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ΙΑΤΡΙΚΗ ΣΧΟΛΗ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΙΩΑΝΝΙΝΩΝ

A **selection model** to explore whether publication bias is more likely **in placebo-controlled trials compared to multi-arm and head-to-head trials**

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I have no actual or potential conflict of interest in relation to this presentation

Meta-analysis and Publication Bias

- Published evidence may represent a **biased sample of the overall evidence**

Trials with **'exciting' results** and **big trials**

are more probable to be published

Publication Bias may exaggerate the effect of a treatment

Network meta-analysis and PB

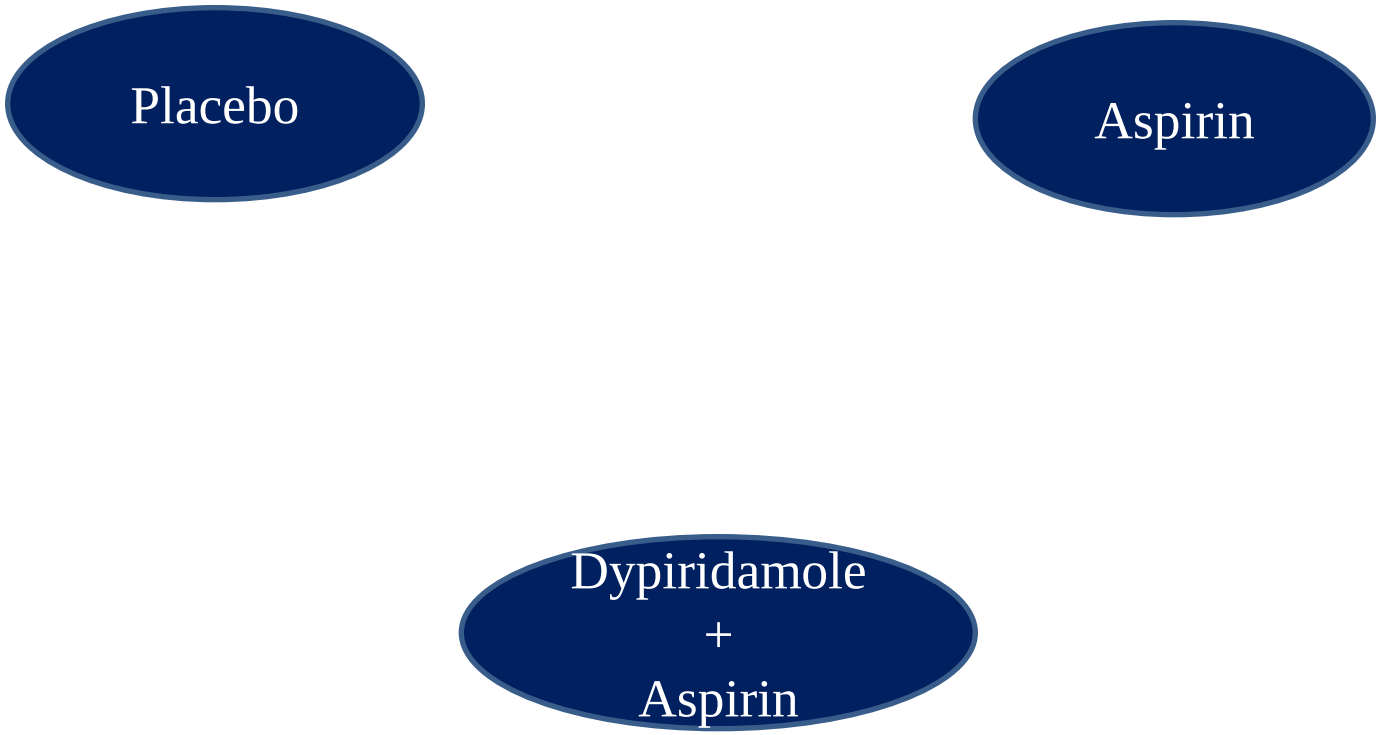
- 86% of Cochrane reviewers acknowledge the need for indirect comparisons
  - Abdelhamid et al RSM 2012

In summary, NMA

- Compares many competing treatments for the same healthcare problem and allows a ranking of all available treatments
- Includes multi-arm studies
- The design of a trial (set of treatments compared) may impact on its likelihood to be published

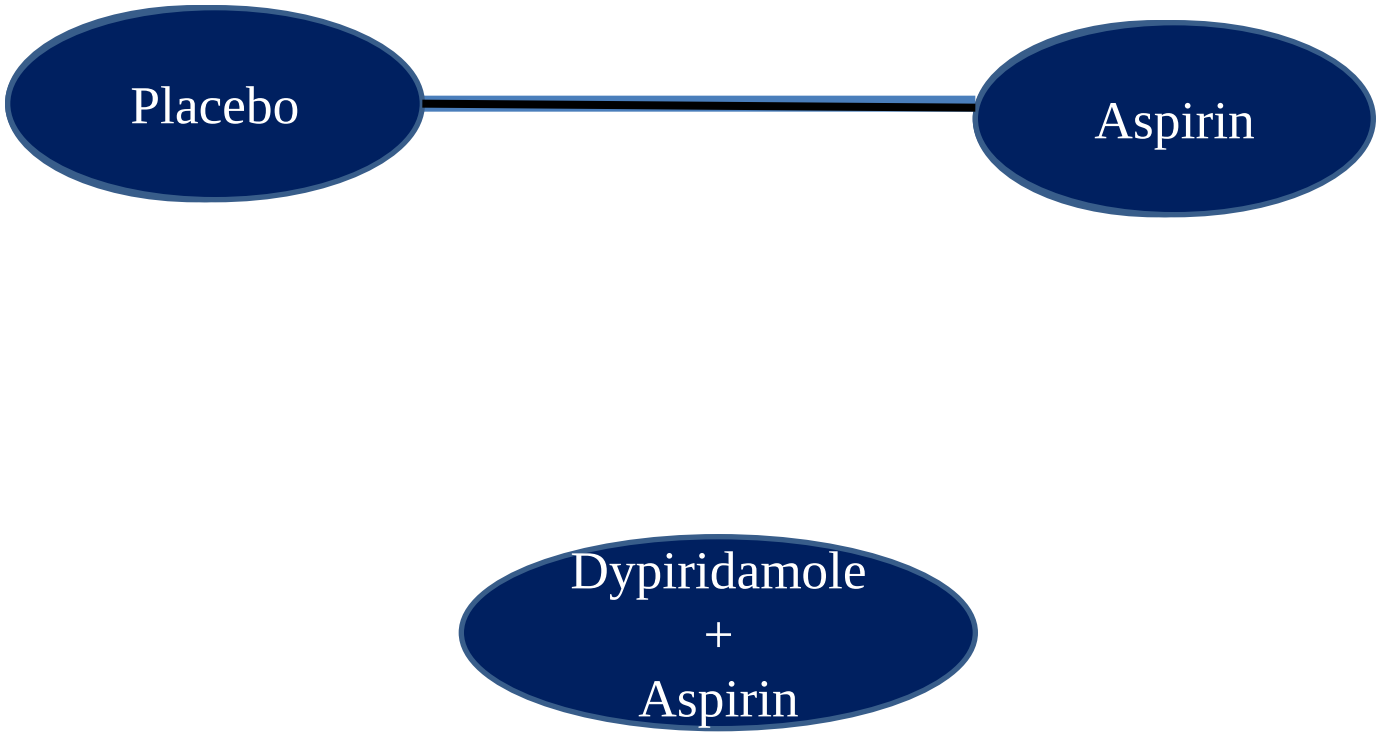
Abdelhamid, A.S. et al (2012). Use of indirect comparison methods in systematic reviews : a survey of Cochrane review authors. *Reserach Synthesis Methods*, **3**(2), 161-176.

Three antiplatalet interventions
Outcome: OR for failure of vascular graft or arterial patency

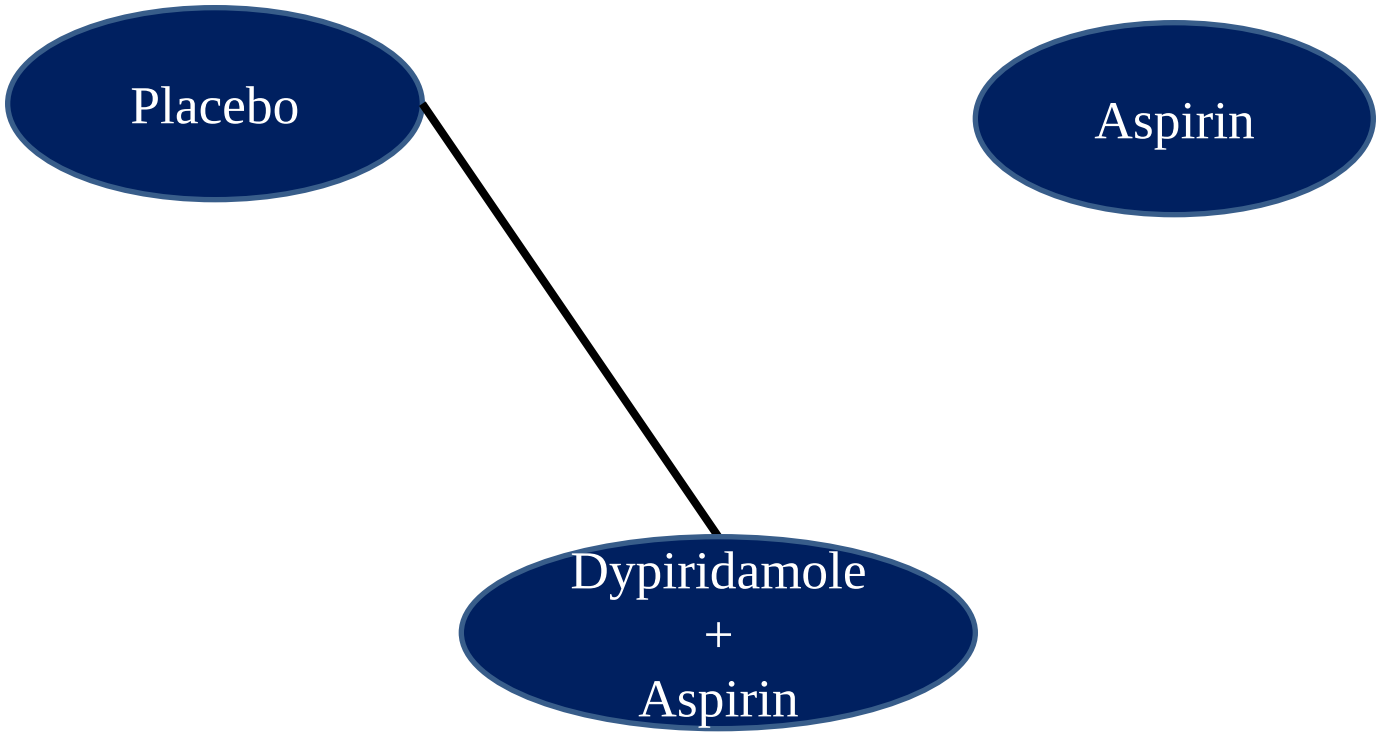


Chootrakool,H., Shi,J.Q. and Yue,R. (2011). Meta-analysis and sensitivity analysis for multi-arm trials with selection bias. *Statistics in Medicine*, **30**(11), 1183-1198.

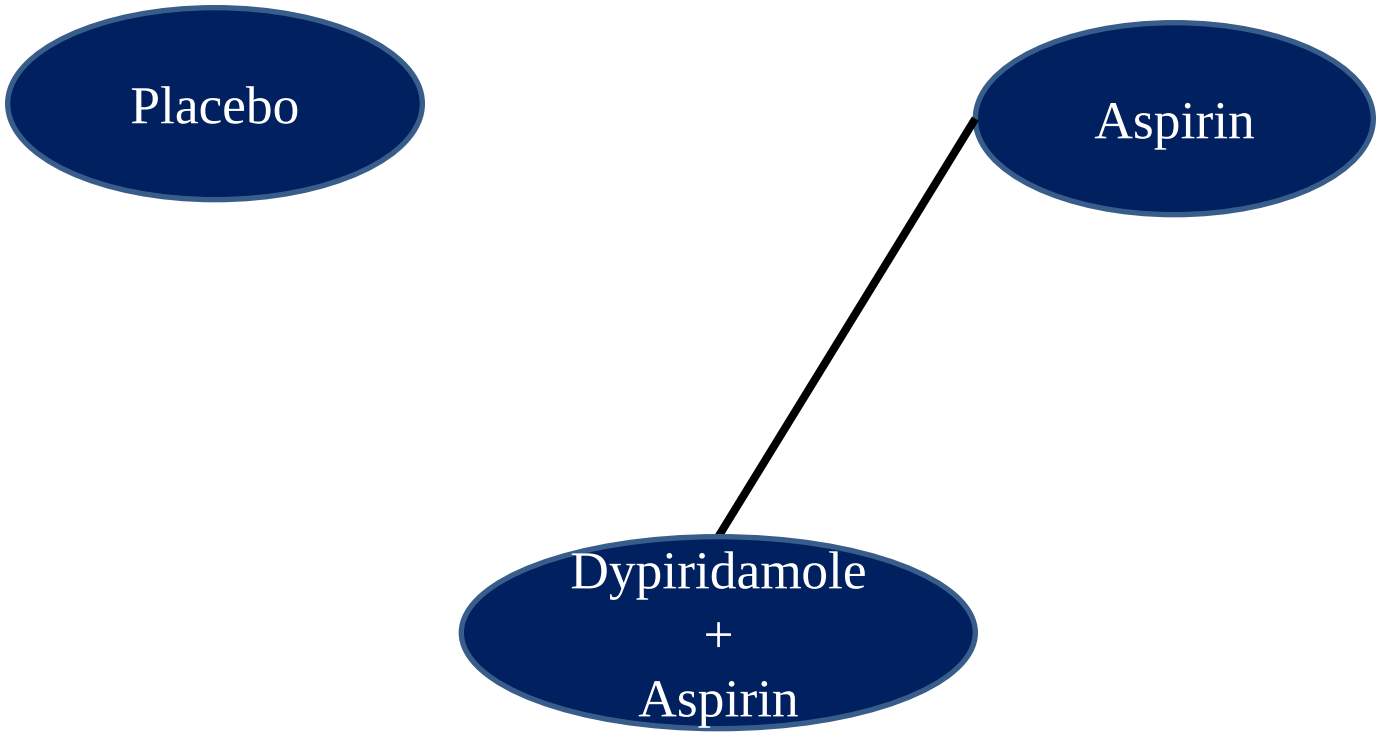
First design – 7 studies



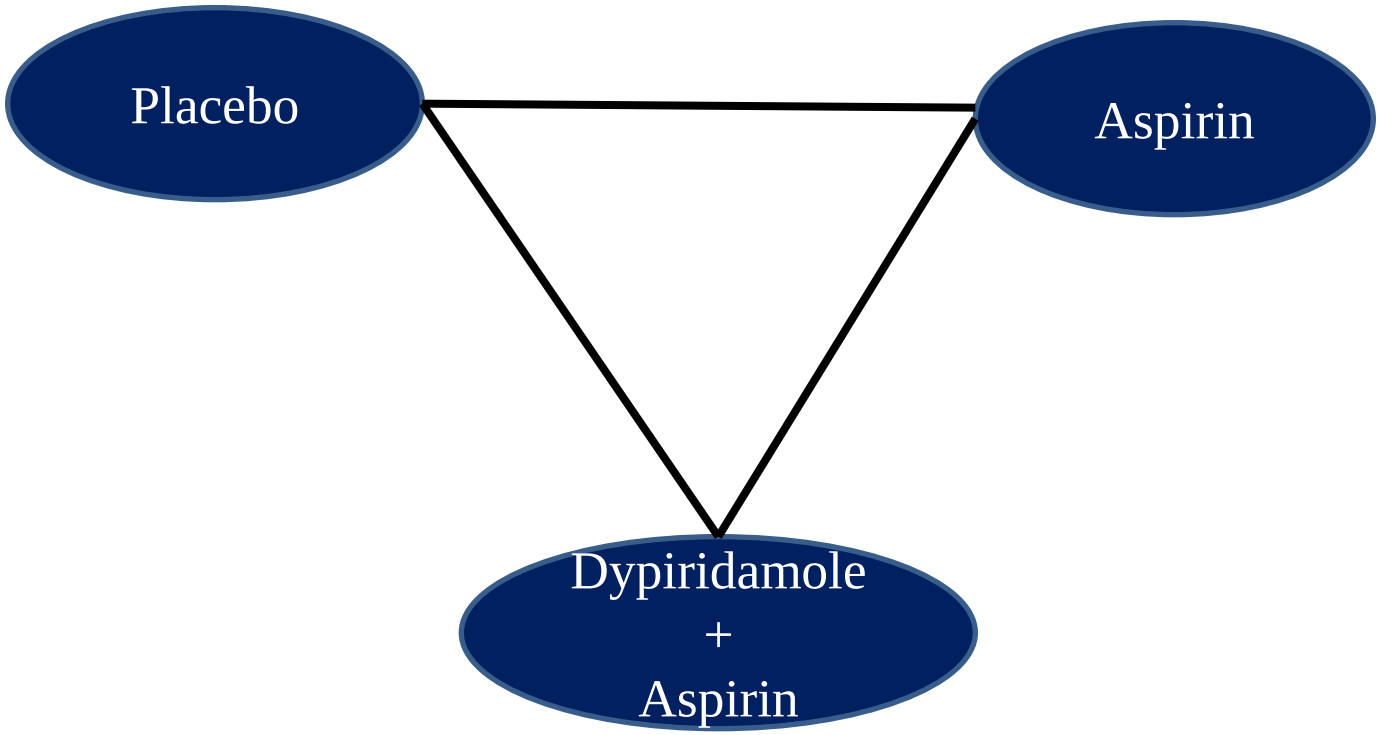
Second design – 14 studies



Third design – 4 studies

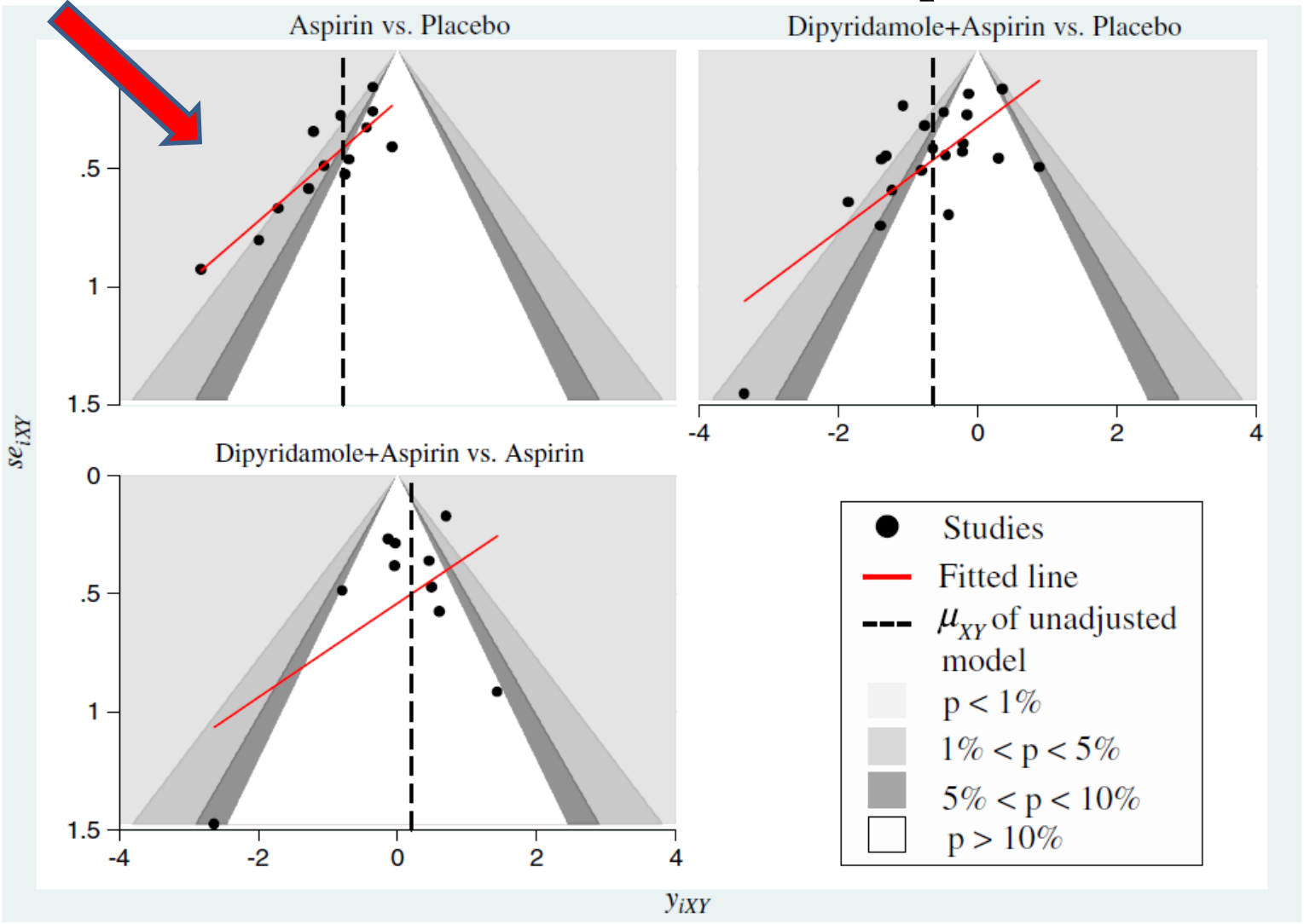


Fourth design – 6 studies



Assumption: Different study designs could be associated with different probabilities of being selected for publication

Contour-enhanced funnel plots



Chaimani,A. and Salanti,G. (2012). Using network meta-analysis to evaluate the existence of small study effects in a network of interventions. *Reserach Synthesis Methods*, **3**(2), 161-176.

Chootrakool,H., Shi,J.Q. and Yue,R. (2011). Meta-analysis and sensitivity analysis for multi-arm trials with selection bias. *Statistics in Medicine*, **30**(11), 1183-1198.

Selection model

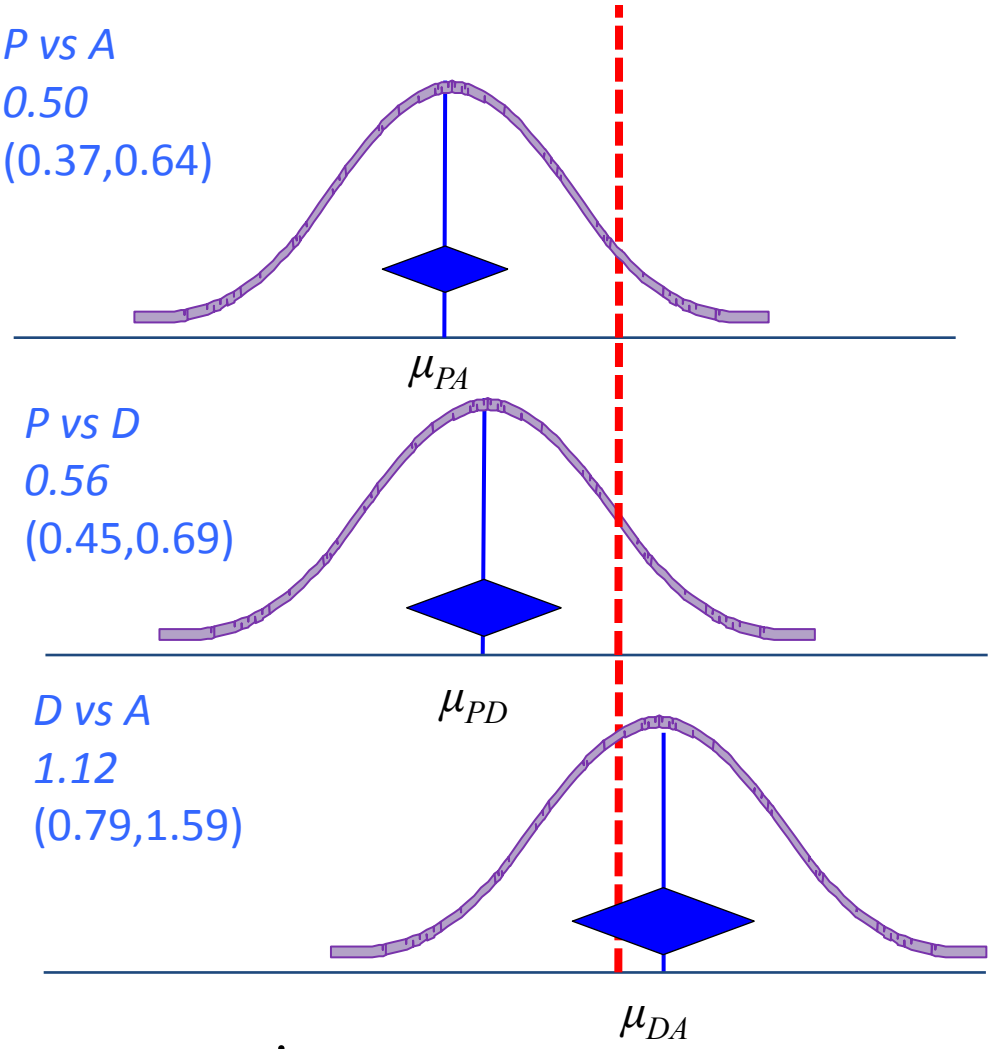
- Models the mechanism by which trials are selected for publication
  - Heckman's selection model (1979) introduced in the meta-analysis literature by Copas and Shi (2000)
  - Mavridis et al (2013) extended the model to star-network meta –analysis

- Each trial has probability p_i of being published
- Bias arises when effect size $\mathbf{y}_i$ is correlated with p_i
- Very large trials have p_i close to one

Copas, J.B. et al (2000). *Meta-analysis, funnel plots and sensitivity analysis.* Biostatistics, 1(3), 247-262.
Heckman,J.J. (1979). *Sample selection bias as a specification error.* Econometrica, **47**, 153-161.
Mavridis et al (2013). *A fully Bayesian application of the Copas selection model for publication bias extended to network meta-analysis*. Statistics in Medicine, **32**(1), 51-66.

NMA of unconditional treatment effects

Effect size	*Standard error*
y_1^{PA}	s_1^{PA}
y_2^{AD}	s_2^{AD}
y_3^{PD}	s_3^{PD}
y_4^{PA}, y_4^{PD}	$s_4^{PA}, s_4^{PD}, cov(y_4^{PA}, y_4^{PD})$
⋮	⋮
$y_n{}^{PA}$	s_n

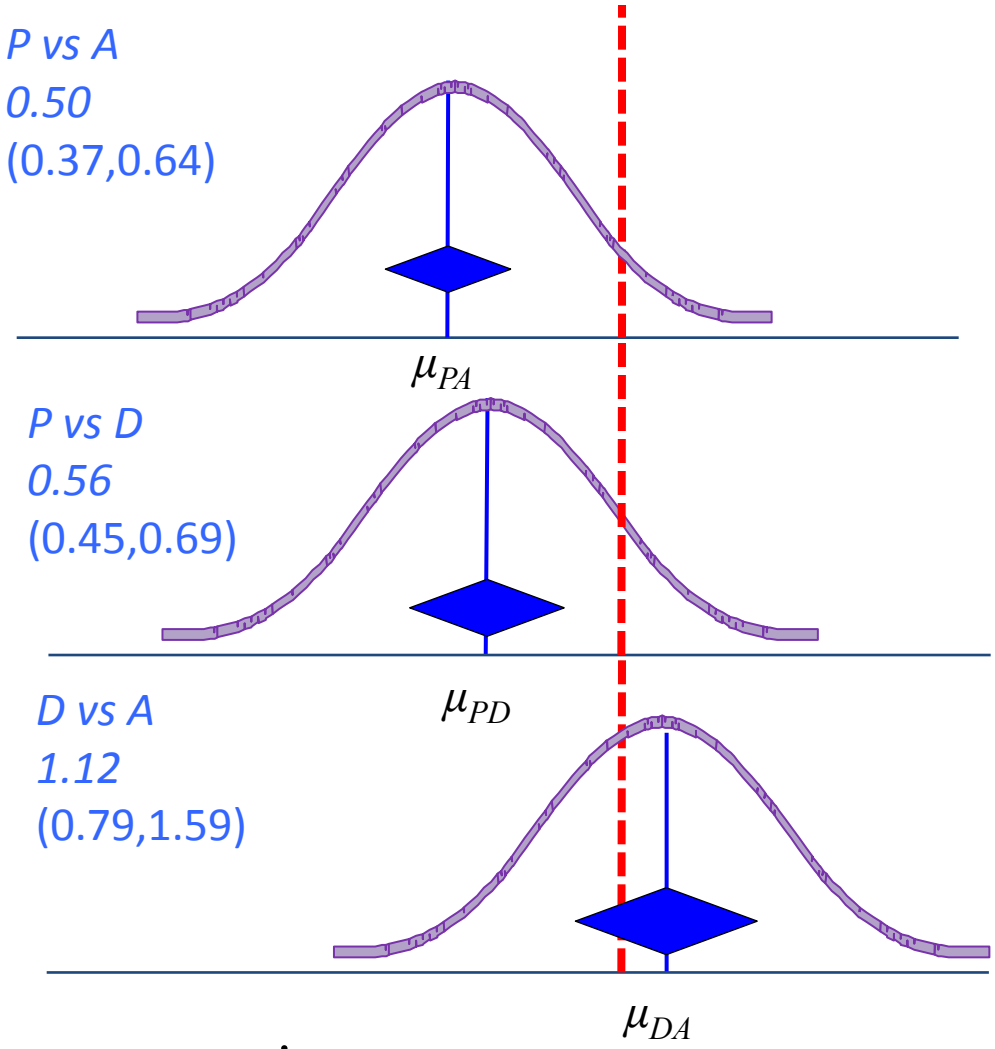


Consistency assumption

$$\mu_{DA} = \mu_{PA} - \mu_{PD}$$

NMA of unconditional treatment effects

Effect size
$y_1^{PA}\|published$
$y_2^{AD}\|$published
$y_3^{PD}\|$published
$y_4^{PA}\|published$, $y_4^{PD}\|published$
⋮
$y_n{}^{PA}\|published$

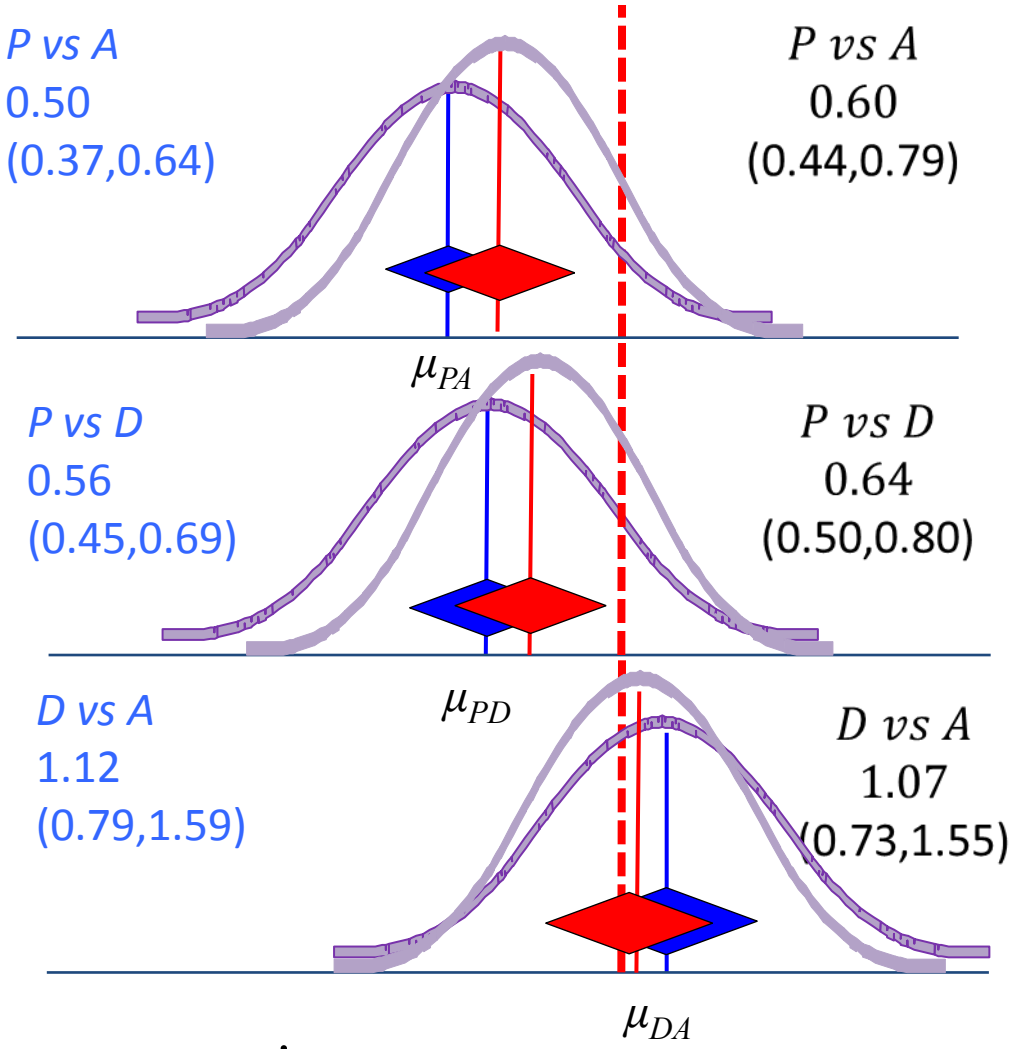


Consistency assumption

$$\mu_{DA} = \mu_{PA} - \mu_{PD}$$

NMA selection model

Effect size
$y_1^{PA} \mid z_1 > 0$
$y_2^{AD} \mid z_2 > 0$
$y_3^{PD} \mid z_3 > 0$
$y_4^{PA} \mid z_4 > 0,$ $y_4^{PD} \mid z_4 > 0$
$\vdots$
$y_n{}^{PA} \mid z_n > 0$



Consistency assumption

$$\mu_{DA|Published} = \mu_{PA|Published} - \mu_{PD|Published}$$

Parameters in NMA selection model

- z_i the propensity of publication
  - $z_i > 0$ the effect size y_i is observed
- We write z_i **as a function of the study precision**, and to be estimated we need to make an assumption about the probability of a large and small study to be published for each design
  - P^{low}
  - P^{large}

Parameters in NMA selection model

- z_i the propensity of publication
- z_i is correlated with y_i

If the estimated ρ is away from null, then this is a sign of selection bias

- *for harmful outcomes, ρ<0*
- *for beneficial outcomes ρ>0*

For three-arm trials we may have three correlations

$$\rho^{PD} s_i^{PD} - \rho^{PA} s_i^{PA} = \rho^{AD} s_i^{AD}$$

Impact of study design

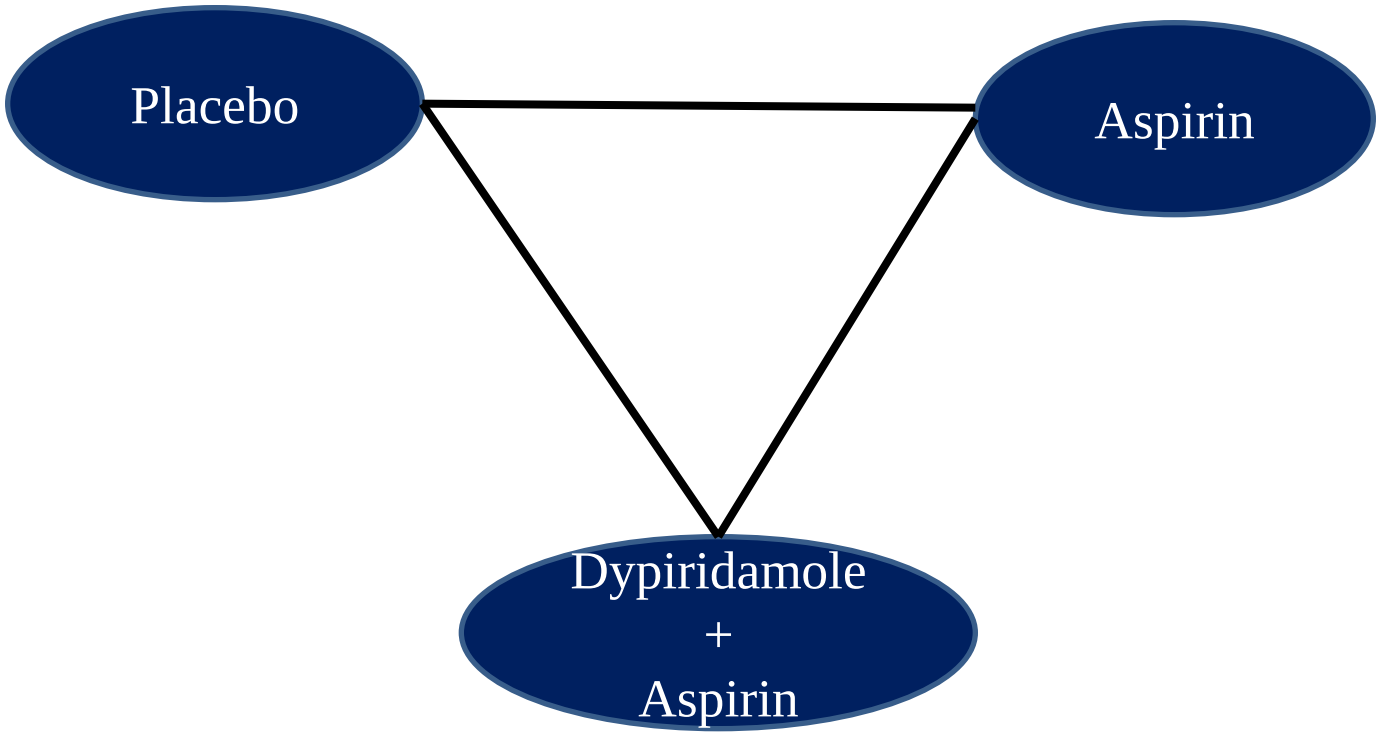
Is publication bias more probable in placebo-controlled trials rather than in head-to-head and multi-arm studies?

Is ρ different across trial designs?

What is the impact on the treatment ranking?

Three antiplatalet interventions

Outcome: OR for failure of vascular graft or arterial patency



Are $\rho_{PA,}\ \rho_{PD,}\ \rho_{DA,}\ \rho_{APD}$ different?

Selection model scenarios

Design	No bias	Moderate selection bias	Severe selection bias	Severe selection bias for all designs
		Selection Probabilities		
Aspirin vs Placebo	$P^{low} = 1$ $P^{large} = 1$	$P^{low} \sim U(0.4,0.5)$ $P^{large} \sim U(0.7,0.8)$	$P^{low} \sim U(0.1,0.2)$ $P^{large} \sim U(0.4,0.5)$	$P^{low} \sim U(0.1,0.2)$ $P^{large} \sim U(0.4,0.5)$
Dip+Asp vs Placebo		$P^{low} = 1$ $P^{large} = 1$	$P^{low} = 1$ $P^{large} = 1$	$P^{low} \sim U(0.1,0.2)$ $P^{large} \sim U(0.4,0.5)$
Dip+Asp vs Aspirin		$P^{low} = 1$ $P^{large} = 1$	$P^{low} = 1$ $P^{large} = 1$	$P^{low} \sim U(0.1,0.2)$ $P^{large} \sim U(0.4,0.5)$
Dip+Asp vs Aspirin vs Placebo		$P^{low} = 1$ $P^{large} = 1$	$P^{low} = 1$ $P^{large} = 1$	$P^{low} \sim U(0.1,0.2)$ $P^{large} \sim U(0.4,0.5)$

Results: correlation ρ

	No selection bias	Moderate selection bias	Severe selection bias	Severe selection bias for all designs
Aspirin vs Placebo	$\rho^{PA} \cong 0$ (-0.95,0.95)	$\rho^{PA} = -0.55$ (-0.98,0.28)	**ρ^{PA} =-0.60 (-0.99,-0.01)**	**$\rho^{PA} = -0.69$ (-0.99,-0.06)**
Dip +Asp vs Placebo	$\rho^{PD} \cong 0$ (-0.95,0.95)	$\rho^{PD} \cong 0$ (-0.95,0.95)	ρ^{PD} =-0.01 (-0.95,0.95)	$\rho^{PD} = -0.09$ (-0.82,-0.77)
Asp+ Dip vs Aspirin	ρ^{DA} =0.01 (-0.95,0.95)	$\rho^{DA} = -0.01$ (-0.95,0.95)	$\rho^{DA} \cong 0$ (-0.94,0.95)	$\rho^{DA} = -0.22$ (-0.71,-0.36)
Dip+Asp vs Aspirin vs Placebo	$\rho^{PA} = 0.02$ $(-0.39,0.39)$	$\rho^{PA} = -0.02$ $(-0.14,0.14)$	$\rho^{PA} = -0.03$ $(-0.14,0.13)$	$\rho^{ABC} = -0.53$ $(-0.82,-0.01)$
	$\rho^{PD} = 0.04$ $(-0.94,0.94)$	$\rho^{PD} = 0.10$ $(-0.63,0.63)$	$\rho^{PD} = 0.12$ $(-0.63,0.64)$	
	$\rho^{DA} = 0.02$ $(-0.54,0.54)$	$\rho^{DA} = 0.10$ $(-0.670.67)$	$\rho^{DA} = 0.13$ $(-0.67,0.67)$	

Results: OR and 95% CrI

	No bias	Moderate selection bias	Severe selection bias	Severe bias for all designs
Placebo	*reference*	*reference*	*reference*	*reference*
Aspirin	0.50 (0.37,0.64)	0.53 (0.40,0.69)	0.58 (0.43,0.74)	0.64 (0.45,0.86)
Aspirin + dipyridamole	0.56 (0.45,0.69)	0.57 (0.45,0.70)	0.58 (0.46,0.71)	0.66 (0.47,0.90)
Heterogeneity τ	0.30 (0.04,0.55)	0.32 (0.11,0.57)	0.31 (0.06,0.55)	0.36 (0.17,0.61)

If a severe selection model scenario is assumed only for Aspirin vs Placebo studies, Aspirin is similarly effective with placebo

Summary

The suggested selection model

- avoids assumptions about p-values and probability of publication
- estimates intervention effects under publication bias scenarios

- Various assumptions can be explored (e.g. all placebo-control trials are equally likely to be published)
- **Extend the selection model** to account for other characteristics associated with publication bias
  - E.g. study quality, conflict of interest etc.