SURROGATE AND COMPOSITE END-POINTS: ARE THEY RELIABLE?

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

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SURROGATE END-POINT

A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Biomarkers definitions working group: biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89-95

SURROGATE END-POINTS

- AS A FACTOR OF STRATICATION
- AS A METHOD TO OBTAIN "ENRICHMENT"
- AS A SUBSTITUTE OF THERAPEUTIC END-POINTS

Surrogate Endpoints vs. Clinical End-points

Surrogate endpoints used in drug therapy

Therapeutic Class	Surrogates/ Biomarkers	Clinical Endpoint
Antihypertensive	↓ blood pressure	↓ stroke
Glaucoma Rx	↓ intraocular pressure	↓ loss of vision
Osteoporosis Rx	↑ bone density	↓ fracture rate
Antiarrythmia Rx	↓ arrythmias	↑ survival
HIV Rx	↑ CD4 ↓ viral RNA	↓ AIDS progression
Hyperlipidemia Rx	↓ cholesterol	↓ coronary artery dis.
Antidiabetic Rx	↓ HbA1c	↓ morbidity
Antibiotics	negative culture	clinical cure
Prostate cancer Rx	↓ PSA	tumor response

Adapted from: Woodcock J. Biomarkers: Physiological & Laboratory Markers of Drug Effect. Food and Drug Administration, February 1, 2007.

Examples of putative surrogate endpoint failures

Disease	Treatment	Effects on		Trials or analyses
		Surrogate endpoint	Clinical endpoint	
Postmyocardial infarction	Anti-arrhythmic agents	Reduced ventricular arrhythmia	Increased sudden death	CAST[41]
Atrial fibrillation	Quinidine	Maintained sinus rhythm at 1 year	Increased mortality	Meta-analysis[2]
Congestive heart failure	Milrinone/Flosequinan/ Epoprostenol	Improved cardiac output/ increased exercise tolerance	Increased mortality	PROMISE[87] PROFILE[88] FIRST[89]
Heart disease in postmenopausal women	Hormone replacement therapy	Favorable effect on serum lipoprotein level	Increased coronary heart disease/myocardial infarction	HERS[90] WHIT[91] PEPI[92]
Heart disease	Cholesterol-lowering agents	Lowering cholesterol level	Increased mortality	WHO[93] Gordon meta-analysis[94]
Osteoporosis	Sodium fluoride	Increased bone mineral density	Increased fracture incidences	95
HIV	Zidovudine	Lowering CD4+ cell counts	Failed to reduce opportunistic infection	British-French Concord Trial[96]
Normotensive patients	Management of glaucoma	Lowering intraocular pressure	No effect of treatment on long-term visual field loss	8

Shi and Sargent, 2009

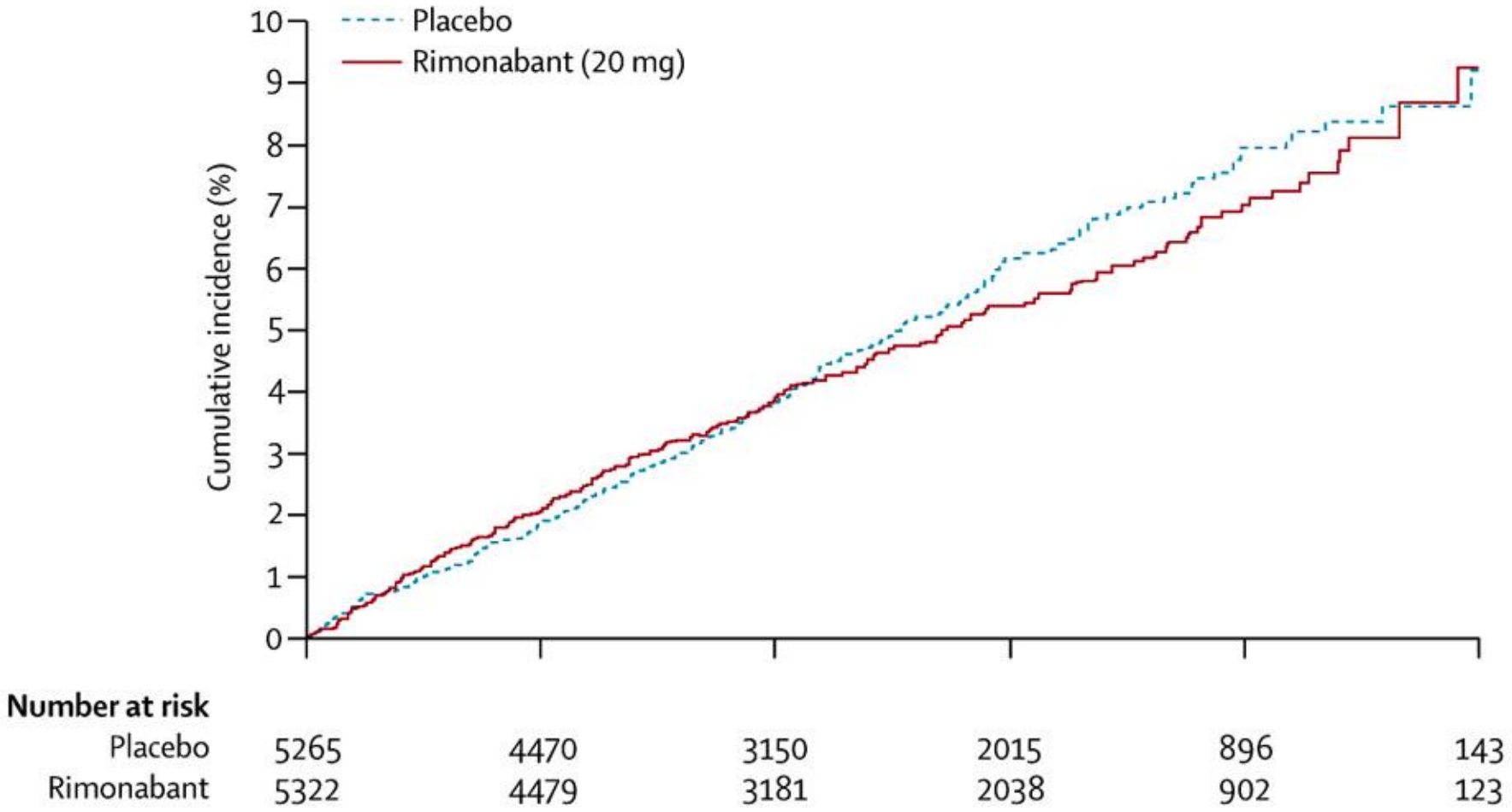
HbA1c IS NOT A SURROGATE END-POINT FOR CARDIOVASCULAR DISEASES IN TYPE 2 DIABETES

SULFONYLUREAS	HbA_{1C}	↓	MYOCARDIAL INFARCTION	↑
ROSIGLITAZONE	HbA_{1C}	↓	HEART FAILURE	↑

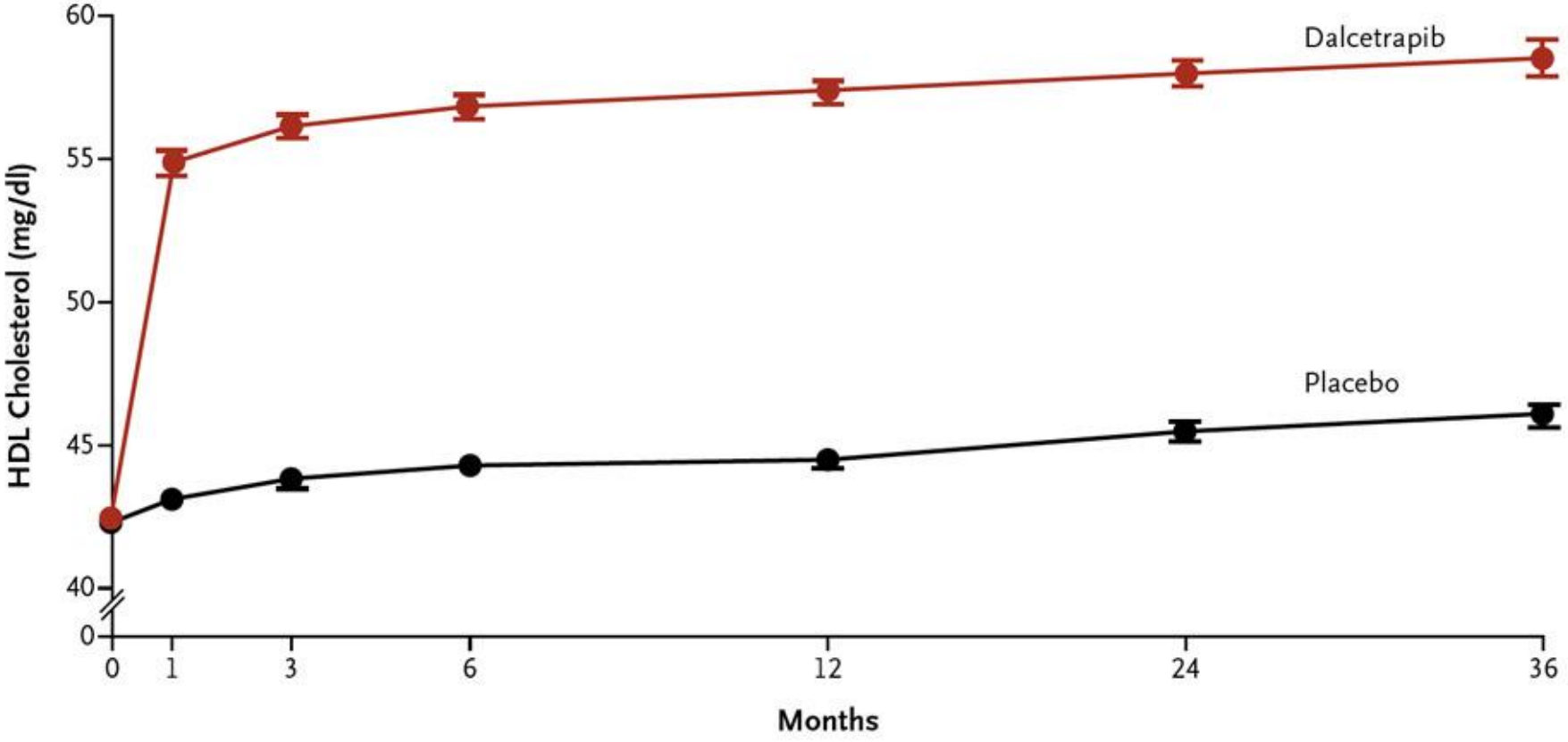
NEED TO EVALUATE PARAMETERS IMPORTANT FOR PATIENTS

RIMONABANT
antagonist of cannabinoid-1 receptor

- DECREASE OF BODY WEIGHT
- INCREASE OF HDL, ADIPONECTIN
- DECREASE OF TRIGLYCERIDES, BLOOD GLUCOSE, FASTING INSULIN, LEPTIN
- DECREASE OF TOTAL VOLUME ATHEROMA



Topol et al., 2010
CRESCENDO TRIAL

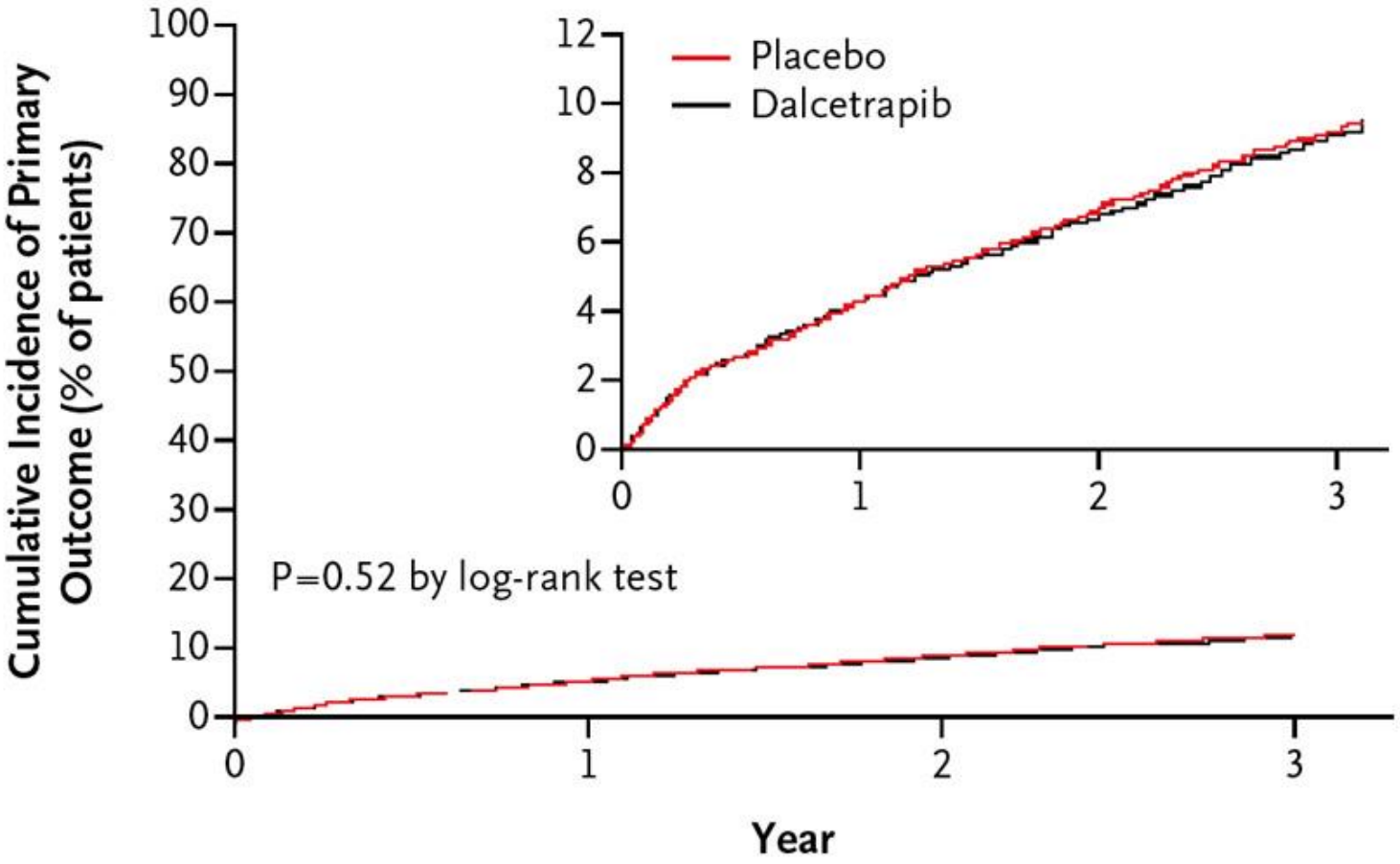


No. at Risk

Placebo	7907 7685	7498	7272	6959	6436	3650
Dalcetrapib	7910 7663	7402	7196	6871	6333	3599

Schwartz et al., 2012

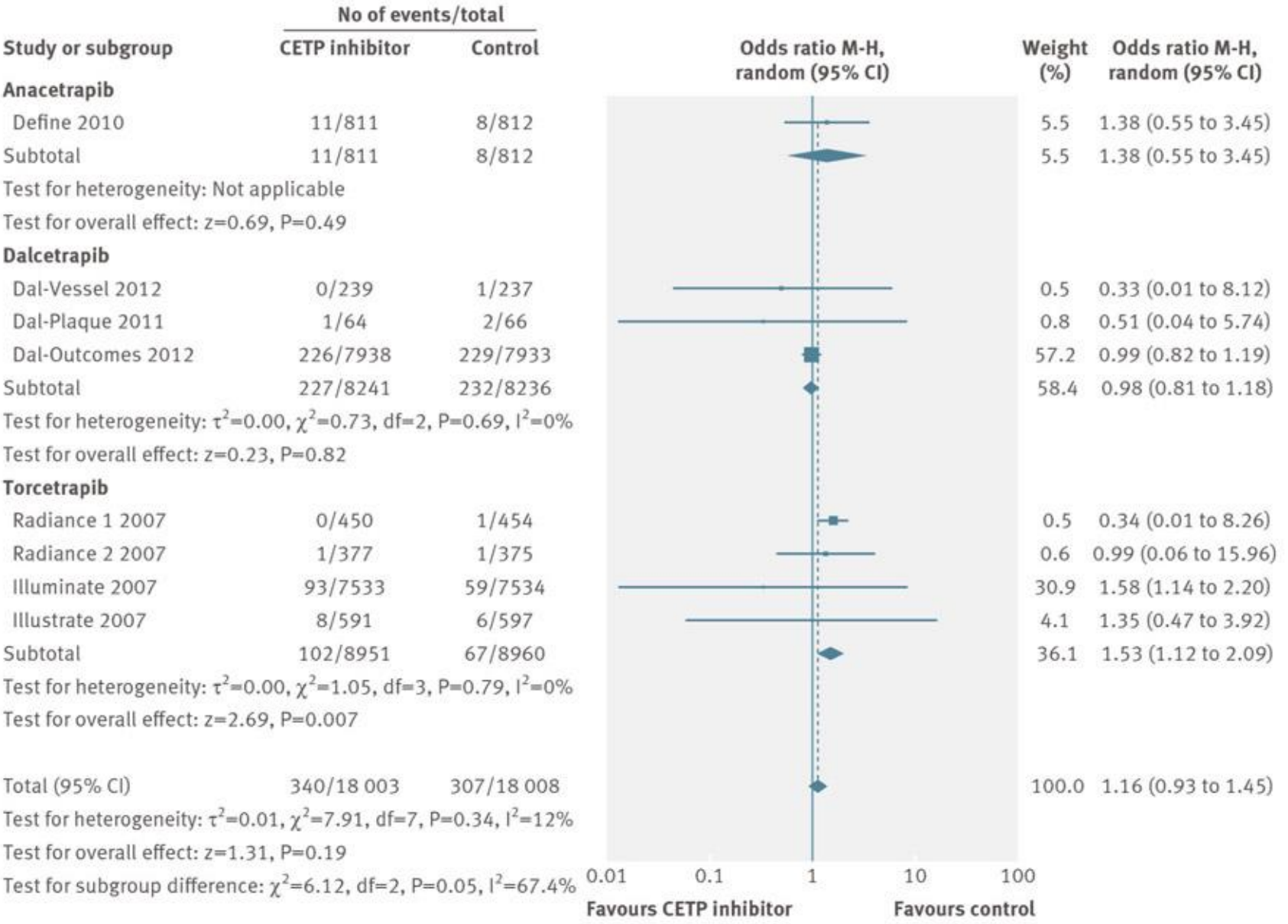
Incidence of the Primary Efficacy End Point



No. at Risk				
Placebo	7933	7386	6551	1743
Dalcetrapib	7938	7372	6495	1736

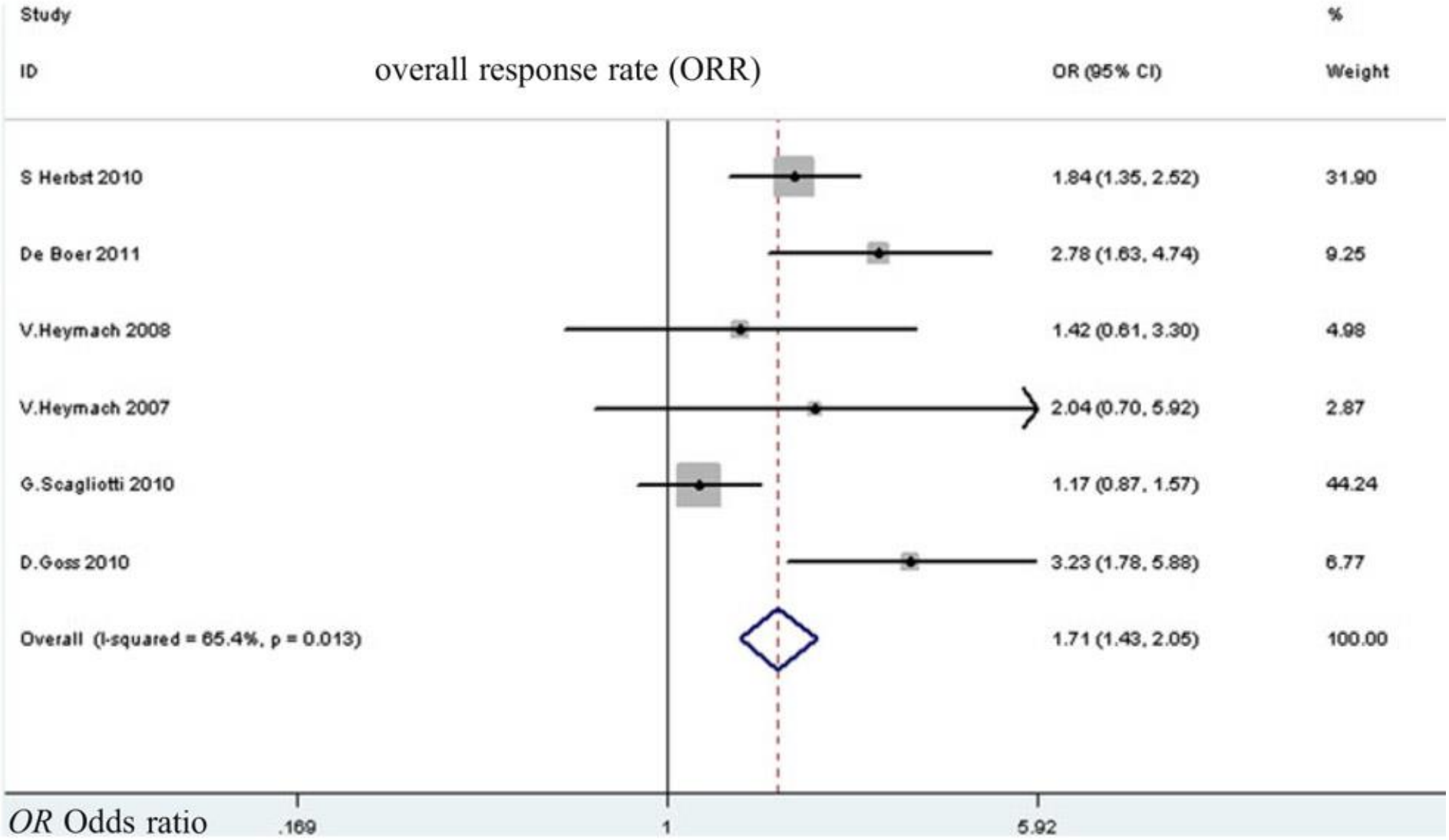
Schwartz et al., 2012

Forest plot showing effect of cholesteryl ester transfer protein (CETP) inhibitors on risk of all cause mortality stratified by CETP inhibitors



Keene et al., 2014

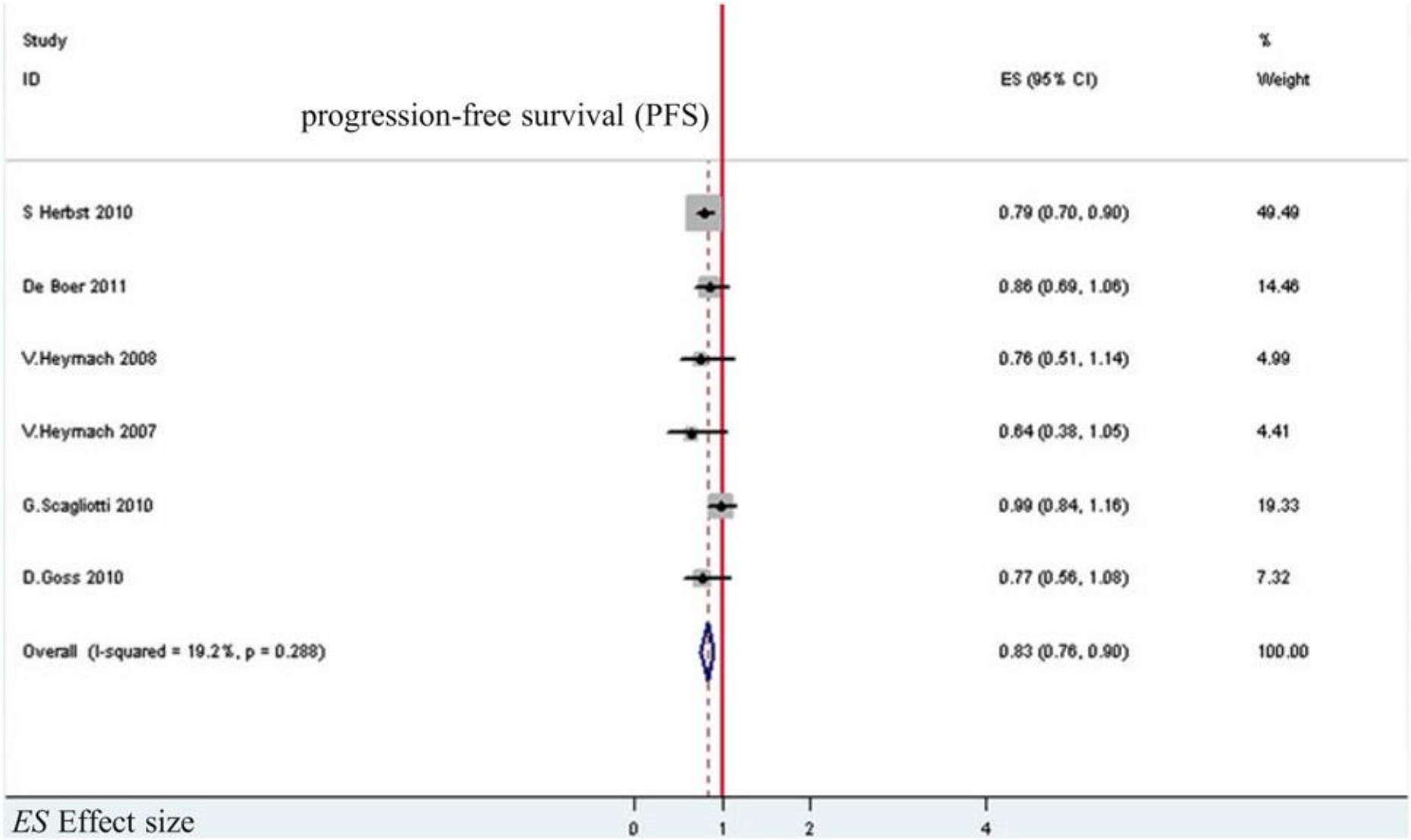
NSCLC and TKI



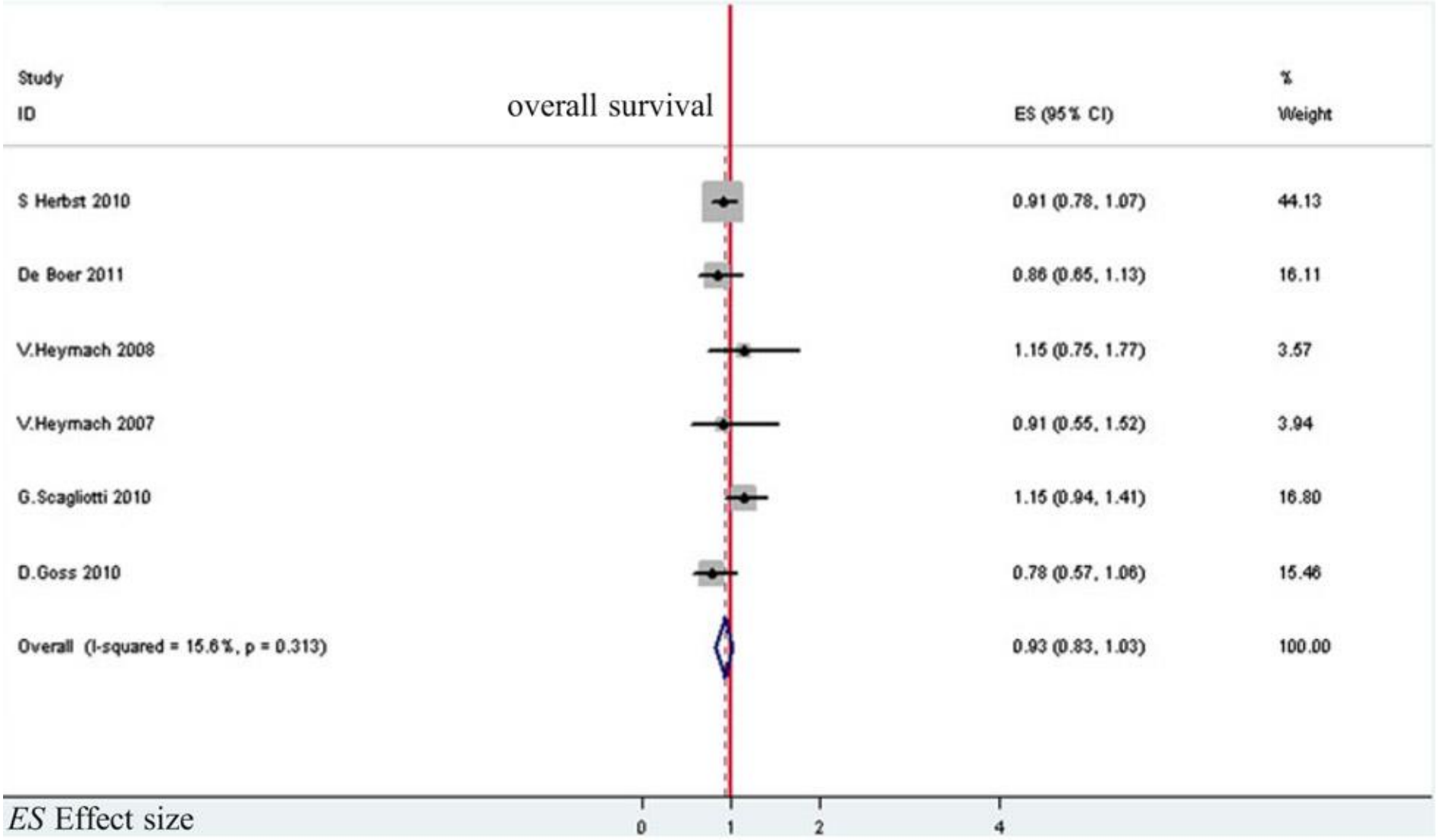
XIAO et al., 2012

patients with advanced non-small-cell lung cancer (NSCLC)

chemotherapy plus multitargeted antiangiogenic tyrosine kinase inhibitors (TKI)



XIAO et al., 2012



XIAO et al., 2012

Tumor Type	R^2 HR PFS → HR OS
CRC Adv	0.98
Breast	0.23
Prostate	0.22
Ovarian	0.95
Renal (Tg agents)*	0.20

**Bria et al 2014: Critical reviews in oncology/hematology*

Comparison of treatment effects of trials using surrogate outcomes with trials using final patient relevant outcomes: primary and sensitivity analyses

Method of analysis	Risk ratio* (95% CI)	
	Surrogate outcomes	Patient relevant outcomes
Primary analysis:		
Binary outcomes (51 surrogate *v* 83 patient relevant)	0.51 (0.42 to 0.60)	0.76 (0.70 to 0.82)
Sensitivity analyses:		
Inclusion of risk ratios as reported by authors (57 *v* 86)	0.56 (0.48 to 0.65)	0.80 (0.75 to 0.86)
Inclusion of continuous outcomes (84 *v* 101)	0.46 (0.39 to 0.54)	0.68 (0.62 to 0.74)
Binary outcomes, matched pairs (43 *v* 43)	0.48 (0.39 to 0.59)	0.68 (0.61 to 0.77)

Ciani et al., 2013

Examples of oncology drugs approved by the FDA from 1990 to 2004 based on endpoints other than overall survival

Cancer type	Endpoints	Approved drugs	FDA approval type
Breast	RR	Anastrozole, exemestane, letrozole, toremefene, fulvestrant, docetaxel,[a] capecitabine[a]	Regular, AA
	TTP	Anastrozole, exemestane, letrozole, toremefene, fulvestrant, paclitaxel	Regular
	DFS	Anastrozole	AA
Ovarian	RR, durable PR	Altretamine, liposomal doxorubicin, paclitaxel	Regular, AA
Leukemia	CR, PR, durable CR	Pentostatin, cladribine, tretinoin, arsenic trioxide, gemtuzumab, fulvestrant, imatinib,[a] alemtuzumab, imatinib mesylate	Regular, AA
	DFS	Busulfan	Regular
Lung	RR	Topotecan, amifostine, gefitinib	Regular, AA
Colon	RR	Irinotecan[a]	AA
	RR and TTP	Oxaliplatin[a]	AA
Lymphoma	RR	Liposomal cytarabine, denileukin diftitox, ibritumomab tiuxetan	AA
Myeloma	RR	Bortezomib	AA
Kaposi's sarcoma	RR	Paclitaxel, liposomal doxorubicin	Regular, AA
MPE	TTR	Bleomycin	Regular
GIST	RR	Imatinib mesylate	AA

Shi and Sargent, 2009

SURROGATE END-POINTS MUST ALWAYS BE VALIDATED FOR ANY GIVEN DRUG OR TREATMENT.

THEY CANNOT BE EXTRAPOLATED TO THERAPEUTIC END-POINTS.

Composite end-point

- A single measure of effect, based on a combination of individual endpoints.
- Particularly useful for drugs that can benefit patients in several ways or if component events are infrequent.
  - "Clinical Worsening" :
    - may include categorical decline in functioning, worsening symptoms, addition of a new medication, hospitalization due to the disease, death, etc.
    - (HRQOL instruments)
- Often analyzed as time to first event.

Breakdown of how individual components contribute to the composite primary endpoint of death, recurrent ischaemia, or coronary-artery occlusion

	Clopidogrel (n=1752)	Placebo (n=1739)	p
Death	45 (2·6%)	38 (2·2%)	0·49
Recurrent ischaemia	44 (2·5%)	63 (3·8%)	0·08
Coronary-artery occlusion*	192 (11·7%)	301 (18·4%)	<0·001
Composite primary endpoint	262 (15·0%)	377 (21·7%)	<0·001

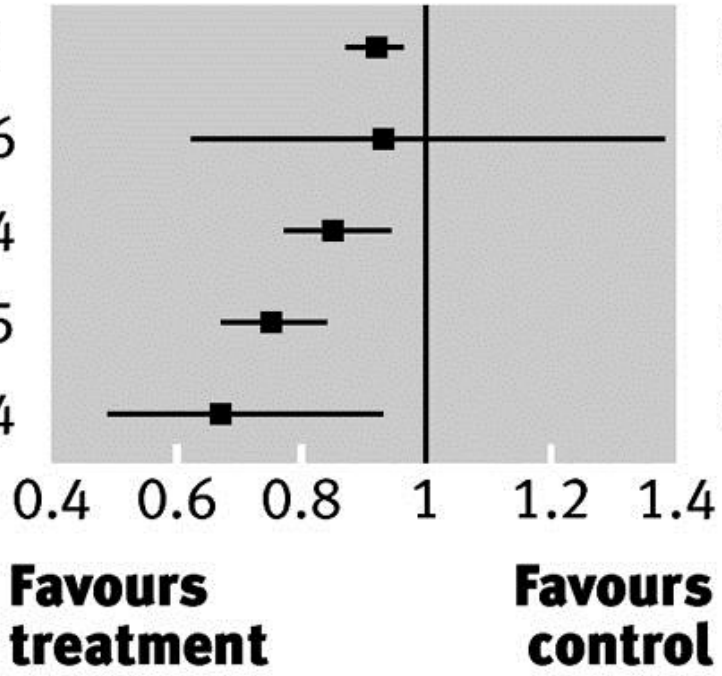
*TIMI grade 0 or 1 on angiography.

Lapostolle et al., 2007

Variability in magnitude of the effect of intervention across categories of importance to patients

COMPOSITE END-POINTS

Severity	No of studies	I^2 (%)	Relative risk or hazard ratio (95% CI)
Death	93	0	0.92 (0.87 to 0.96)
Critical	11	36	0.93 (0.62 to 1.38)
Major	70	44	0.85 (0.77 to 0.94)
Moderate	46	45	0.75 (0.67 to 0.84)
Minor	9	44	0.67 (0.49 to 0.93)



Ferreira-Gonzàlez et al., 2007

Composite end-point considerations

- Each component should itself be clinically meaningful.
  - Ideally, each component would be approximately equally meaningful.
- “Success” should not be concluded if driven by a less meaningful component, if there is evidence of a therapeutic disadvantage on a more meaningful component.
- The composite should not include individual components for which a treatment effect is not expected.
- May complicate communication of the established benefit of a drug.
- There may often be inadequate evidence to establish a treatment effect on any of the components individually.