Do Randomized and Non-Randomized Trials Yield Different Answers in Similar Populations? – Evidence from a 'Meta-Propensity Score' Analysis in Cardiac Surgery

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Introduction I: RCTs and Non-RCTs

- Effects of therapeutic interventions should be checked (if possible) in randomized controlled trials (RCTs).
- RCTs sometimes have limited **external** validity (Rothwell, 2005).
- Consequence for all systematic comparisons of RCTs and Non-RCTs: Limited **internal** validity!

  If RCTs are conducted in highly selected populations, but Non-RCTs in general populations, potential differences between RCTs and Non-RCTs are not necessarily due to missing randomisation.
  They might also arise from the different populations involved!

Introduction II: 'Meta-Randomization'?

- Ideally we would like to have a 'Meta-randomized' trial: Investigators willing to conduct a study on a specific clinical question would be randomly selected to perform a RCT or a Non-RCT:
  → Balancing of 'Meta-confounders' (All properties of investigator's setting and patients)
  → Causal effect of randomization could be validly measured

- Technically feasible? Ethically acceptable?

Introduction III: 'Meta-Propensity Score'!

- Our Solution: Matched 'Meta-Propensity Score-Analyse'

  1. Match RCTs and Non-RCTs for relevant 'Meta-confounders'
     (summarized by a 'Meta-Propensity Score')
  2. Compare treatment effects in the
     'Meta-matched' population

Introduction IV: Clinical topic

- Comparison of on- and off-pump (beating heart, no use of the heart-lung-machine) technique in coronary artery bypass grafting

- " … one of the most hotly debated and polarizing issues in cardiac surgery …" (Sellke et al., 2005).

- Public health relevance: In Germany, 51.273 (isolated) bypass surgerys were conducted in 2006, of which 10.1% were off-pump (Gummert et al., 2007).

Methods I: Studies

- Systematic search for all RCTs (all studies from the three largest, most recent systematic reviews on the topic + own MEDLINE search)
- Systematic search for all PS-analyses (Kuss et al., 2008(?))
- Inclusion criteria for studies:
  - Information given on study population and setting ('Meta-confounders')
  - Information given on at least one of 10 binary clinical in-hospital outcomes (Postoperative death, stroke, myocardial infarction, renal failure, …)

Methods II: Studies

- Structured data extraction (pretested data extraction form, two blinded reviewers (OK, TL), differences resolved by consensus with a third reviewer (JB))

- Extracted data:
  - General information (time of study, number of centers, number of patients, country, …)
  - Study population (baseline risk factors)
  - Outcomes (Absolute numbers or effect estimates for each available clinical outcome)

Methoden III: Meta-PS-Analysis

- Inclusion criterion for 'Meta-confounders': Information in at least 2/3 of all RCTs and PS-Analyses
- Simplifying assumption: Mean = Median
- If necessary: transformation of categorical 'Meta-confounders' in continuous ones under the assumption of uniform distribution in the categories
- Multiple imputation of missing values in the 'Meta-PS-Model‘ (SAS® PROC MI)
- 'Meta-PS model' as logistic model with continuous 'Meta-confounders' up to third order (optimal c-statistic=89.6%)
- 'Meta-matching' with an optimal matching algorithm with variable number of controls (Soledad Cepeda et al., 2006)

Methods IV: Meta-PS-Analysis

- “Reconstruction” of four-fold-tables in the PS analyses by the Di Pietrantonj method (Di Pietrantonj, 2006).
- Estimated treatment effects from RCTs and PS analyses were compared in the 'Meta-matched' sample as **differences in odds ratios** (with 95%-confidence intervals) with a 3-level (patients are correlated within studies, studies are correlated within matching stratum) random effects logistic regression model
- Parameter estimation by PQL (SAS® PROC GLIMMIX)
- Confidence intervals by the multivariate delta method

Results I: Studies

- Initially retrieved: 28 PS-Analyses and 51 RCTs
- 7 'Meta-confounders' had data in at least 2/3 of all RCTs and PS-Analyses
- After 'Meta-matching':
  10 PS-Analyses (25.552 patients) and
  29 RCTs (2.723 patients)
- 186 effect estimates from all clinical outcomes:
  Post-op. death (38), stroke (28), MI (27), atrial fibrillation (16), …

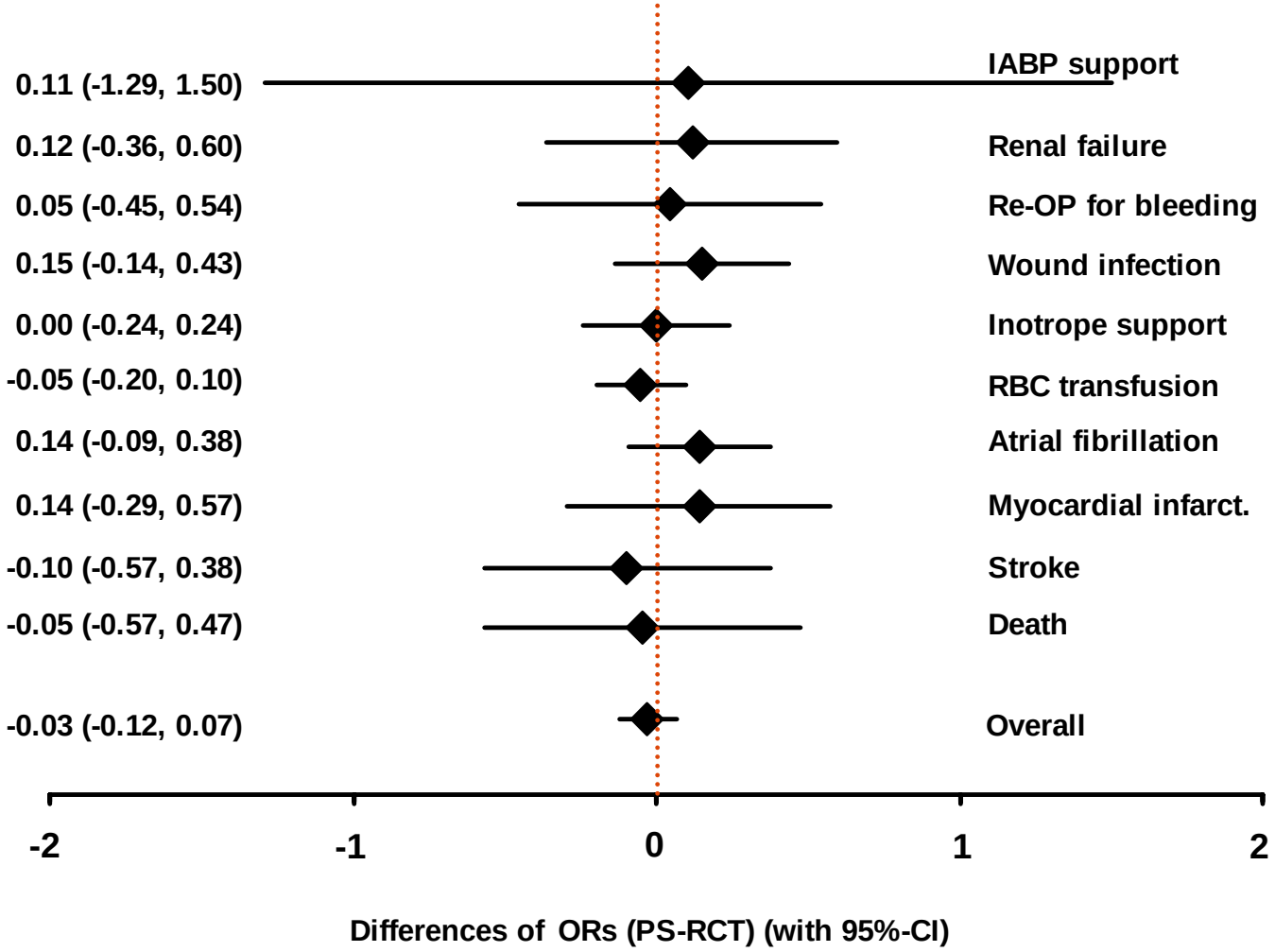
Results II: Studies *before* 'Meta-matching'

Meta-confounder	PS analyses (N=28)	RCTs (N=51)	p-value	Standard. diff. (%)
Study region			0.007	
Europe	17 (61%)	36 (71%)		
Northern America	10 (36%)	5 (10%)		
Others	1 (3%)	10 (19%)		
Number of centers				
1	18 (65%)	47 (92%)	0.006	
>1	9 (32%)	3 (6%)		
Missing	1 (3%)	1 (2%)		
Mean age (years)	65.8	63.1	0.002	75.1
Mean prop. males (%)	72.1	77.1	0.138	-37.0
Mean prop. pre-op. MI (%)	44.5	41.6	0.480	21.0
Mean LVEF (%)	58.8	62.7	0.033	-55.9
Mean prop. diabetic pers. (%)	26.2	24.4	0.595	13.9

Results III: Studies *after* 'Meta-matching'

Meta-confounder	PS analyses (N=10)	RCTs (N=29)	p-value	Standard. diff. (%)
Study region			0.999	
Europe	8 (80%)	23 (80%)		
Northern America	1 (10%)	3 (10%)		
Others	1 (10%)	3 (10%)		
Number of centers				
1	8 (80%)	25 (86%)	0.631	
>1	2 (20%)	3 (10%)		
Missing	0 (0%)	1 (4%)		
Mean age (years)	64.1	63.9	0.916	3.9
Mean prop. males (%)	80.5	76.9	0.431	30.5
Mean prop. pre-op. MI (%)	44.0	39.9	0.530	27.6
Mean LVEF (%)	61.1	60.7	0.861	6.8
Mean prop. diabetic pers. (%)	24.8	25.2	0.925	-3.7

Results IV: Differences of ORs (PS-RCT) in the 'Meta-matched' sample



Conclusion I

- In our example, treatment effects from RCTs and PS analyses were very similar in a ‘Meta-matched' population, indicating a small effect of randomisation itself. (difference in ORs [95%-CI]: -0.027 [-0.119, 0.066])

- Besides 'Meta-matching':
  - Identical design of Non-RCTs (PS)
  - Identical intervention and control group,
  - Identical responses in RCTs and Non-RCTs
  - Identical length of follow-up
  - Valid outcomes used
  - Overlap (though not perfect) in observation intervals

Conclusion II

- **Limitations:**
  - Publication bias?
  - Simplifying assumptions too simple?
  - 'Meta-Residual Confounding'?
    (We did not conduct a 'Meta-randomized' trial!)
  - Balancing of 'Meta-Confounders' in the 'Meta-matched' sample does not assure balancing for the individual outcome!

Conclusion III

- **In the future:**
  Our study needs independent replication in a different (preferably non-surgical) setting.

  Even if replicated we do not think that RCTs would be obsolete, but the current practice of excluding well conducted Non-RCTs from systematic reviews of treatment effects could at least be questioned.

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