Magnitude of bias in trials stopped early for benefit reviews

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Stopping early apparent benefit

- ethical mandate
  - unethical to randomize to control
  - priority to get effective treatment to patients
- increasing proportion of trials stopping early
- danger
  - arbitrary stopping violates statistical principles
  - statistically sound stopping rules
- remaining danger
  - rules may not be observed
  - simulations suggest still overestimate effect
  - systematic review suggests overestimate in real world: almost 50% of 143 trials RRR > 50%; 25% RRR > 70%

Addressing uncertainty

- survey didn't prove overestimates
- survey suggested large less problems
  - OR 31 for RRR > 47% for events < 66
  - also not proved
- what is average overestimate?
  - what factors associated?

Study design

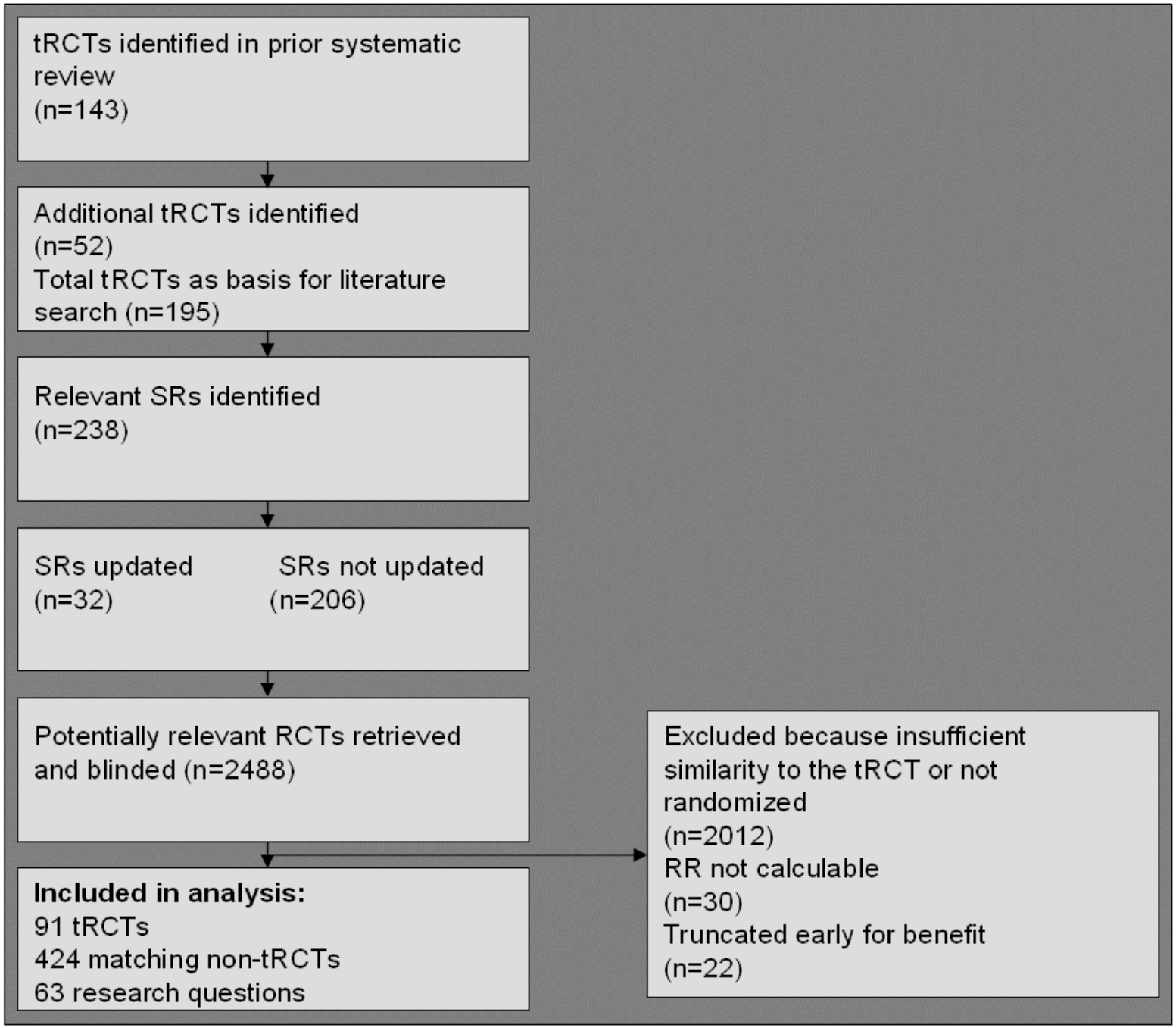
- obtain all trials stopped early for benefit
- obtain meta-analyses
  - same question (population, intervention, comparator)
  - outcome that drove early stopping
  - if tRCT non included, update meta-analysis
- compare effects
  - tRCTs versus non-tRCTs
  - predictors of difference
    - rigorous rule yes/no
    - sample size/number of events
    - methodologic quality

Details of methods

- search included MEDLINE, Embase, Current Contents
  - databases including full text of journals (*OVID, ScienceDirect, Ingenta, and Highwire Press, Lancet, New England Journal of Medicine, JAMA, Annals of Internal Medicine, BMJ)*
- duplicate assessment of eligibility
  - blind to results
  - reviewers content area expertise
- duplicate data abstraction

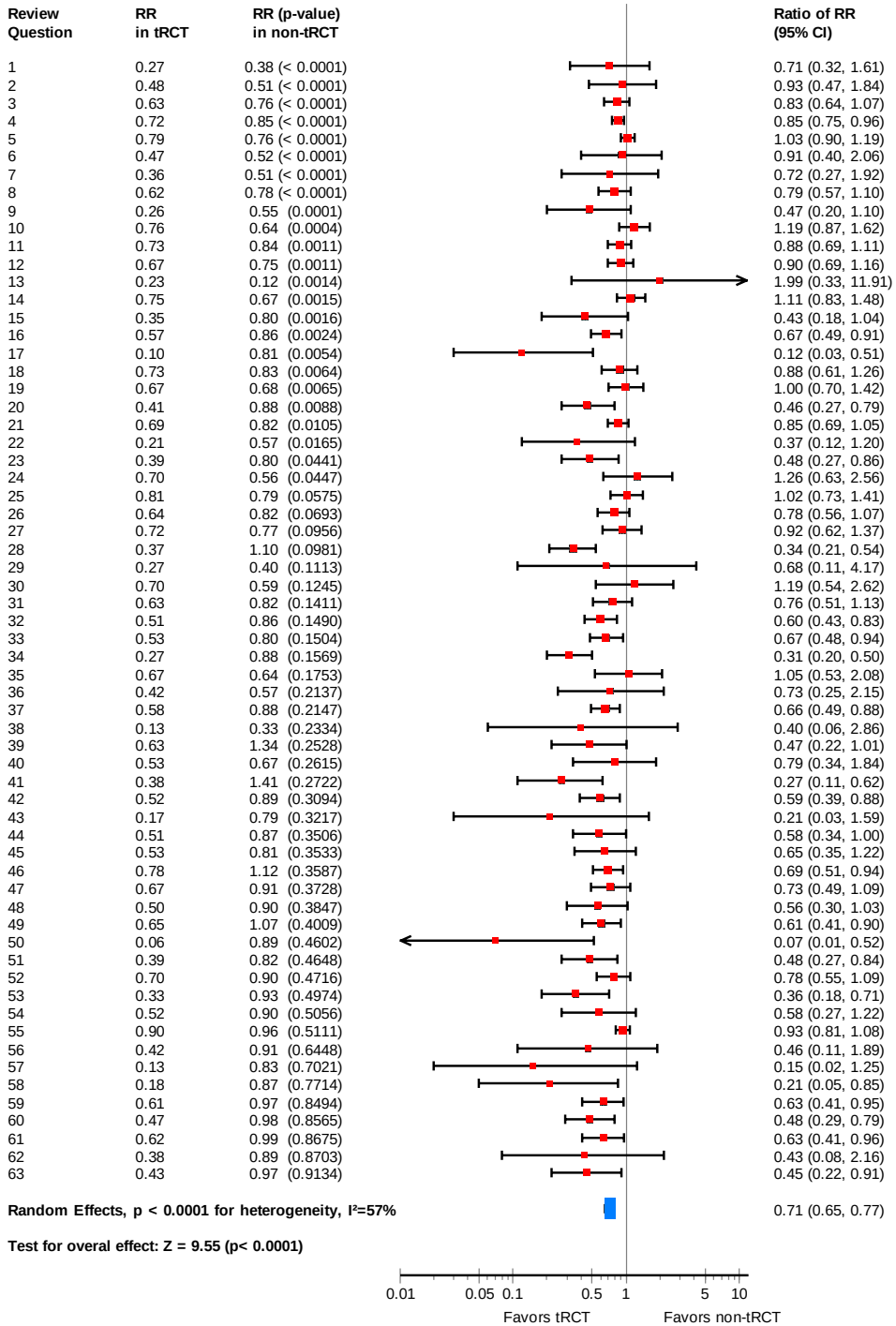
Analysis

- ratio of RRs of individual tRCTs to corresponding non-tRCTs:
  log(ratio of RRs) = log(RR of tRCT / RR of pooled non-tRCTs)
  = log(RR of tRCT) – log(RR of pooled non-tRCTs)
- overall estimate
  - log(ratio of RRs) inverse variance-weighted average of log(ratio of RRs)
  - back transformed to the overall ratio of RRs
- two meta-regressions
- first dependent variable log of difference in RRs of tRCTs and non-tRCTs
  - independent variables use of stopping rule, number of events
- second hierarchicial meta-regression
  - meta-analysis and individual study were levels in hierarchy
  - dependent variable log RR of each individual study
  - independent variables added concealment, blinding, stopping early


tRCTs identified in prior systematic review
(n=143)
Additional tRCTs identified
(n=52)
Total tRCTs as basis for literature search (n=195)
Relevant SRs identified
(n=238)
SRs updated
(n=32)
SRs not updated
(n=206)
Potentially relevant RCTs retrieved and blinded (n=2488)
Excluded because insufficient similarity to the tRCT or not randomized
(n=2012)
RR not calculable
(n=30)
Truncated early for benefit
(n=22)
Included in analysis:
91 tRCTs
424 matching non-tRCTs
63 research questions

Study Characteristics

- area of study
  - cardiology > 35%, no other concentration
- publication in high impact journals
  - 62 tRCTs (68%), 128 non-tRCTs (30%)
- methods
  - concealment 53% and 34%; blinding 60%
- preplanned stopping rule
  - 76% of tRCTs, 13% of non-tRCTs



55/63 "favor" tRCT

20/63 significantly "favor" tRCT

if RR non-tRCT 0.8
RR tRCT 0.57
more than double RRR

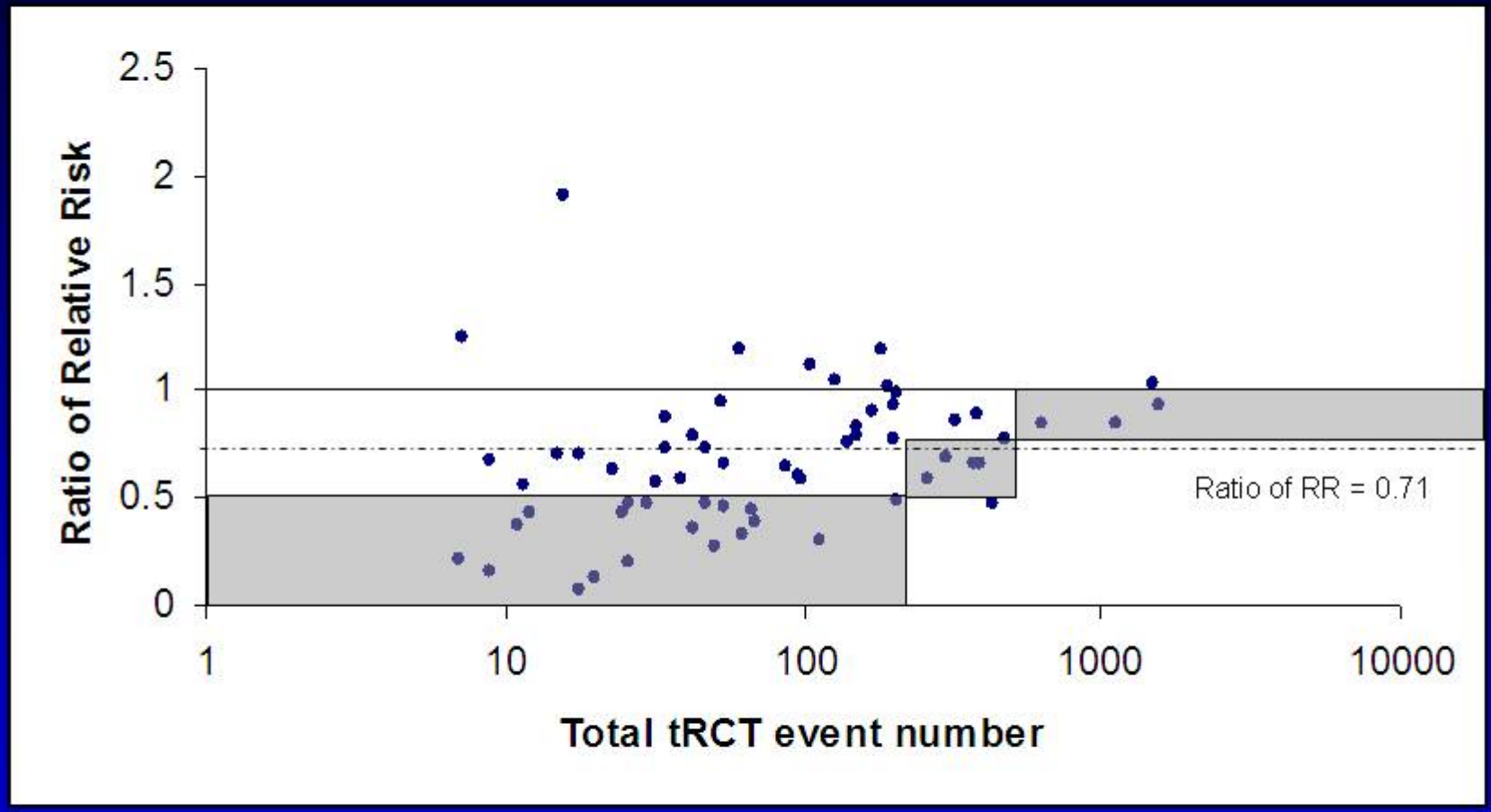
39/63 (62%) results of non-tRCTs > 0.05

16/63 (25%) non-tRCTs RR > 0.90

Predictors of difference

Independent variable	Parameter (95%CI)	p-value	R-square*
Univariable Model			
Stopping rule	0.14 (0.02, 0.27)	0.02	0.08
Univariable Model			
Every 100 events in the tRCT	0.0169 (0.0088, 0.025)	< 0.0001	0.22
Multivariable Model			
Stopping rule	0.07 (-0.05, 0.19)	0.25	0.24
Every 100 events in the tRCT	0.0151 (0.0066, 0.0237)	< 0.0001	

Concealment p = .96
Blinding p = 0.32


Ratio of Relative Risk
2.5
2
1.5
1
0.5
0
1
10
100
1000
10000
Total tRCT event number
Ratio of RR = 0.71

Conclusions

- trials stopped early for benefit overestimate magnitude of treatment effects
  - overestimates substantial, potentially effect treatment decisions
  - may sometime create completely spurious treatment effects
- overestimates less with large sample size
  - but overestimates still substantial
  - probably need > 500 events before safe from major overestimates

Editorial comments

- problem made worse by
  - publication in top journals
  - may obscure adverse effects
- ethics questionable
  - scientific value (overestimated compromise)
  - value to society (dissemination of overestimates)
- if really unethical to continue
  - should be no subsequent trials addressing question
- DMCs stop only when completely confident
  - our results suggest never that confident

Alternative comparison

- ideal comparator
  - no stopping rule, not stopped
  - unidentifiable, not feasible
- alternative
  - all trials including stopped early for benefit
  - rationale non-tRCTs will underestimate, simulations
  - RR 0.85 (95% CI: 0.81 – 0.91)
  - 16 of 63 (25%) p>0.05
- simulations suggest low weight tRCTs
  - 28% (interquartile range 12% to 40%)
  - 37 (60%) tRCTs more than 20% of weight
  - possibly stopped early phenomenon