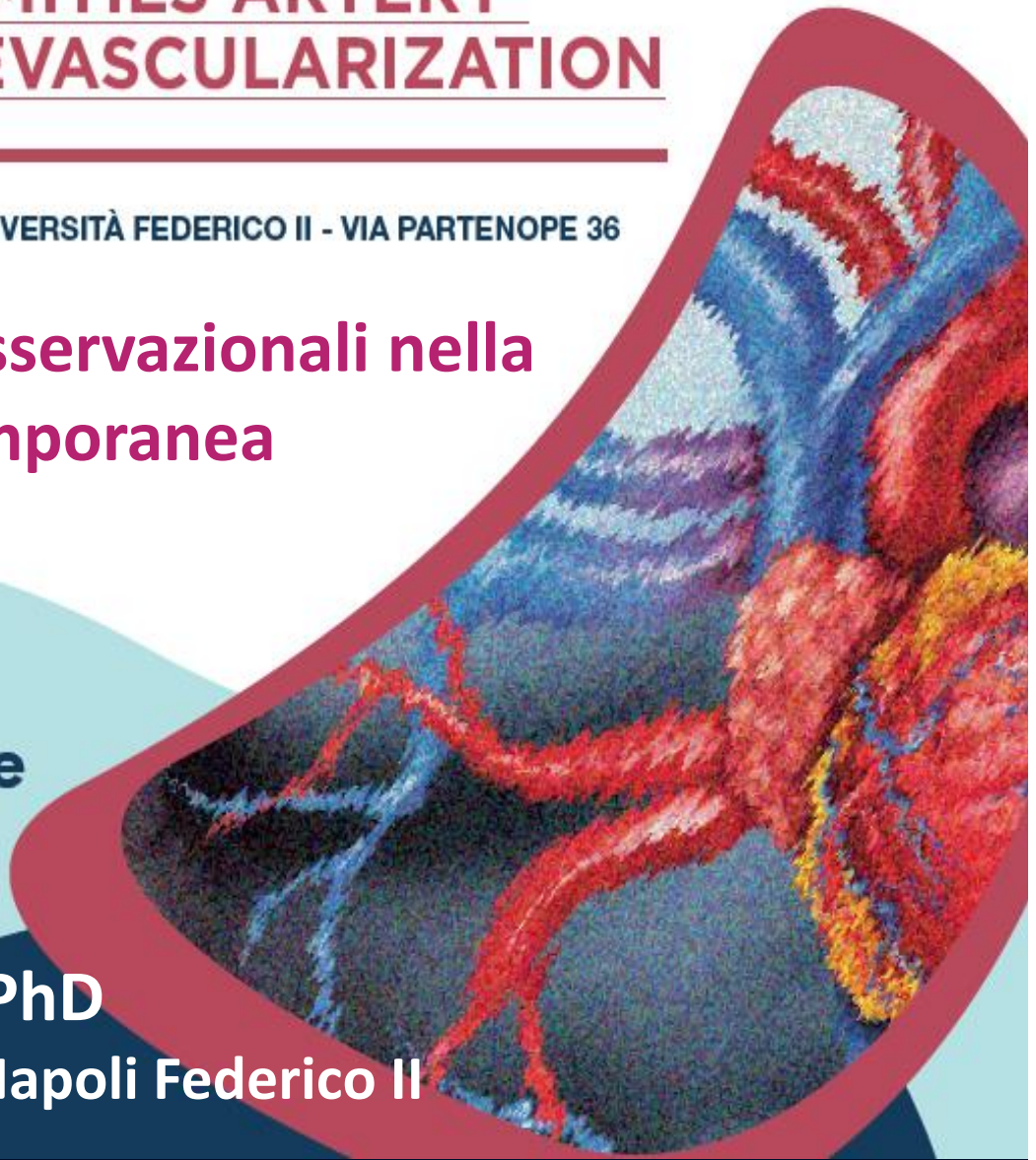
THE ADHERENCE TO MEDICAL THERAPY AFTER LOWER EXTREMITIES ARTERY DISEASE REVASCULARIZATION

CENTRO CONGRESSI UNIVERSITÀ FEDERICO II - VIA PARTENOPE 36

Il ruolo dei registri osservazionali nella ricerca clinica contemporanea



Napoli
25 novembre
2021

Raffaele Piccolo, MD PhD
Università degli Studi di Napoli Federico II

Randomized Trials, Observational Studies and Levels of Evidence

Randomized studies

Contribute to Levels of Evidence A & B

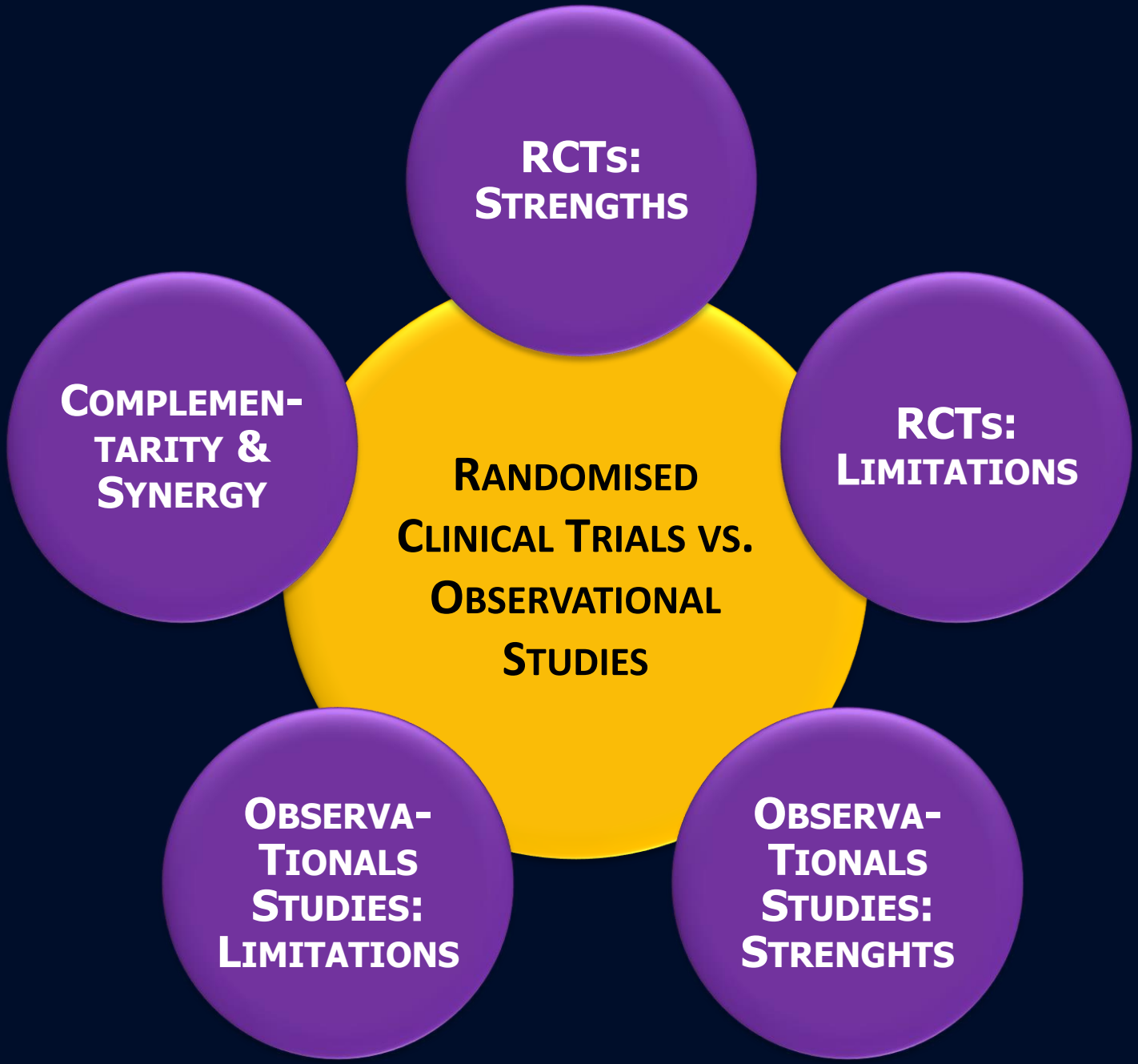
Observational studies

Contribute to Levels of Evidence B & C

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

Main Differences Between RCTs and Observational Studies

Randomized study **Observational study**


RCTs: Strengths
RCTs: Limitations
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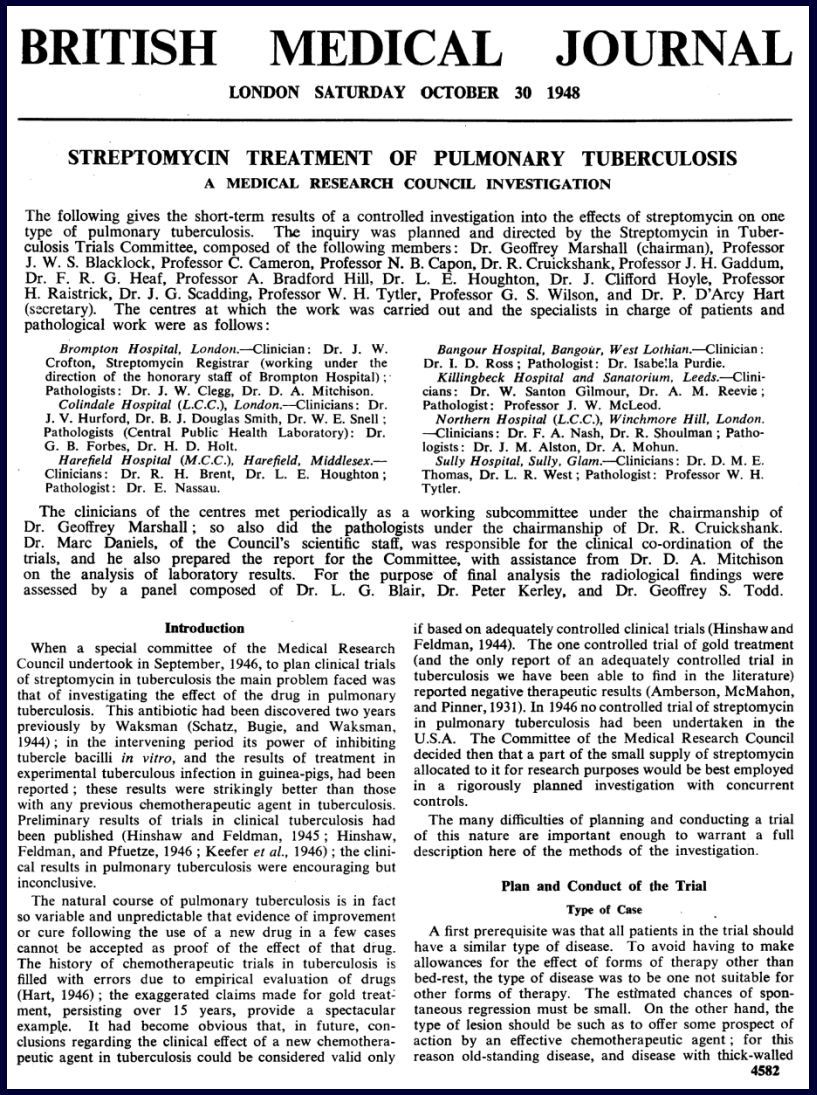
Randomised Clinical Trials vs. Observational Studies

The History of Randomized Clinical Trials



BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchison.

Colindale Hospital (L.C.C.), London.—Clinicians: Dr. J. V. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Snell; Pathologists (Central Public Health Laboratory): Dr. G. B. Forbes, Dr. H. D. Holt.

Harefield Hospital (M.C.C.), Harefield, Middlesex.—Clinicians: Dr. R. H. Brent, Dr. L. E. Houghton; Pathologist: Dr. E. Nassau.

Bangour Hospital, Bangour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reevie; Pathologist: Professor J. W. McLeod.

Northern Hospital (L.C.C.), Winchmore Hill, London.—Clinicians: Dr. F. A. Nash, Dr. R. Shoulman; Pathologists: Dr. J. M. Alston, Dr. A. Mohun.

Sully Hospital, Sully, Glam.—Clinicians: Dr. D. M. E. Thomas, Dr. L. R. West; Pathologist: Professor W. H. Tytler.

The clinicians of the centres met periodically as a working subcommittee under the chairmanship of Dr. Geoffrey Marshall; so also did the pathologists under the chairmanship of Dr. R. Cruickshank. Dr. Marc Daniels, of the Council's scientific staff, was responsible for the clinical co-ordination of the trials, and he also prepared the report for the Committee, with assistance from Dr. D. A. Mitchison on the analysis of laboratory results. For the purpose of final analysis the radiological findings were assessed by a panel composed of Dr. L. G. Blair, Dr. Peter Kerley, and Dr. Geoffrey S. Todd.

Introduction

When a special committee of the Medical Research Council undertook in September, 1946, to plan clinical trials of streptomycin in tuberculosis the main problem faced was that of investigating the effect of the drug in pulmonary tuberculosis. This antibiotic had been discovered two years previously by Waksman (Schatz, Bugie, and Waksman, 1944); in the intervening period its power of inhibiting tubercle bacilli *in vitro*, and the results of treatment in experimental tuberculous infection in guinea-pigs, had been reported; these results were strikingly better than those with any previous chemotherapeutic agent in tuberculosis. Preliminary results of trials in clinical tuberculosis had been published (Hinshaw and Feldman, 1945; Hinshaw, Feldman, and Pfuetze, 1946; Keefer *et al.*, 1946); the clinical results in pulmonary tuberculosis were encouraging but inconclusive.

The natural course of pulmonary tuberculosis is in fact so variable and unpredictable that evidence of improvement or cure following the use of a new drug in a few cases cannot be accepted as proof of the effect of that drug. The history of chemotherapeutic trials in tuberculosis is filled with errors due to empirical evaluation of drugs (Hart, 1946); the exaggerated claims made for gold treatment, persisting over 15 years, provide a spectacular example. It had become obvious that, in future, conclusions regarding the clinical effect of a new chemotherapeutic agent in tuberculosis could be considered valid only if based on adequately controlled clinical trials (Hinshaw and Feldman, 1944). The one controlled trial of gold treatment (and the only report of an adequately controlled trial in tuberculosis we have been able to find in the literature) reported negative therapeutic results (Amberson, McMahon, and Pinner, 1931). In 1946 no controlled trial of streptomycin in pulmonary tuberculosis had been undertaken in the U.S.A. The Committee of the Medical Research Council decided then that a part of the small supply of streptomycin allocated to it for research purposes would be best employed in a rigorously planned investigation with concurrent controls.

The many difficulties of planning and conducting a trial of this nature are important enough to warrant a full description here of the methods of the investigation.

Plan and Conduct of the Trial

Type of Case

A first prerequisite was that all patients in the trial should have a similar type of disease. To avoid having to make allowances for the effect of forms of therapy other than bed-rest, the type of disease was to be one not suitable for other forms of therapy. The estimated chances of spontaneous regression must be small. On the other hand, the type of lesion should be such as to offer some prospect of action by an effective chemotherapeutic agent; for this reason old-standing disease, and disease with thick-walled

4582

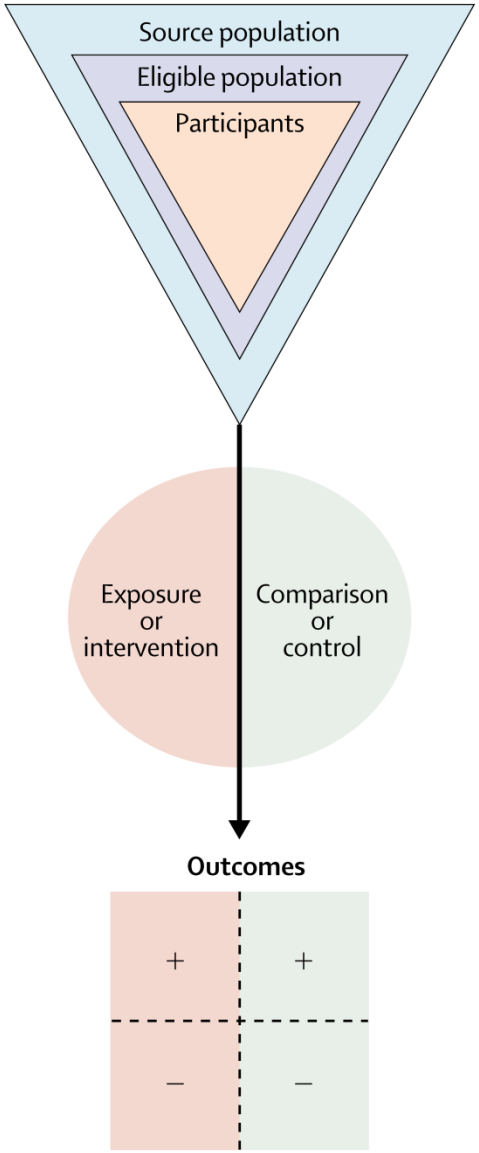
BMJ 1948:2(4582):769-782

The first modern RCT

- *Antibiotic treatment for pulmonary tubercolosis (n =107)*
- *1948 – First use of a randomized control group*
- *Experimental arm: streptomycin*
- *Control arm: bed rest*
- *At 6-month 51% of streptomycin group and 8% of the control group were «considerably improved» relative to admission, as judged by chest roentenograms*
- *Physicians reading the films were masked to which treatment patients had received*

Interpretation of a RCT: Graphic Appraisal Tool For Epidemiology (GATE)

Summerskill W et al. *Lancet* 2005;382:13-14



Nested triangles

- *Triangles are designed to help clinicians consider how generalisable findings from any particular trial might be to their own patients*

Circles

- *The circle, divided in two by a vertical line, separates the study participants according to the exposure of interest into an intervention (I) group on the left and a comparison (or control [C]) on the right*

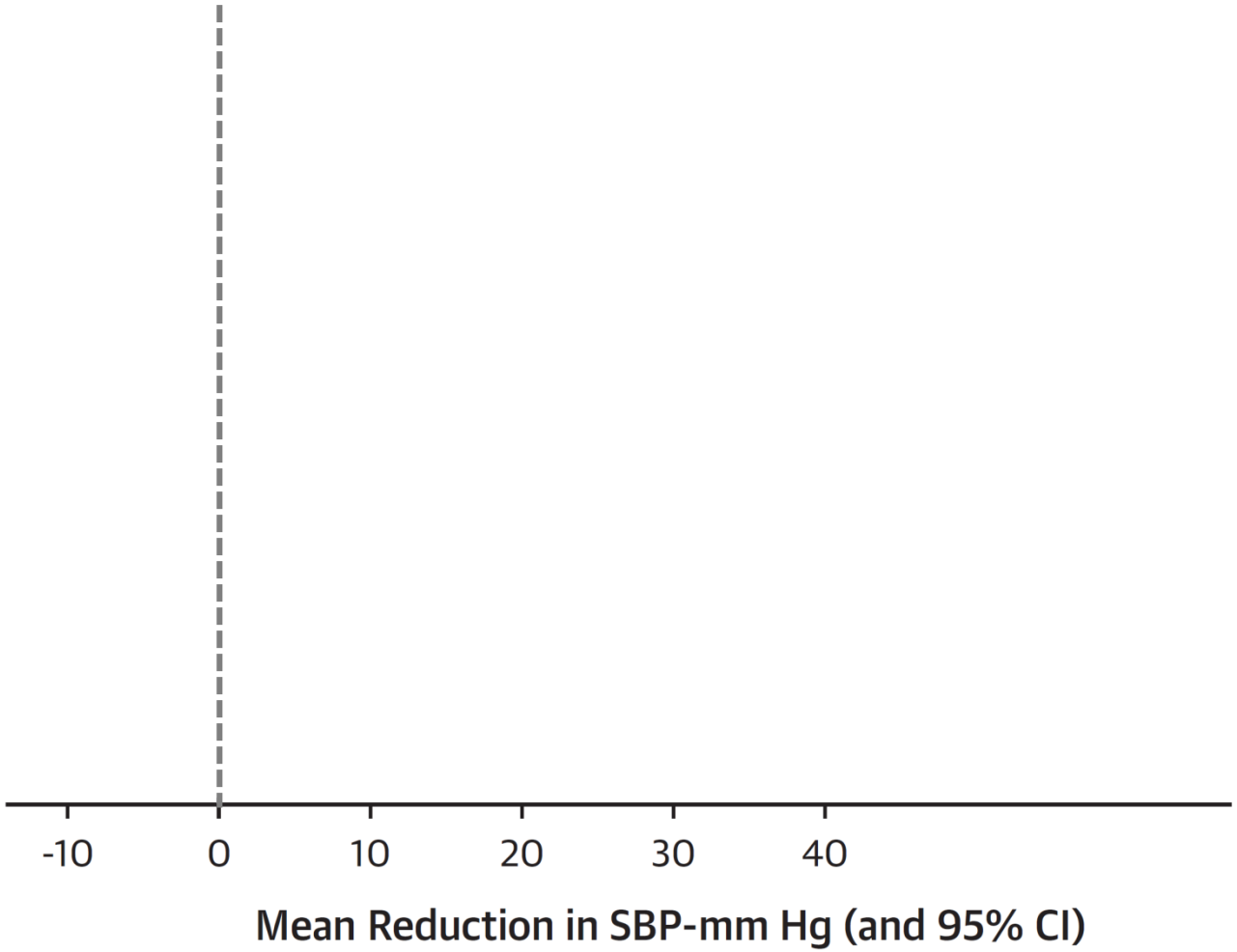
Squares

- *The squares represents the outcomes of the study and consistes of the generic 2 x 2 table*

WHY DO WE NEED RANDOMIZED TRIALS?

Pocock S et al. *J Am Coll Caridol* 2014;64:1615-28

The Case of Renal Denervation for Resistant Hypertension



WHY DO WE NEED RANDOMIZED TRIALS?

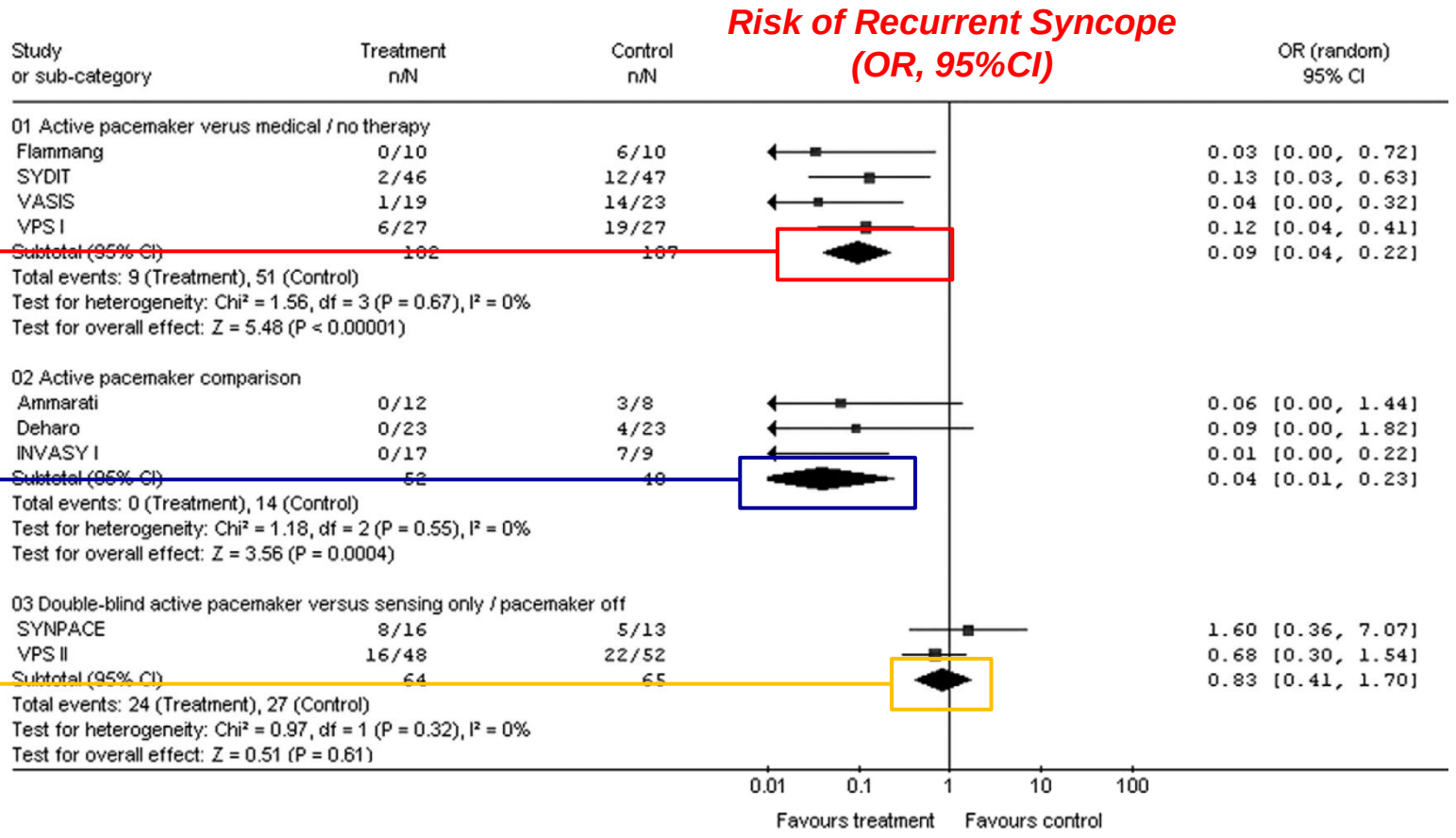
Sud S et al. *Am J Med* 2007;120:54-62

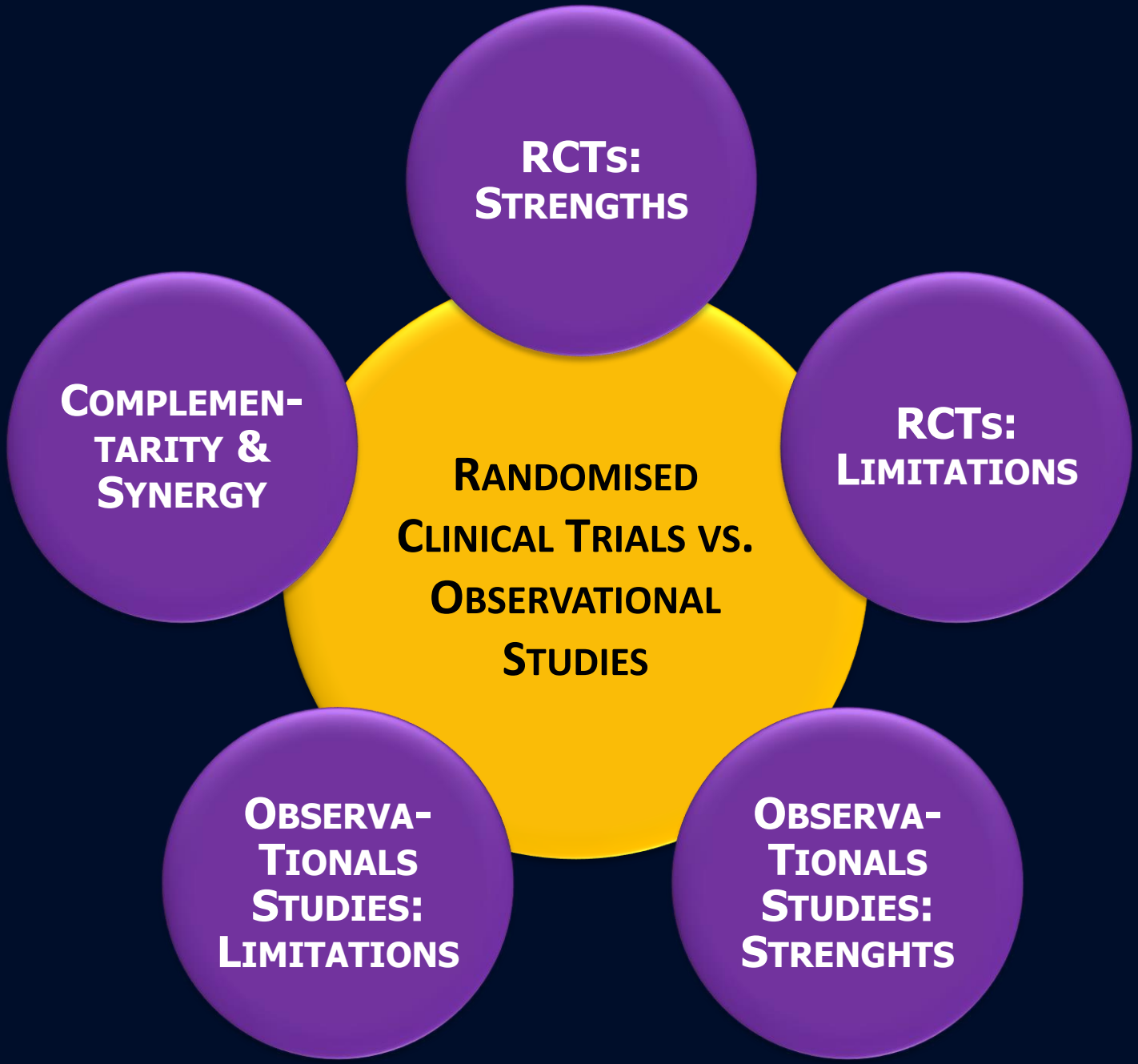
The Expectation Effect and Cardiac Pacing for Refractory Vasovagal Syncope

Active PM vs No treatment

Active PM vs Inactive PM (unblinded)

Double blind RCTs

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External Validity of Randomised Controlled Trials

Rothwell P *Lancet 2005;*365:82–93

Setting of the trial

- *Healthcare system*
- *Country*
- *Recruitment from primary, secondary, or tertiary care*
- *Selection of participating centres*
- *Selection of participating clinicians*

Selection of patients

- *Methods of prerandomisation diagnosis and investigation*
- *Eligibility criteria*
- *Exclusion criteria*
- *Placebo run-in period*
- *Treatment run-in period*
- *Enrichment strategies*
- *Ratio of randomised patients to eligible non-randomised*
- *patients in participating centres*
- *Proportion of patients who declined randomisation*

Characteristics of randomised patients

- *Baseline clinical characteristics*
- *Racial group*
- *Uniformity of underlying pathology*
- *Stage in the natural history of their disease*
- *Severity of disease*
- *Comorbidity*
- *Absolute risks of a poor outcome in the control group*

Differences between the trial protocol and routine practice

- *Trial intervention*
- *Timing of treatment*
- *Appropriateness/relevance of control intervention*
- *Adequacy of non-trial treatment—both intended and actual*
- *Prohibition of certain non-trial treatments*
- *Therapeutic or diagnostic advances since trial was done*

Outcome measures and follow-up

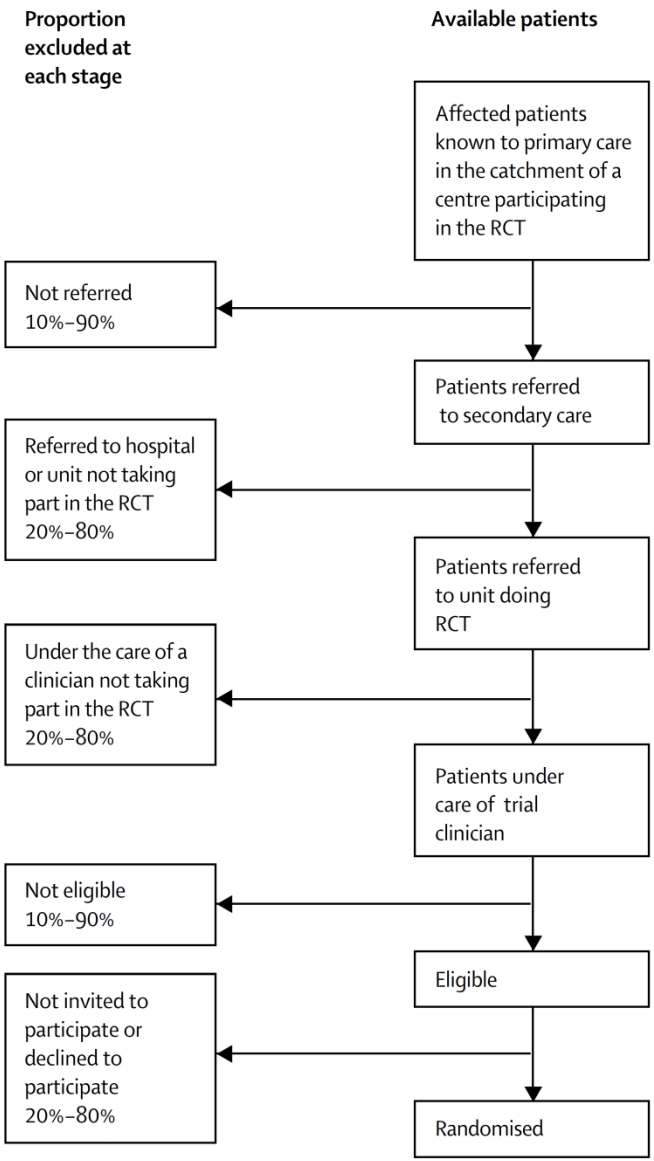
- *Clinical relevance of surrogate outcomes*
- *Clinical relevance, validity, and reproducibility of complex scales*
- *Effect of intervention on most relevant components of composite outcomes*
- *Who measured outcome*
- *Use of patient-centred outcomes*
- *Frequency of follow-up*
- *Adequacy of the length of follow-up*

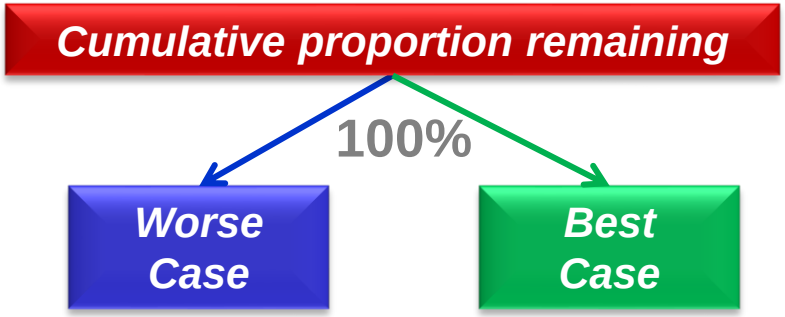
Adverse effects of treatment

- *Completeness of reporting of relevant adverse effects*
- *Rates of discontinuation of treatment*
- *Selection of trial centres and/or clinicians on the basis of skill or experience*
- *Exclusion of patients at risk of complications*
- *Exclusion of patients who experienced adverse effects*
- *during a run-in period*
- *Intensity of trial safety procedures*

Selection of Patients in RCTs

Rothwell P *Lancet 2005*;365:82–93





IMPACT OF PATIENT EXCLUSION FROM RCT

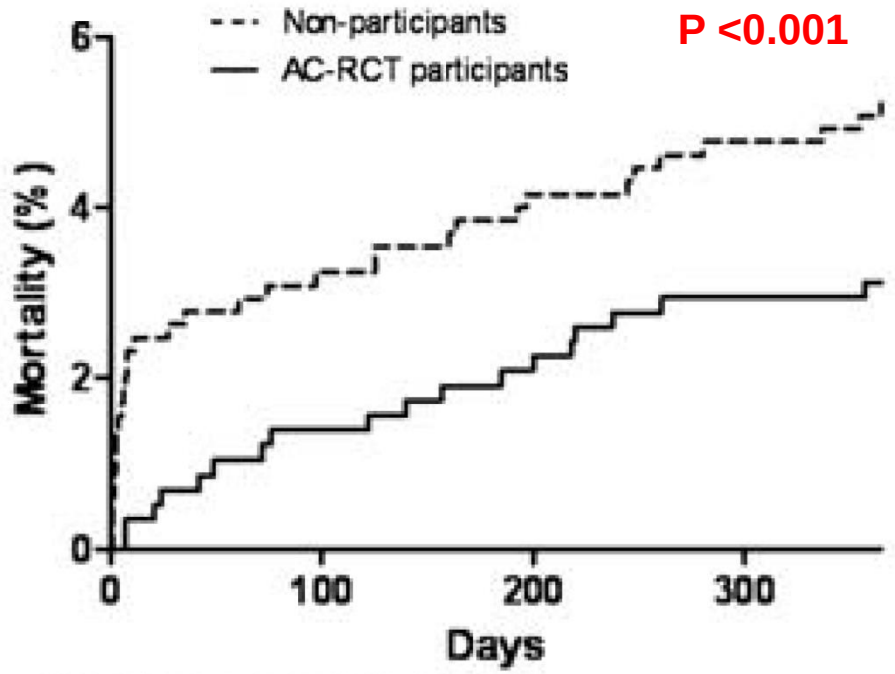
de Boer S *Eur Heart J 2011;*32:2161–67

Analysis of patients (n =1,242) included in All-comers RCTs (48%) for stent comparisons (LEADERS and RESOLUTE)

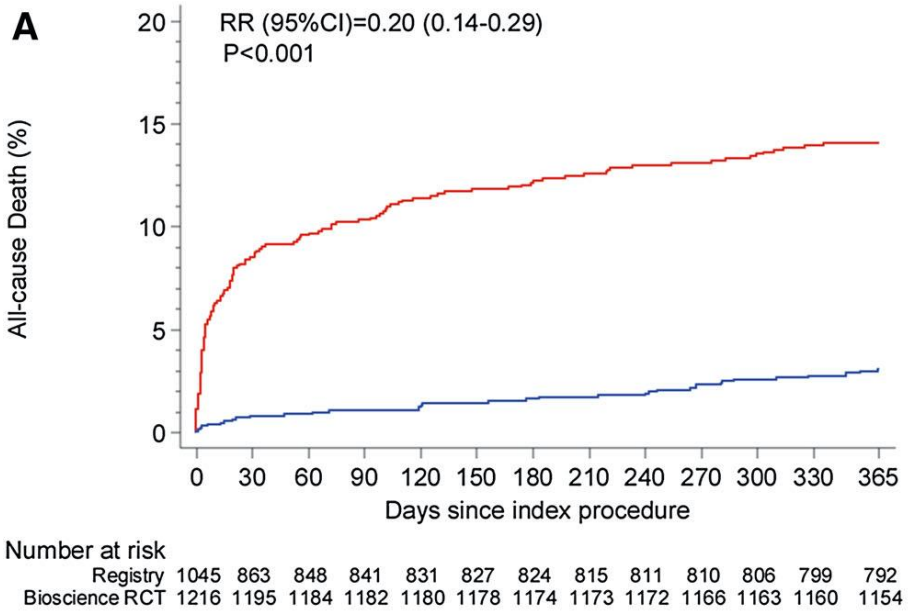
Predictors of Pts Exclusion

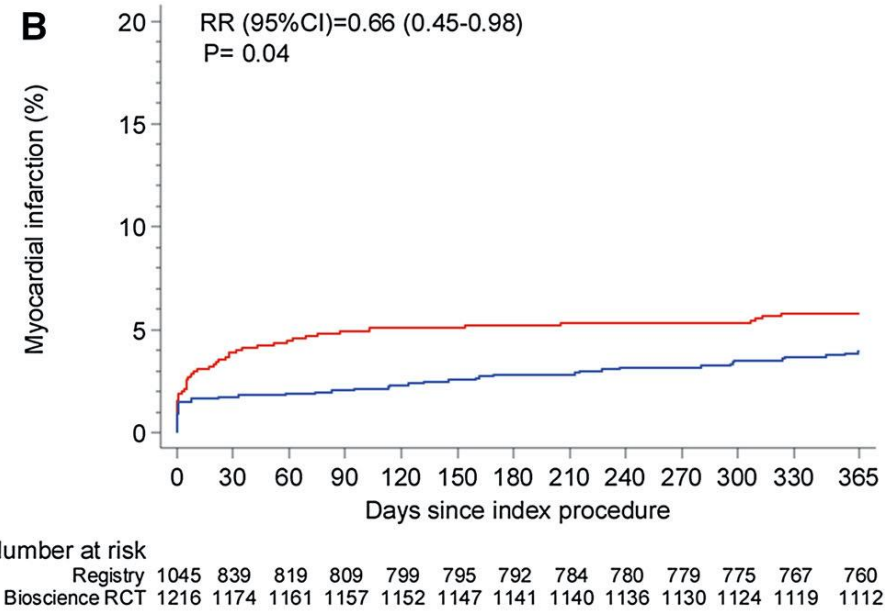
Characteristic	Adjusted for confounders OR, 95% CI
Age (per year)	0.99 (0.98–1.00)
Sex (male)	1.17 (0.90–1.52)
Indication for PCI	
Acute MI	0.71 (0.51–0.99)
Unstable angina pectoris	0.94 (0.70–1.26)
Stable angina pectoris	1
Hypertension (yes)	1.20 (0.95–1.52)
Positive family history for CHD (yes)	1.37 (1.08–1.74)
Heart failure (yes)	0.42 (0.21–0.84)
Treatment during off-hours (yes)	0.77 (0.55–1.07)

Clinical Correlates



EXTERNAL VALIDITY OF THE "ALL-COMERS" DESIGN: INSIGHTS FROM THE BIOSCIENCE TRIAL





Franzone et al., Clin Res Cardiol. 2016

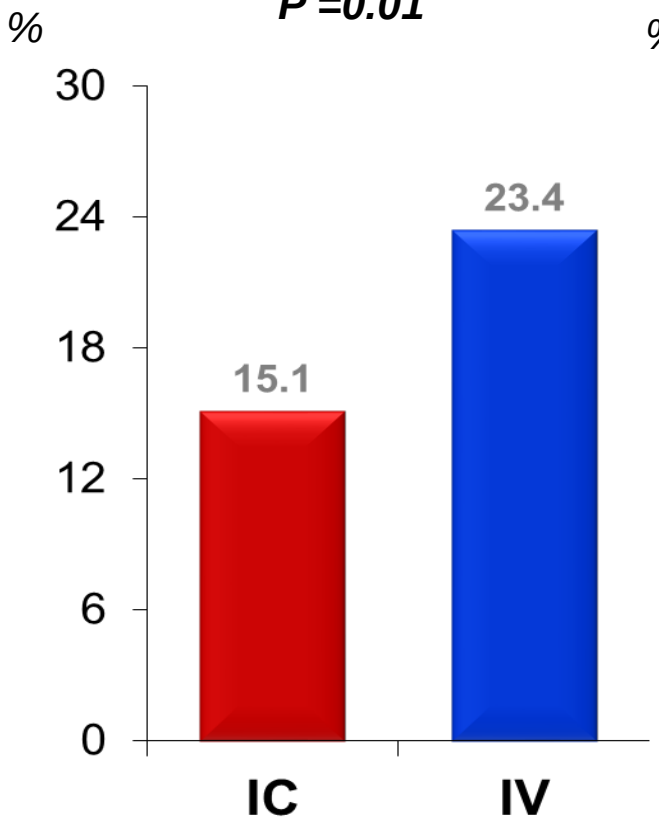
USE OF SURROGATE ENDPOINTS

Trials comparing IC vs IV Abciximab in STEMI

%Infact size assessed with MRI

Thiele H et al. Circulation 2008

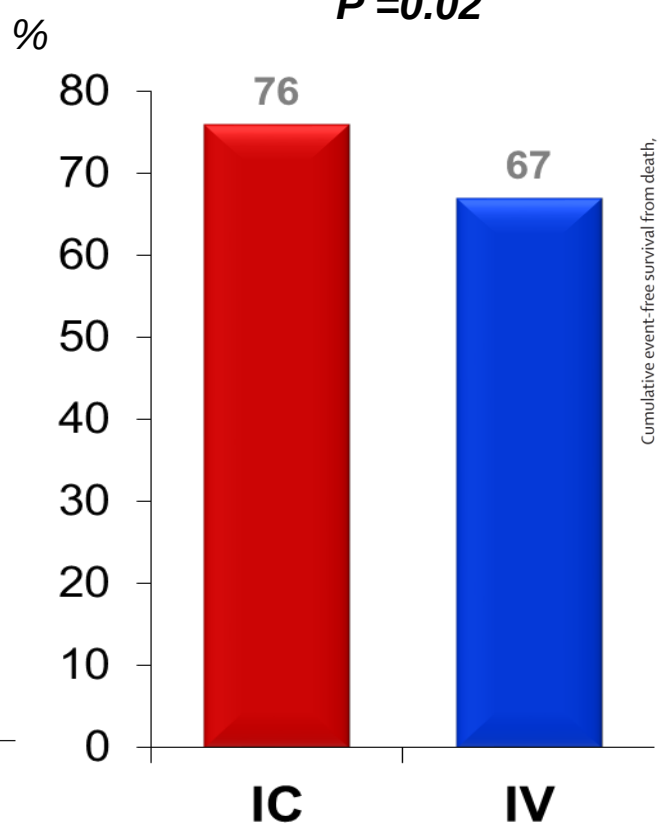
P =0.01



Myocardial Blush Grade 2/3

Gu Y et al. Circulation 2010

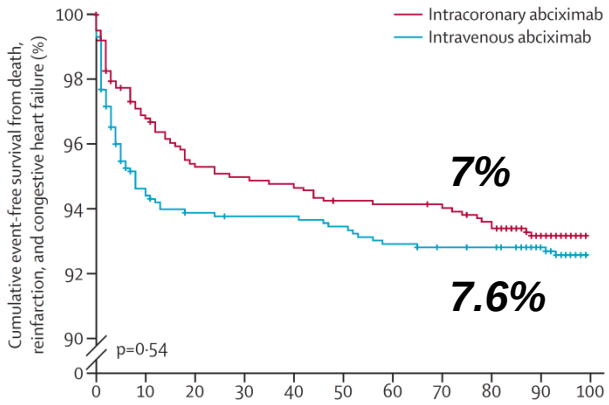
P =0.02



AIDA STEMI MACE

Thiele H et al. Lancet 2012

P =0.54



No differences for the composite of death, reinfarction or Congestive heart failure

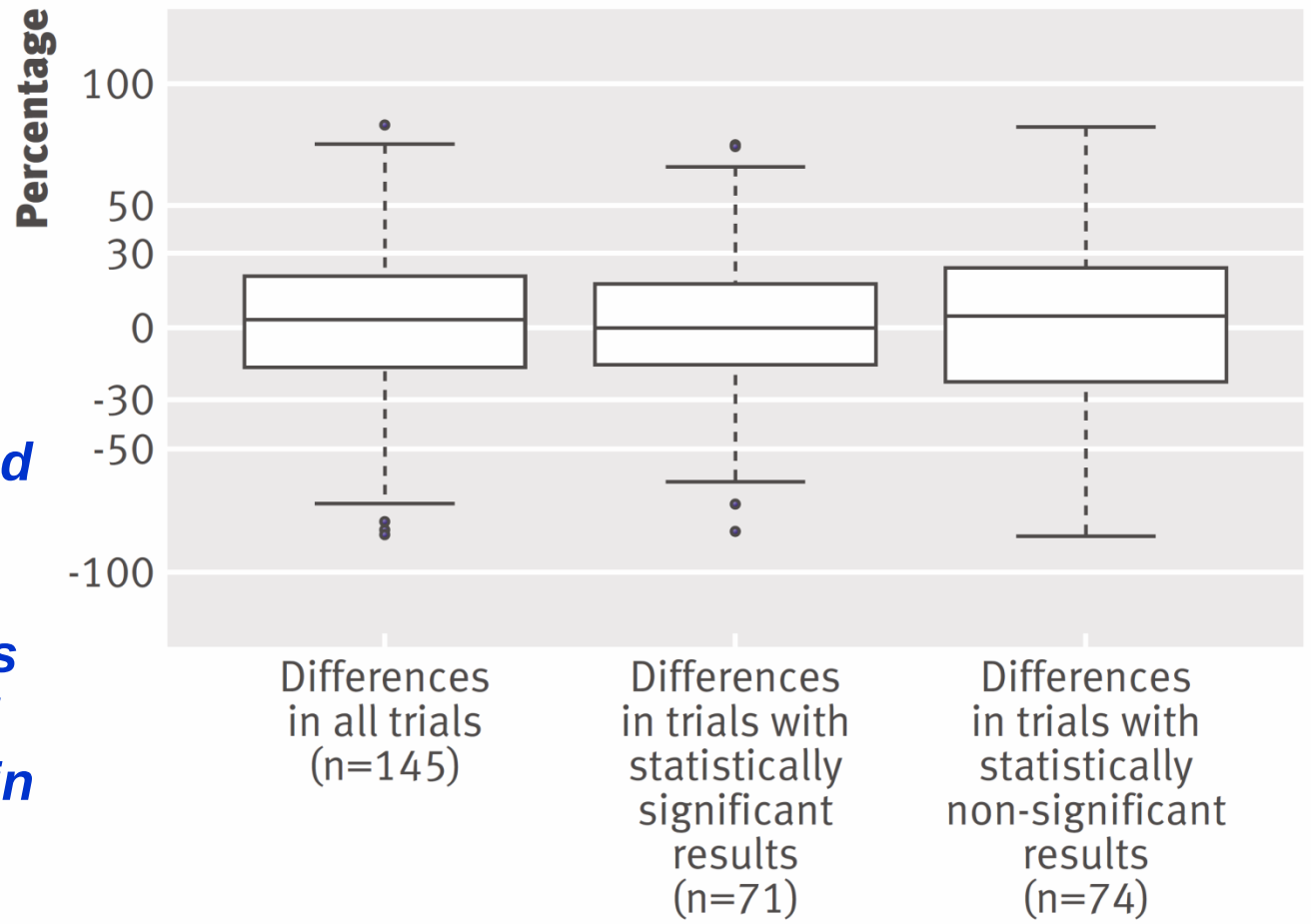
SAMPLE SIZE IN RCTS

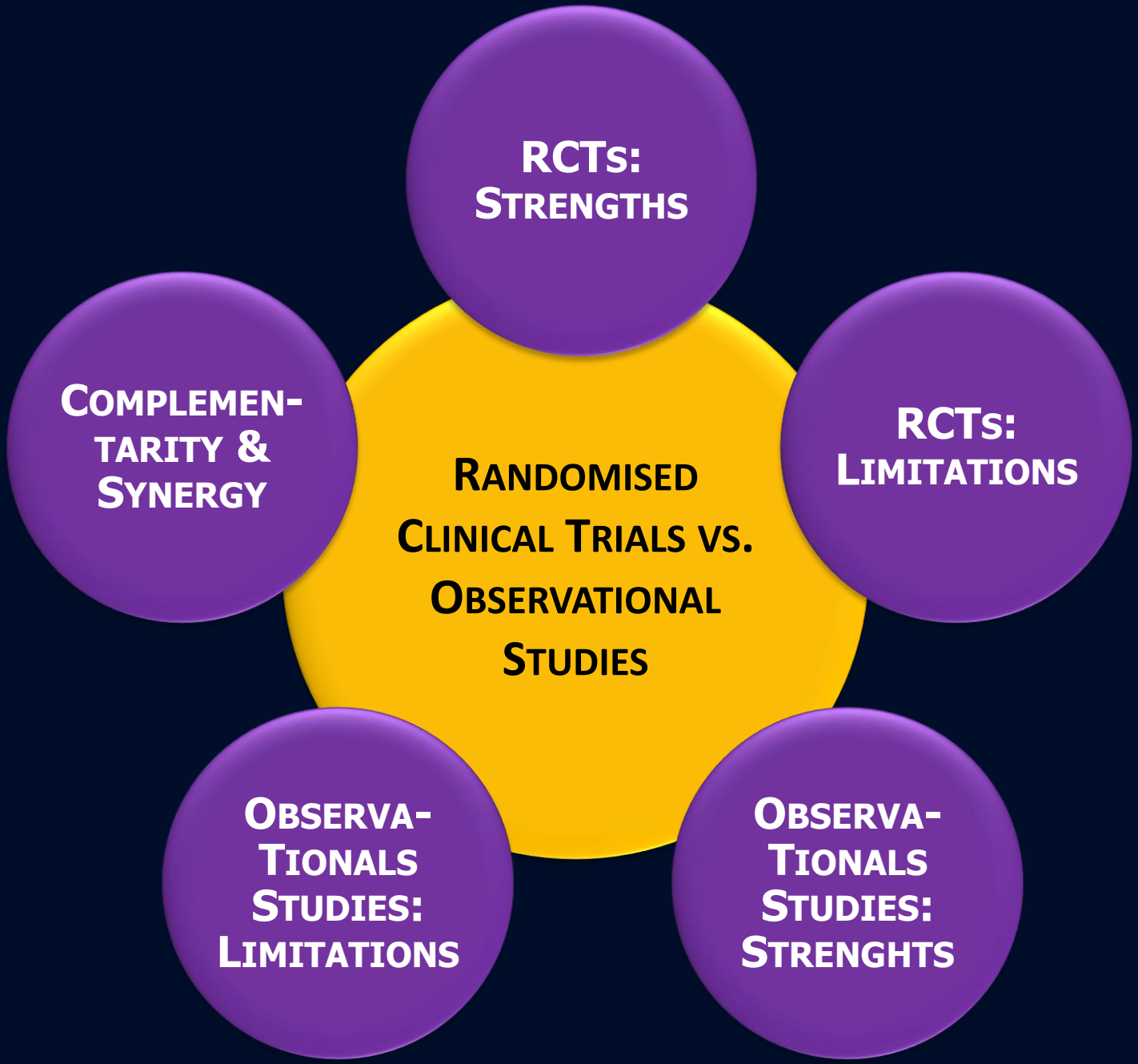
Charles P et al. *BMJ* 2009;338:b1732

- ***215 selected articles***
- ***5% No sample size calculation***
- ***Only 43% RCTs repored all data required for sample size calculation***

The Difference between assumed and observed events for the control grup was >30% in 31% of RCTs and >50% in 17% of RCTs

Relative differences between assumptions and results for control groups in RCTs

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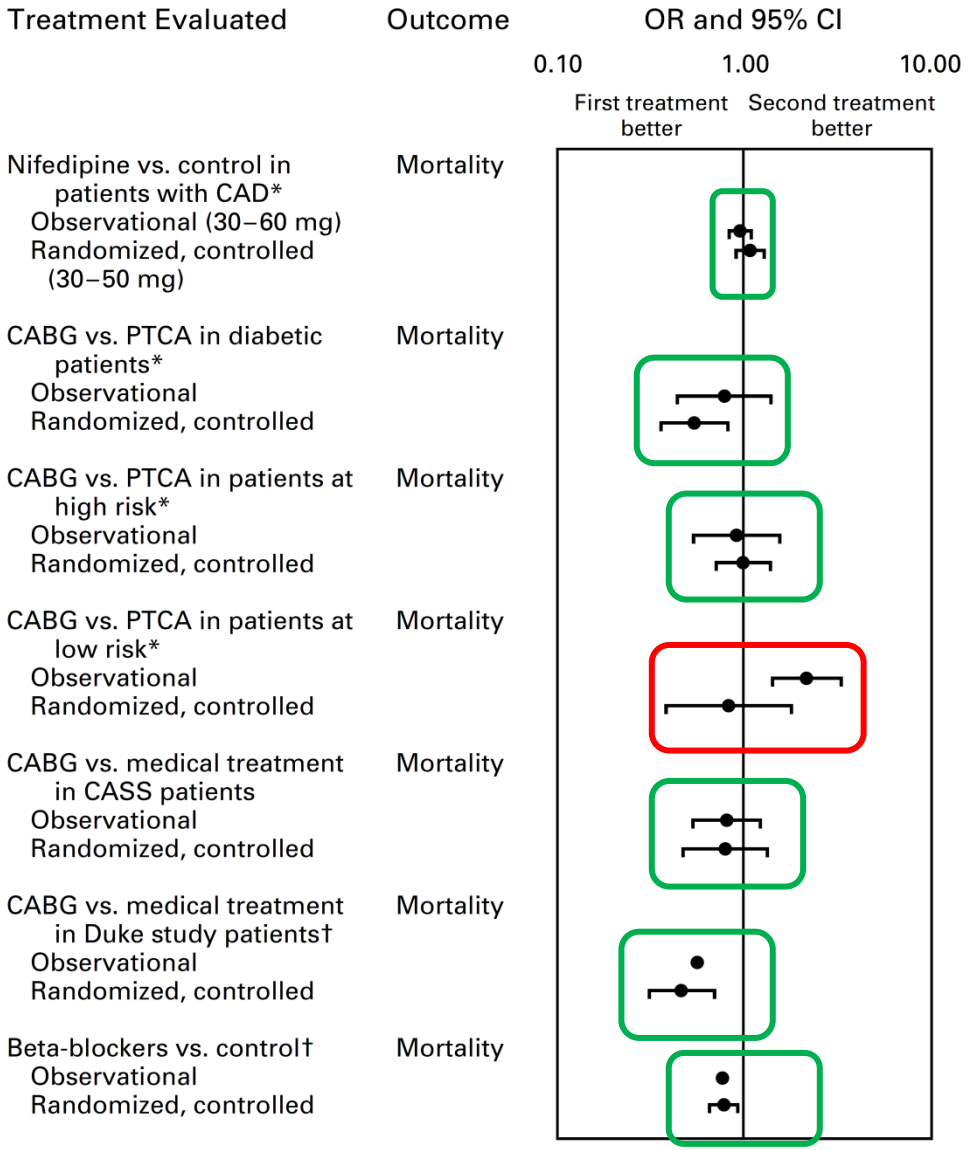
OBSERVATIONAL STUDIES: STRENGTHS

Benson K et al. *NEJM* 2000;342:1878-86



Results in observational studies vs randomized trials

- *Systematic evaluation of 136 reports published between 1985 and 1998 comparing the 2 or more treatments or intervention for the same condition;*
- *The results of well-designed, large observational studies do not systematically overestimate the magnitude of the effects of treatment as compared with those in RCTs*
- *In the comparison of 7 cardiologic treatments, the observational results fell within the 95% of the RCTs in all cases with the exception of the comparison of CABG vs PTCA in patients at low-risk*

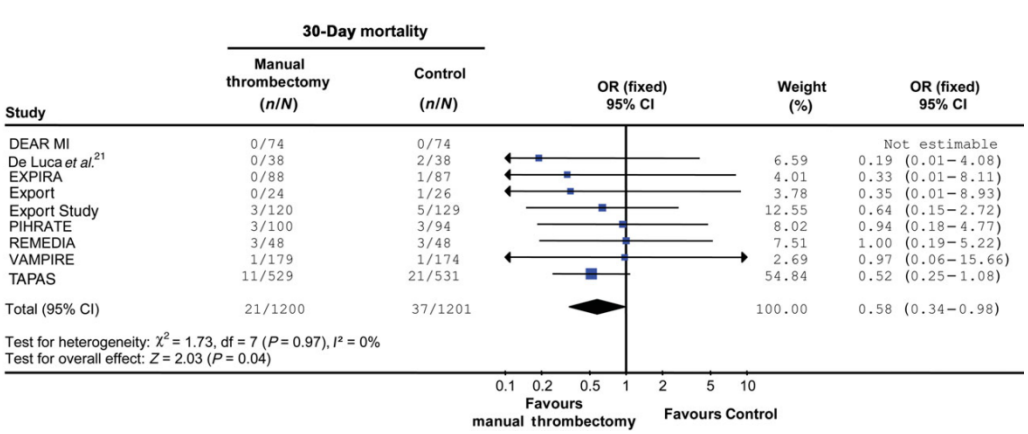
EXAMPLE: THROMBECTOMY IN PRIMARY PCI

Randomized Evidence before TASTE and TOTAL

Meta-analysis 2008

De Luca G et al. *EHJ* 2008;29:3002-10

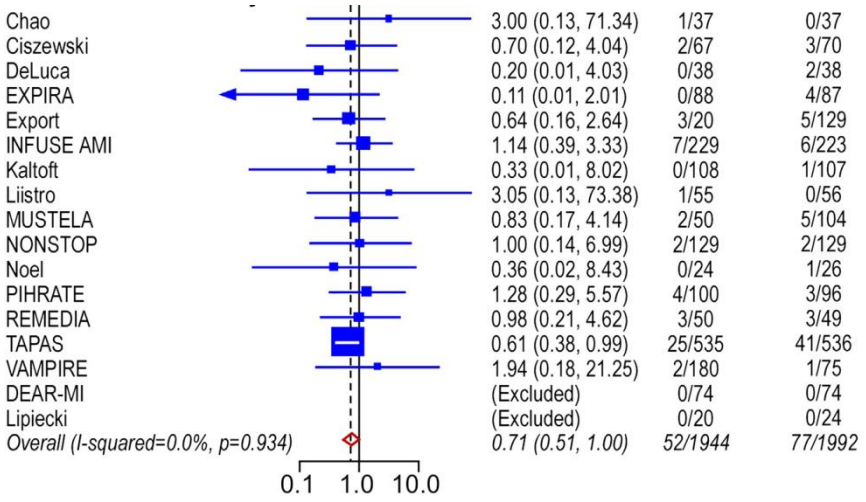
9 RCTs (n =2,417)
30-day mortality reduced with thrombus aspiration
(OR 0.58, 95%CI 0.34-0.98, p =0.04)



Meta-analysis 2013

Kumbhani D et al. *JACC* 2013;62:1409-18

18 RCTs (n =3,936)
All-cause mortality reduced with thrombus aspiration
(RR 0.71, 95%CI 0.51-0.99, p =0.049)

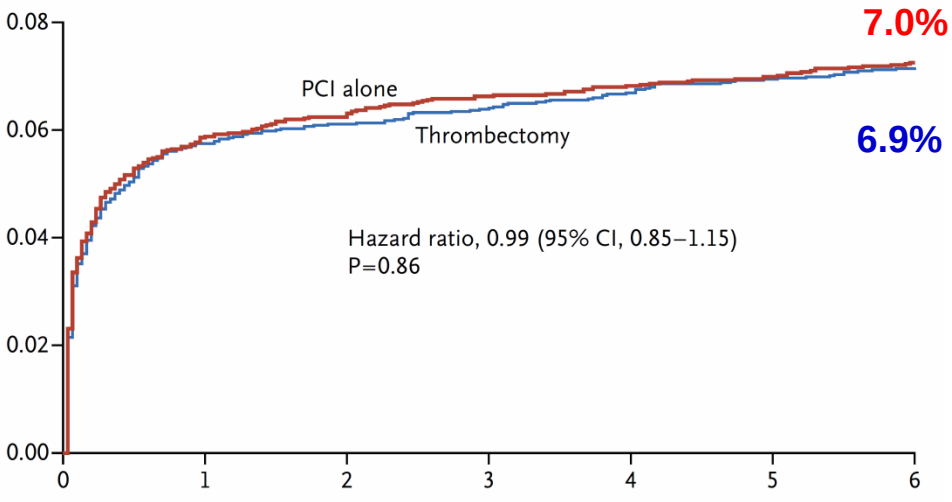


EXAMPLE: THROMBECTOMY IN PRIMARY PCI

TOTAL Trial

Jolly SS et al. *N Engl J Med* 2015;372:1389-98

10,732 STEMI patients randomized to thrombectomy (n =5,033) or PCI alone (n =5,030)

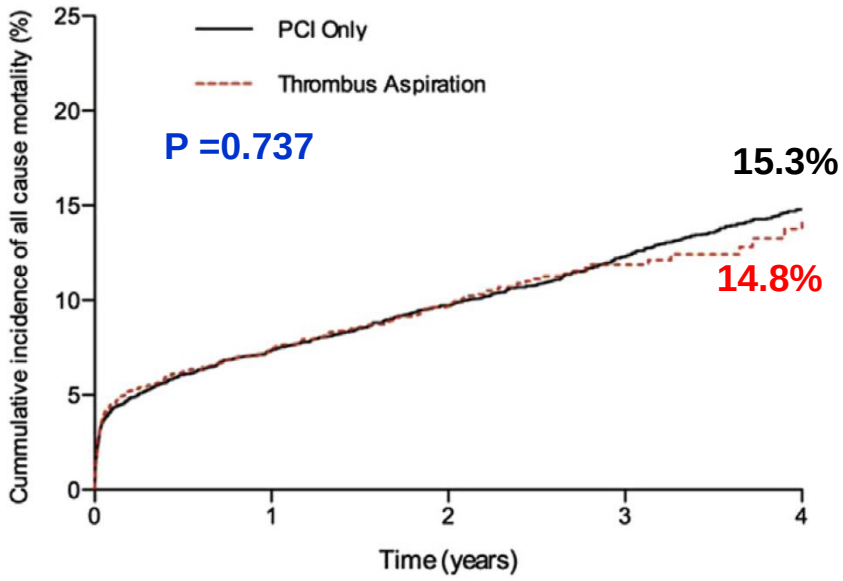


Primary Endpoint CV death, MI, cardiogenic shock, or heart failure (NYHA IV)

UK BCIS Registry

Jones DA et al. *JACC Intv* 2015;8:575-84

10,929 STEMI patients of which 3,572 patients (32.7%) underwent thrombectomy

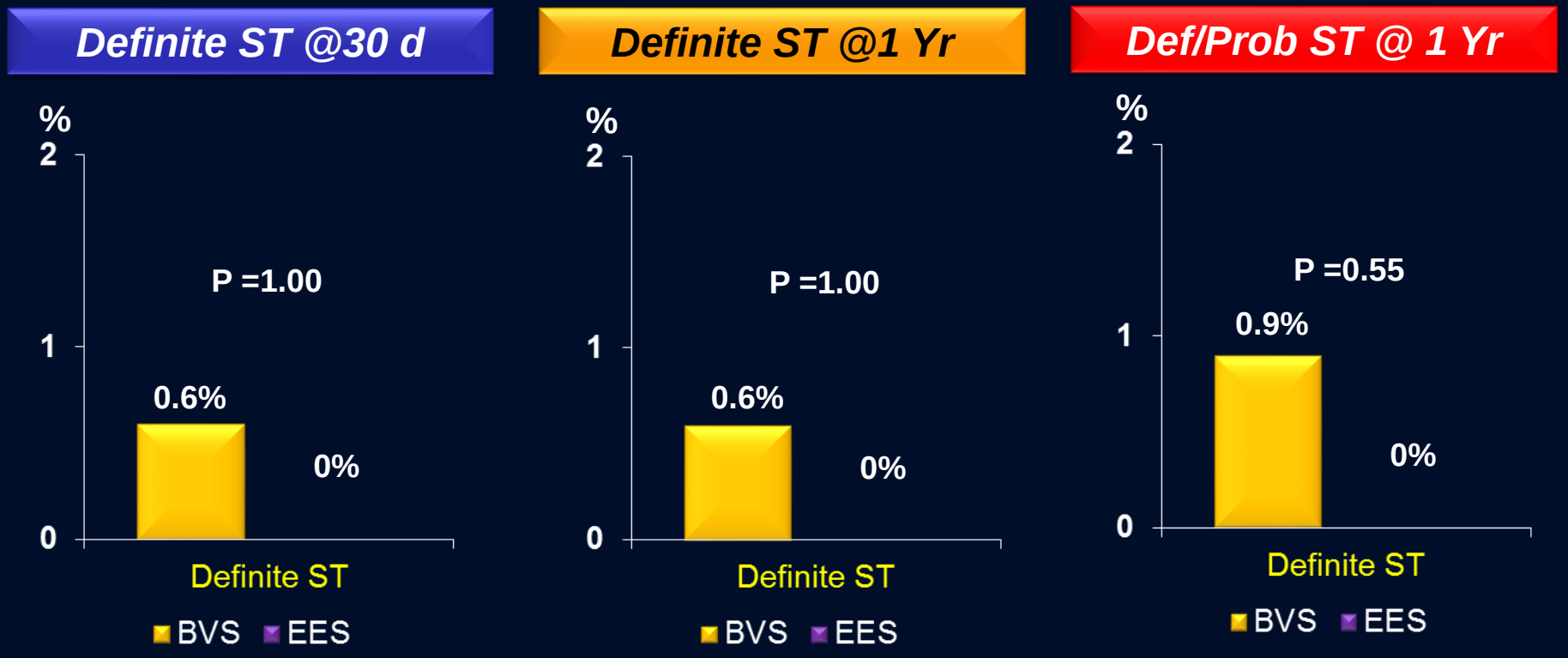


All-cause mortality at 4-years

Rare Events in Randomized Trials

Serruys PW et al. *Lancet* 2015; 385:43–54

ABSORB II trial (BVS n=335; EES n=166)



Definite Stent thromboses: 2 cases, one <24h and the second on day 2

Probable Stent thrombosis: One case on day 355

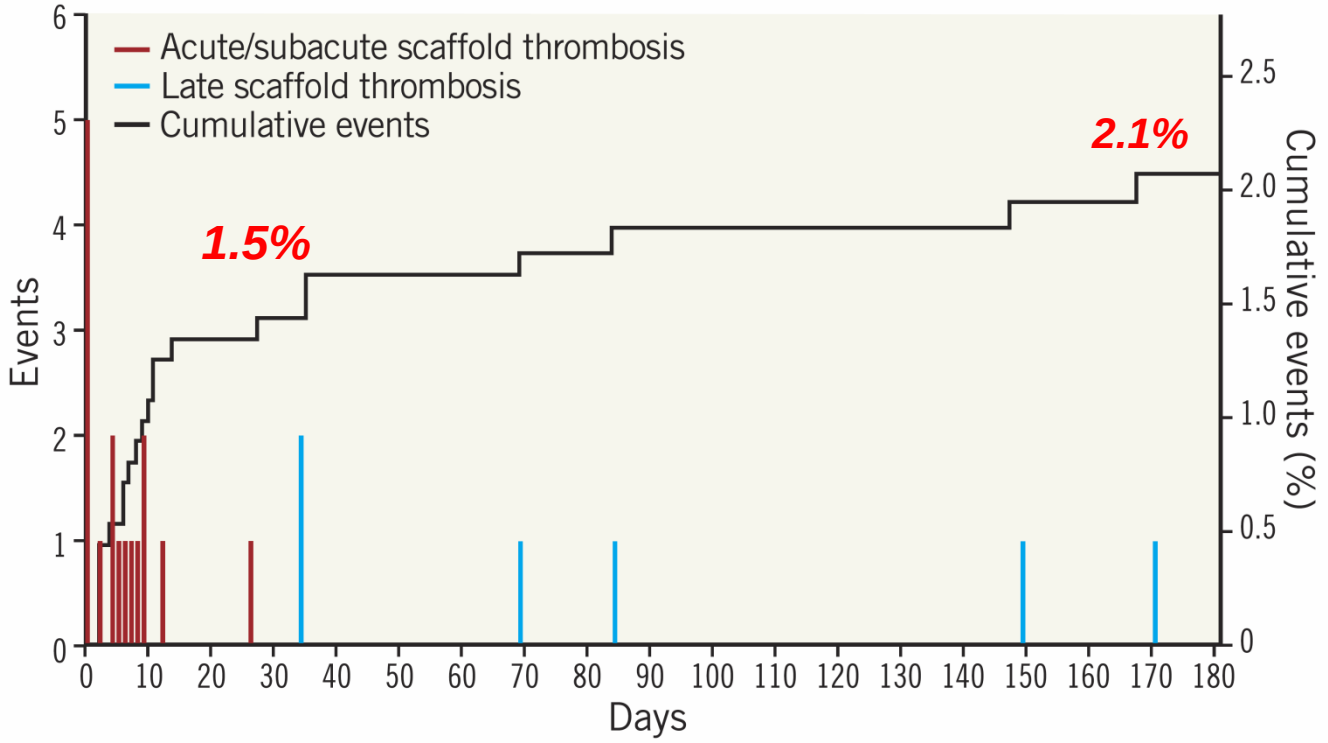
Rare Events in Observational Studies

Capodanno D et al. *EuroIntervention* 2015;10:1144-53

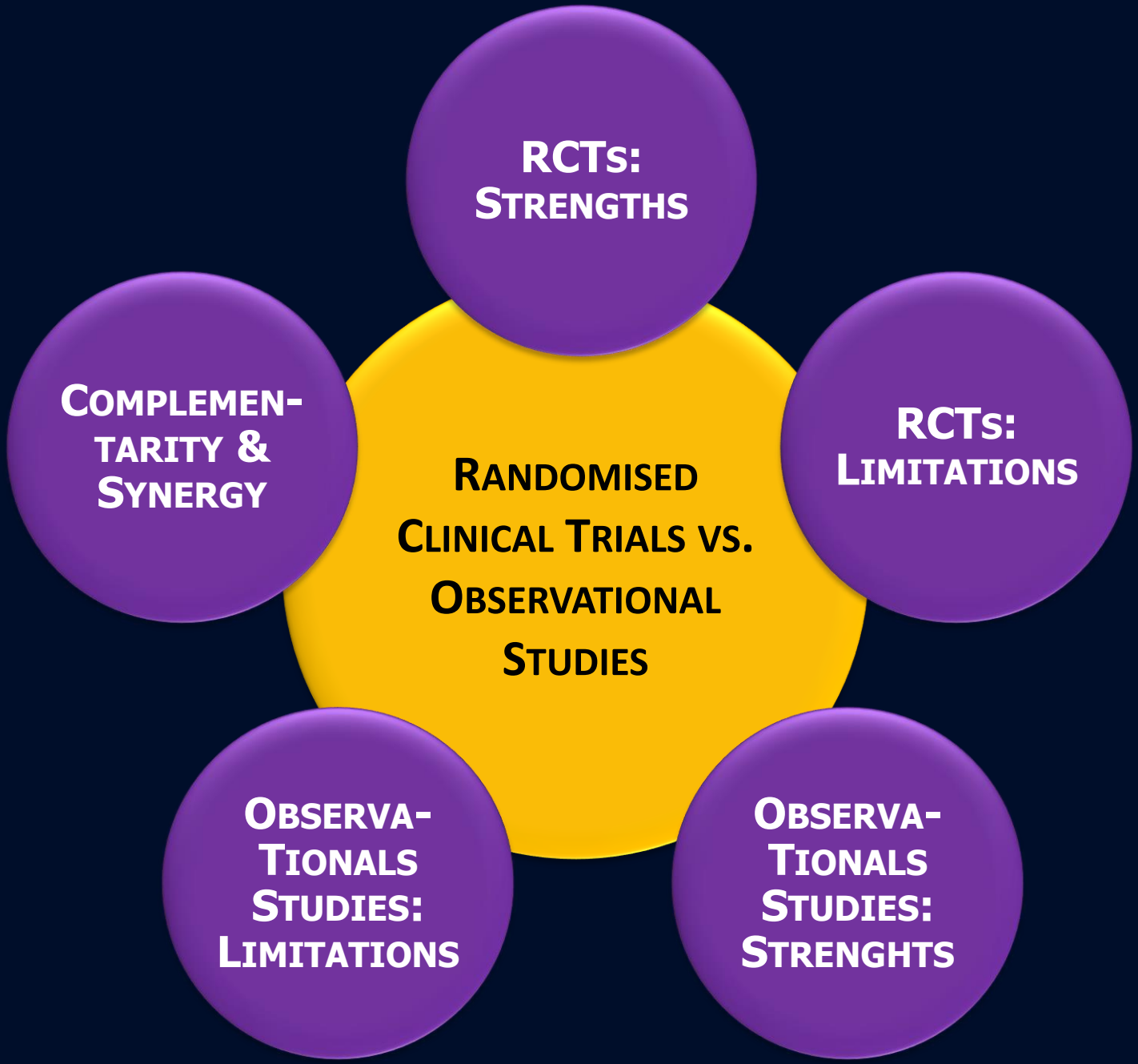
GHOST-EU Registry (n =1,189)

Stent Thrombosis

Definite or Probable Stent Thrombosis



- ***23 cases of Definite or Probable ST:***
  - *20 Definite ST*
  - *3 Probable ST*
- ***87% of ST occurred on DAPT***
- ***Median Time to ST: 6.5 days (IQR: 1.5-34)***
- ***ST resulted in cardiac death in 23 Pts (13%) and non-fatal MI in 15 Pts (65%)***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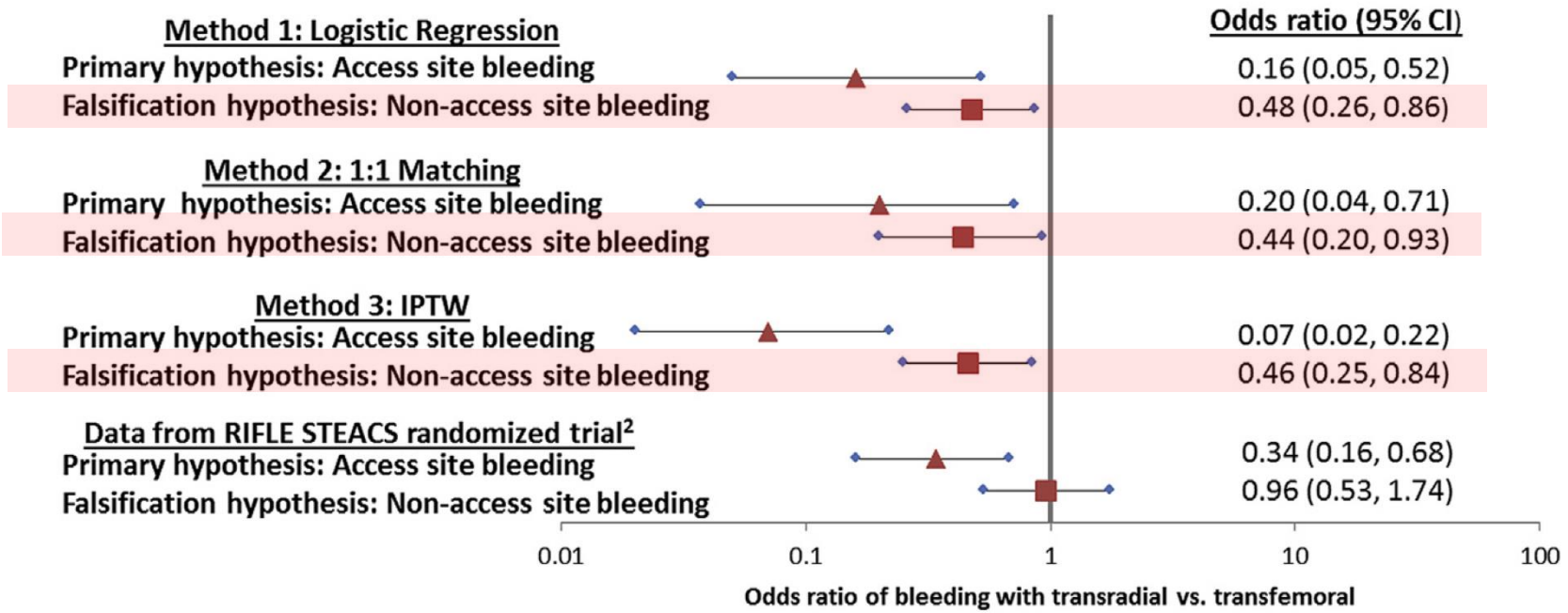
OBSERVATIONAL STUDIES: LIMITATIONS

Wimmer N et al. *J Am Coll Cardiol* 2013;62:2147-50

Residual Confounding

Data from CathPCI Registry 2008-2011

- *17,509 PCI patients.17.8% of procedures performed via the transradial approach (TRA);*
- *By applying 3 different statistical methods TRA reduced the risk of non-access site bleeding, suggesting residual confounding;*
- *"Falsification hypotheses can help adjudicate whether observational associations are robust or whether they reflect selection bias among patients who receive an intervention" (Jena, JAMA 2013).*



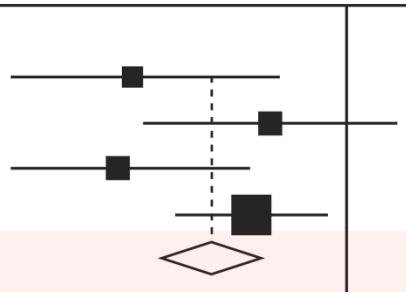
BLEEDING WITH RADIAL APPROACH: MATRIX

Valgimigli M et al. *Lancet* 2015

Non-CABG major bleeding (n =19,328)

Meta-analysis

Subgroup	Radial (n/N)	Femoral (n/N)	Risk ratio (95% CI)	p value
Non-CABG major bleeds				
Pre-RIVAL trials	11/974	32/999	0·41 (0·22–0·76)	
RIVAL	24/3507	33/3514	0·73 (0·43–1·23)	
Post-RIVAL trials	17/960	45/970	0·39 (0·23–0·67)	
MATRIX	64/4197	95/4207	0·68 (0·49–0·92)	
Combined	116/9638	205/9690	0·58 (0·46–0·72)	<0·0001



BARC Bleeding

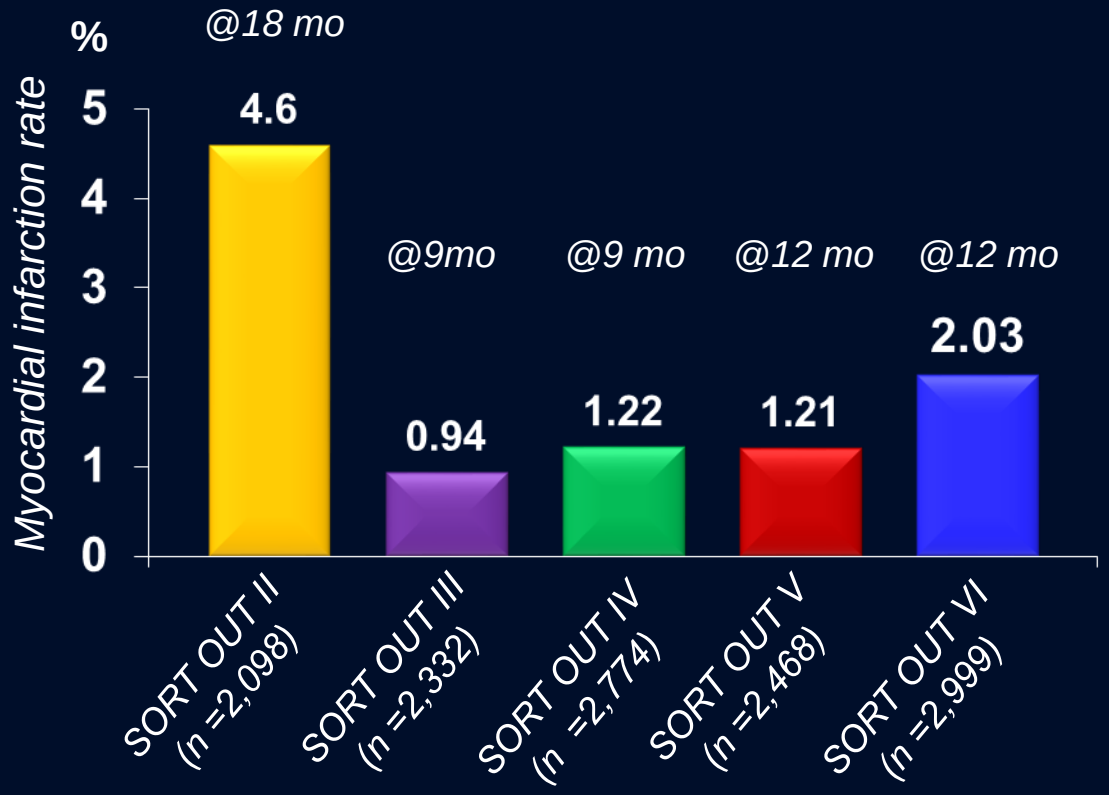
Analysis in the MATRIX (n =8,404) according to access sites events

	Radial access (n=4197)	Femoral access (n=4207)	Rate ratio (95% CI)	p value
Type 3 or 5	64 (1·6%)	95 (2·3%)	0·67 (0·49–0·92)	0·0128
Related to access site	16 (0·4%)	43 (1·1%)	0·37 (0·21–0·66)	0·0004
Not related to access site	48 (1·2%)	52 (1·3%)	0·92 (0·62–1·36)	0·68
Type 2, 3, or 5	189 (4·6%)	307 (7·4%)	0·60 (0·50–0·73)	<0·0001
Related to access site	69 (1·7%)	197 (4·8%)	0·34 (0·26–0·45)	<0·0001
Not related to access site	121 (2·9%)	115 (2·8%)	1·05 (0·81–1·36)	0·70

Event Detection in Randomized Registry Trials

Myocardial infarction detection in SORT OUT vs Other RCTs

SORT OUT RCTs*



MI Rates in other RCTs

EVOLVE II	5.2%
LEADERS	5.1%
TWENTE	4.6%
RESOLUTE-AC	4.2%
BIOSCIENCE	4.0%
ISAR TEST 5	3.9%
COMPARE II	2.7%
CENTURY II	2.4%

(All MI events reported @9-12 months)

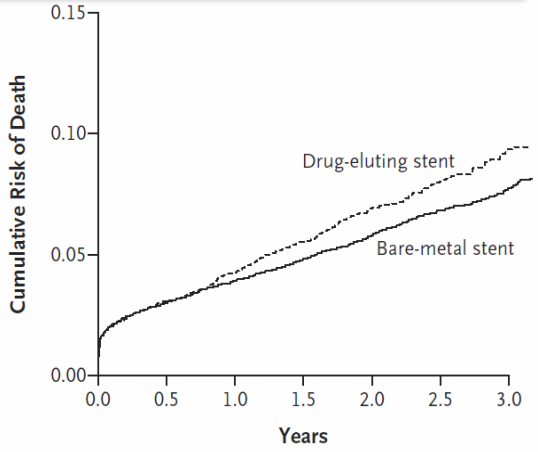
**SORT OUT I not reported because only in-hospital FU was available*

OBSERVATIONAL STUDIES: LIMITATIONS

Drug-Eluting Stents vs. Bare Metal Stents

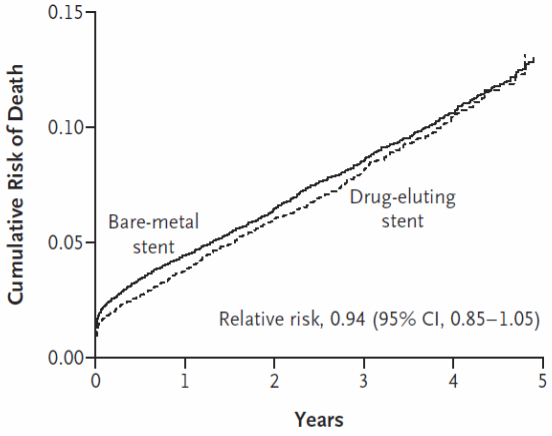
Nationwide Registry: The SCAAR Experience

NEJM 2007



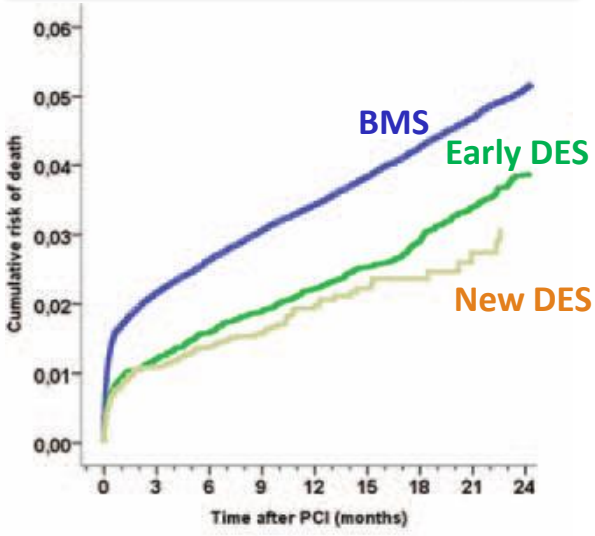
No. at Risk							
Bare-metal stent	12,880	12,473	12,354	12,228	9298	5966	3199
Drug-eluting stent	5,770	5,605	5,541	5,471	3434	1777	626

NEJM 2009



No. at Risk						
Bare-metal stent	18,659	17,830	12,825	8,890	4,391	6
Drug-eluting stent	10,294	9,902	6,717	3,180	1,016	0

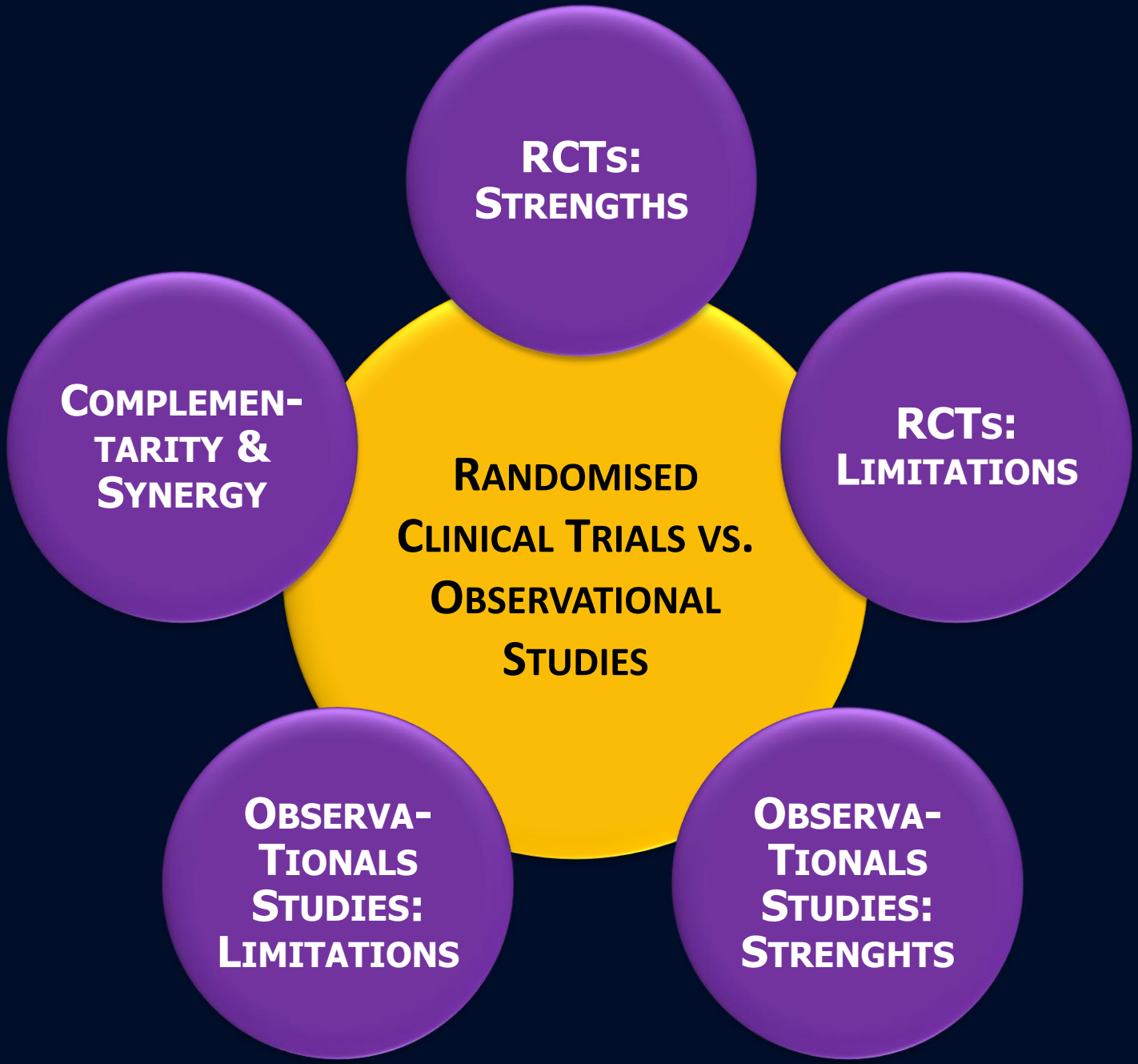
Eur Heart J 2011



↑ ***Early DES vs. BMS***
RR 1.18 (1.04-1.35)

= ***Early DES vs. BMS***
RR 0.94 (0.85-1.05)

↓ ***DES vs. BMS***
HR 0.55 (0.46-0.67)


RCTs: Strengths
RCTs: Limitations
Observa-tionals Studies: Strenghts
Observa-tionals Studies: Limitations
Complemen-tarity & Synergy
Randomised Clinical Trials vs. Observational Studies

Complementarity of Randomized And Observational Studies

Hannan E *JACC Intv* 2008;1:211-217

Randomized and observational studies can be used synergistically to obtain more and better information about the relative merits of alternative interventions.

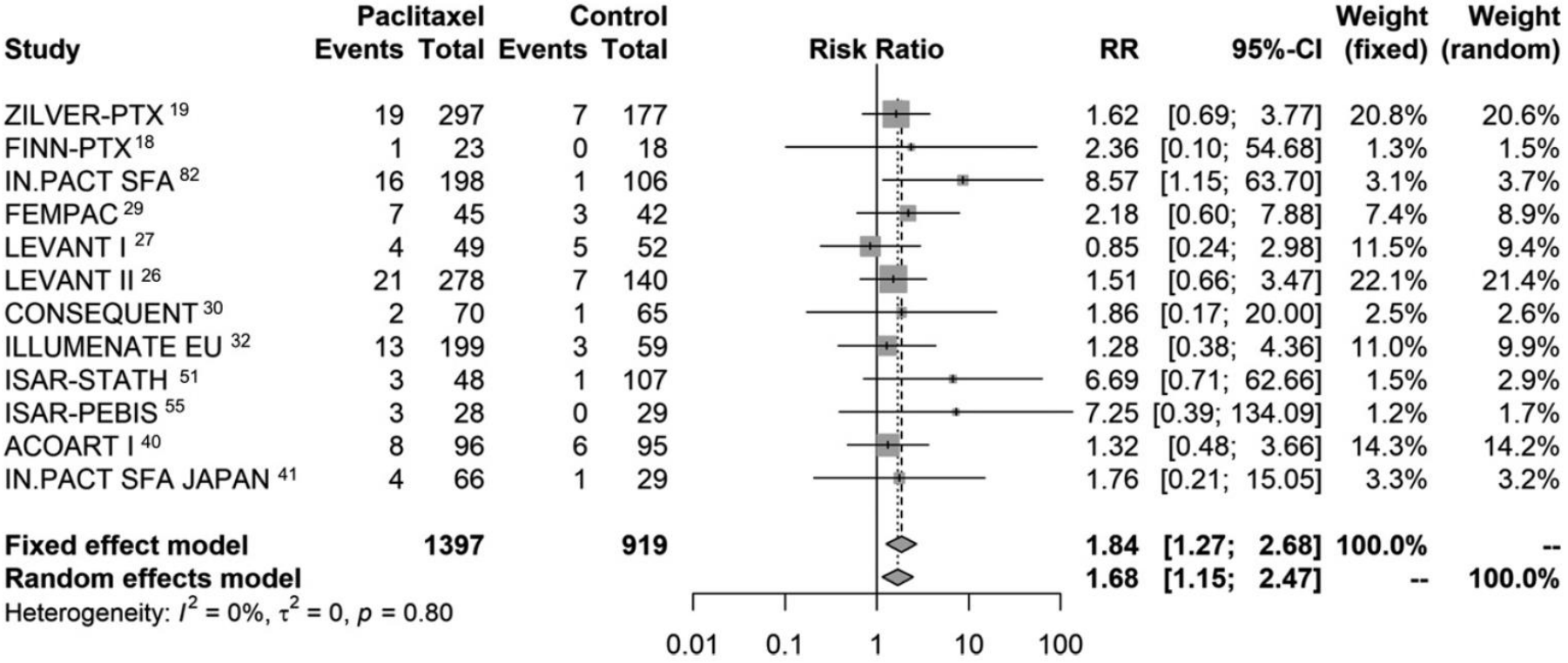
Observational studies can be used to:

- ***Test the external validity of RCTs by expanding the settings to a more representative population***
- ***Formulate hypotheses for RCTs to test***
- ***Identify structures, processes, and outcomes to study***
- ***Help establish the appropriate sample size for RCT***
- ***Examine patients subsets to dermine precisely which patients benefit from each alternative intervention***

Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg

Katsanos K *J Am Heart Assoc*. 2018;7:e011245

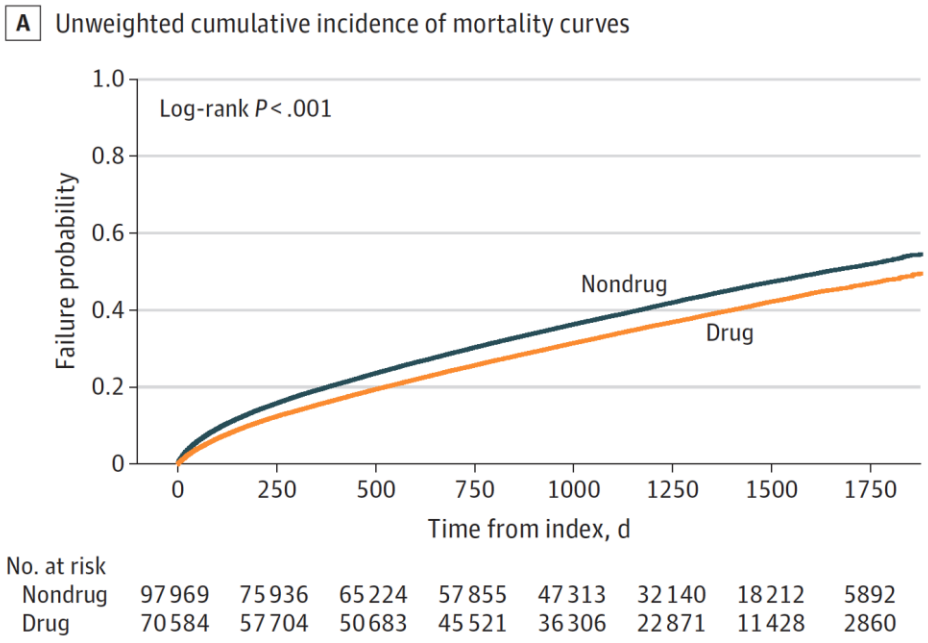
Mortality at 2-Year Follow-up

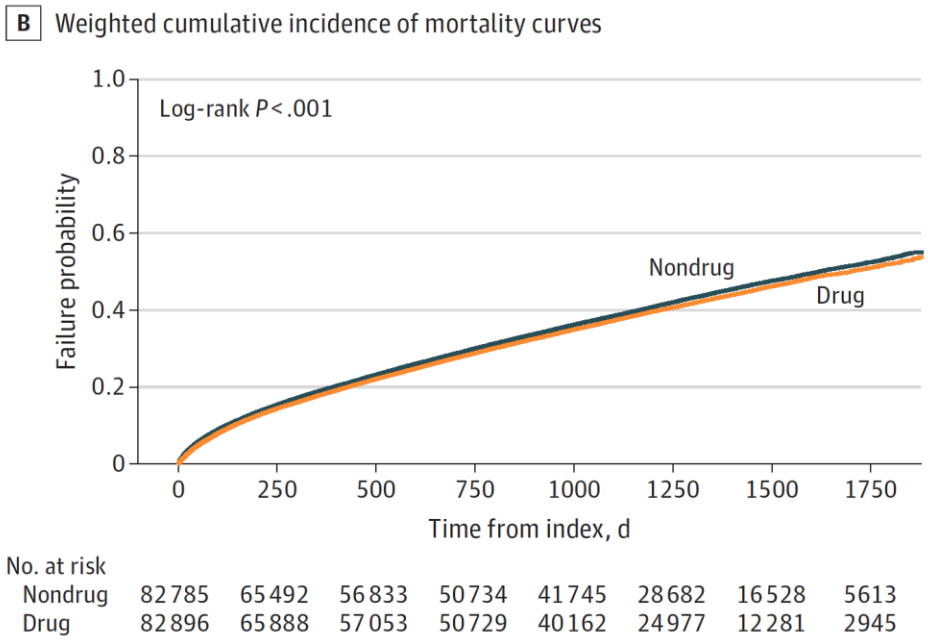


PACLITAXEL-COATED DEVICES VS. UNCOATED DEVICES FOR FEMOROPOPLITEAL ENDOVASCULAR TREATMENT: SAFE-PAD

Secemsky E. et al. *JAMA Intern Med.* 2021;181(8):1071-1080

168,533 patients from 2015 to 2018 – 43% (N=70,584) treated with drug-coated devices



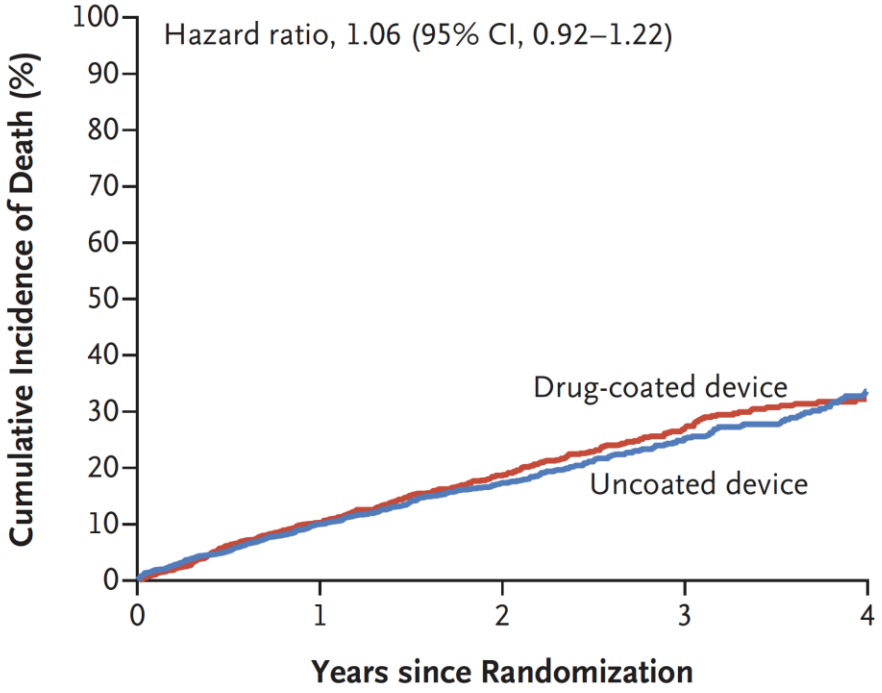


PACLITAXEL-COATED DEVICES VS. UNCOATED DEVICES FOR PERIPHERAL ARTERY DISEASE: SWEDEPAD

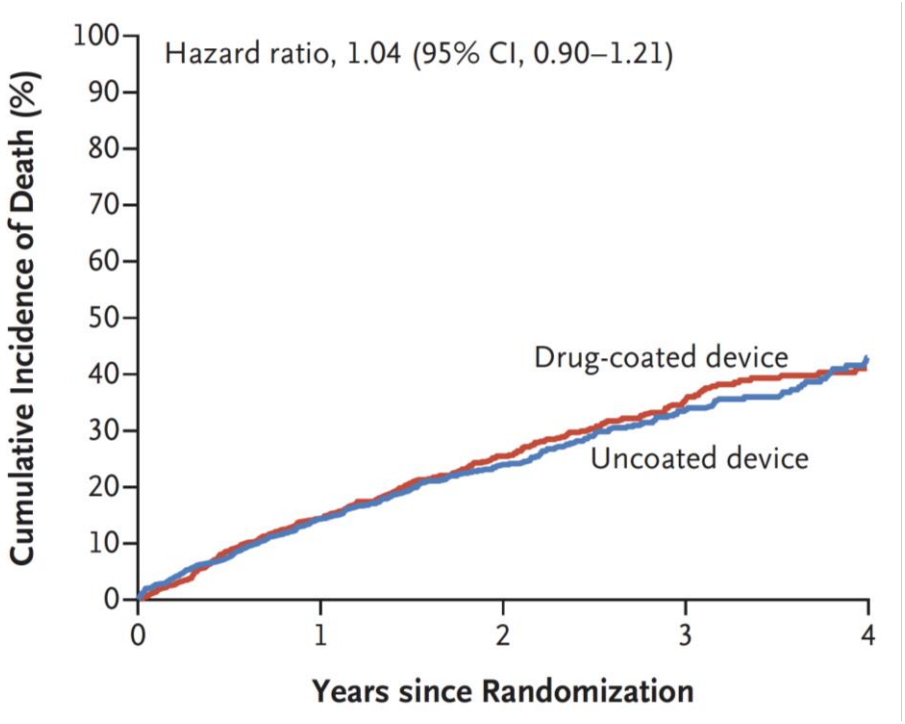
Nordanstig J. et al. *New Engl J Med.* 2020;383:2538-46

Registry-Based Clinical Trial (N=2,289)

Overall Population

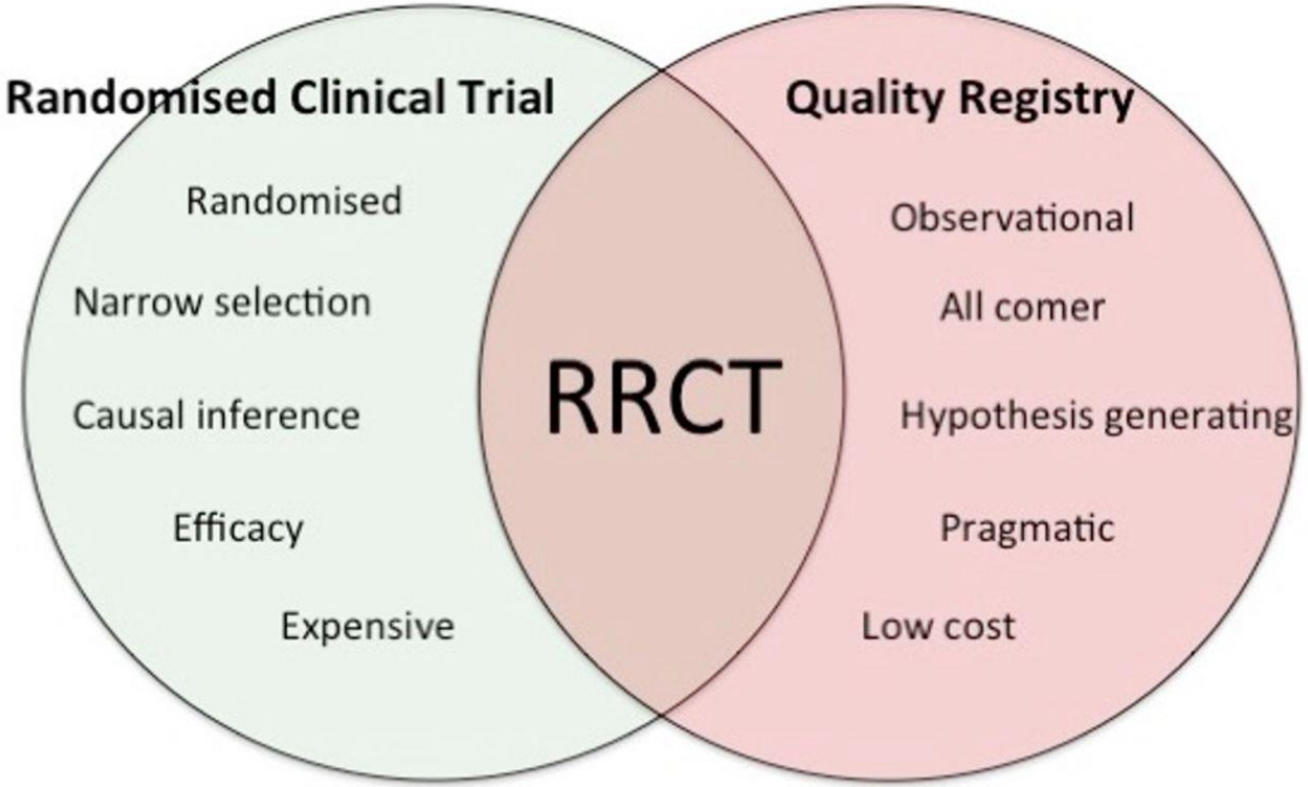


Patients with Chronic Limb-Threatening Ischemia



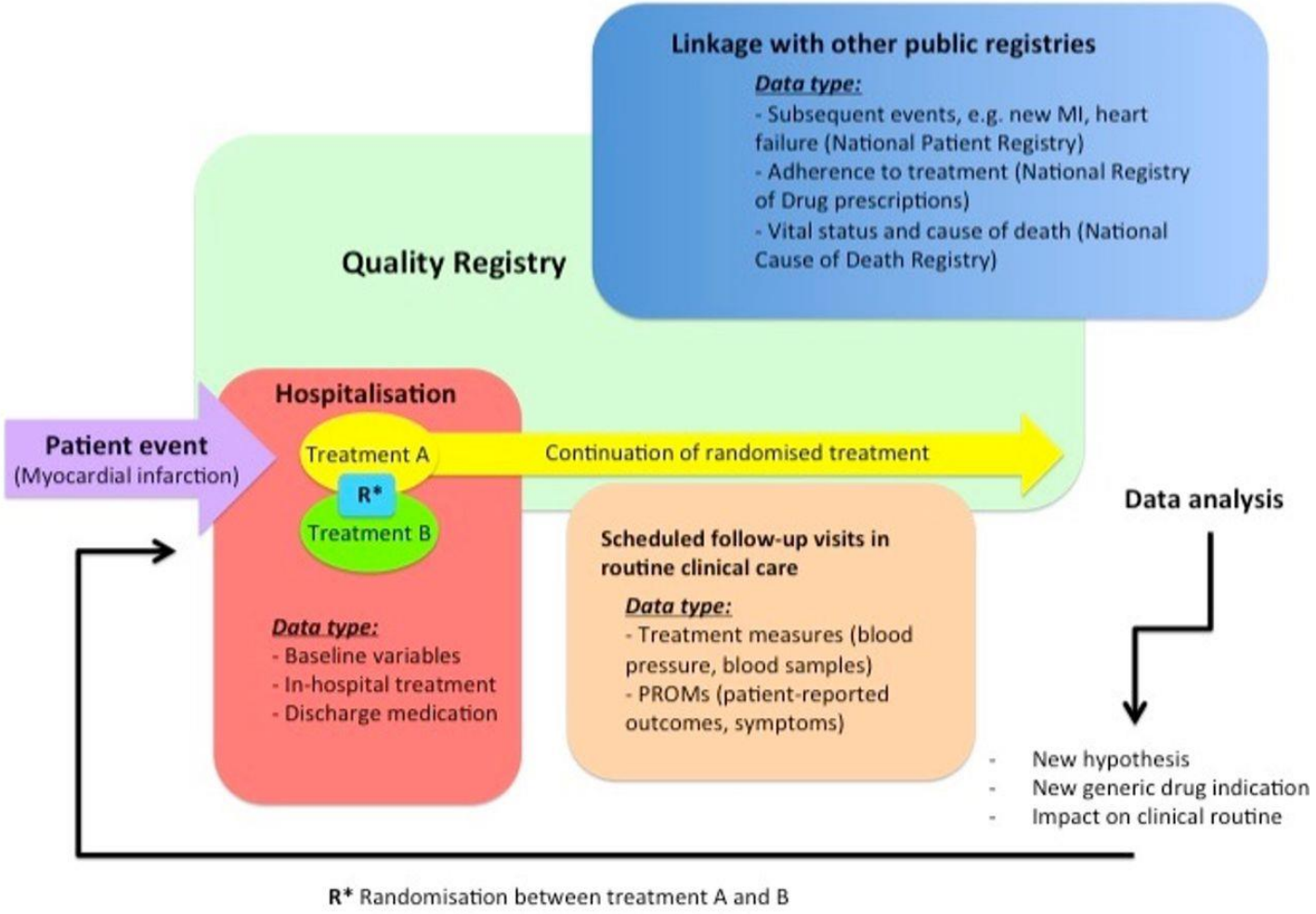
Registry-Based Randomized Clinical Trial (RRCT)

Yndigegn T, et al. *Heart* 2018;104:1562–1567



REGISTRY-BASED RANDOMIZED CLINICAL TRIAL (RRCT)

Yndigegn T, et al. *Heart* 2018;104:1562–1567



Without Trials and Observational Studies We Would Continue to Treat Myocardial Infarction as Done in the Past

Dwight D. Eisenhower

Messerli F et al. *N Engl J Med* 2005;353:1205

- On 25 September 1955 awakened by chest pain treated at home with nitrates, morphine and papaverine
- ECG due to persistent chest pain performed >12 hours after onset of symptoms established diagnosis of anterolateral MI
- Dow Jones lost 6 points ($14 billion), the largest decline since 1929
- «Chair rest» versus «bed rest»
- Died at age 78 of CHF after at least 7 recurrent MIs and 14 cardiac arrests on 28 March 1969