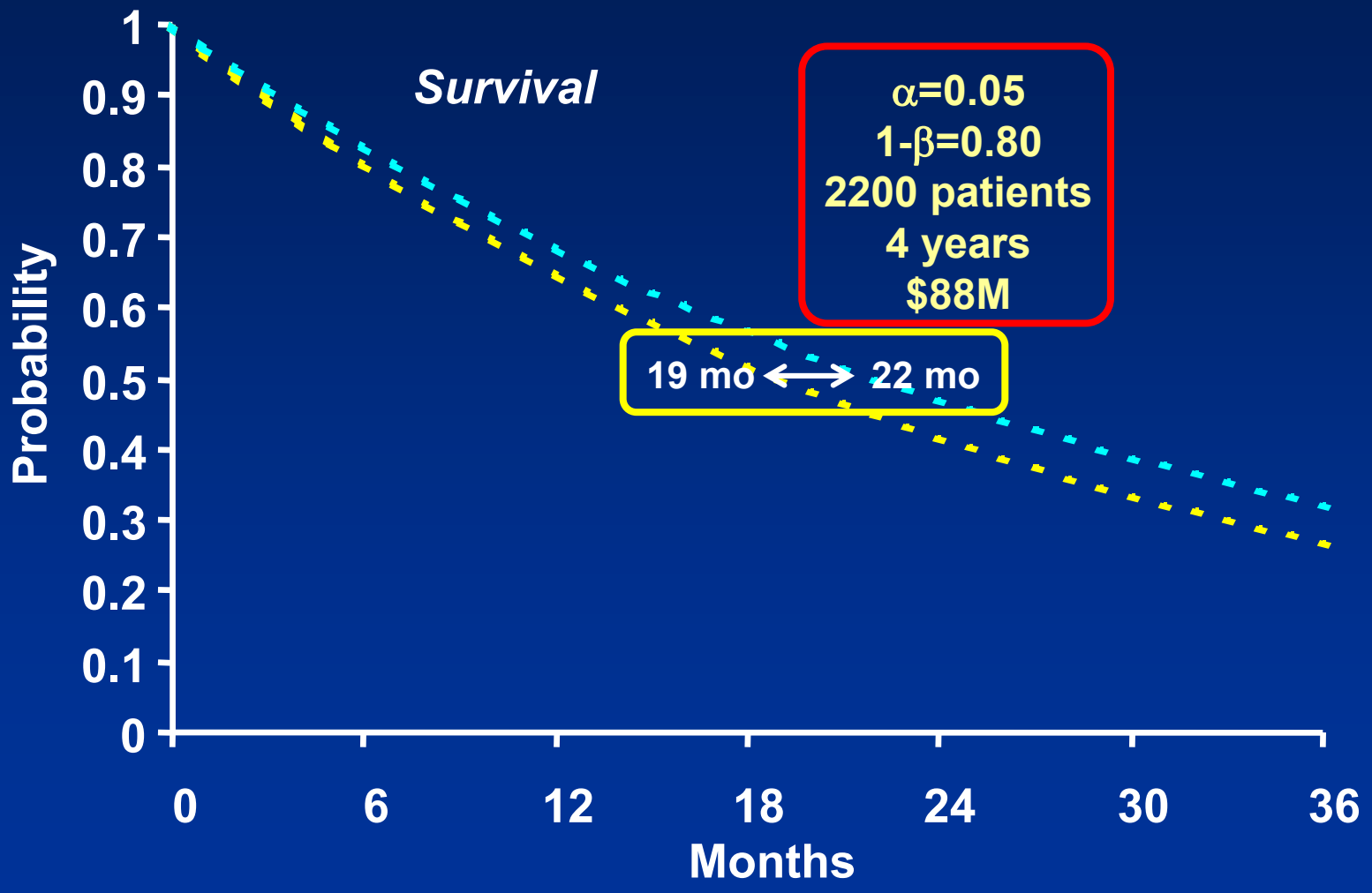
Regular Approval Basis – "Clinical Benefit"

- **Longer life**
- Better life
- Established Surrogate for one of above

Survival Superiority Study Offers Too Little, Too Late, For Too Much



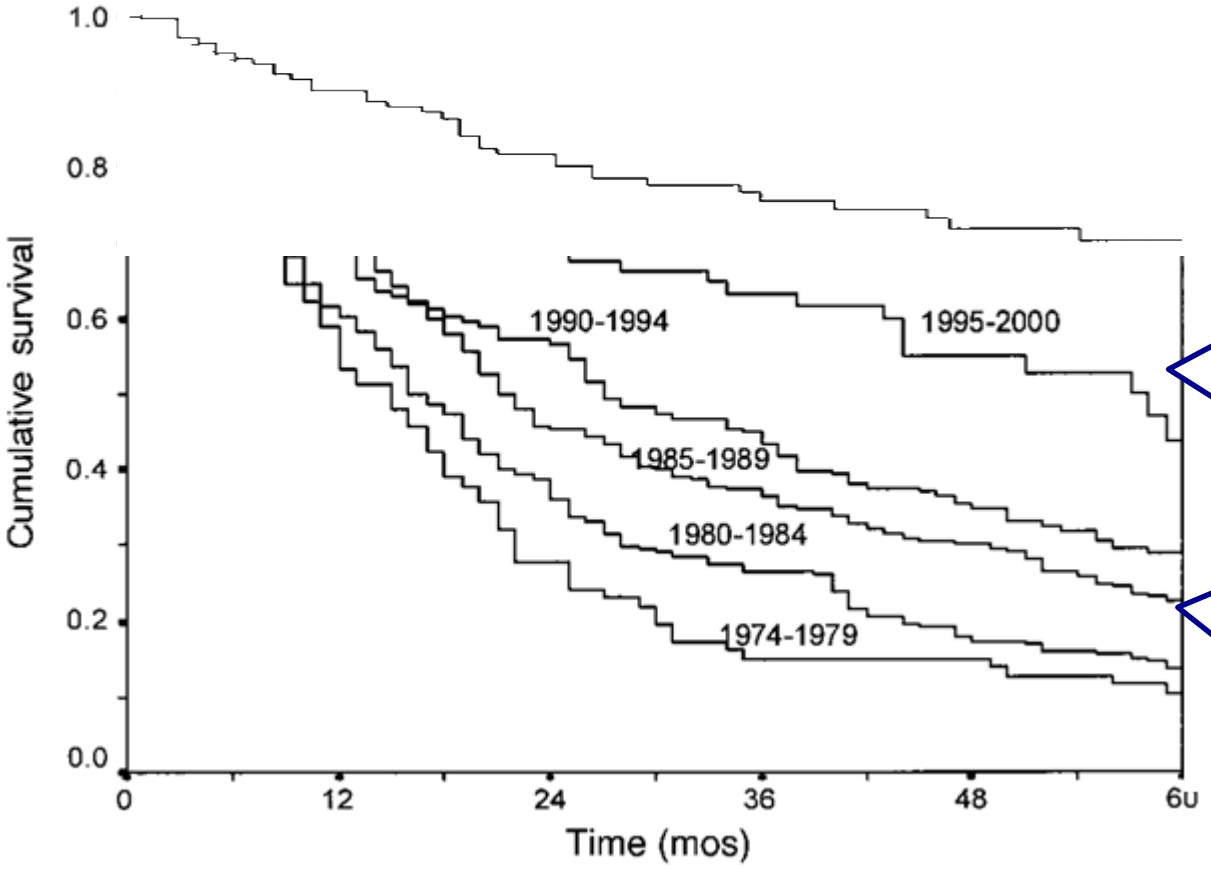
Assumes accrual = 100 patients/mo; follow-up = largest median + 2 mo (TTP) or 4 mo (survival)

L.L. Miller, 2003

Trends in Breast Cancer Survival/Giordano et al.
CANCER January 1, 2004 / Volume 100 / Number 1

Overall survival from time of recurrence

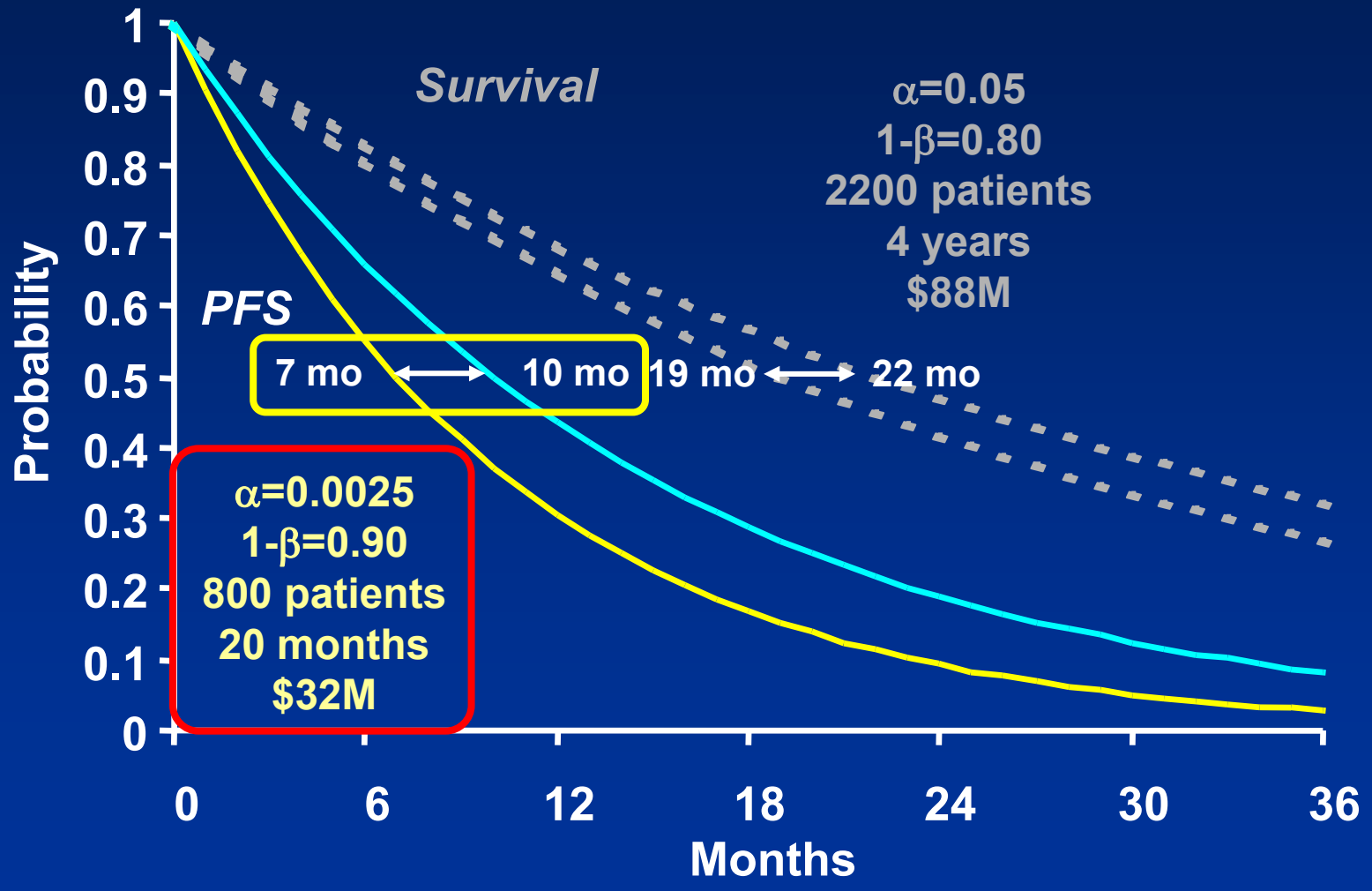
… e al giorno



Più difficile ottenere un beneficio relativo di Sopravvivenza

(abbastanza) facile ottenere un beneficio relativo di Sopravvivenza

Single Superiority Study Can Offer Highly Robust PFS Assessment (α=0.0025)



Assumes accrual = 100 patients/mo; follow-up = largest median + 2 mo (TTP) or 4 mo (survival)

L.L. Miller, 2003

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

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

The primary endpoint was the

with alirocumab compared h ezetimibe.

LDL-C…

- **Endpoint di attività?**
- **Endpoint di efficacia?**
- **Endpoint “intermedio” (surrogato?)**

The Treat-to-Target Trial

Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients

MATTHEW C. RIDDLE, MD[1] JOHN GERICH, MD[2]
JULIO ROSENSTOCK, MD[2]
ON BEHALF OF THE INSULIN GLARGINE 4002 STUDY INVESTIGATORS*

DIABETES CARE, VOLUME 26, NUMBER 11, NOVEMBER 2003

The primary outcome measure was the percentage of subjects achieving ≤7.0% without a single instance of [illegible]mp-tomatic nocturnal hypogl[illegible]on-

HbA_{1c}…

- **Endpoint di attività?**
- **Endpoint di efficacia?**
- **Endpoint "intermedio" (surrogato?)**

Regular Approval Basis – "Clinical Benefit"

- **Longer life**
- Better life
- **Established Surrogate** for one of above


Cremino Gandola
GANDOLA
5
Cremini
Cremino

Validation of Surrogate Endpoints

Property of a Valid Surrogate

Effect of the Intervention
on the Clinical Endpoint

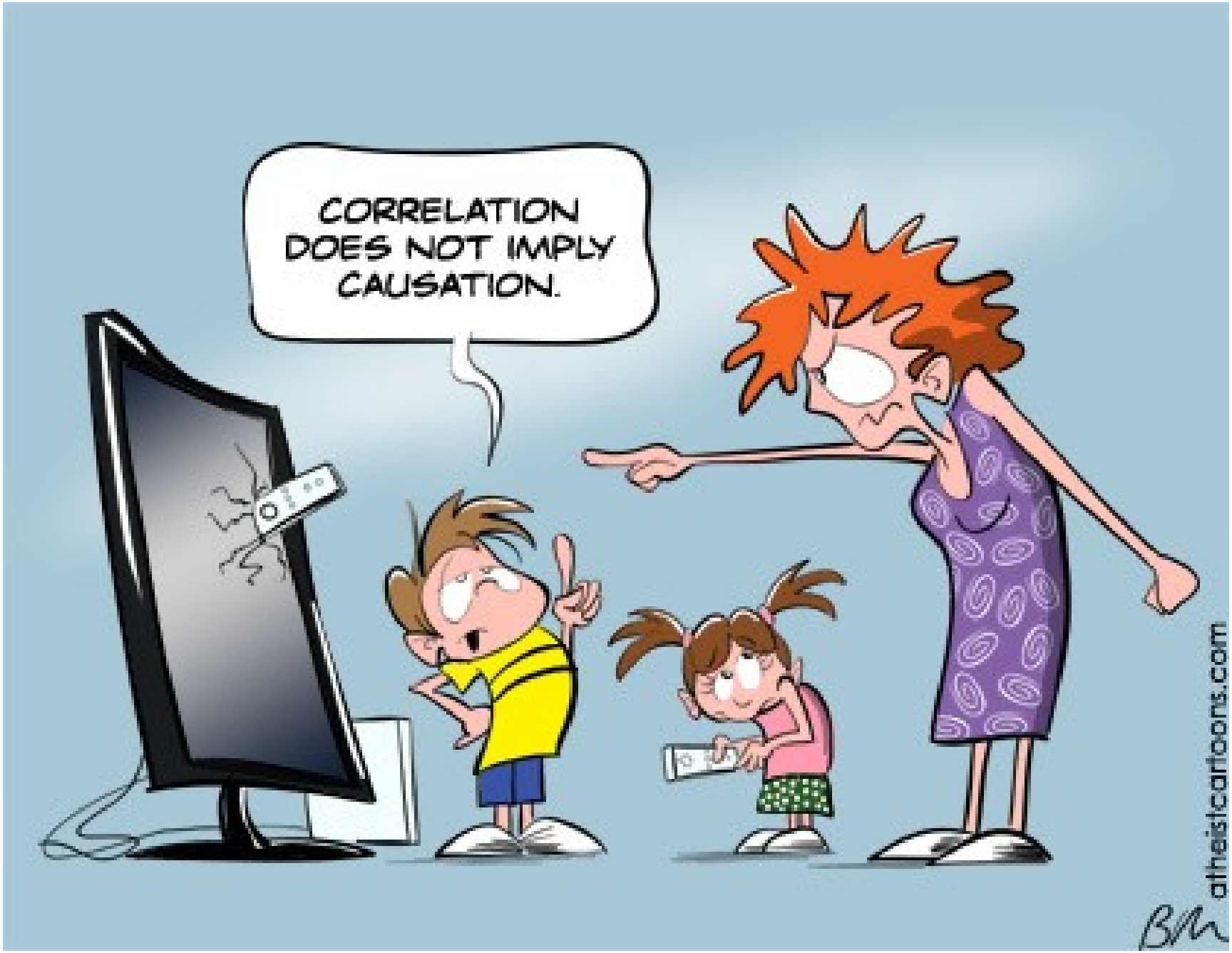
is reliably predicted by the

Effect of the Intervention
on the Surrogate Endpoint

D. Sargent, ASCO 2011

Prentice's Criteria

- To be a direct substitute for a clinical benefit endpoint on inferences of superiority and inferiority
  - The surrogate endpoint must be correlated with the clinical outcome
  - The surrogate endpoint must fully capture the net effect of treatment on the clinical outcome

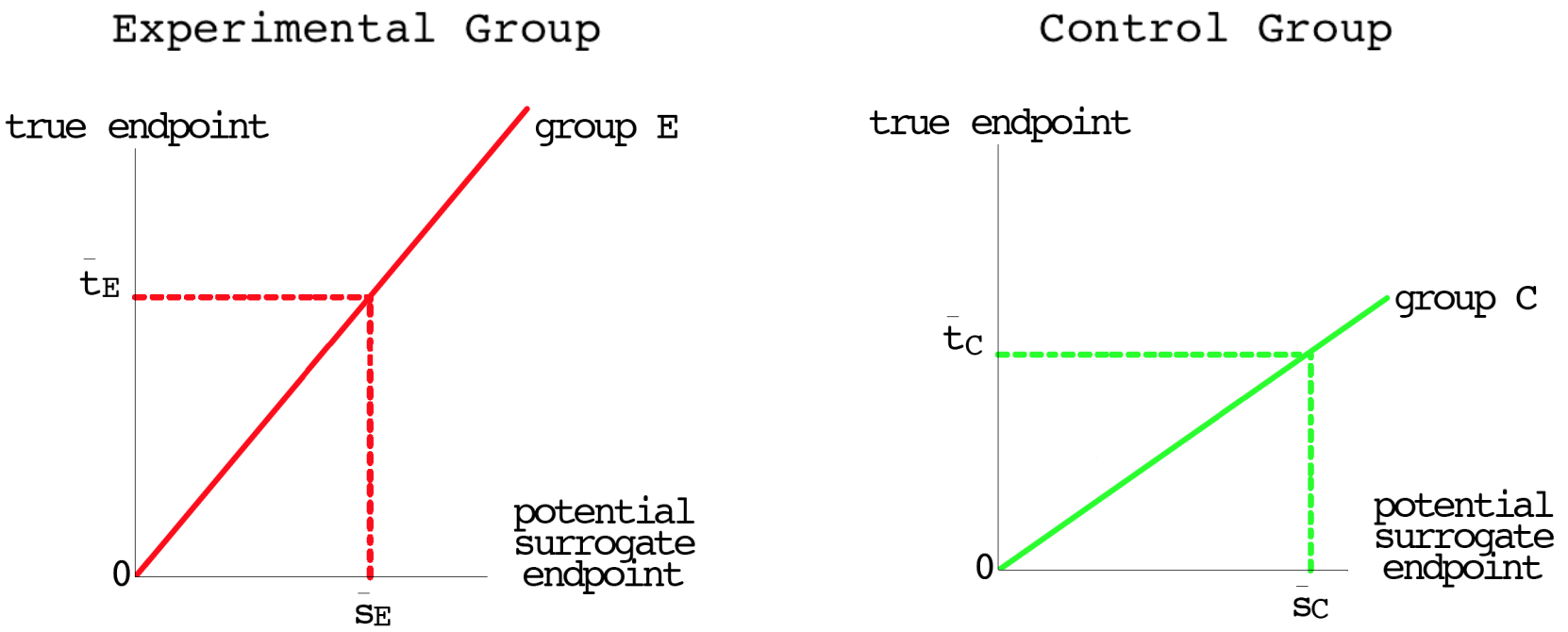

CORRELATION DOES NOT IMPLY CAUSATION.
atheistcartoons.com

A perfect correlate does not a surrogate make

Stuart G Baker*[1] and Barnett S Kramer[2]

BMC Medical Research Methodology 2003, **3**:16

Background: There is common belief among some medical researchers that if a potential surrogate endpoint is highly correlated with a true endpoint, then a positive (or negative) difference in potential surrogate endpoints between randomization groups would imply a positive (or negative) difference in unobserved true endpoints between randomization groups.



A perfect correlate does not a surrogate make

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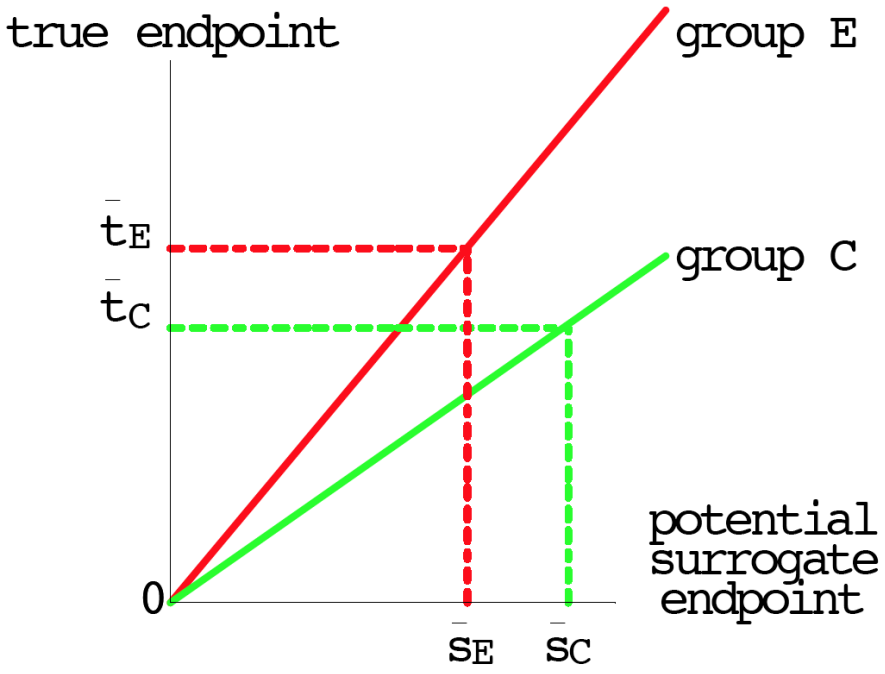
BMC Medical Research Methodology 2003, **3**:16

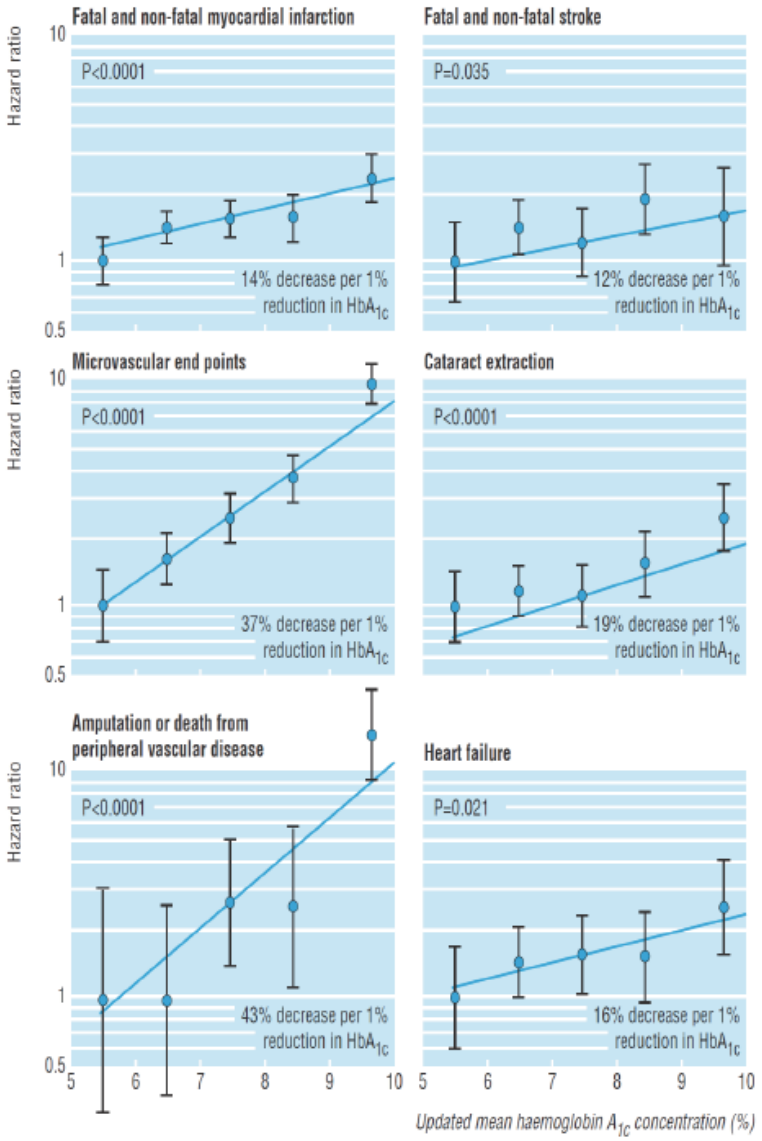


The mean surrogate outcome in the E group $\bar{s}_E$ is smaller than the mean surrogate outcome in the C group $\bar{s}_C$. However the mean true outcome in the E group $\bar{t}_E$ is larger than the mean true outcome in the C group $\bar{t}_C$, yielding the opposite conclusion for the effect of experimental intervention.

Conclusion: Perfect correlation between potential surrogate and unobserved true outcomes within randomized groups does not guarantee correct inference based on a potential surrogate endpoint.

HbA1c as Surrogate Endpoint in DM

- Measures average glucose level over 3 months
- Validated as a diagnostic marker and therapeutic target as recommended by
  - The American Diabetes Association (ADA)
  - World Health Organizations (WHO)
  - The American College of Endocrinologists (ACE)
  - Food and Drug Administration (FDA)
- Strongly associated with clinical outcomes
  - Microvascular complications
  - Macrovascular complications



Surrogate endpoints and emerging surrogate endpoints for risk reduction of cardiovascular disease

Crystal M Rasnake, Paula R Trumbo, and Therese M Heinonen

Nutrition Reviews® Vol. 66(2):76–81

Blood LDL cholesterol, as a surrogate marker for CVD risk, is supported by clinical trials of cholesterol-lowering drugs (e.g., bile acid sequestrants) that resulted in the lowering of blood LDL cholesterol concentration, as well as reduction in the rate of CHD. Furthermore, observational studies have positively correlated LDL cholesterol concentration with CHD rates.

EUROPEAN UROLOGY 68 (2015) 775–776

Postprostatectomy Radiotherapy for Patients with High-risk Features on Definitive Pathology: A Plea for Evidence-based Medicine

Alberto Bossi[a,*], *Thomas Wiegel*[b], *Mack Roach*[c]

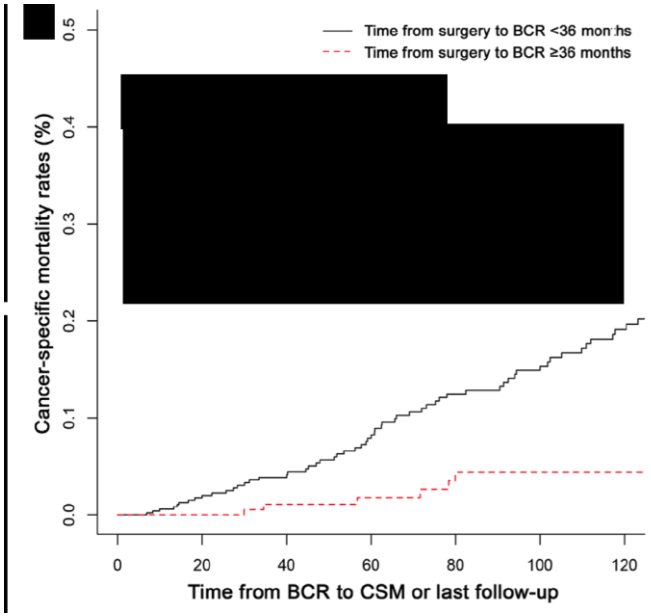
It is noteworthy that multivariate analysis clearly demonstrated a [redacted] between (early) biochemical recurrence and the risk of dying fromPCa

Urologic Oncology: Seminars and Original Investigations 33 (2015) 163.e7–163.e13

Natural history of surgically treated high-risk prostate cancer

Alberto Briganti, M.D.[a,*,1], Robert Jeffrey Karnes, M.D.[b,1], Giorgio Gandaglia, M.D.[a], Martin Spahn, M.D.[c], Paolo Gontero, M.D.[d], Lorenzo Tosco, M.D.[e], Burkhard Kneitz, M.D.[f], Felix K.H. Chun, M.D.[g], Emanuele Zaffuto, M.D.[a], Maxine Sun, M.D.[h], Markus Graefen, M.D.[i], Giansilvio Marchioro, M.D.[j], Detlef Frohneberg, M.D.[k], Simone Giona, M.D.[d], Pierre I. Karakiewicz, M.D.[h], Hein Van Poppel, M.D.[e], Francesco Montorsi, M.D.[a], Steven Joniau, M.D.[e], on behalf of the European Multicenter Prostate Cancer Clinical and Translational Research Group (EMPaCT)

Individuals who experienced BCR within 3 years from surgery had significantly higher CSM rates compared with those who developed late BCR. At competing-risks regression analyses, [redacted] after accounting for the risk of OCM.



Prostate-Specific Antigen (PSA) as a Surrogate End Point for Survival in Prostate Cancer Clinical Trials

Laurence Collette

EUROPEAN UROLOGY 53 (2008) 6–9

Prognostic versus surrogate

A [redacted] is a set of physical signs or laboratory measurements that occur in association with a pathologic process and are significantly [redacted] and survival of a patient. For example, biochemical relapse after radical prostatectomy is prognostic for clinical relapse.

A [redacted] a "(set of) biochemical measurements or clinical signs used as [redacted] in the assessment of a therapeutic benefit."

Prentice's Criteria

- To be a direct substitute for a clinical benefit endpoint on inferences of superiority and inferiority
  - The surrogate endpoint must be correlated with the clinical outcome
  - The surrogate endpoint must fully capture the net effect of treatment on the clinical outcome

EUROPEAN JOURNAL OF CANCER 42 (2006) 1344–1350

Prostate-specific antigen (PSA) alone is not an appropriate surrogate marker of long-term therapeutic benefit in prostate cancer trials

Laurence Collette[a,*], *Tomasz Burzykowski*[b], *Fritz H. Schröder*[c]

We review the published literature pertaining to the validation of PSA endpoints as surrogate in all disease stages.

We discuss the limitations of these studies and conclude that so far, [redacted] in any of the disease settings and treatment conditions considered.

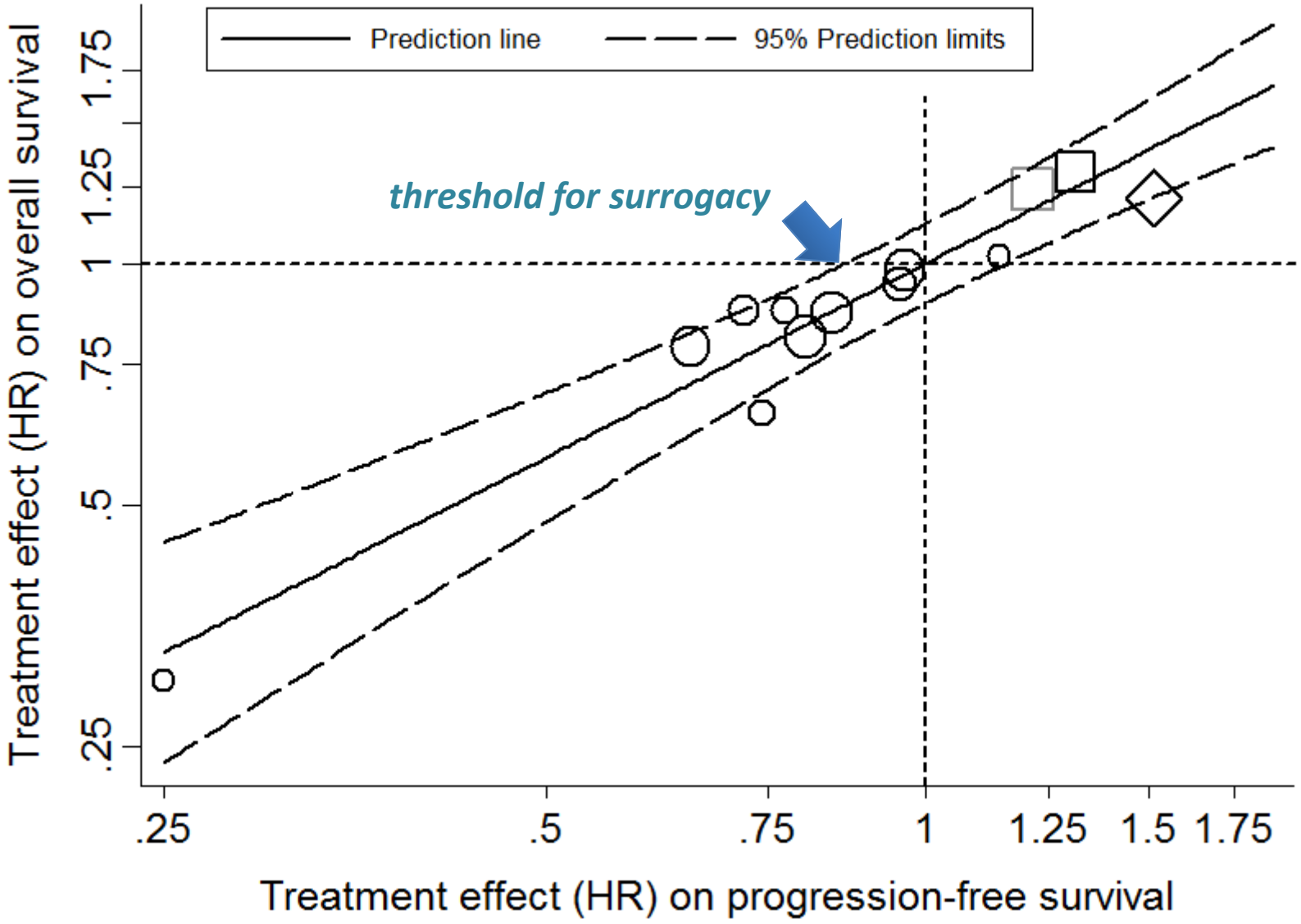
Quando si hanno dati di molti RCT…

… si deriva un modello di regressione:

- **che possa predire la magnitudine**
- **dell'effetto del trattamento sull'endpoint "vero"**
- **in base all'effetto del trattamento sull'end-point (candidato) surrogato**

Il surrogato è tale se la predizione è sufficientemente precisa

TRIAL LEVEL CORRELATION BETWEEN EFFECTS

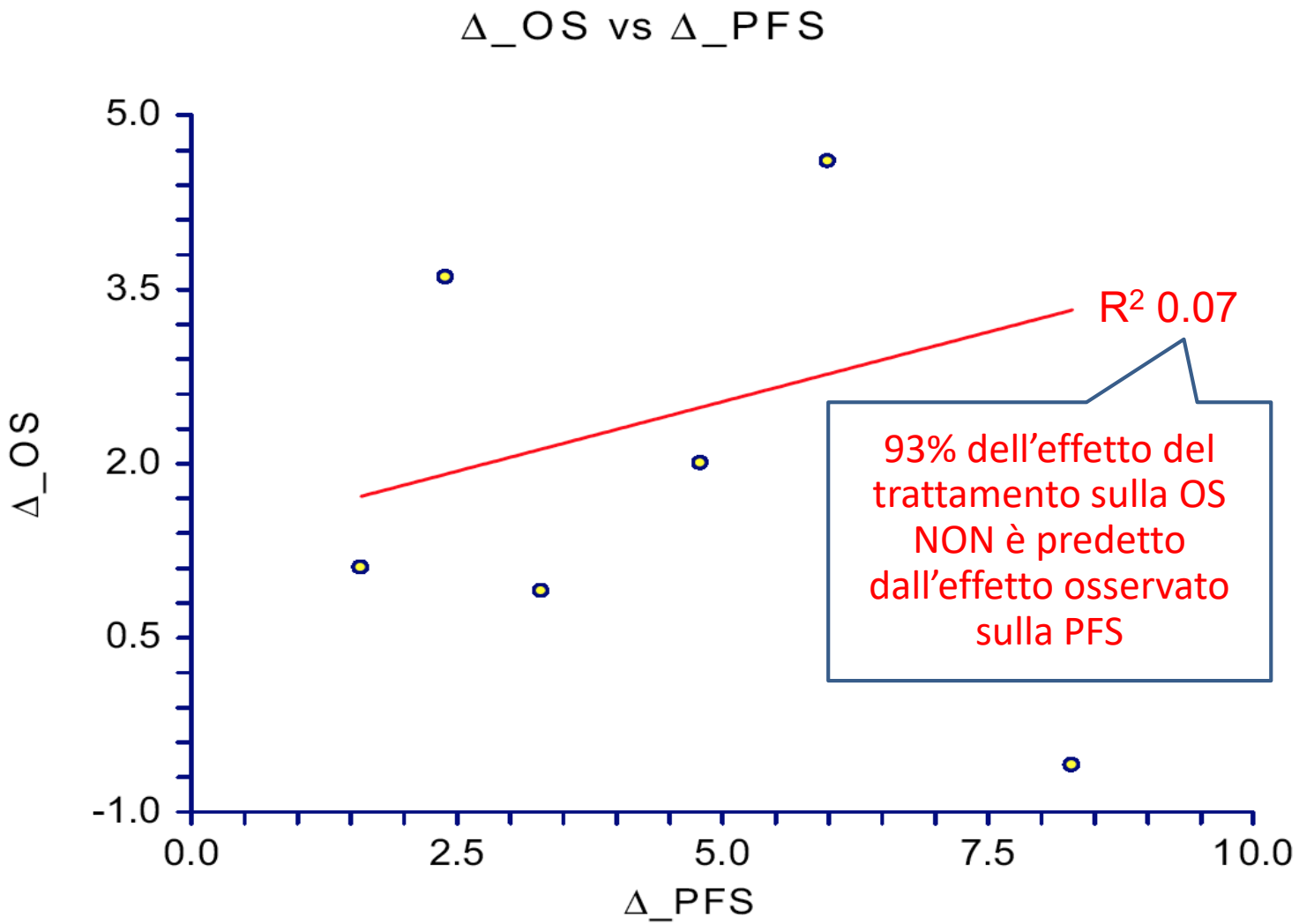


Burzykowski and Buyse, Pharmaceutical Statist 2006;5:173

Surrogate End Points in Renal Cell Carcinoma: An Analysis of First-Line Trials With Targeted Therapies

Fausto Petrelli, Sandro Barni

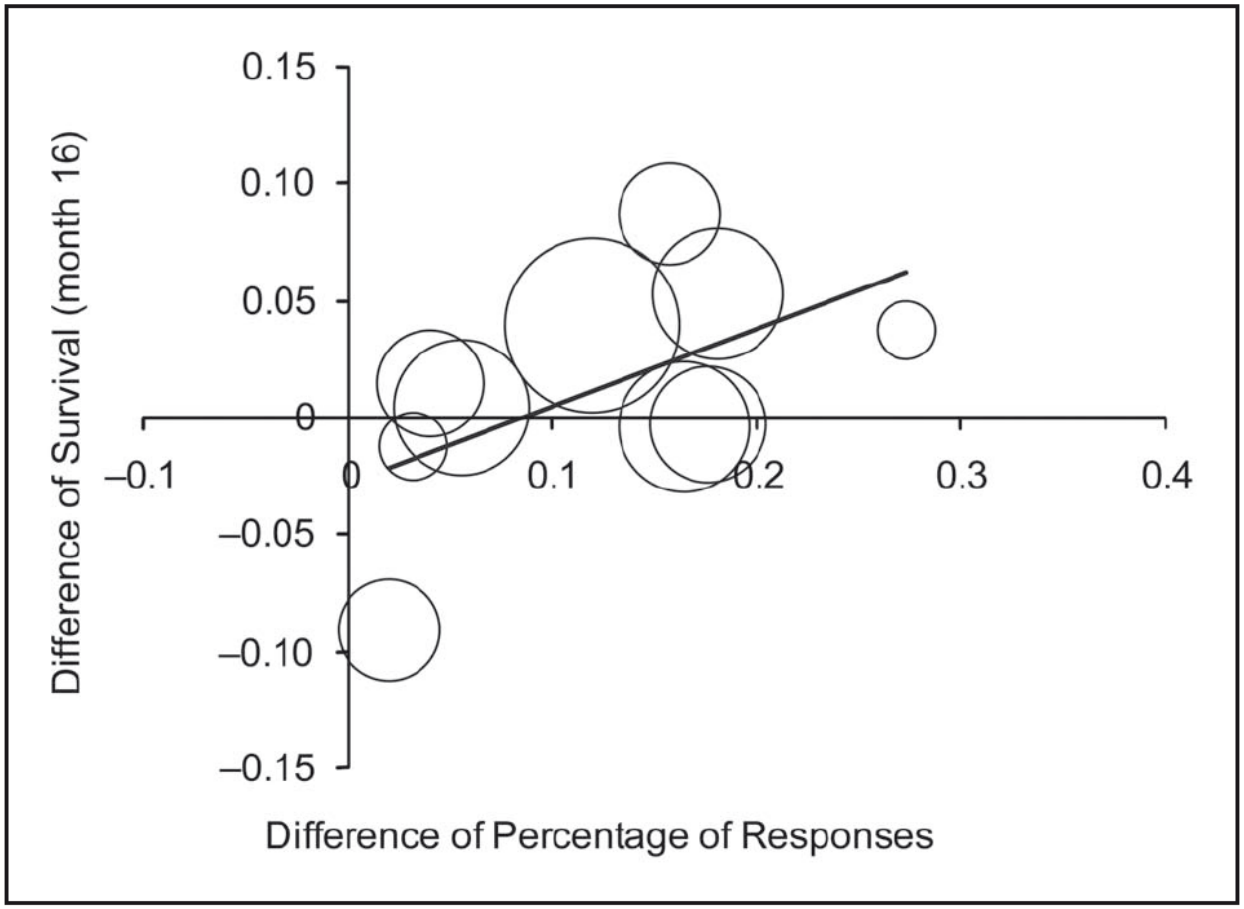
Clinical Genitourinary Cancer, Vol. 11, No. 4, 385-9 © 2013 Elsevier Inc.



Objective Response to Chemotherapy As a Potential Surrogate End Point of Survival in Metastatic Breast Cancer Patients

Paolo Bruzzi, Lucia Del Mastro, Maria P. Sormani, Lars Bastholt, Marco Danova, Christian Focan, George Fountzilas, James Paul, Riccardo Rosso, and Marco Venturini

J Clin Oncol 23:5117-5125. © 2005 by American Society of Clinical Oncology

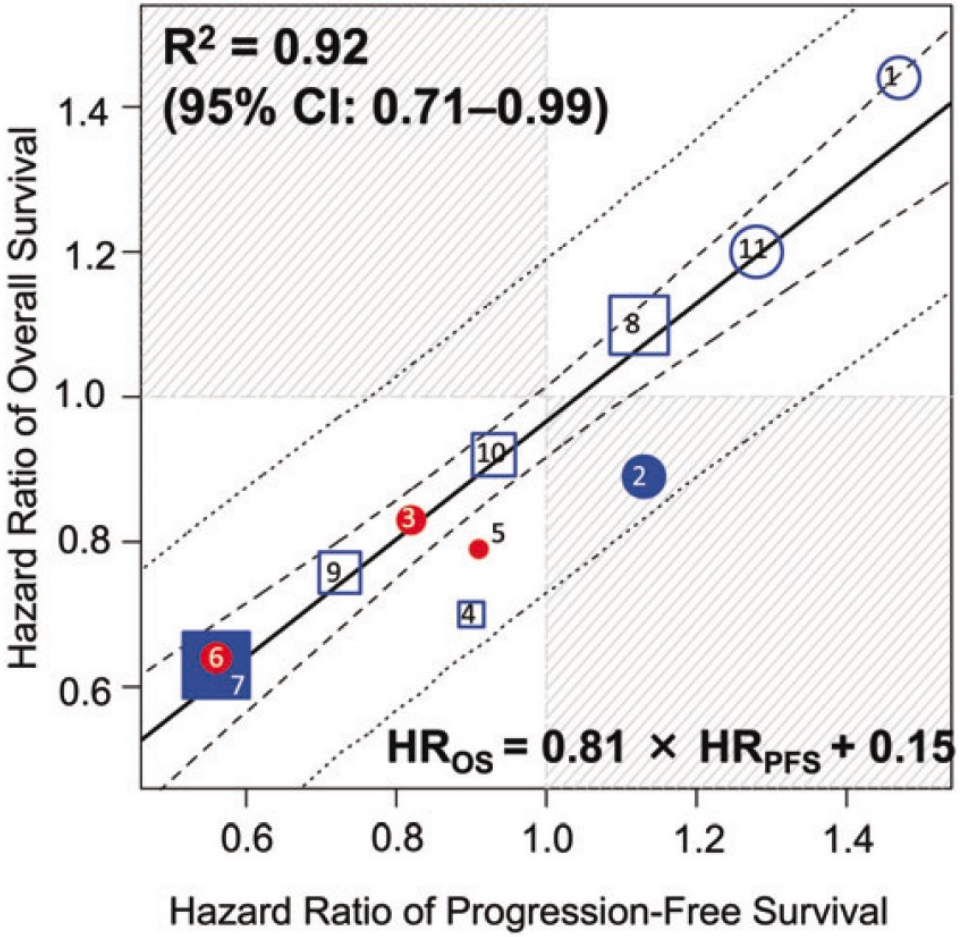


($R^2 = 0.20$; 95% CI, 0 to 0.65)

Progression-free survival as a surrogate endpoint for overall survival in glioblastoma: a literature-based meta-analysis from 91 trials

Kelong Han, Melanie Ren, Wolfgang Wick, Lauren Abrey, Asha Das, Jin Jin, and David A. Reardon

Neuro-Oncology 16(5), 696–706, 2014



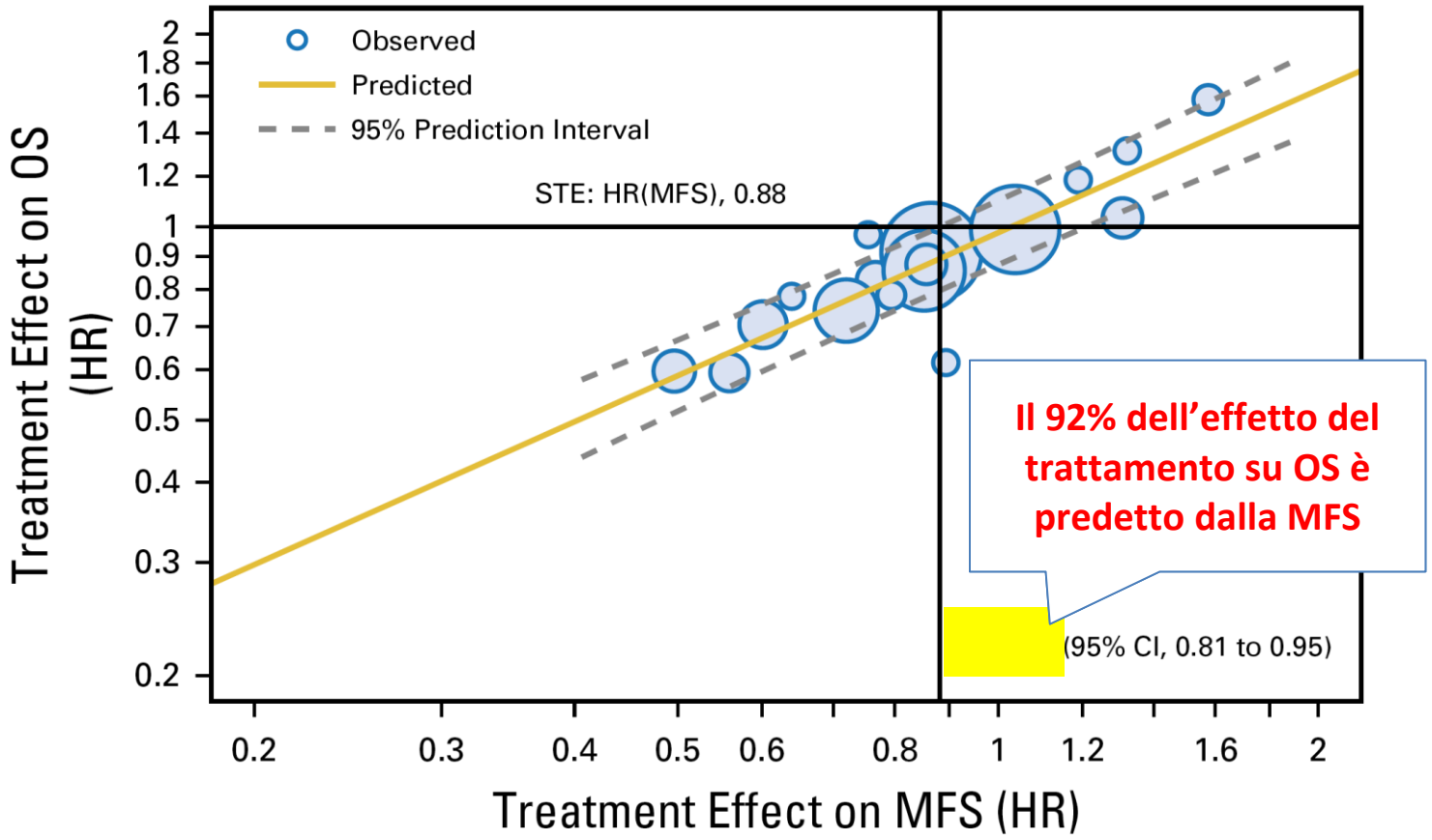
Round symbols:	Glioblastoma
Square symbols:	Mixed high-grade glioma
Solid symbols:	Newly diagnosed
Hollow symbols:	Recurrent
———	Weighted linear fit
- - - - -	95% confidence interval
----------	95% prediction interval
Blue symbols:	Head-to-head comparison
Red symbols:	Single-arm trials using historical data as control

Linear regression determined that a 10% PFS risk reduction would yield an 8.1% ± 0.8% OS risk reduction.

Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer

Wanling Xie, Meredith M. Regan, Marc Buyse, Susan Halabi, Philip W. Kantoff, Oliver Sartor, Howard Soule, Noel W. Clarke, Laurence Collette, James J. Dignam, Karim Fizazi, Wendy R. Paruleker, Howard M. Sandler, Matthew R. Sydes, Bertrand Tombal, Scott G. Williams, and Christopher J. Sweeney, on behalf of the ICECaP Working Group

J Clin Oncol 35:3097-3104. © 2017 by American Society of Clinical Oncology

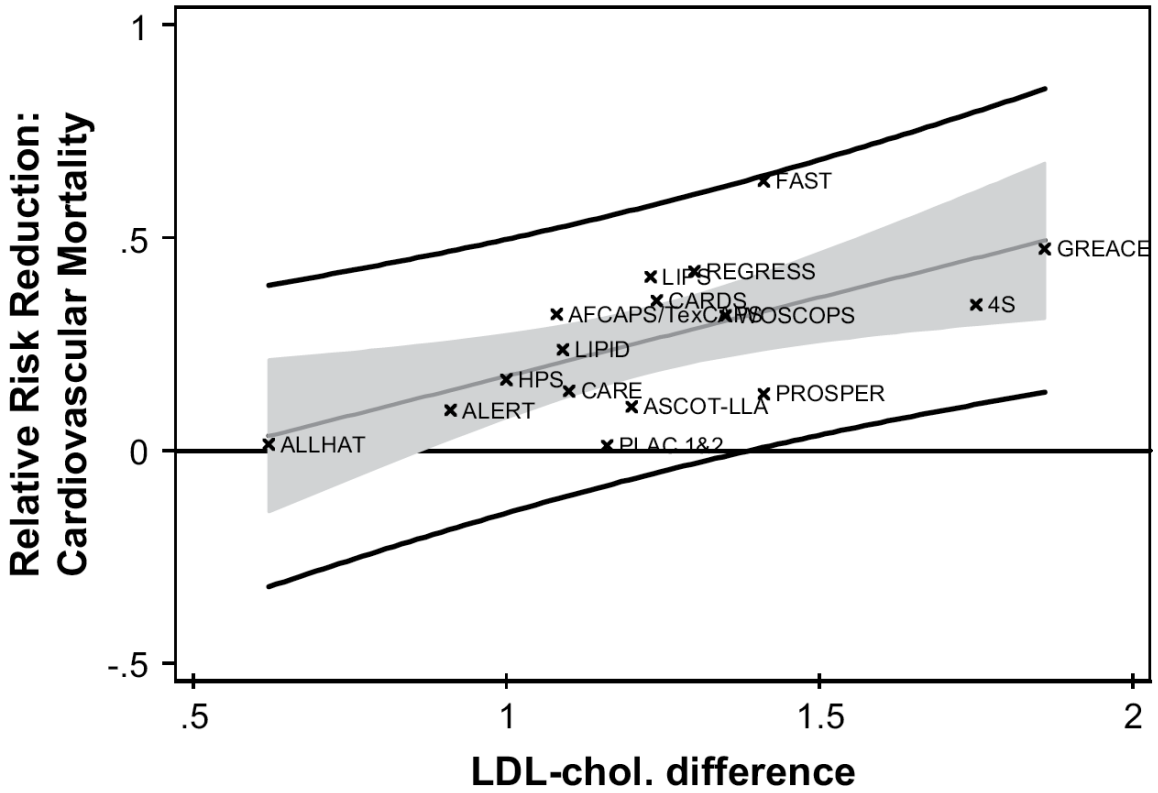


LDL-cholesterol differences predicted survival benefit in statin trials by the surrogate threshold effect (STE)

Kent R. Johnson[a,*], Nick Freemantle[b], Danielle M. Anthony[a], Marissa N.D. Lassere[c]

[a]*Department of Clinical Pharmacology, University of Newcastle, Mater Hospital, Waratah NSW 2298, Australia*
[b]*Department of Primary Care and General Practice, University of Birmingham, Birmingham B15 2TT, UK*
[c]*Department of Rheumatology, University of New South Wales, St. George Hospital, Kogarah NSW 2217, Australia*

Journal of Clinical Epidemiology 62 (2009) 328−336



In 16 qualifying trials, regression analysis yielded a cardiovascular mortality model whose prediction bands demonstrated no cardiovascular survival benefit with LDL-cholesterol difference values below 1.4 mmol/L.

Reducing LDL with PCSK9 Inhibitors — The Clinical Benefit of Lipid Drugs

Brendan M. Everett, M.D., M.P.H., Robert J. Smith, M.D., and William R. Hiatt, M.D.

N ENGL J MED 373;17 NEJM.ORG OCTOBER 22, 2015

Aside from IMPROVE-IT, several trials with other non-statin medications that lower LDL cholesterol do not fully support the hypothesis that LDL cholesterol reduction will reduce cardiovascular risk regardless of a drug's mechanism of action.

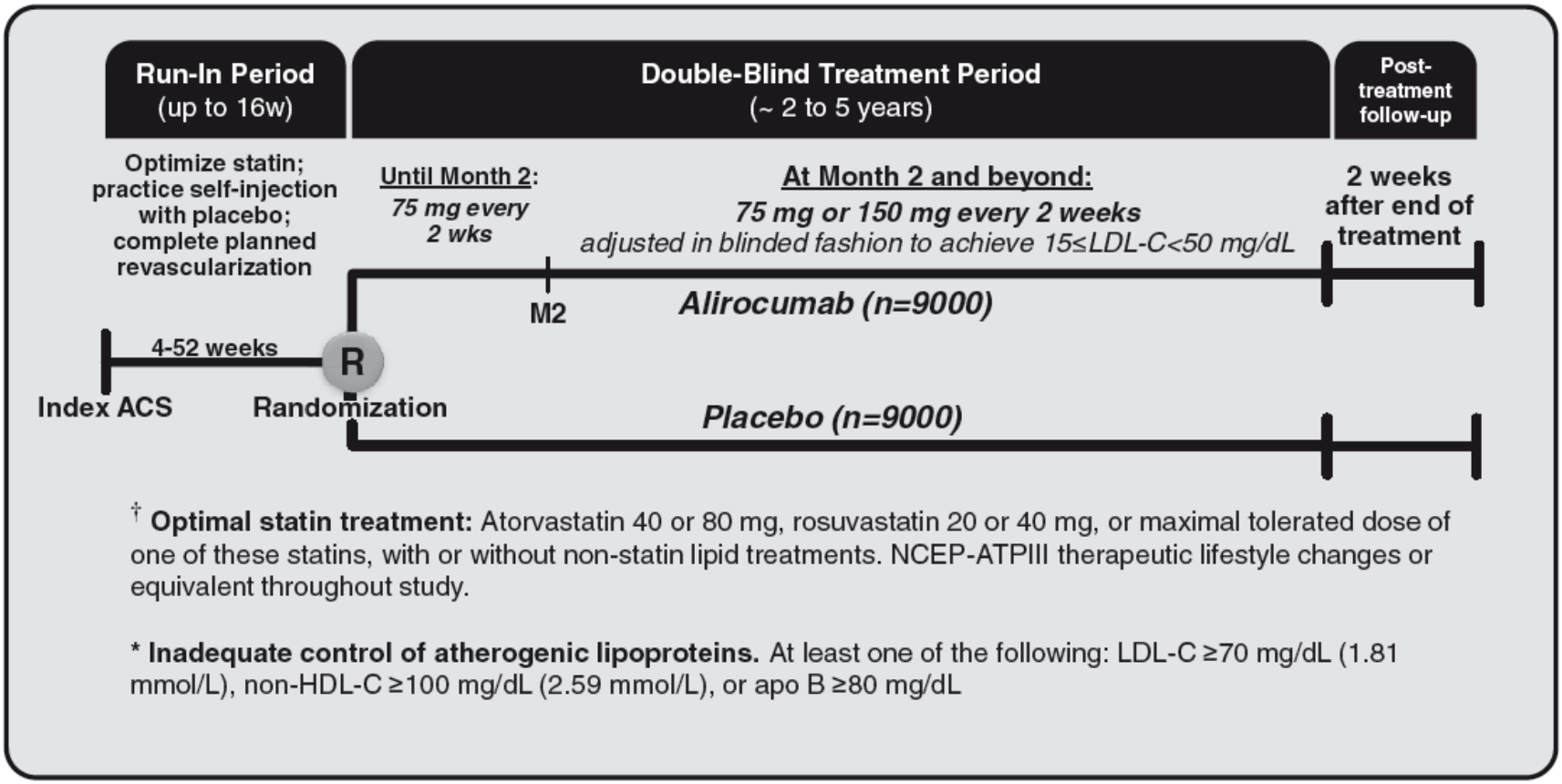
Selected Clinical Trials of Medications for Lowering LDL Cholesterol Levels Other Than Statins Alone and Their Effects on Cardiovascular Events.*

Trial	Study Drug	Comparison	Primary End Point	% Difference in LDL Cholesterol	Cardiovascular Outcome	
					Hazard Ratio (95% CI)	P Value
HERS	Estrogen (alone or in combination with medroxyprogesterone)	Placebo	Nonfatal myocardial infarction or death due to coronary heart disease	–11	0.99 (0.80–1.22)	0.91
FIELD	Fenofibrate	Placebo	Nonfatal myocardial infarction or death due to coronary heart disease	–12	0.89 (0.75–1.05)	0.16
ILLUMINATE	Torcetrapib–atorvastatin	Placebo plus atorvastatin	Nonfatal myocardial infarction, stroke, hospitalization for unstable angina, or death due to coronary heart disease	–27	1.25 (1.09–1.44)	0.001
HPS-2 THRIVE	Niacin–laropiprant	Placebo	Nonfatal myocardial infarction, death from coronary causes, stroke, or arterial revascularization	–16	0.96 (0.90–1.03)	0.29
IMPROVE-IT	Ezetimibe–simvastatin	Placebo plus simvastatin	Death due to cardiovascular causes, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke	–24	0.94 (0.89–0.99)	0.02

Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: Rationale and design of the ODYSSEY Outcomes trial

Gregory G. Schwartz, MD, PhD,[a,q] Laurence Bessac, MD,[b,c] Lisa G. Berdan, PA, MHS,[d] Deepak L. Bhatt, MD, MPH,[e] Vera Bittner, MD,[f] Rafael Diaz, MD,[g] Shaun G. Goodman, MD, MSc,[h] Corinne Hanotin, MD,[b,c] Robert A. Harrington, MD,[i] J. Wouter Jukema, MD, PhD,[j] Kenneth W. Mahaffey, MD,[i] Angèle Moryusef, MD,[b,c] Robert Pordy, MD,[k] Matthew T. Roe, MD, MPH,[d] Tyrus Rorick, RN,[d] William J. Sasiela, PhD,[k] Cheerag Shirodaria, MBBS,[l] Michael Szarek, PhD,[m] Jean-François Tamby, MD,[b,c] Pierluigi Tricoci, MD,[d] Harvey White, MBBS, DSc,[n] Andreas Zeiher, MD,[o] and Philippe Gabriel Steg, MD[p,q] *Denver, CO; Paris, France; Bridgewater, NJ; Durham, NC; Boston, MA; Birmingham, AL; Rosario, Argentina; Toronto, Canada; Stanford, CA; Leiden, the Netherlands; Tarrytown, NY; Oxford, United Kingdom; Brooklyn, NY; Auckland, New Zealand; and Frankfurt, Germany*

(Am Heart J 2014;168:682-689.e1.)



† **Optimal statin treatment:** Atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg, or maximal tolerated dose of one of these statins, with or without non-statin lipid treatments. NCEP-ATPIII therapeutic lifestyle changes or equivalent throughout study.

* **Inadequate control of atherogenic lipoproteins.** At least one of the following: LDL-C ≥70 mg/dL (1.81 mmol/L), non-HDL-C ≥100 mg/dL (2.59 mmol/L), or apo B ≥80 mg/dL

Prostate-Specific Antigen (PSA) as a Surrogate End Point for Survival in Prostate Cancer Clinical Trials

Laurence Collette

EUROPEAN UROLOGY 53 (2008) 6–9

Prognostic versus surrogate

A [redacted] is a set of physical signs or laboratory measurements that occur in association with a [redacted] and are significantly ass[redacted]lution and survival of [redacted]emical relapse after radical prostatectomy is prognostic for clinical relapse.

…in the individual patient

A [redacted] a "(set of) biochemical measurements [redacted] clinical signs used as [redacted]t in the assess-me[redacted]

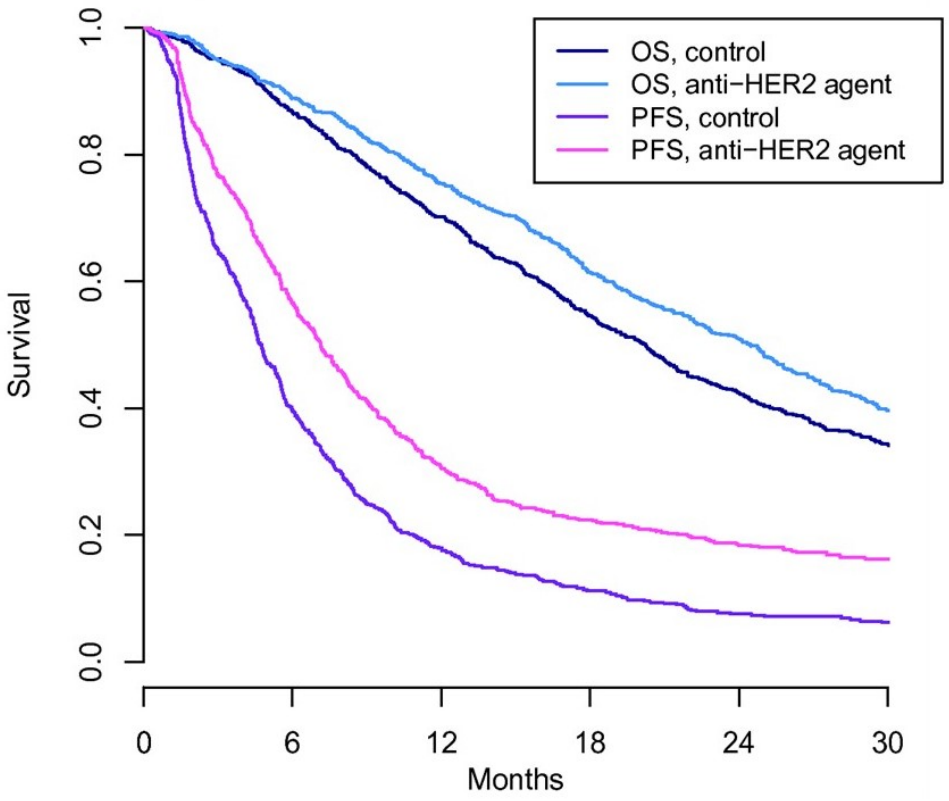
…across groups of patients

Progression-free survival (PFS) as surrogate endpoint for overall survival (OS) in clinical trials of HER2-targeted agents in HER2-positive metastatic breast cancer (MBC): An individual patient data (IPD) analysis.

S. Michiels[1,2], L. Pugliano[1,3], D. Grun[1], S. Marguet[2], J. Barinoff[4], D. Cameron[5], M. Cobleigh[6], A. Di Leo[7], S. Johnston[8], G. Gasparini[9], B.Kaufman[10], M. Marty[11], V. Nekjudova[12], S. Paluch-Shimon[13], F.Penault-Llorca[14], D. Slamon[15], C. Vogel[16], G. von Minckwitz[12], M. Buyse[17], M. Piccart[1,3]

ASCO 2013
CHICAGO
30 MAY - 04 JUN

Individual level ρ=0.66 (95% CI 0.65-0.66)

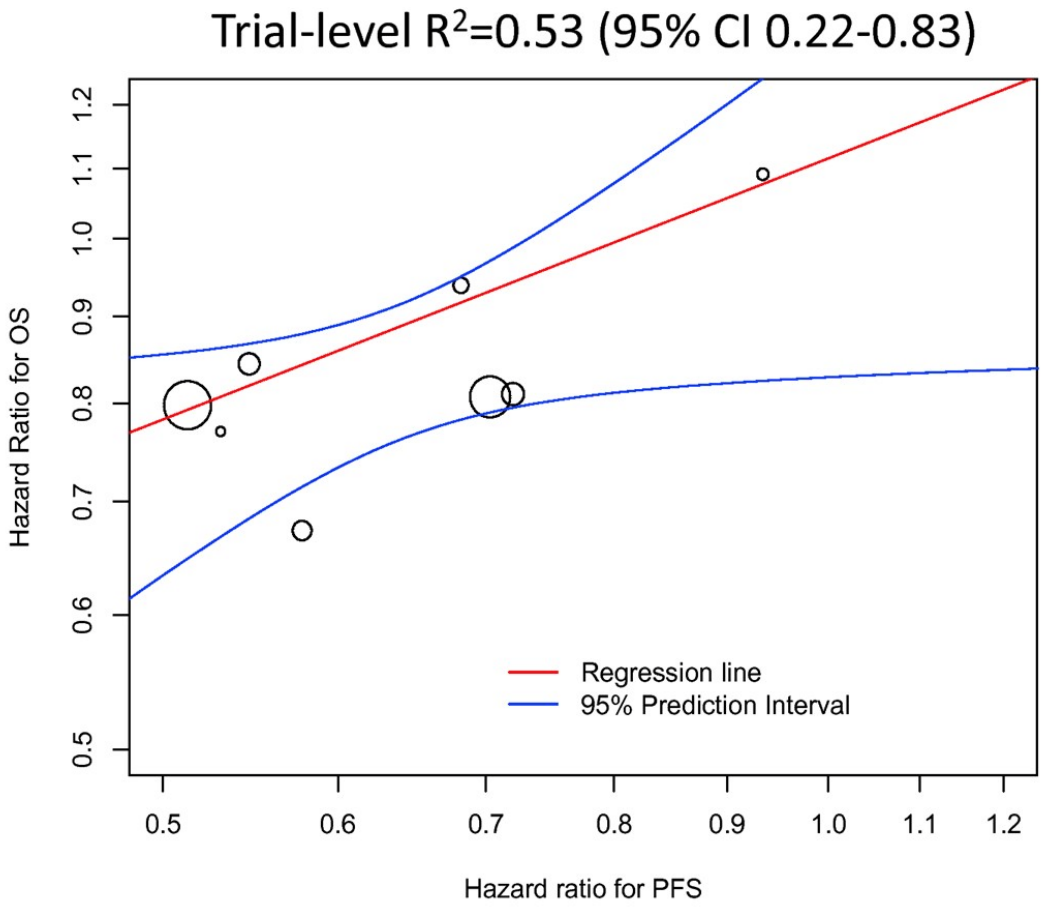


- For HER2-targeted therapies in HER2+ MBC, PFS is moderately correlated with OS at the individual level (ρ=0.66)

Progression-free survival (PFS) as surrogate endpoint for overall survival (OS) in clinical trials of HER2-targeted agents in HER2-positive metastatic breast cancer (MBC): An individual patient data (IPD) analysis.

S. Michiels[1,2], L. Pugliano[1,3], D. Grun[1], S. Marguet[2], J. Barinoff[4], D. Cameron[5], M. Cobleigh[6], A. Di Leo[7], S. Johnston[8], G. Gasparini[9], B.Kaufman[10], M. Marty[11], V. Nekjudova[12], S. Paluch-Shimon[13], F.Penault-Llorca[14], D. Slamon[15], C. Vogel[16], G. von Minckwitz[12], M. Buyse[17], M. Piccart[1,3]

ASCO 2013
CHICAGO
30 MAY - 04 JUN



- At the trial level, only 53% of the variation in treatment effects on OS can be explained by effects on PFS (trial-level R^2=0.53).

Surrogate outcome markers in research and clinical practice

Scott Twaddell

(Aust Prescr 2009;32:47–50)

Table 1

Surrogate markers often used in clinical practice

Generally accepted as valid		Doubt still exists about validity	
Surrogate marker	**Predicts**	**Surrogate marker**	**Predicts**
HbA1c	Diabetic microvascular complications	HbA1c	Diabetic macrovascular complications
FEV_1	Mortality in chronic obstructive pulmonary disease	Bone mineral density	Fracture risk
Blood pressure	Primary and secondary cardiovascular events	Prostate specific antigen	Prognosis of prostate cancer
Viral load	Survival in HIV infection	Suppression of arrhythmia	Long-term survival
Cholesterol concentration	Primary and secondary cardiovascular events	Carotid intima-media thickness	Coronary artery disease
Intraocular pressure	Visual loss in glaucoma	Albuminuria	Cardiovascular events

HbA1c glycated haemoglobin

FEV_1 forced expiratory volume in one second

Co-primary endpoints can be different medical assessments angled at different aspects of a disease, therefore, are used collectively to strengthen evidence for the treatment effect.

Li QH. Evaluating co-primary endpoints collectively in clinical trials. Biom J. 2009 Feb;51(1):137-45.

Guidance for Industry

E9 Statistical Principles for Clinical Trials

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
September 1998
ICH

5. *Multiple Primary Variables (2.2.5)*

It may sometimes be desirable to use more than one primary variable, (or a subset of which) of the therapies.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy

Charles J. Ryan, M.D., Matthew R. Smith, M.D., Ph.D., Johann S. de Bono, M.B., Ch.B., Ph.D., Arturo Molina, M.D., Christopher J. Logothetis, M.D., Paul de Souza, M.B., Ph.D., Karim Fizazi, M.D., Ph.D., Paul Mainwaring, M.D., Josep M. Piulats, M.D., Ph.D., Siobhan Ng, M.D., Joan Carles, M.D., Peter F.A. Mulders, M.D., Ph.D., Ethan Basch, M.D., Eric J. Small, M.D., Fred Saad, M.D., Dirk Schrijvers, M.D., Ph.D., Hendrik Van Poppel, M.D., Ph.D., Som D. Mukherjee, M.D., Henrik Suttmann, M.D., Winald R. Gerritsen, M.D., Ph.D., Thomas W. Flaig, M.D., Daniel J. George, M.D., Evan Y. Yu, M.D., Eleni Efstathiou, M.D., Ph.D., Allan Pantuck, M.D., Eric Winquist, M.D., Celestia S. Higano, M.D., Mary-Ellen Taplin, M.D., Youn Park, Ph.D., Thian Kheoh, Ph.D., Thomas Griffin, M.D., Howard I. Scher, M.D., and Dana E. Rathkopf, M.D., for the COU-AA-302 Investigators*

METHODS

In this double-blind study, we randomly assigned 1088 patients to receive abiraterone acetate (1000 mg) plus prednisone (5 mg twice daily) or placebo plus prednisone. The

Apixaban for Extended Treatment of Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators*

N Engl J Med 2013;368:699-708.

OUTCOME MEASURES

[redacted]— an outcome consistent with that recommended in regulatory guidelines for trials of extended treatment for venous thromboembolic diseases.[16] Recurrent venous thromboembolism included fatal and nonfatal pulmonary embolism and deep-vein thrombosis. Death was classified as related to venous thromboembolism, related to cardiovascular disease, due to bleeding, or due to other causes.

APPLIED CLINICAL TRIALS Online

Composite Endpoints: Proceed with Caution

By Peter Kleist May 1, 2006

Multiple single endpoints are combined in order to confront an investigational drug with a higher number of events expected during the trial.

Statistical precision and efficiency will be increased, trials become smaller, less costly, and the results of promising new treatments will be available earlier.

The selected individual components of a composite endpoint, as reported in the biomedical literature, are not always clinically meaningful.

Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial

The TIME Investigators

Lancet 2001; **358:** 951–957

The frequency of the composite endpoint (death, nonfatal myocardial infarction, and hospital admission for ACS) was much lower with revascularization; however, this was due to a marked difference in hospital admissions, which accounted for 75% of the events in the medical treatment group. In contrast, there were twice as many deaths in the invasive treatment group.

The question remains how to interpret the results and inform a patient who has to decide between conservative or surgical therapy.