A tale of two meta-analyses

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It is the best of times, It is the worst of times

- it was the age of wisdom, it was the age of foolishness,
- it was the epoch of belief, it was the epoch of incredulity
- It was the season of light, it was the season of darkness
- It was the spring of hope, it was the winter of despair

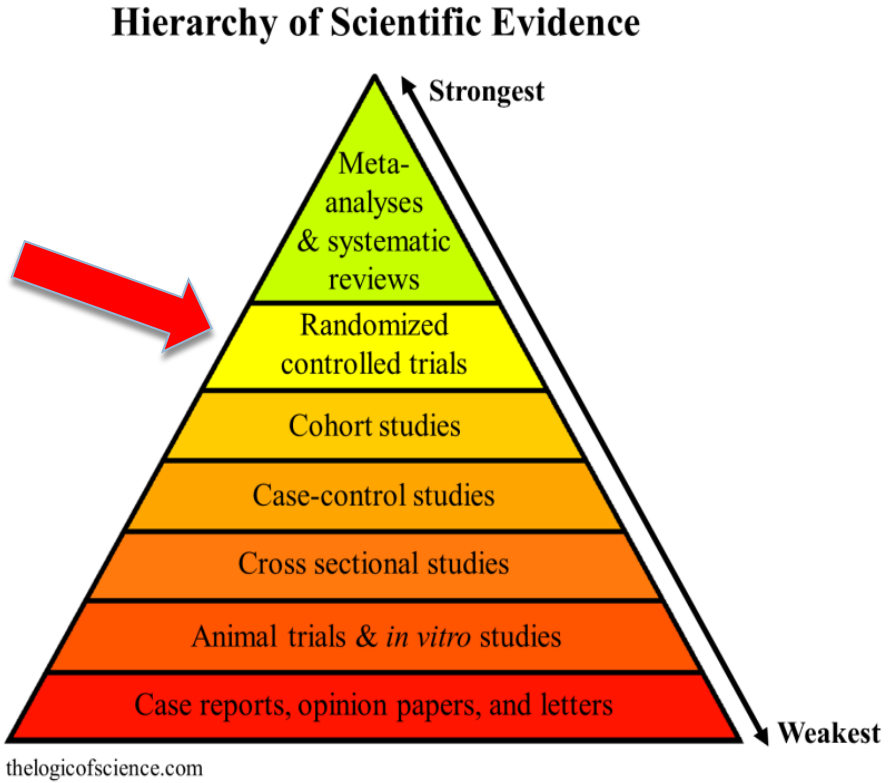
A tale of two cities

- Charles Dickens
  - Published 1859
- Not too dissimilar to the situation with present day clinical trials ……

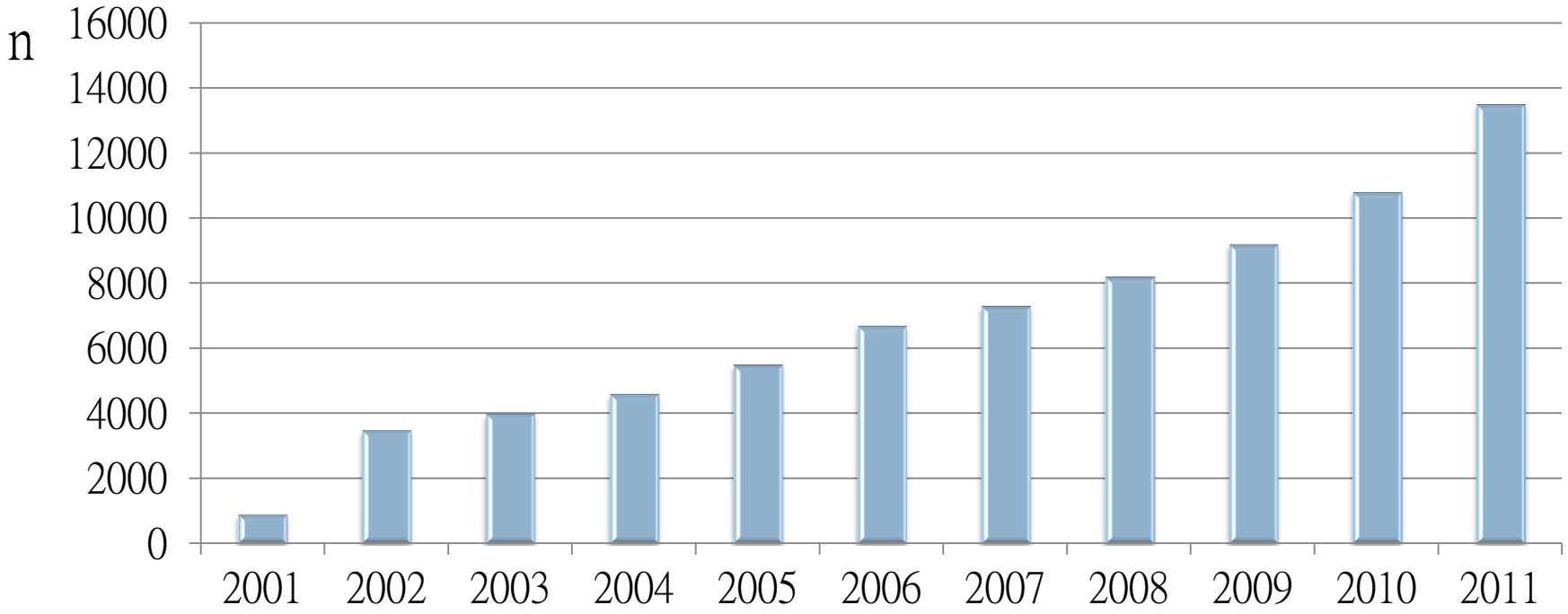
Selected clinical trials with acronyms starting with "A"

A-COMET-I, A-COMET-II, A-HEFT, AAA, AAASPS, AACHEN, AASK, ABACAS, ABCD, ABOARD, ACADEMIC, ACAS, ACC AMI GAP, ACCEL-AMI, ACCEL-RESISTACE, ACCEPT, ACCLAIM, ACCOMPLISH, ACCORD, ACCT, ACCURACY, ACE, ACES, ACIP, ACME, ACME-2, ACORN, ACT, ACTION, ACTIVATE, ACTIVE-W, ACTIV in CHF, ACUTE, ACUITY, ADAM, ADAPT, ADIOS, ADMIRAL, ADMIT, ADOPT, ADVANCE, ADVENT,AF-CHF, AFASAK, AFASAK-2, AFCAPS, AFFIRM, AFREGS, AGENT, AGENT-2, AGENT -3,AIDA-STEMI, AIM-HIGH, A-HeFT, AiMI, AIMS, AIRCRAFT, AIRE, Air-PAMI, ALBION, ALERT, ALIVE, ALKK, ALLAY, ALLHAT, ALLIANCE, ALPHABET, ALPHEE, ALTITUDE, AMEDIEUS, AMIGO, AMIHOT, AMIOVERT, AISTAD I, AMISTAD II, AMRO, ANBP2, ANTIBIO, ANTIPAF, ANZ-Carvedilol, APAF, APEX-AMI, APLAUSE, APPRAISE, APRICOT, APRICOT-2, ARBITER 2, ARCH, ARCHIPELAGO, ARCHer, ARCTIC, ARG, ARGAMI-2, ARIC, ARISE, ARISTOTLE, ARMYDA, ARMYDA-2, ARPEGGIO, ARREST, ART, ARTIST, ARTISTIC, ARTS, ARTS II, ARVD, ASAP, ASCOT-BP, ASCOT-LLA, ASIS, ASPAC, ASPECT, ASPECT-2, ASPIRE, ASSENT-1, ASSENT-2, ASSENT-3, ASSENT 3 PLUS, ASSENT-4, ASSENT-4 PCI, ASSERT, ASSET, ASSIST, ASTAMI, ASTRAL, ATBC, ATHENA, ATHEROMA, ATLANTIC, ATLAS,

Pyramid of evidence



Meta-analyses publications



- How can this NOT be the best of times ...
- Not be the age of wisdom, the epoch of belief, the season of light and the spring of hope …

A tale of two meta-analyses

- Thiazolidinediones (TZDs) and CV death

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

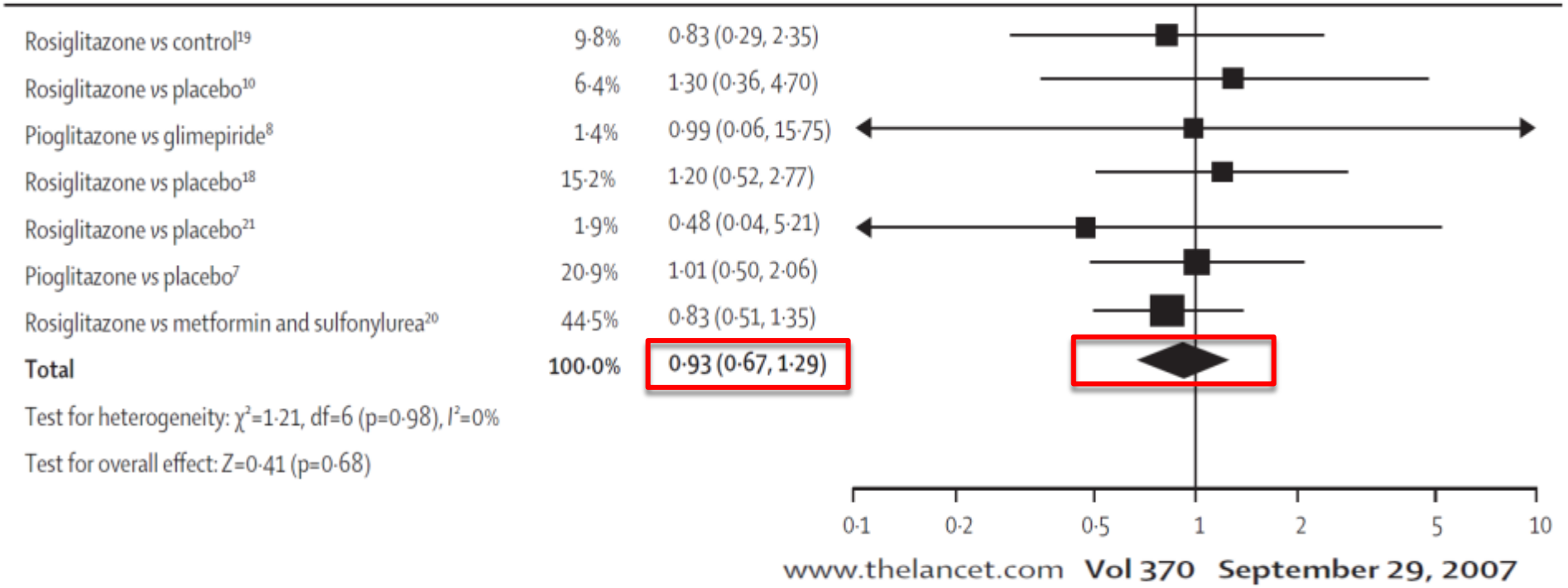
Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Tabl

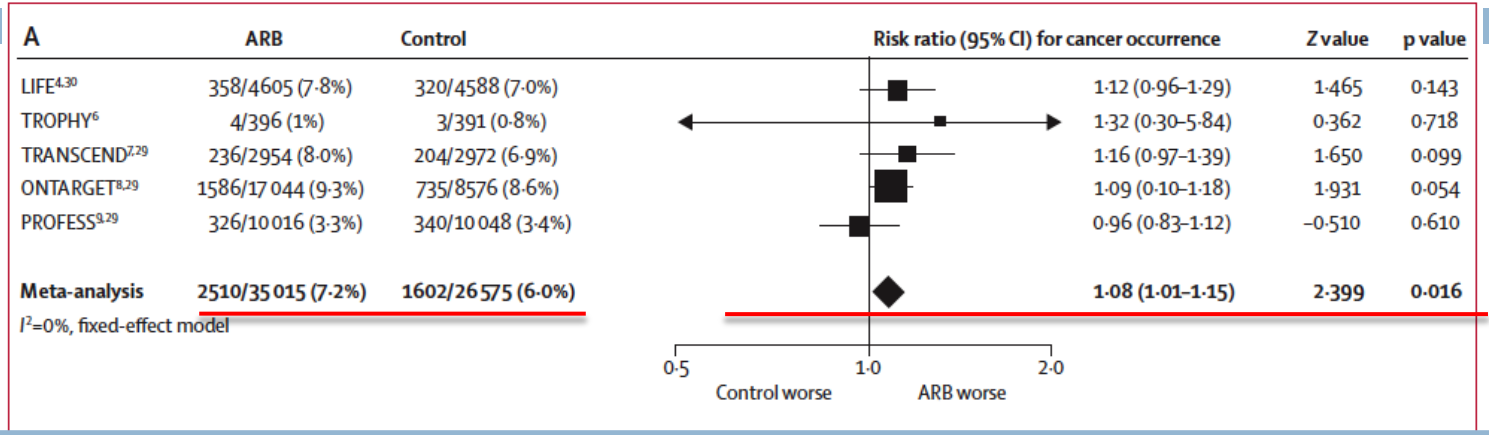
Stud				P Value
Myo				
Sma				0.15
DRE				0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials

A *Rodrigo M Lago, Premranjan P Singh, Richard W Nesto*



Angiotensin receptor blockers and cancer



A	ARB	Control	Risk ratio (95% CI) for cancer occurrence	Z value	p value
LIFE[4,30]	358/4605 (7·8%)	320/4588 (7·0%)	1·12 (0·96–1·29)	1·465	0·143
TROPHY[6]	4/396 (1%)	3/391 (0·8%)	1·32 (0·30–5·84)	0·362	0·718
TRANSCEND[7,29]	236/2954 (8·0%)	204/2972 (6·9%)	1·16 (0·97–1·39)	1·650	0·099
ONTARGET[8,29]	1586/17 044 (9·3%)	735/8576 (8·6%)	1·09 (0·10–1·18)	1·931	0·054
PROFESS[9,29]	326/10 016 (3·3%)	340/10 048 (3·4%)	0·96 (0·83–1·12)	−0·510	0·610
Meta-analysis	**2510/35 015 (7·2%)**	**1602/26 575 (6·0%)**	**1·08 (1·01–1·15)**	**2·399**	**0·016**

I^2=0%, fixed-effect model

Lancet Oncol 2010; 11: 627–36

Alarming claim

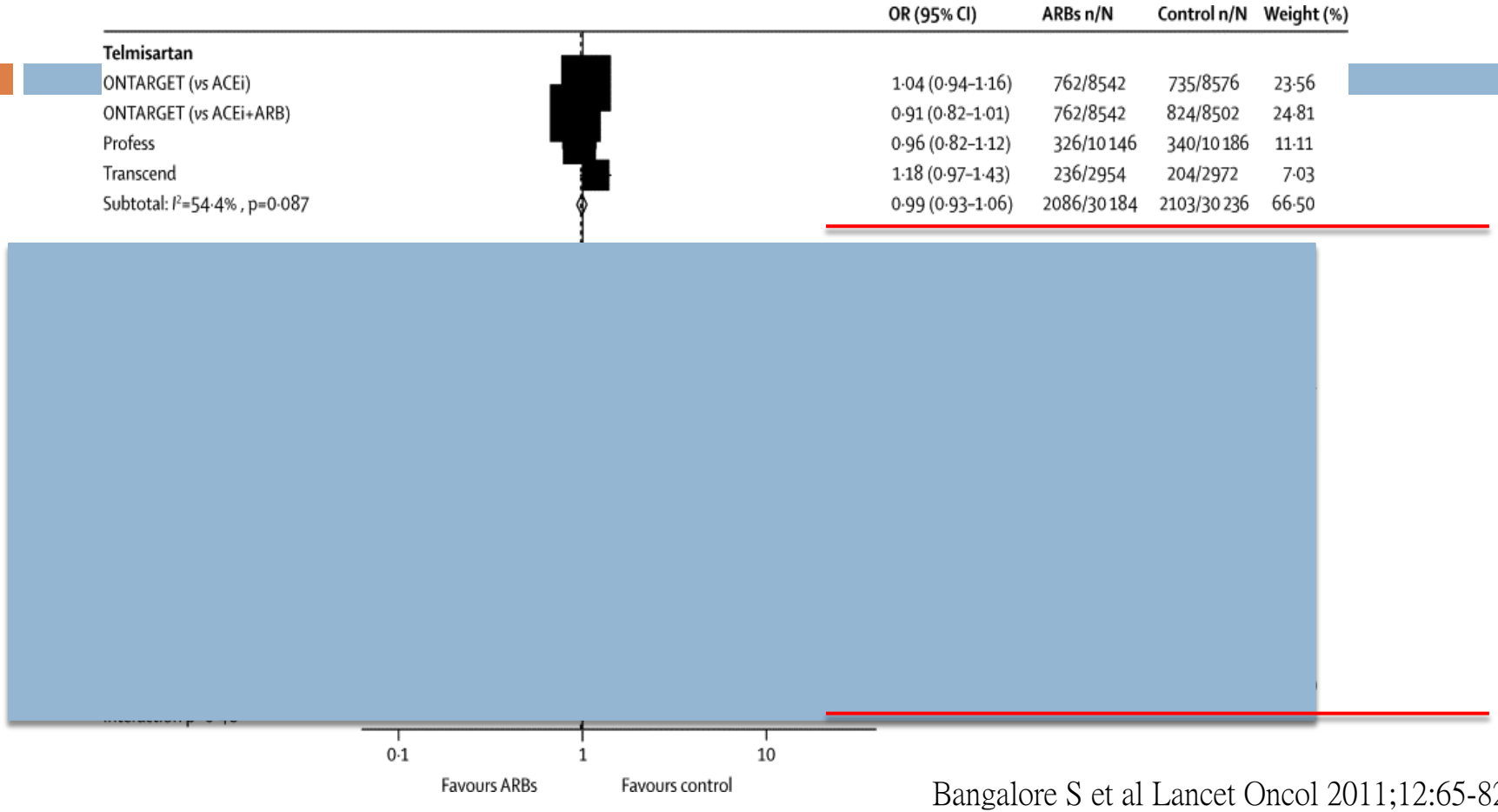
- Numbers needed to treat to cause one excess cancer
- 143 patients for 4 years

Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324 168 participants from randomised trials

Sripal Bangalore, Sunil Kumar, Sverre E Kjeldsen, Harikrishna Makani, Ehud Grossman, Jørn Wetterslev, Ajay K Gupta, Peter S Sever, Christian Gluud, Franz H Messerli

Bangalore S et al Lancet Oncol 2011;12:65-82

ARBs and cancer risks



Bangalore S et al Lancet Oncol 2011;12:65-82

ARBs and cancer

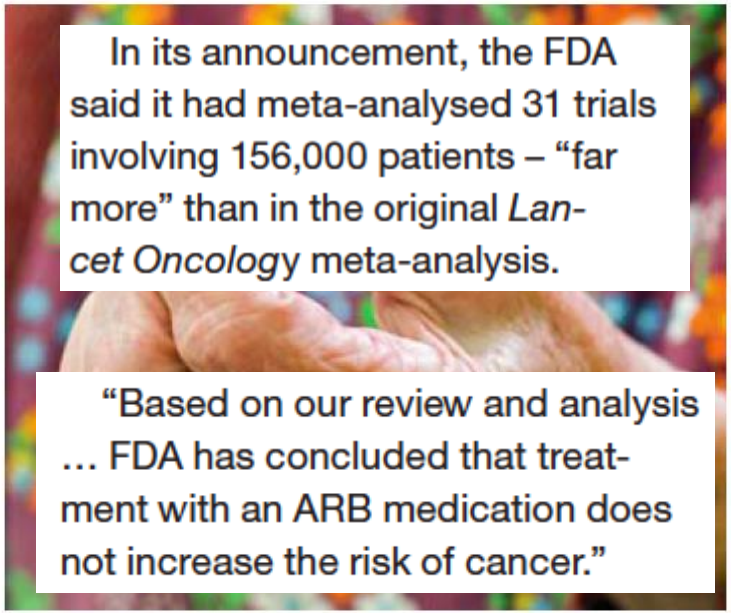
ARBs don't increase cancer risk: review

David Brill

Authorities have shot down a possible link between ARBs and lung cancer, after a controversial meta-analysis raised widespread concerns last year.

A review released yesterday by the US Food and Drug Administration concluded that treatment with an ARB "does not increase the risk of cancer" – putting an end to months of heated debate in the medical literature.

The saga began last June with a meta-analysis in the *Lancet Oncology*, linking ARBs to a small but

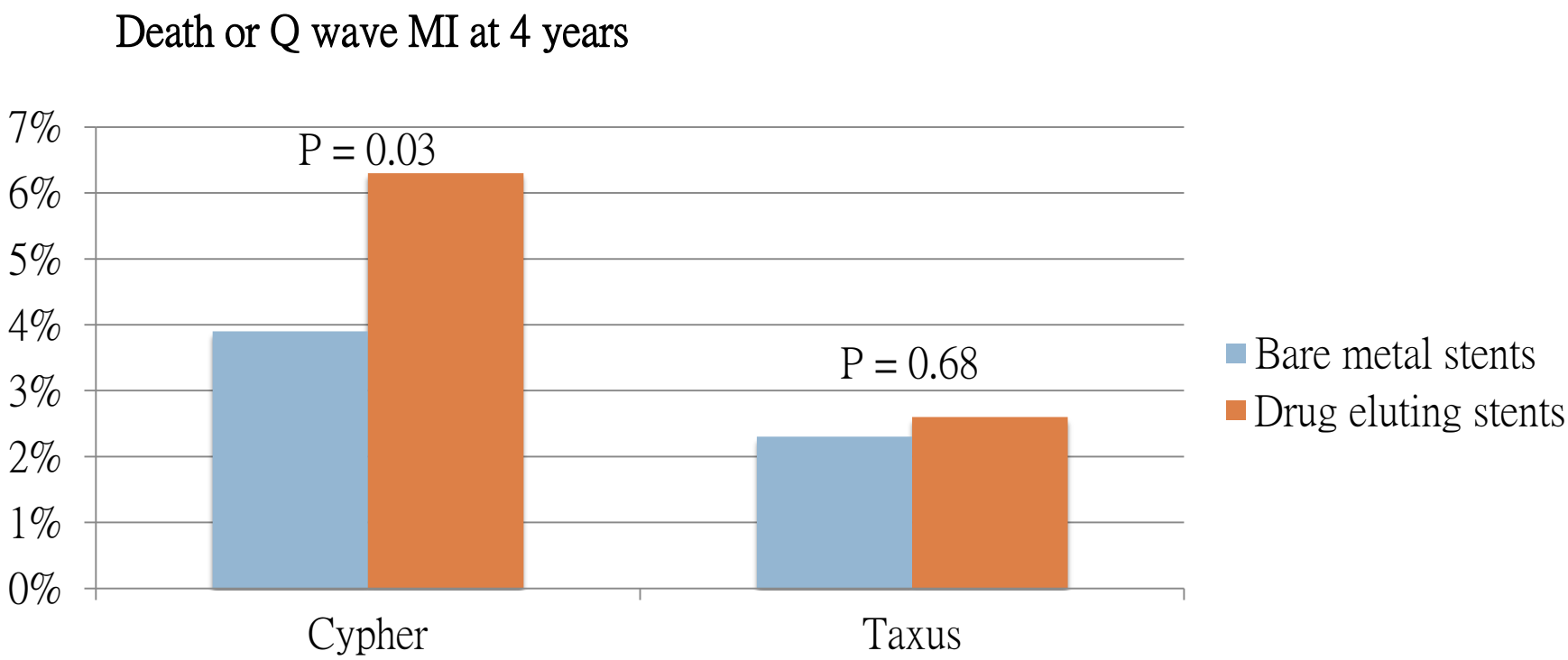


Several subsequent studies had failed to replicate the findings of a link between ARBs and lung cancer

Drug eluting stents increased mortality

- 2 meta-analyses presented in ESC 2006 in Barcelona
- Camenzind meta-analysis
- Nordmann meta-analysis

Camenzind meta-analysis



European Heart Journal (2006) **27**, 2784–2814
doi:10.1093/eurheartj/ehl282

EUROPEAN SOCIETY OF CARDIOLOGY®

Clinical research
Interventional cardiology

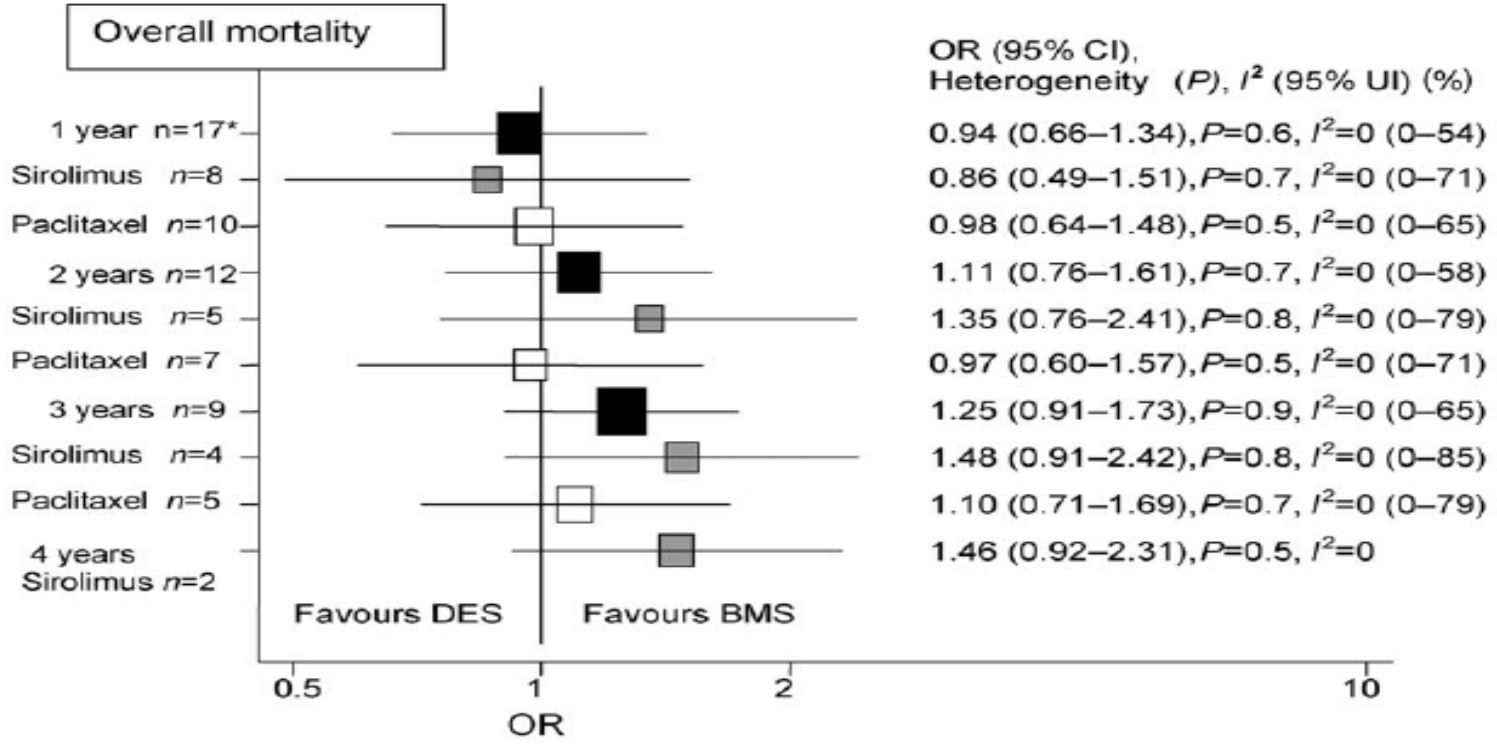
Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis

Alain Joel Nordmann*, Matthias Briel, and Heiner Claudins Bucher

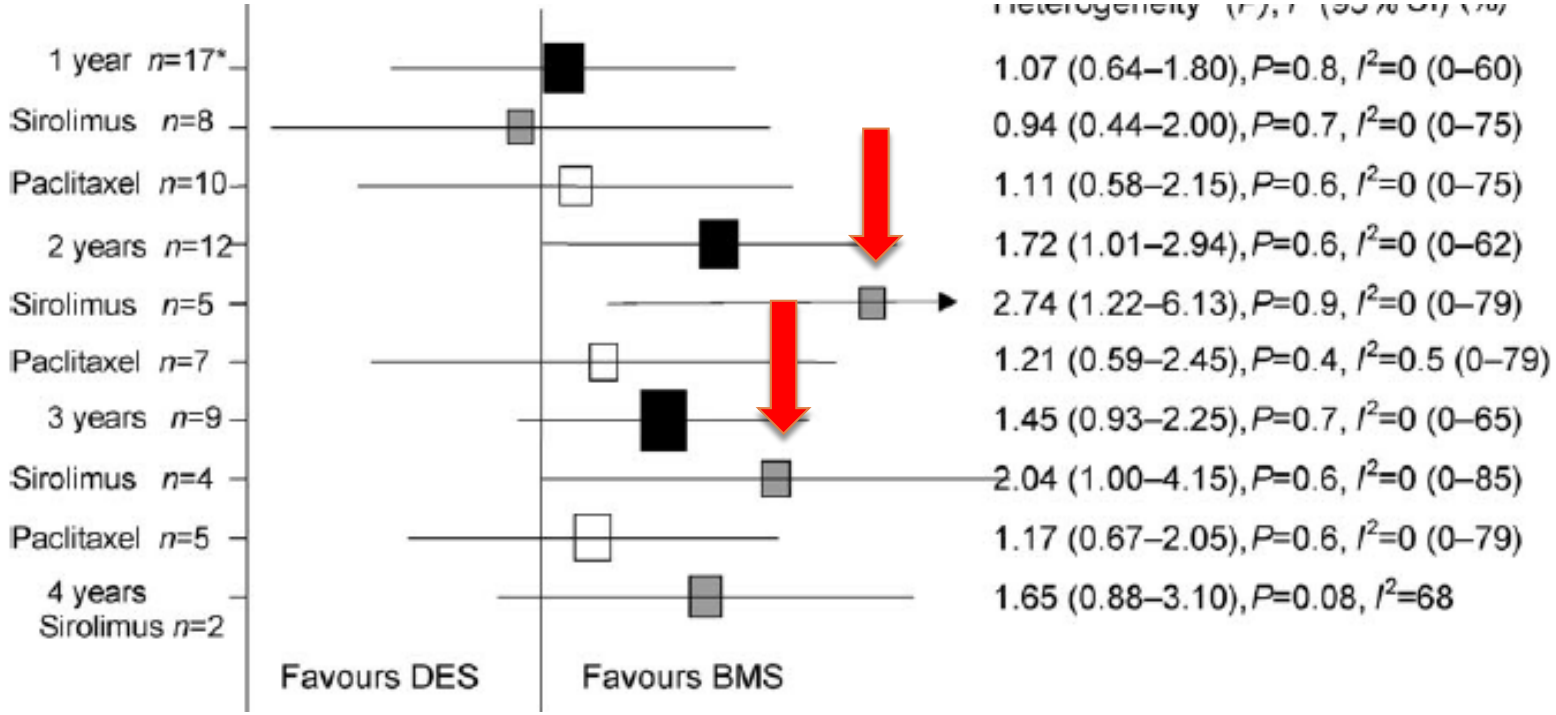
Basel Institute for Clinical Epidemiology, University Hospital Basel, Hebelstrasse 10, 4031 Basel, Switzerland

Received 28 April 2006; revised 20 July 2006; accepted 11 September 2006; online publish-ahead-of-print 4 October 2006

See page 2737 for the editorial comment on this article (doi:10.1093/eurheartj/ehl378)


Overall mortality
OR (95% CI),
Heterogeneity (P), I² (95% UI) (%)
1 year n=17*
0.94 (0.66–1.34), P=0.6, I²=0 (0–54)
Sirolimus n=8
0.86 (0.49–1.51), P=0.7, I²=0 (0–71)
Paclitaxel n=10
0.98 (0.64–1.48), P=0.5, I²=0 (0–65)
2 years n=12
1.11 (0.76–1.61), P=0.7, I²=0 (0–58)
Sirolimus n=5
1.35 (0.76–2.41), P=0.8, I²=0 (0–79)
Paclitaxel n=7
0.97 (0.60–1.57), P=0.5, I²=0 (0–71)
3 years n=9
1.25 (0.91–1.73), P=0.9, I²=0 (0–65)
Sirolimus n=4
1.48 (0.91–2.42), P=0.8, I²=0 (0–85)
Paclitaxel n=5
1.10 (0.71–1.69), P=0.7, I²=0 (0–79)
4 years
Sirolimus n=2
1.46 (0.92–2.31), P=0.5, I²=0
Favours DES
Favours BMS
0.5
1
2
10
OR

Non cardiac mortality



Nordmann meta analysis: conclusions

- Drug eluting stents do not decrease mortality
- Sirolimus, not paclitaxel, stents increased non cardiac mortality at 2 and 3 years

Comprehensive Meta-Analysis on Drug-Eluting Stents versus Bare-Metal Stents during Extended Follow-up

Henri Roukoz, MD,[a] Anthony A. Bavry, MD, MPH,[b] Michael L. Sarkees, MD,[c] Girish R. Mood, MD,[d] Dharam J. Kumbhani, MD, SM,[d] Mark G. Rabbat, MD,[e] Deepak L. Bhatt, MD, MPH[f]

- 28 trials, 10727 patients
- No excess mortality with drug eluting stents

The American Journal of Medicine (2009) 122, 581.e1-581.e10

History is full of concerns raised by meta-analysis

- Statins caused increased cancer deaths, violent and traumatic deaths
- Ezetimibe increased cancer risks
- Angiotensin converting enzyme inhibitor increased lung cancer risks
- Calcium blockers increased breast cancer risks

Calcium Channel Blockers and Risk of Breast Cancer: A Meta-Analysis of 17 Observational Studies

Wen Li[1¶], Qi Shi[1], Weibing Wang[2], Jianrong Liu[1], Qi Li[3], Fenggang Hou[1*]

1 Oncology Department of Shanghai Municipal Hospital of Traditional Chinese Medicine affiliated to Shanghai TCM University, Shanghai, China, 2 Department of Epidemiology, School of Public Health, Fudan University, Shanghai, China, 3 Oncology Department of Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China

RETRACTION

Retraction: Calcium Channel Blockers and Risk of Breast Cancer: A Meta-Analysis of 17 Observational Studies

The *PLOS ONE* Editors

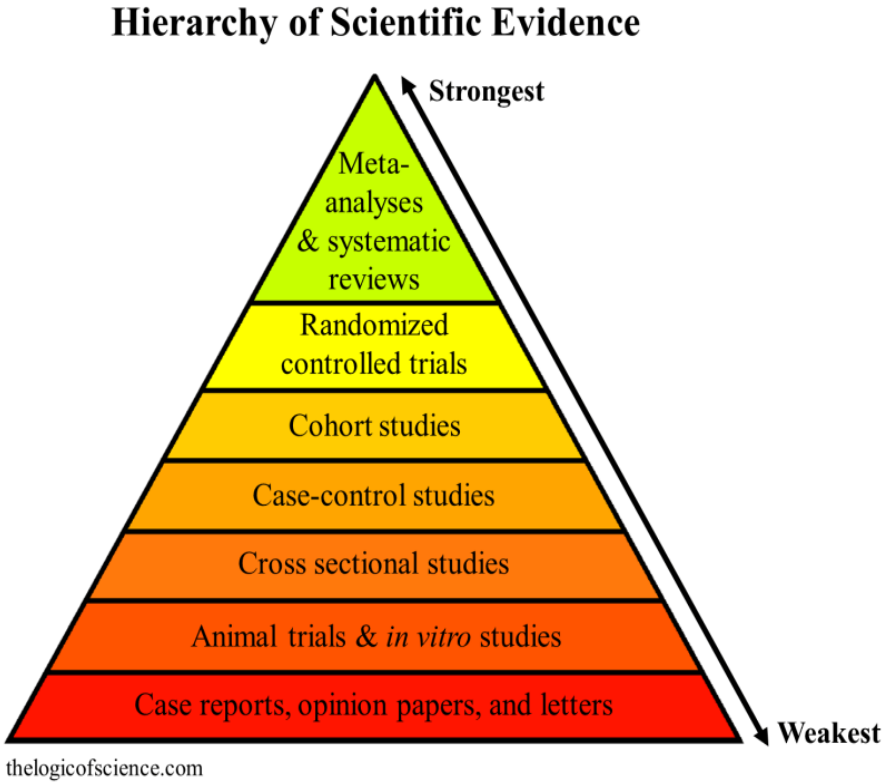
Citation: The *PLOS ONE* Editors (2018) Retraction: Calcium Channel Blockers and Risk of Breast Cancer: A Meta-Analysis of 17 Observational Studies. PLoS ONE 13(5): e0198220. https://doi.org/10.1371/journal.pone.0198220

Published: May 23, 2018

Meta-analysis

- Meta-analyses are not worth the paper the are printed on !
- Meta-analyses are like sausages……
- Only God and the butcher know what goes into them and neither would ever eat any !

Pyramid of evidence



How do we reconcile the difference ?

Steps of a meta-analysis (same as primary studies)

- Hypotheses
- Design
  - Inclusion and exclusion criteria
- Data collection
- Statistical analysis (meta analysis)
- Conclusions and report

Results of a meta analysis

- Mean effect size
- Estimate of the variability (heterogeneity)

Mean effect size of a meta-analysis

- Not an average of effect sizes all the studies included !
- Weights are attached to each study
  - Weighted mean
- Weights are given according to the variance of each study

Heterogeneity in meta-analyses

- Within study
- Between study
  - Heterogeneity of the true effect sizes
  - Random sampling errors

Interpreting meta-analyses

- Heterogeneity
- Random vs fixed effect model
- Publication bias

Fixed effect model

- Common (singular) effect
- Assume *ONE* true effect size in real life
  - True effect does NOT vary between study
- Heterogeneity observed entirely due to random sampling errors

Random effects model

- The true effects are “random” (distributed normally)
- The observed heterogeneity
  - True heterogeneity + Random sampling error
- Most (if not all) clinical scenarios

Fixed Vs random effects models

- Fixed effect model
  - A narrower confidence interval
  - More likely to yield significant p values
- Random effects model
  - More conservative estimate of effect size
  - Wider confidence interval
  - Less likely to yield significant p values

Number of studies in a meta-analysis

- Less important in fixed effect model
- Singular effect assumed
  - Large studies assume most weights
- Random effects models need larger number of studies
  - Individual studies of large sample size assume less weights

Statistical measures of heterogeneity

- Cochrane Q
  - Null hypothesis: observed heterogeneity between studies due to random sampling errors alone
  - P value < 0.1 : significant heterogeneity
- I^2 percentage
  - Percentage of observed heterogeneity due to real heterogeneity rather than sampling error
  - > 50% (25%) indicates significant heterogeneity

Is heterogeneity a bad thing ?

- No !
- It is what is expected in a real life clinical situation
- What to do if there is significant heterogeneity ?

How to determine if a fixed effect or random effects model should be used ?

- Determined by the clinical scenario
  - Fixed effect models seldom applicable
- Should not depend on assessment of heterogeneity !
- Wrong to use fixed effect models even if there is no significant heterogeneity

A

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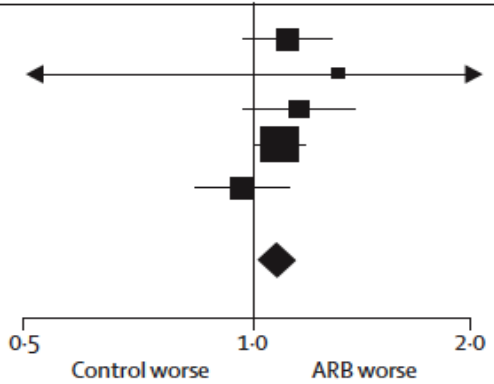
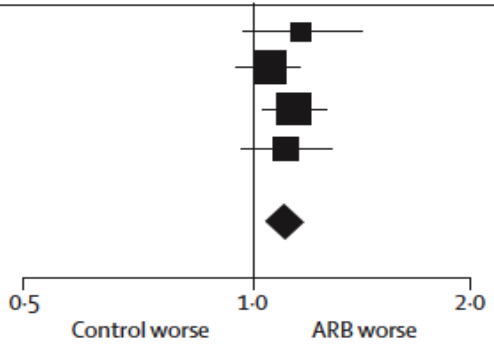


B

	Risk ratio (95% CI) for cancer occurrence	Z value	p value
TRANSCEND[7,29]	1·17 (0·97–1·41)	1·645	0·100
ONTARGET[8,29] (telmisartan *vs* ramipril)	1·05 (0·95–1·16)	0·933	0·351
ONTARGET[8,29] (telmisartan+ramipril *vs* ramipril)	1·14 (1·03–1·26)	2·548	0·011
LIFE[4,30]	1·12 (0·96–1·29)	1·465	0·143
Meta-analysis	**1·11 (1·04–1·18)**	**3·244**	**0·001**

I^2=0%, fixed-effect model



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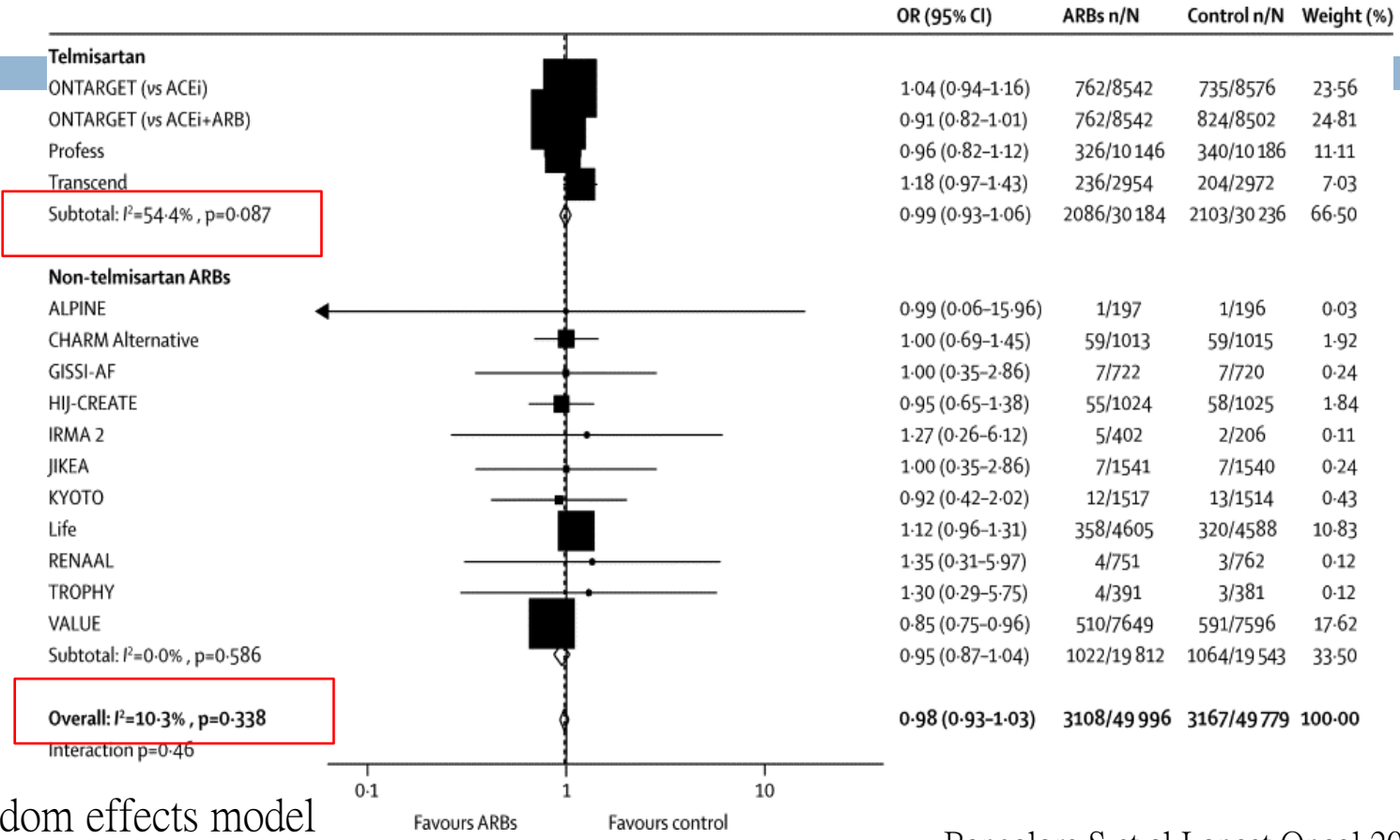
ARBs and cancer risks



Random effects model

Bangalore S et al Lancet Oncol 2011;12:65-82

Nissen meta-analysis on TZDs

- Fixed effect model
- Cochrane Q statistics used to assess heterogeneity
  - Justified use of fixed effect model as $p > 0.1$
- No information on the weighting of the trials

Suggestions to intelligently interpret meta-analyses

- Hypotheses are biologically plausible and supported by existing data
- Understand the search criteria used and possible biases from a limited search
- Heterogeneity of included studies
- Fixed vs random effects model
- Number of studies vs number of patients in each study
- Publication bias
- Interpretation and conclusions supported by data presented

Continued…

- Just be an intelligent consumer
- Do not just believe what you are told
- Do not be lured into complacency by the sheer number of patients in a meta-analysis
  - No guarantee of good data

Thank you for your attention

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