Definizione del quesito clinico e degli outcome di interesse

Defining the review question

A clearly defined, focused review begins with a well framed question.

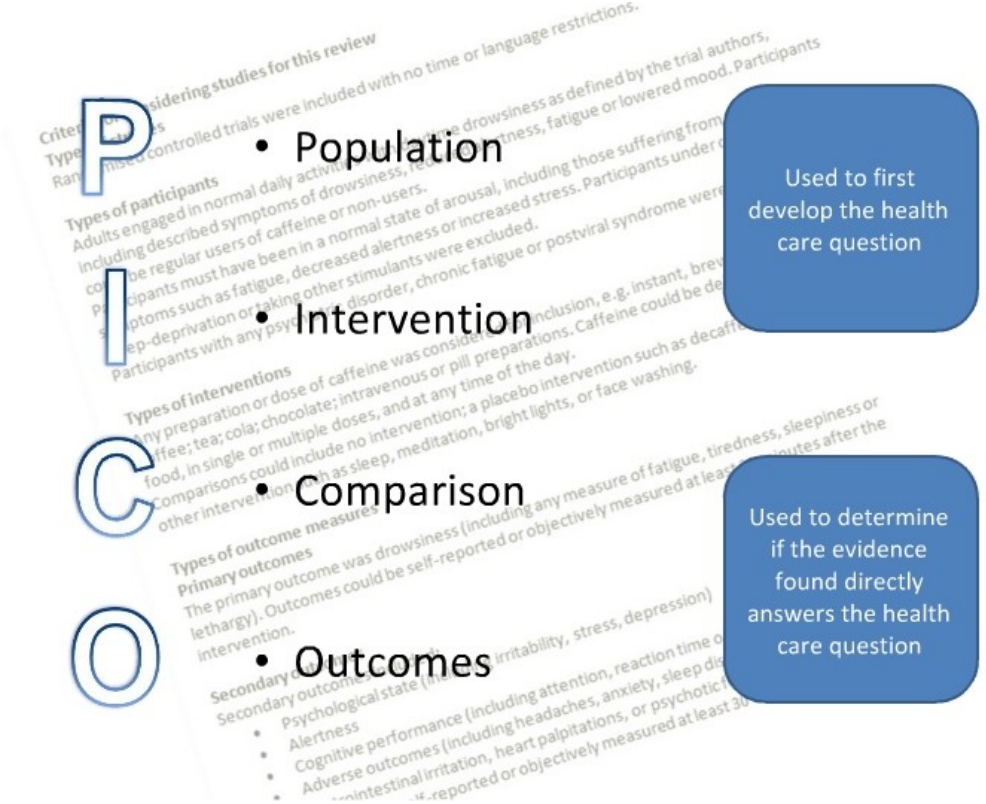
The review question should specify:

- types of population (participants),
- types of interventions (and comparisons),
- types of outcomes that are of interest.

These components of the question, with the additional specification of types of study that will be included, form the basis of the pre-specified eligibility criteria for the review.

The ‘clinical question’ should specify the types of population (participants), types of interventions (and comparisons), and the types of outcomes that are of interest.

The acronym PICO (**P**articipants, **I**nterventions, **C**omparisons and **O**utcomes) helps to serve as a reminder of these.



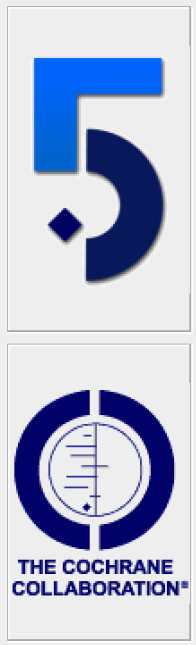
Defining the review question

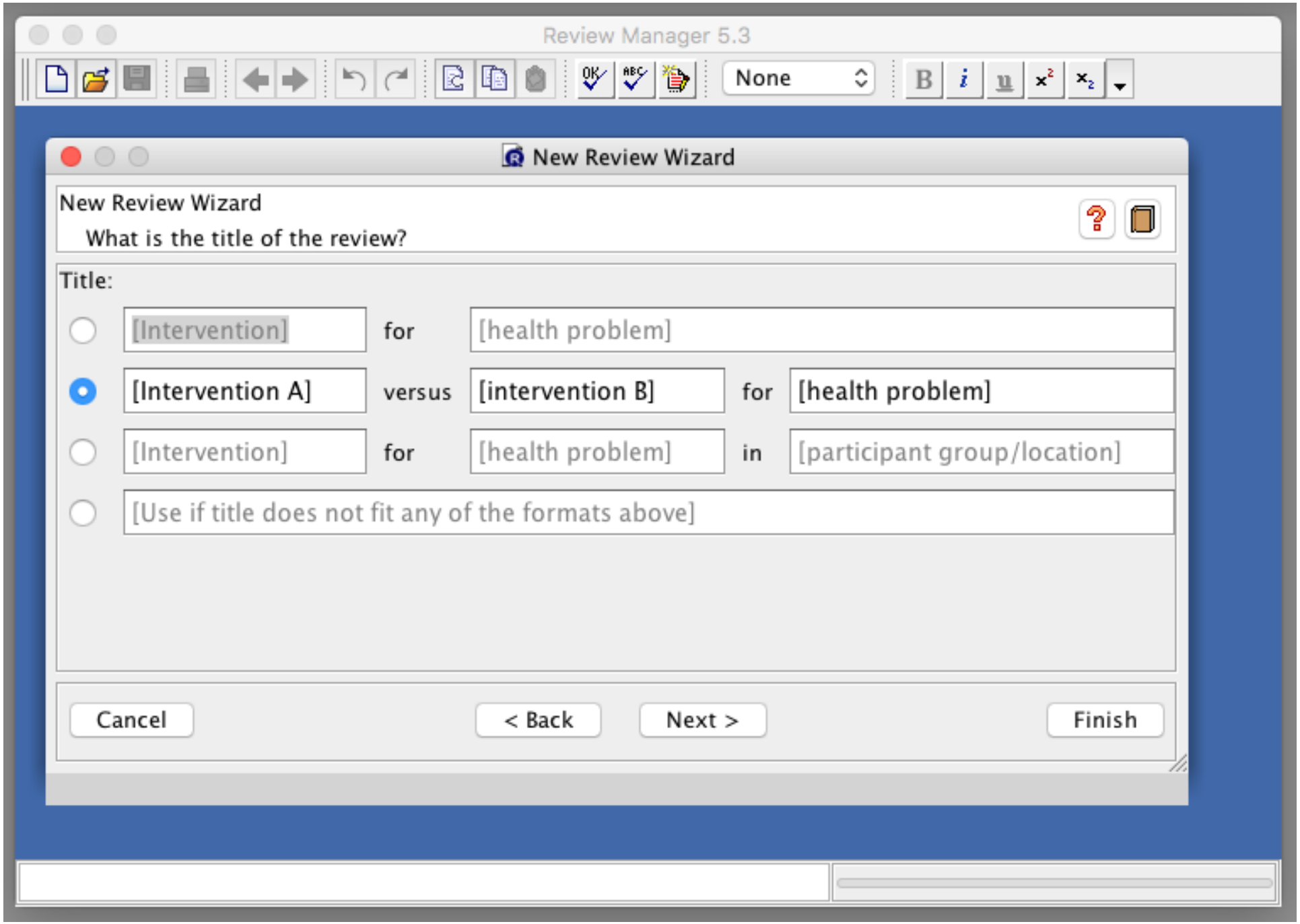
A statement of the review's objectives should begin with a precise statement of the primary objective, ideally in a single sentence.

Where possible the style should be of the form:

'To assess the effects of [*intervention or comparison*] for [*health problem*] in [*types of people, disease or problem and setting if specified*]'.

This might be followed by one or more secondary objectives, for example relating to different participant groups, different comparisons of interventions or different outcome measures.


THE COCHRANE
COLLABORATION®


Review Manager 5.3
None
New Review Wizard
New Review Wizard
What is the title of the review?
Title:
[Intervention]
for
[health problem]
[Intervention A]
versus
[intervention B]
for
[health problem]
[Intervention]
for
[health problem]
in
[participant group/location]
[Use if title does not fit any of the formats above]
Cancel
< Back
Next >
Finish

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'To assess the effects of [*intervention or comparison*] for [*health problem*] in [*types of people, disease or problem and setting if specified*]'.

This might be followed by one or more secondary objectives, for example relating to different participant groups, different comparisons of interventions or different outcome measures.

Defining the scope of a review question (broad versus narrow)

The questions addressed by a review may be broad or narrow in scope.

- ✓ *A review might address a broad question regarding whether antiplatelet agents in general are effective in preventing all thrombotic events in humans .*
- ✓ *A review might address whether a particular antiplatelet agent, such as aspirin, is effective in decreasing the risks of a particular thrombotic event, stroke, in elderly persons with a previous history of stroke .*

Screening for prostate cancer (Review)
Ilic D, Neuberger MM, Djulbegovic M, Dahm P
Cochrane Database of Systematic Reviews 2013, Issue 1.

OBJECTIVES

The primary objective of this review was to determine the efficacy of screening men for prostate cancer in reducing prostate cancer-specific and all-cause mortality.

The secondary objectives of this review were to:

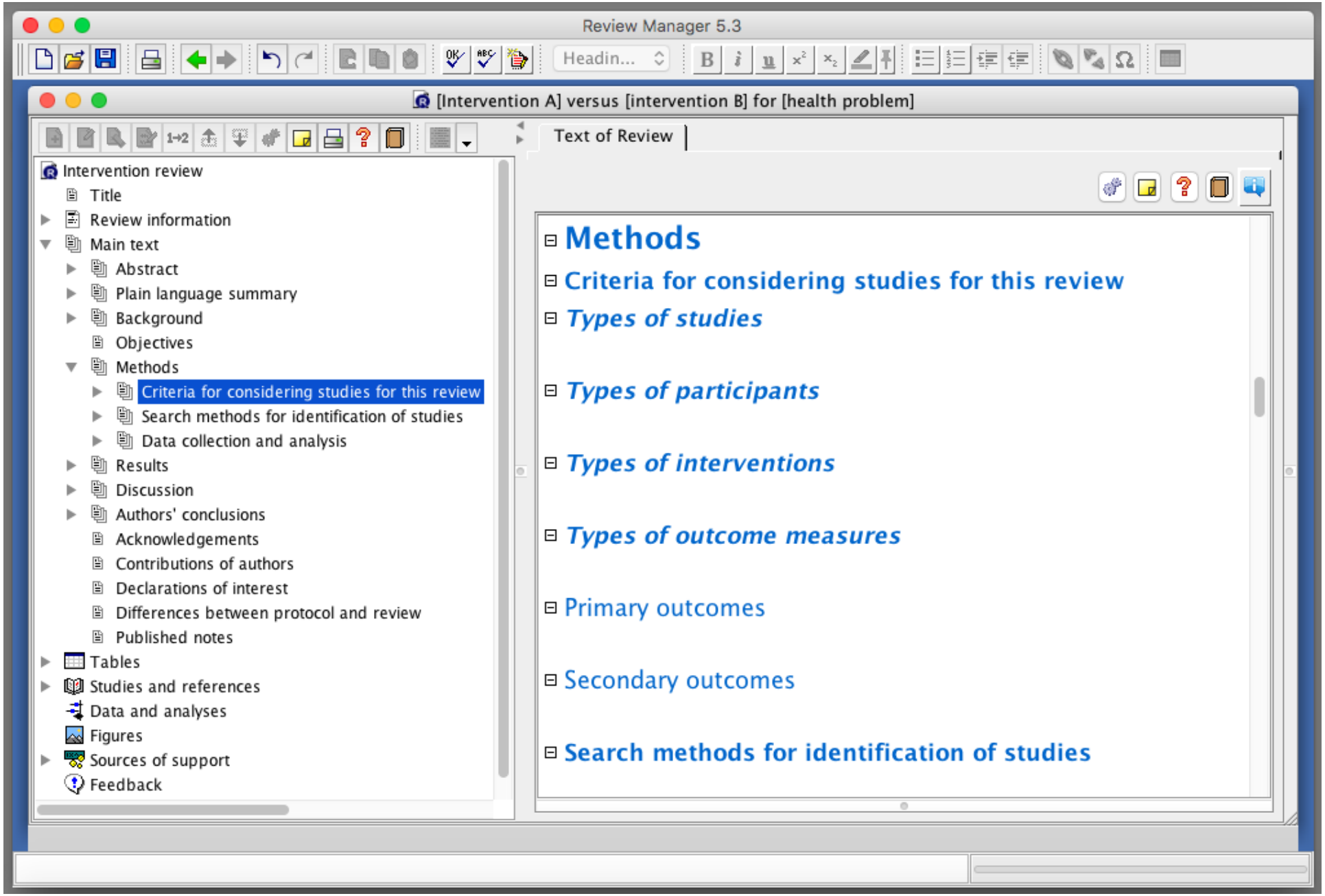
- determine the impact of prostate cancer screening on quality of life and adverse effects; and
- document the costs of screening for prostate cancer.

Which Populations?

The criteria for considering types of people included in studies in a review should be sufficiently broad to encompass the likely diversity of studies, but sufficiently narrow to ensure that a meaningful answer can be obtained when studies are considered in aggregate.

It is often helpful to define the types of people that are of interest in two steps:

- ✓ diseases or conditions of interest using explicit criteria for establishing their presence or not;
- ✓ the broad population and setting of interest


Review Manager 5.3
[Intervention A] versus [intervention B] for [health problem]
Text of Review
Intervention review
Title
Review information
Main text
Abstract
Plain language summary
Background
Objectives
Methods
Criteria for considering studies for this review
Search methods for identification of studies
Data collection and analysis
Results
Discussion
Authors' conclusions
Acknowledgements
Contributions of authors
Declarations of interest
Differences between protocol and review
Published notes
Tables
Studies and references
Data and analyses
Figures
Sources of support
Feedback
Methods
Criteria for considering studies for this review
Types of studies
Types of participants
Types of interventions
Types of outcome measures
Primary outcomes
Secondary outcomes
Search methods for identification of studies

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Screening for prostate cancer (Review)

Ilic D, Neuberger MM, Djulbegovic M, Dahm P

Cochrane Database of Systematic Reviews 2013, Issue 1.

Types of participants

All men enrolled in studies of prostate cancer screening were eligible for this review, with no exclusions based on ethnicity, age, or presence of lower urinary tract symptoms. Studies including men with a previous diagnosis and treatment of prostate cancer were excluded.

Which comparisons to make?

The second key component of a well-formulated question is to specify the interventions of interest and the interventions against which these will be compared (comparisons).

- ✓ *Consider exactly what is delivered, at what intensity, how often it is delivered, who delivers it, etc.*
- ✓ *Are the interventions to be compared with an inactive control intervention (e.g. placebo, no treatment), or with an active control intervention (e.g. a different variant of the same intervention, a different drug, a different kind of therapy)?*

Screening for prostate cancer (Review)
Ilic D, Neuberger MM, Djulbegovic M, Dahm P
Cochrane Database of Systematic Reviews 2013, Issue 1.

Types of interventions

Studies that used any of the following screening procedures, individually or in combination, were included:

- digital rectal examination (DRE);
- prostate-specific antigen (PSA) test (including total, velocity, density, and percentage free and complex); and
- transrectal ultrasound (TRUS)-guided biopsy.

L’importanza della formulazione del Quesito

P. Pazienti con mHSPC ad alto volume/rischio

I. AAP/Doce + ADT

C. ADT

O. OS, PFS, QoL, Tollerabilità

Evidenze **direttamente trasferibili** nel caso la sola ADT rappresenti l’alternativa terapeutica *standard*

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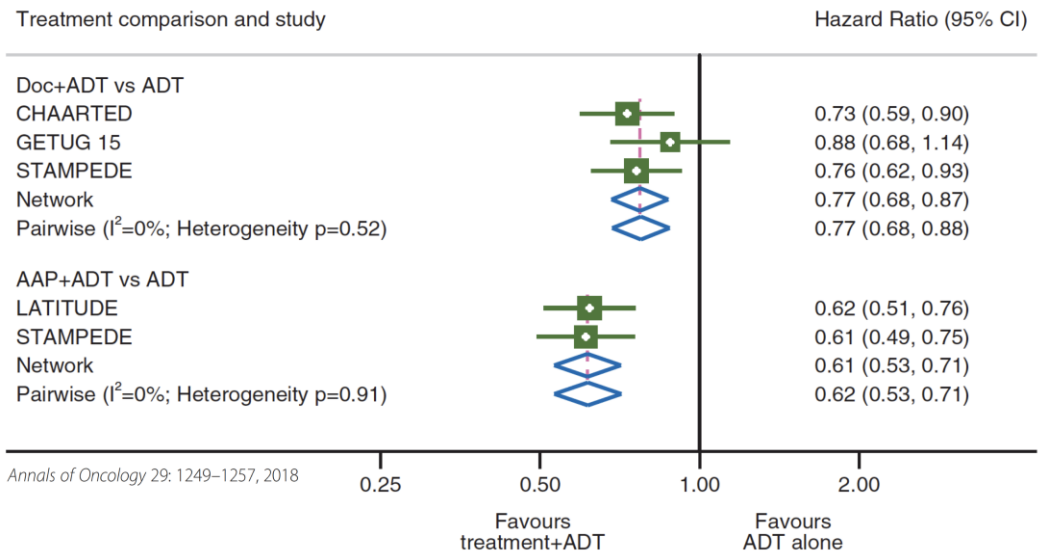

GRADE

Important Questions

Should be from practice NOT evidence driven

L’importanza della formulazione del Quesito

P. Pazienti con mHSPC ad alto volume/rischio

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C. Doce + ADT

O. OS, PFS, QoL, Tollerabilità

Evidenze disponibili **NON direttamente trasferibili** alle richieste del quesito P.I.C.O (*indirectness* di **C.**)

L’importanza della formulazione del Quesito

P. Pazienti con mHSPC ad alto volume/rischio

I. AAP/Doce + ADT

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O. OS, PFS, QoL, Tollerabilità

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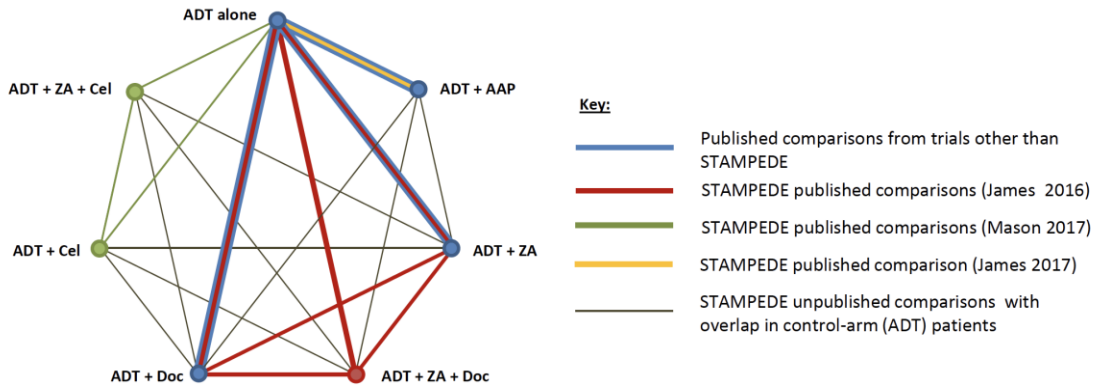


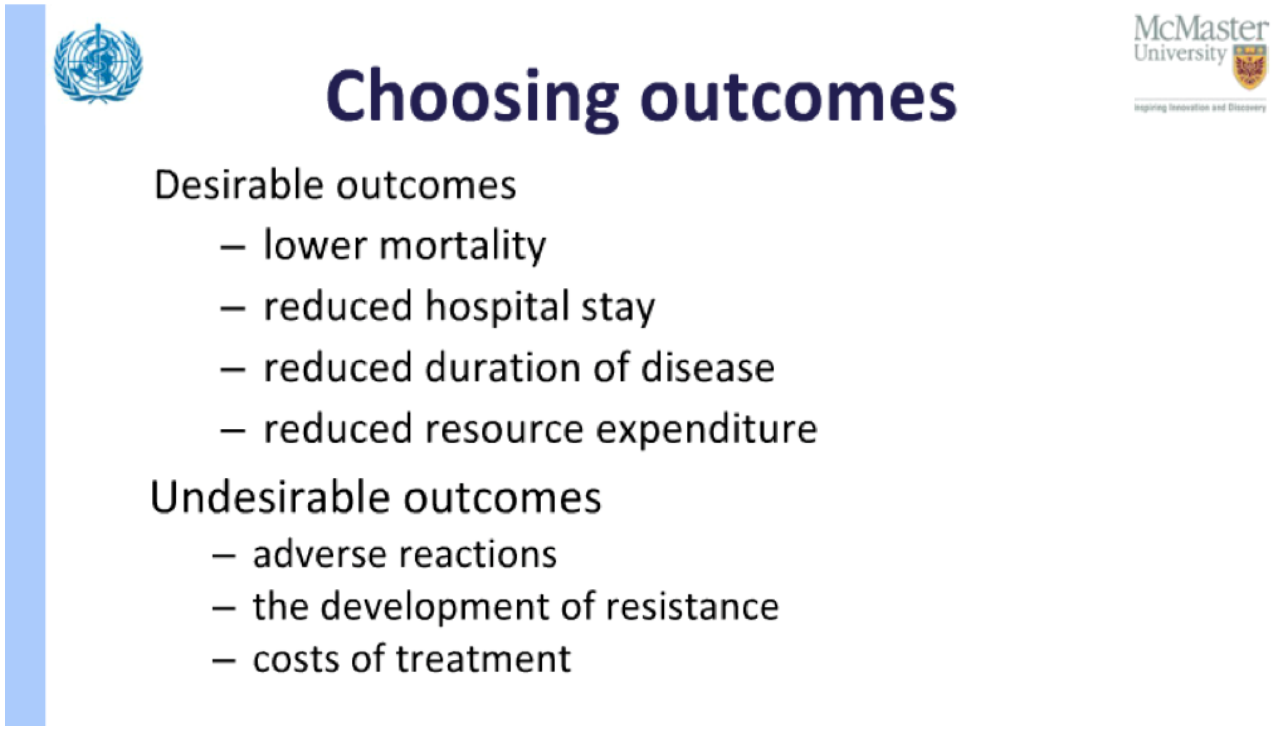
Which outcome measures are most important?

The third key component of a well-formulated question is the delineation of particular outcomes that are of interest.

- ✓ *Outcomes considered to be meaningful, and therefore addressed in a review, will not necessarily have been reported in individual studies.*
- ✓ *Including all important outcomes in a review will highlight gaps in the primary research and encourage researchers to address these gaps in future studies.*

Which outcome measures are most important?

It is critical that outcomes used to assess adverse effects as well as outcomes used to assess beneficial effects are among those addressed by a review



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Outcomes

Should be importance driven NOT evidence driven

Journal of Clinical Epidemiology 64 (2011) 395–400

GRADE guidelines: 2. Framing the question and deciding on important outcomes

Gordon H. Guyatt[a,*], Andrew D. Oxman[b], Regina Kunz[c], David Atkins[d], Jan Brozek[a], Gunn Vist[b], Philip Alderson[e], Paul Glasziou[f], Yngve Falck-Ytter[g], Holger J. Schünemann[a]

If evidence is lacking for an important outcome, this should be acknowledged, rather than ignoring the outcome - that uncertainty may have a bearing on the ultimate recommendation.

Primary outcomes

Primary outcome measures for this review were prostate cancer-specific and all-cause mortality.

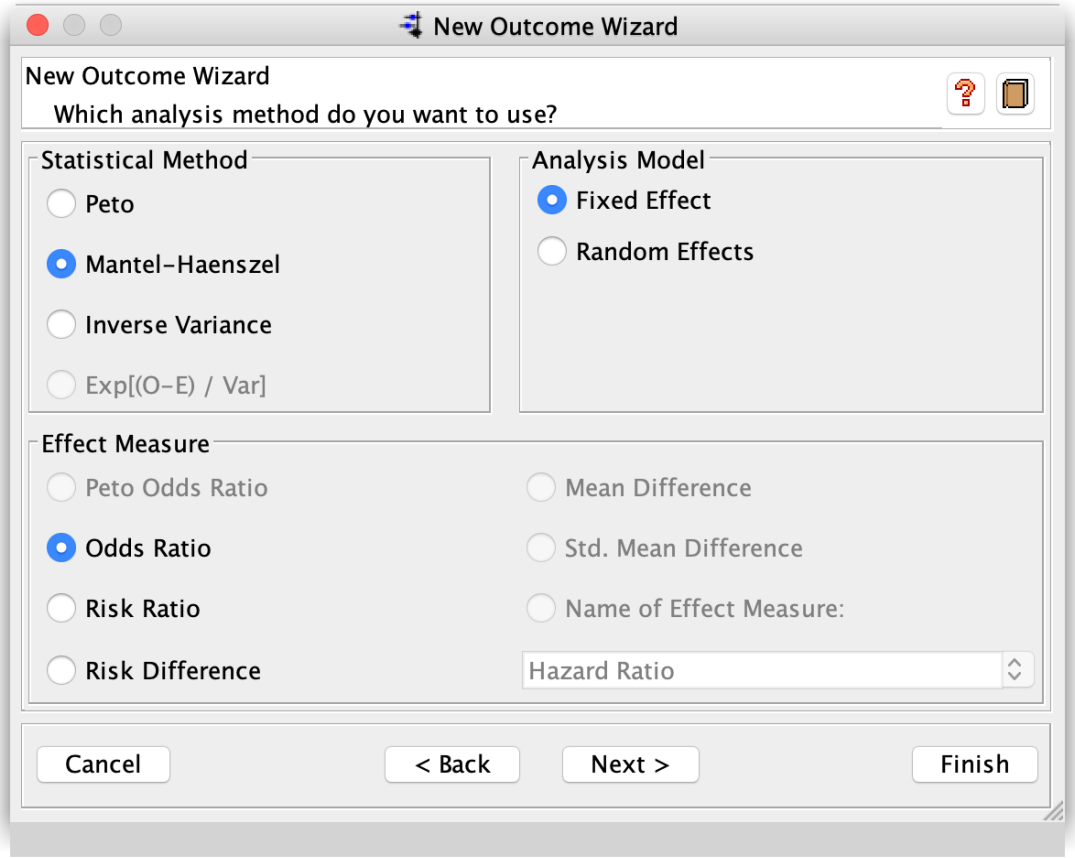
Secondary outcomes

Secondary outcome measures included:

- incident prostate cancers by stage and grade at diagnosis;
- metastatic disease at follow-up;
- quality of life;
- harms of screening (including both adverse outcomes from false-positive or false-negative results and their impact upon resulting treatment procedures); and
- costs associated with screening programs.

Misure riassuntive di effetto per varie tipologie di variabili statistiche


New Outcome Wizard
New Outcome Wizard
What type of outcome do you want to create?
Data Type:
Dichotomous
Continuous
O-E and Variance
Generic Inverse Variance
Other Data
Description:
Enter observed minus expected and its variance (e.g. calculated from individual patient data). Optionally enter number of participants with events and total number of participants in experimental and control groups.
Cancel
< Back
Next >
Finish


New Outcome Wizard
New Outcome Wizard
Which analysis method do you want to use?
Statistical Method
Peto
Mantel-Haenszel
Inverse Variance
Exp[(O-E) / Var]
Analysis Model
Fixed Effect
Random Effects
Effect Measure
Peto Odds Ratio
Odds Ratio
Risk Ratio
Risk Difference
Mean Difference
Std. Mean Difference
Name of Effect Measure:
Hazard Ratio
Cancel
< Back
Next >
Finish

VARIABILE DI RISPOSTA

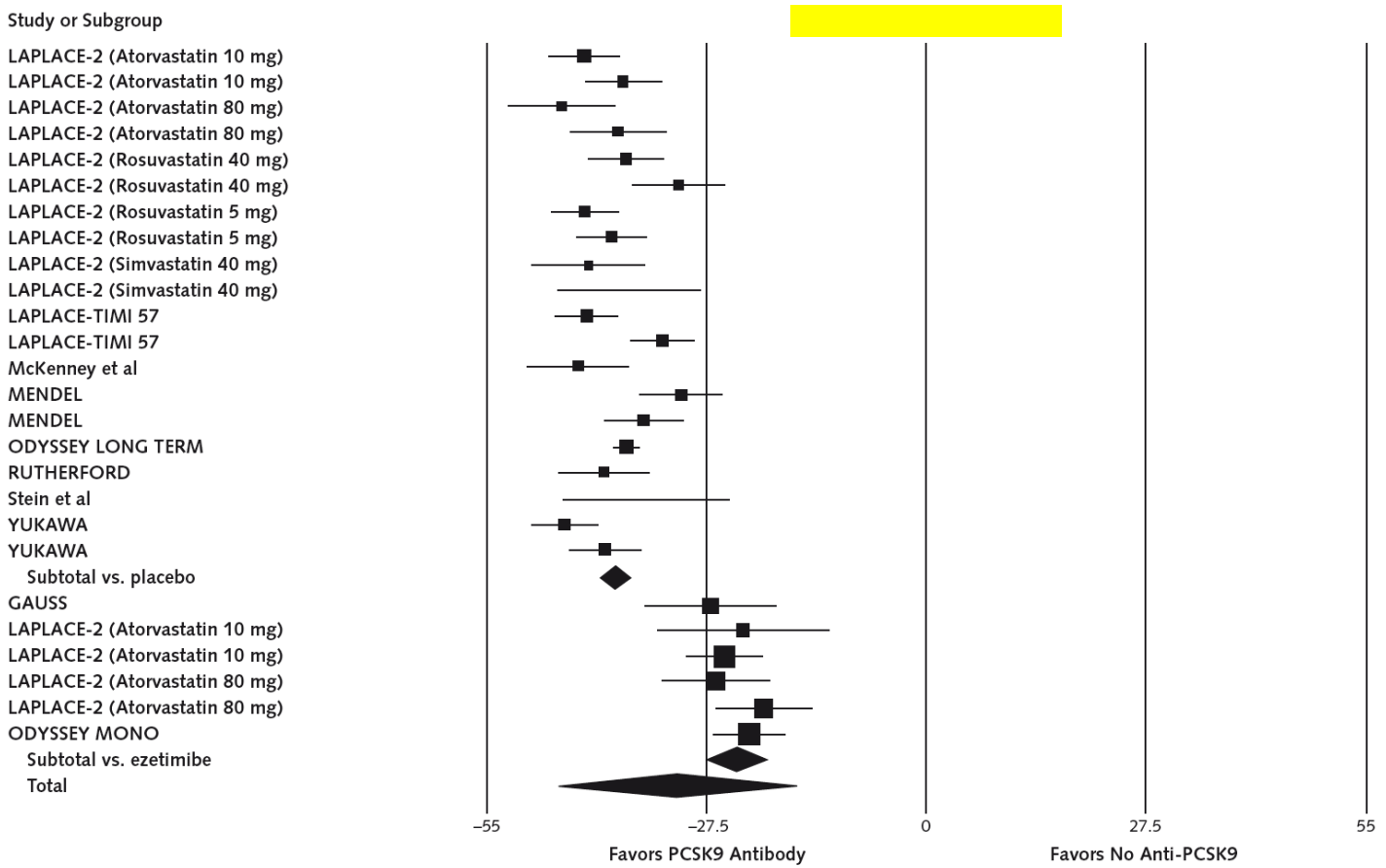
- di tipo **quantitativo**
  - assume uno spettro continuo di valori e viene misurata in riferimento a una scala a intervalli costanti.
- di tipo **qualitativo**
  - esprime categorie di risposta del tipo successo / insuccesso (di un trattamento somministrato).
- del tipo **"tempo a evento"**
  - rappresenta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

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

	Malaria cases			Healthy controls				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	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: $Tau^2 = 0.44$; $Chi^2 = 897.72$, df = 14 ($P < 0.00001$); $I^2 = 98\%$

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

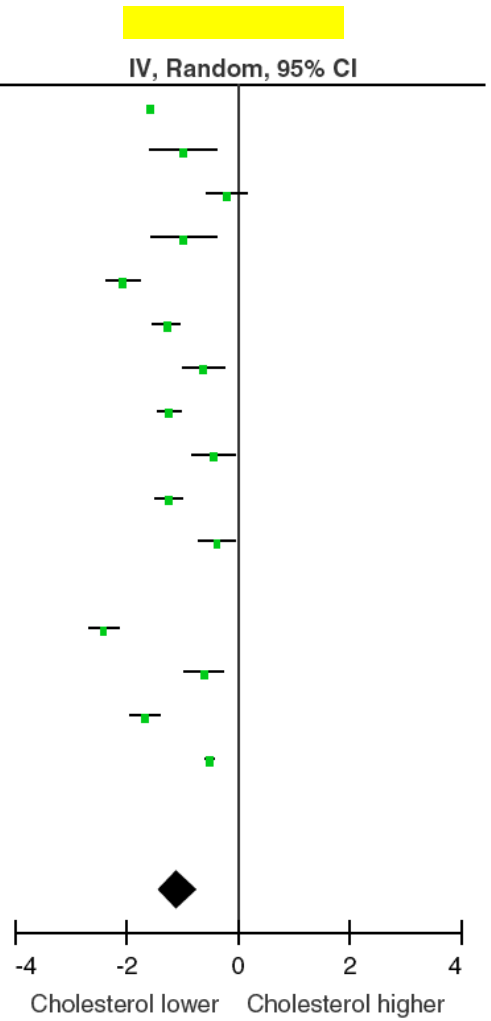
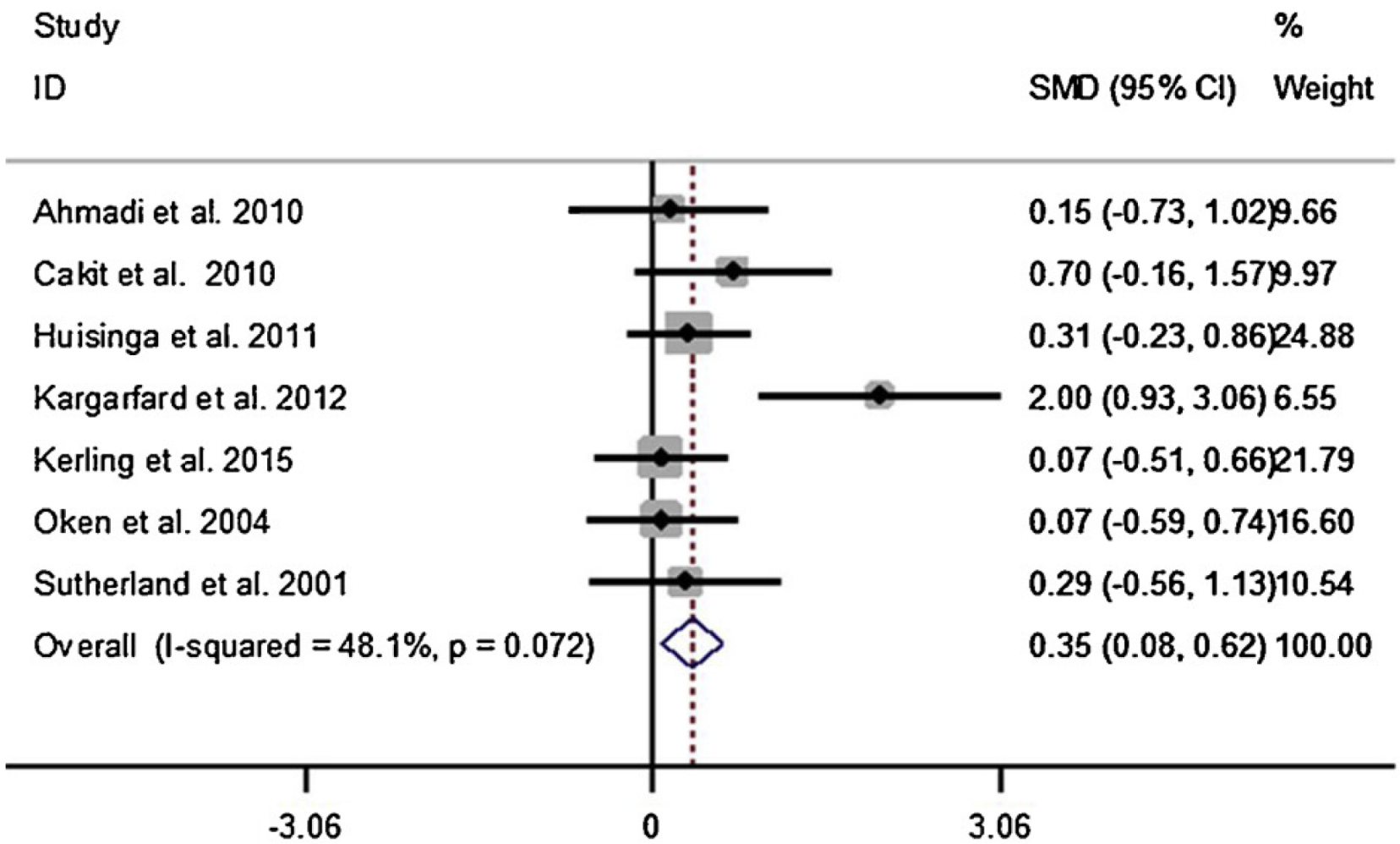


Figure 2 Forest plot Mean difference for cholesterol (mmol/l) between malaria patients and healthy controls. Random-effect model.

The effect of exercise, yoga and physiotherapy on the quality of life of people with multiple sclerosis: Systematic review and meta-analysis

Khrisha B. Alphonsus[a,*], Yingying Su[a], Carl D'Arcy[a,b]

Complementary Therapies in Medicine 43 (2019) 188–195



VARIABILE DI RISPOSTA

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- di tipo **qualitativo**
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  - rappresenta il tempo trascorso fino al verificarsi (o meno) di un evento.

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

INCIDENZA CUMULATIVA (IC)

Probabilità (rischio) di sviluppare la malattia in uno specifico periodo di tempo *t*

- assume follow-up completo
- è una proporzione perciò può assumere valori da 0 ad 1
- deve riferirsi ad uno specifico periodo di tempo

$$IC = \frac{\text{N° di persone che ammalano tra il } t_0 \text{ e } t_1}{\text{N° di persone non malate all'inizio del periodo } t_0}$$

Es. 5 si ammalano / 10 inizialmente non malati = 0.5

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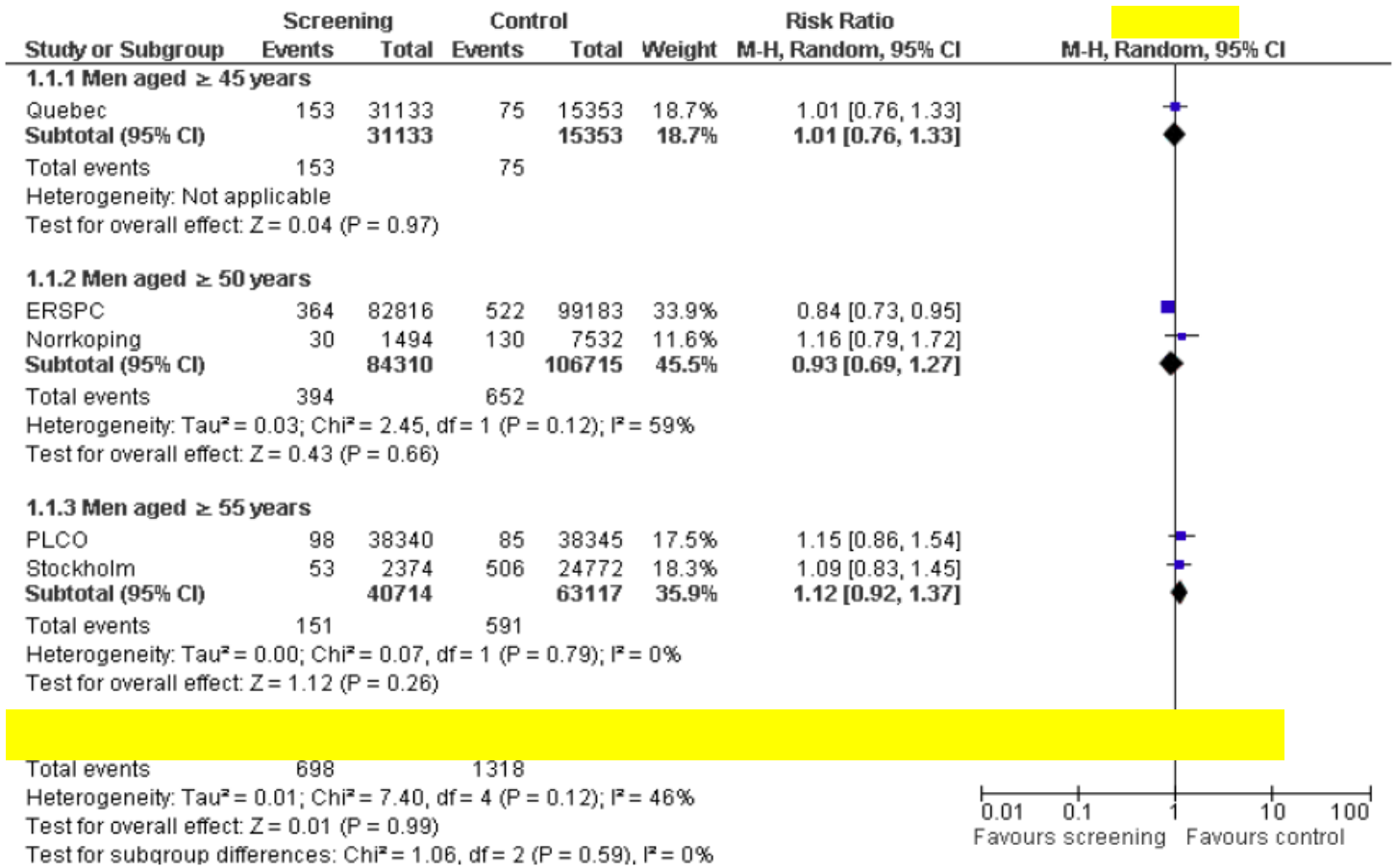
Screening for prostate cancer (Review)

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)



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

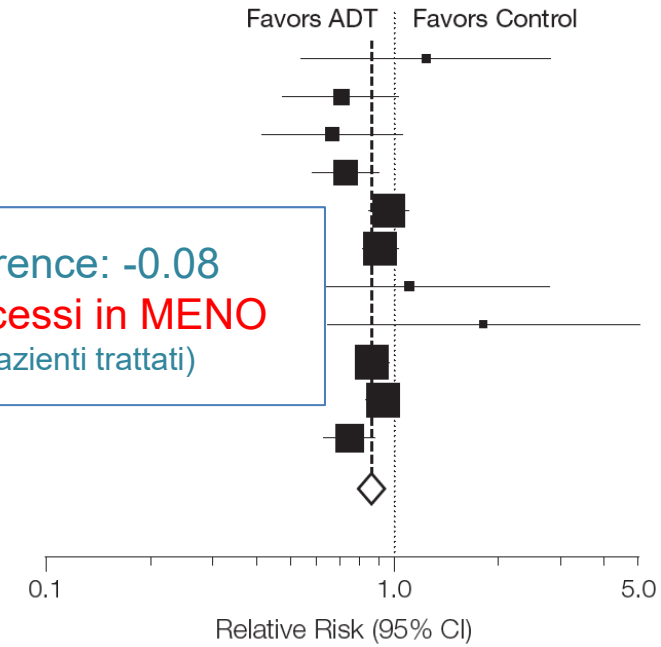
JAMA. 2011;306(21):2359-2366

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

Source	No./Total No. of Events: ADT	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.[illegible]-0.87)

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)



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  - ***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

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

Risks, Rates and Odds

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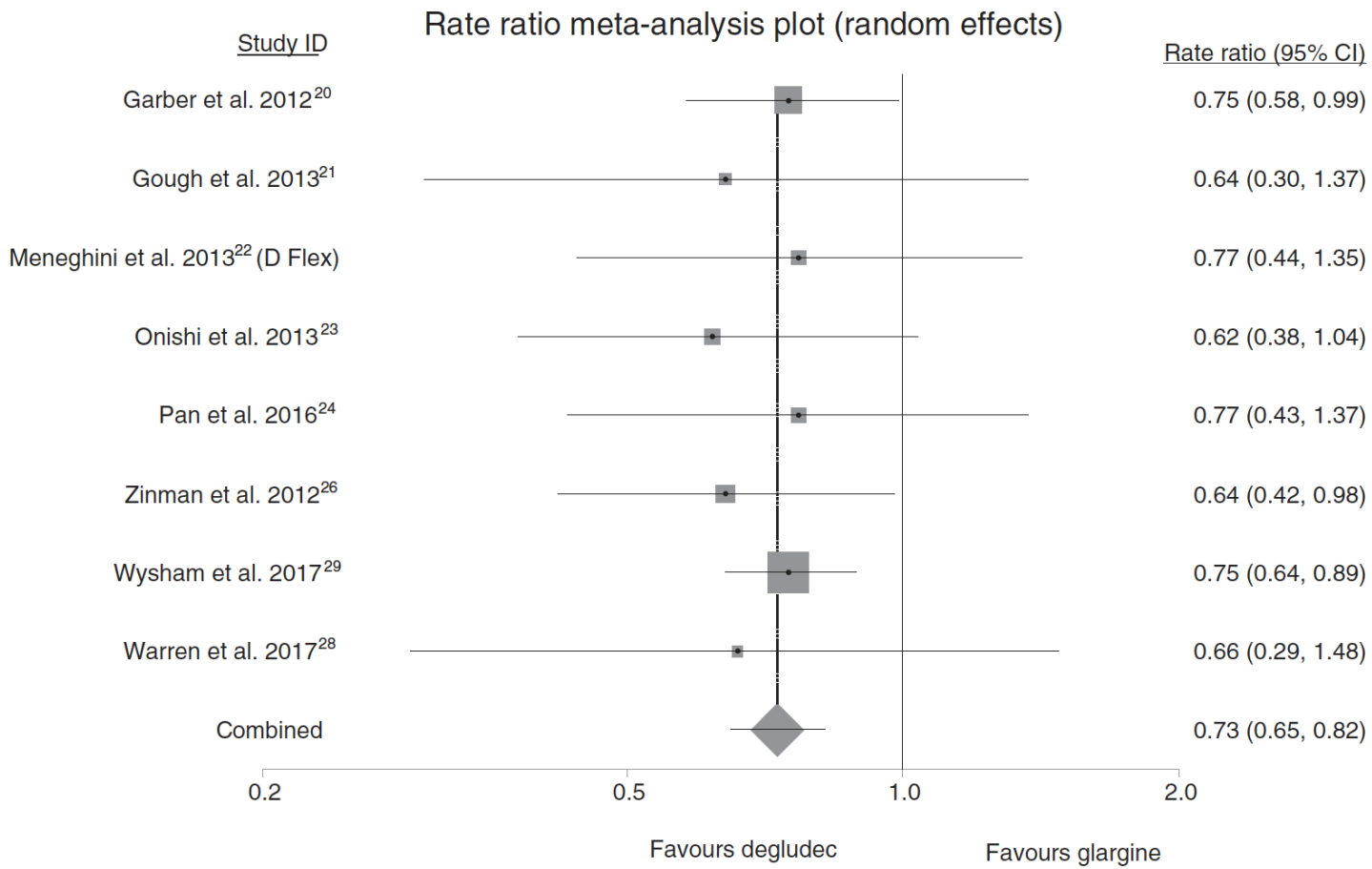
Comparative effectiveness and harms of long-acting insulins for type 1 and type 2 diabetes: A systematic review and meta-analysis

Rebecca S. Holmes MD | Elizabeth Crabtree PhD | Marian S. McDonagh PharmD

Diabetes Obes Metab. 2019;21:984–992.



Nocturnal hypoglycaemia event rates in adult patients with type 2 diabetes treated with daily degludec compared with glargine

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  - ***Odds Ratio*** = ratio of 2 odds

Risks, Rates and Odds

- ***Risk*** (proportion of persons with disease = *cumulative incidence*)

es =

- ***R***

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**

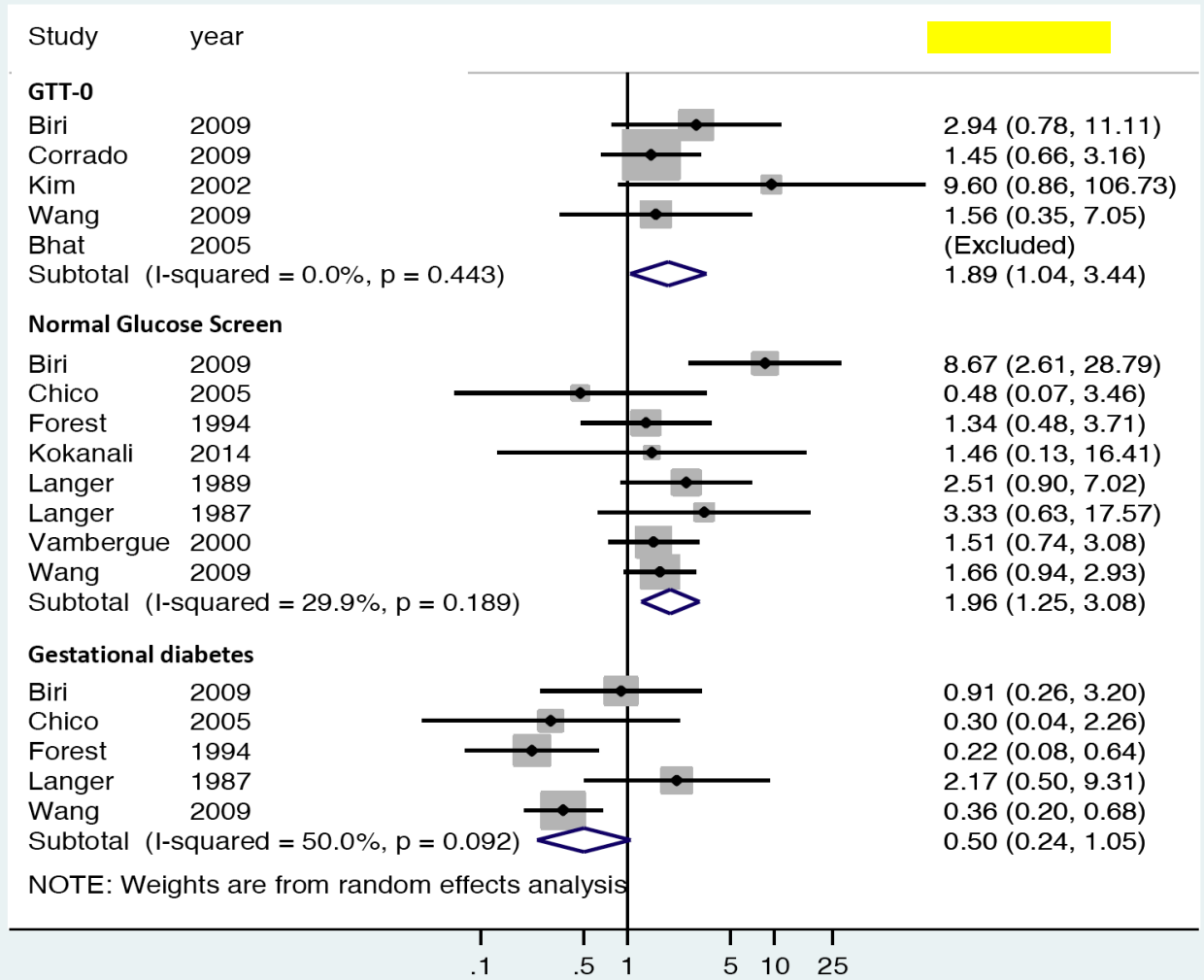
- ***Odds*** (the events divided by the number of non events)
  - ***Odds Ratio*** = ratio of 2 odds

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

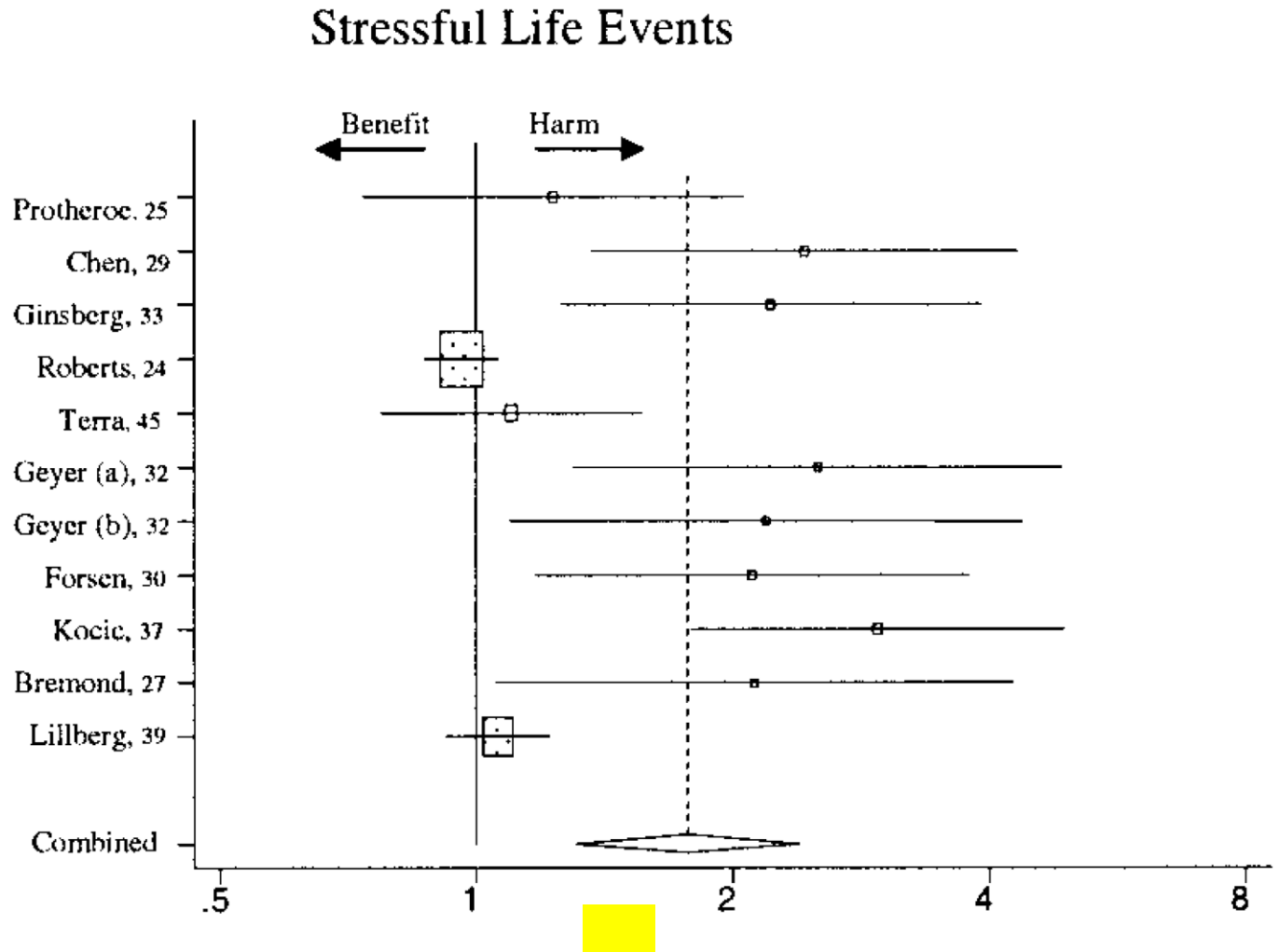


Int. J. Cancer: **107,** 1023–1029 (2003)

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

- 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.

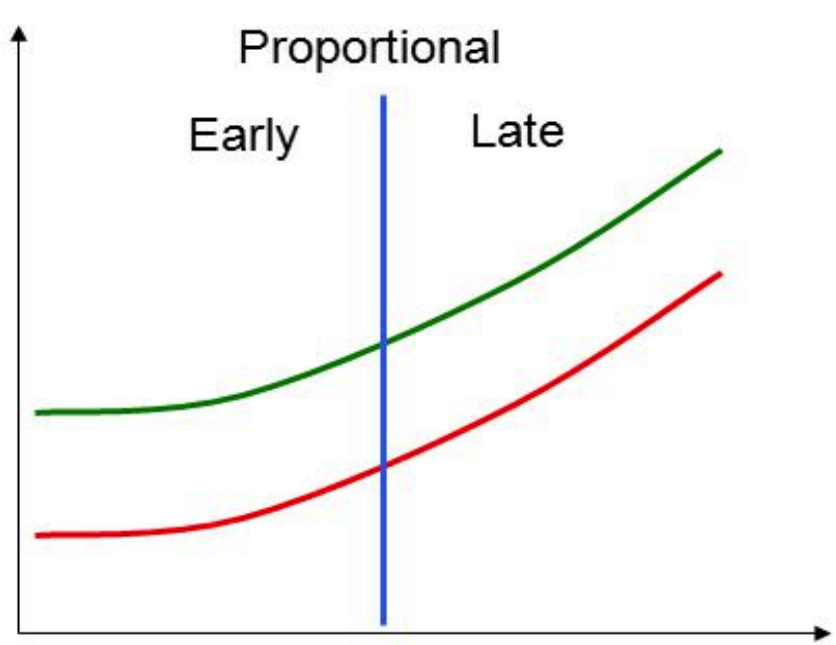
Indicatori riassuntivi di effetto di variabili tempo-a-evento

- Differenza tra stime della mediana di s
- D ted *m*
- D) al tempo *t* *estone* Survival)
- **Hazard Ratio** (KM+Cox)

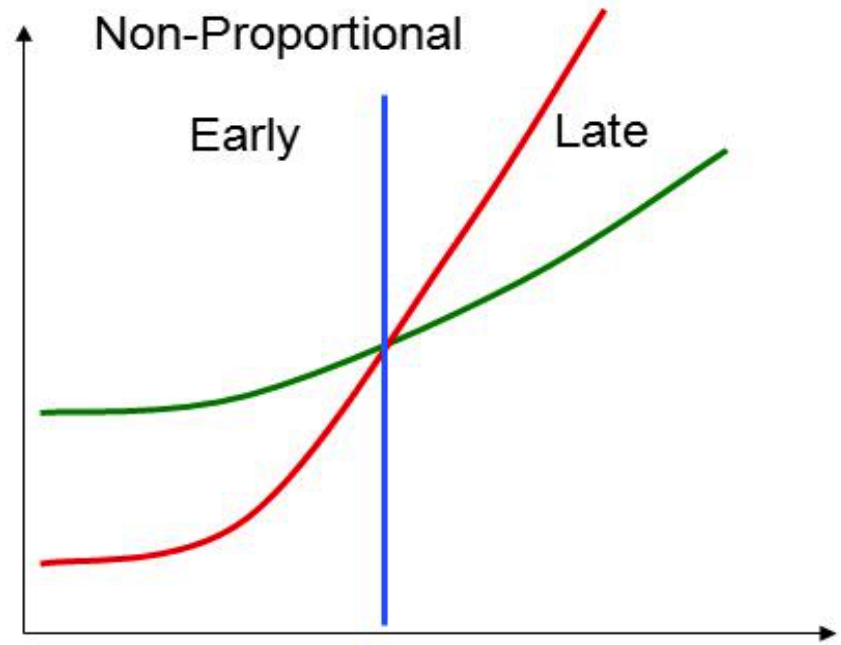
Appropriato quando il rapporto tra gli *hazard* dei due gruppi si mantiene (relativamente) costante

Proportional Hazard Assumption

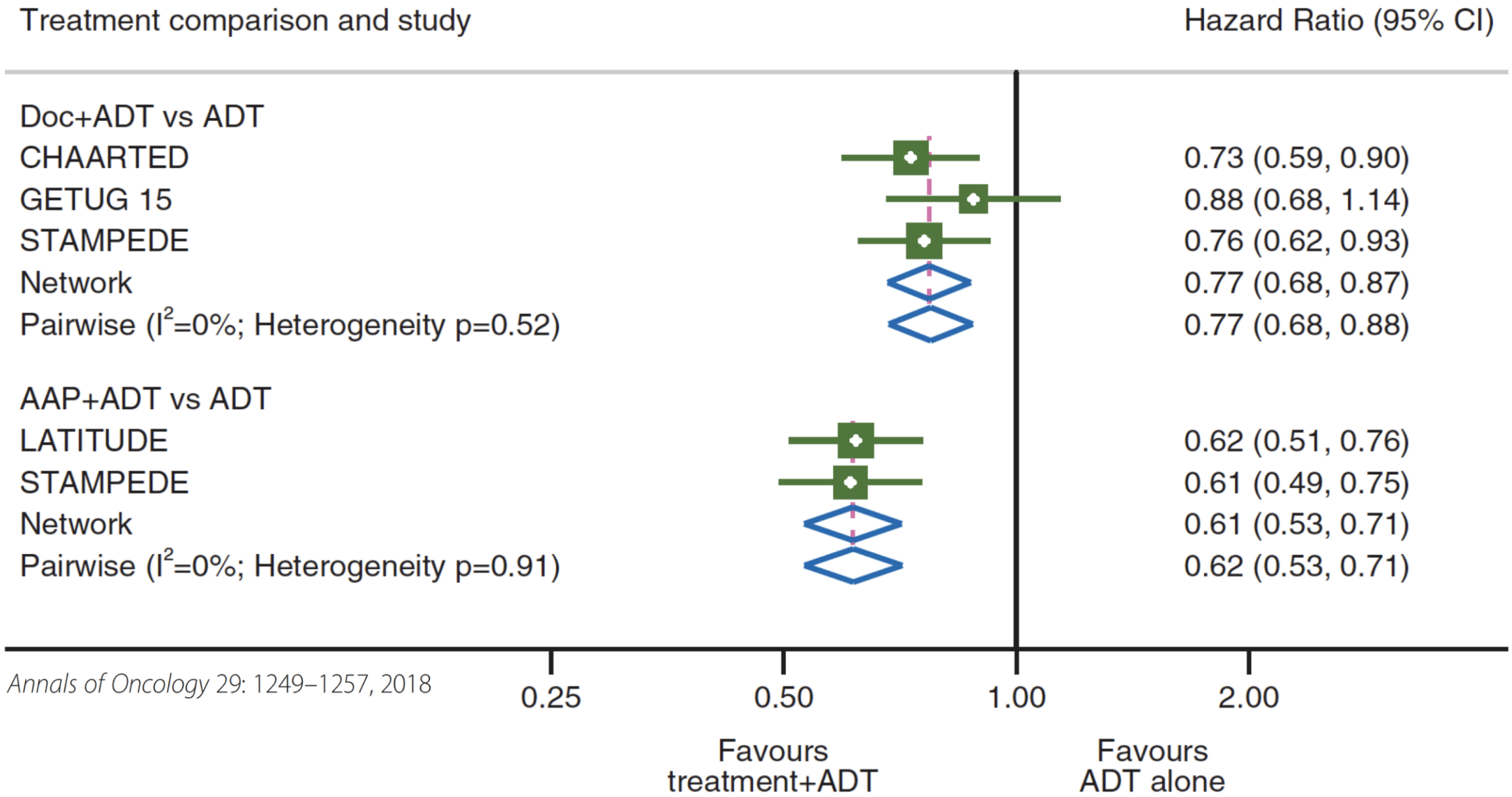
If we are comparing a new treatment with the standard treatment, it is assumed that the ratio of the hazard for an individual on a new treatment to that for an individual on the standard treatment remains constant over time



Here, the effect is the same in both time periods



Here, the effect is negative in the early period and positive in the late period



Annals of Oncology 29: 1249–1257, 2018

Treatment comparison and study

Hazard Ratio (95% CI)

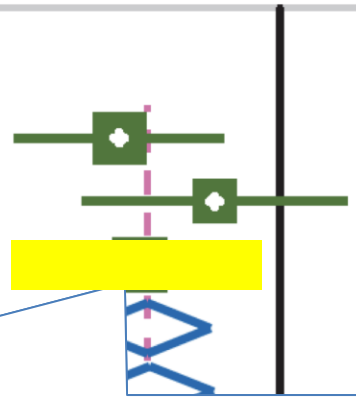
Doc+ADT vs ADT

CHAARTED

GETUG 15

Network

Pairwise (I^2=0%; Heterogeneity p=0.52)



0.73 (0.59, 0.90)

0.88 (0.68, 1.14)

0.76 (0.62, 0.93)

0.77 (0.68, 0.87)

0.77 (0.68, 0.88)

0.62 (0.51, 0.76)

0.61 (0.49, 0.75)

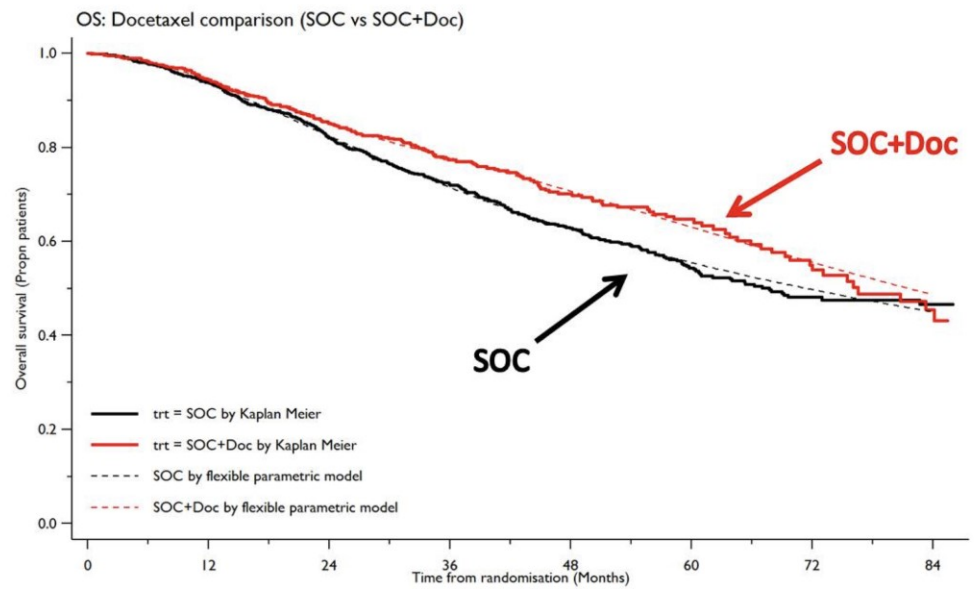
0.61 (0.53, 0.71)

0.62 (0.53, 0.71)

2.00

Favours
DT alone

Docetaxel: Survival



HR (95%CI) **0.78** (0.66, 0.93)
P-value **0.006**