

# Challenges of defining a non-inferiority margin: a case study of non-inferiority randomized controlled trials of oral anticoagulants for prophylaxis of venous thromboembolic events after orthopedic surgery

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project  
escher



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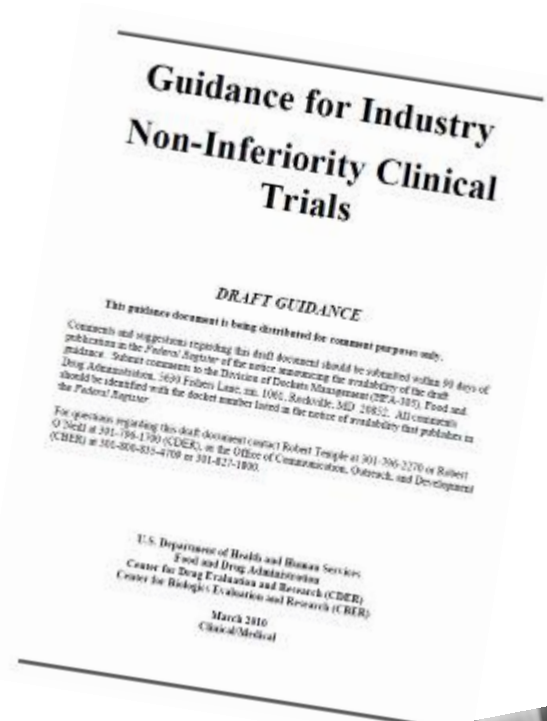
# Background and aim

- Non-inferiority (NI) margin
- Draft FDA guideline 2010
- Aim of study :  
identify problems and difficulties  
in determining NI margin



## case study on

RCTs of oral anticoagulants for prophylaxis of venous thromboembolic events (VTE) after orthopedic surgery.



# Search strategy & publication selection (NI trials)

## Pubmed search term :

("Hirudin"[All Fields] OR "bivalirudin"[All Fields] OR "lepirudin"[All Fields] OR "desirudin "[All Fields] OR "argatroban "[All Fields] OR "dabigatran"[All Fields] OR "melagatran"[All Fields] OR "ximelagatran"[All Fields] OR "apixaban"[All Fields] OR "edoxaban"[All Fields] OR "otamixaban"[All Fields] OR "rivaroxaban"[All Fields]) AND "humans"[MeSH Terms] AND English[lang] AND Randomized Controlled Trial[Publication Type]

326 articles

## Cochrane search term :

"hirudin or bivalirudin or lepirudin or desirudin or argatroban or dabigatran or melagatran or ximelagatran or apixaban or edoxaban or otamixaban or rivaroxaban" in Title, Abstract or Keywords in Cochrane Central Register of Controlled Trials"

592 articles

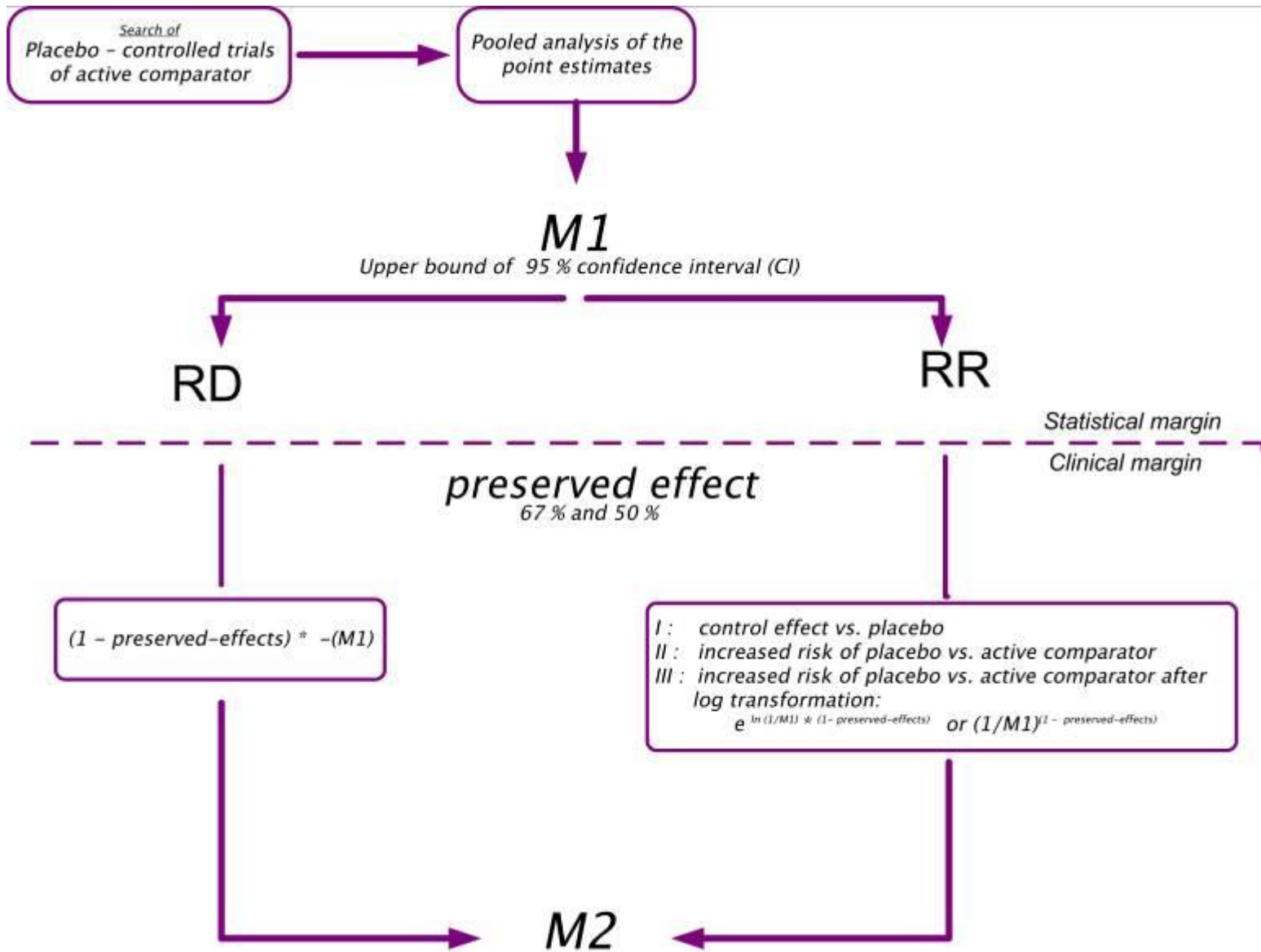
### **Excluded 906 publications :**

Other indication : 332  
Review and non – RCT articles : 68  
Healthy volunteers: 105  
Not in English : 6  
Superiority trials : 8  
Double publication : 387

**12 articles /NI trials**

# Results – NI trials

Name of Trial	Name of drug	Study ID	Dose	NI margin	Method to determine NI margin	Study Date	NI	NI
Colwell, et.al.	Ximelagatran	10-12	40 mg qd	RD = 5%	Used the same NI margin as published NI trial on Tinzarapin vs Enoxaparin	Apr 2004	67	50
EXPRESS	Dabigatran	8-12	40 mg qd	RD = 2%	Not described	Apr 2004	67	50
REMODEL	Dabigatran	6-10	40 mg qd	RD = 9.2%	- 67% preserved-effect of difference between enoxaparin and placebo	Nov 2004	68	65
RE MOBILIZE	Dabigatran	12-15	30 mg bid	RD = 9.2%	- 67% preserved-effect of difference between enoxaparin and placebo - Based on one published placebo controlled trial	Nov 2004	66	58
Re-Novate	Dabigatran	28-35	40 mg qd	RD = 7.7%	67% preserved-effect of difference between enoxaparin and placebo - Based on pooled analysis of 3 placebo controlled trials	Dec 2004	64	56
EXTEND	Ximelagatran	32-38	40 mg qd	RD = 2%	Not described	Sep 2005	65	54
RECORD 1	Rivaroxaban	35	40 mg qd	RD = 3.5%	Not described	Feb 2006	63	56
RECORD 3	Rivaroxaban	10 - 14	40 mg qd	RD = 4%	Not described	Feb 2006	68	68
RECORD 4	Rivaroxaban	11-15	30 mg bid	RD = 4%	Not described	Jun 2006	65	65
ADVANCE 1	Apixaban	10 - 14	30 mg bid	RD = 5.6% RR = 1.25	Not described	Nov-2006 <sup>1</sup>	66	61
ADVANCE 3	Apixaban	32-38	40 mg qd	RR = 1.25	Not described	Mar 2007	61	53
ADVANCE 2	Apixaban	10 - 14	40 mg qd	RD = 5.6% RR = 1.25	Not described	Jun 2007	67	72



# Search strategy & publication selection (placebo-controlled trials of enoxaparin)

## Pubmed search term :

("low-molecular weight heparin"[All Fields] OR "low molecular weight heparin"[All Fields] OR "enoxaparin"[All Fields]) AND ("placebos"[All Fields] OR "placebo"[All Fields]) AND "humans"[MeSH Terms]

409 articles

## Cochrane search term :

("low-molecular weight heparin" OR "low molecular weight heparin" OR "enoxaparin") AND "placebo" in Title, Abstract or Keywords in Cochrane Central Register of Controlled Trials

249 articles

### **Excluded 648 publications :**

Different drug (LMWH but not Enoxaparin) : 109

Other indication : 13

Review and non – RCT articles : 315

Different treatment procedure and timing : 6 Double publication : 205

**10 articles/ 6 placebo-controlled trials**

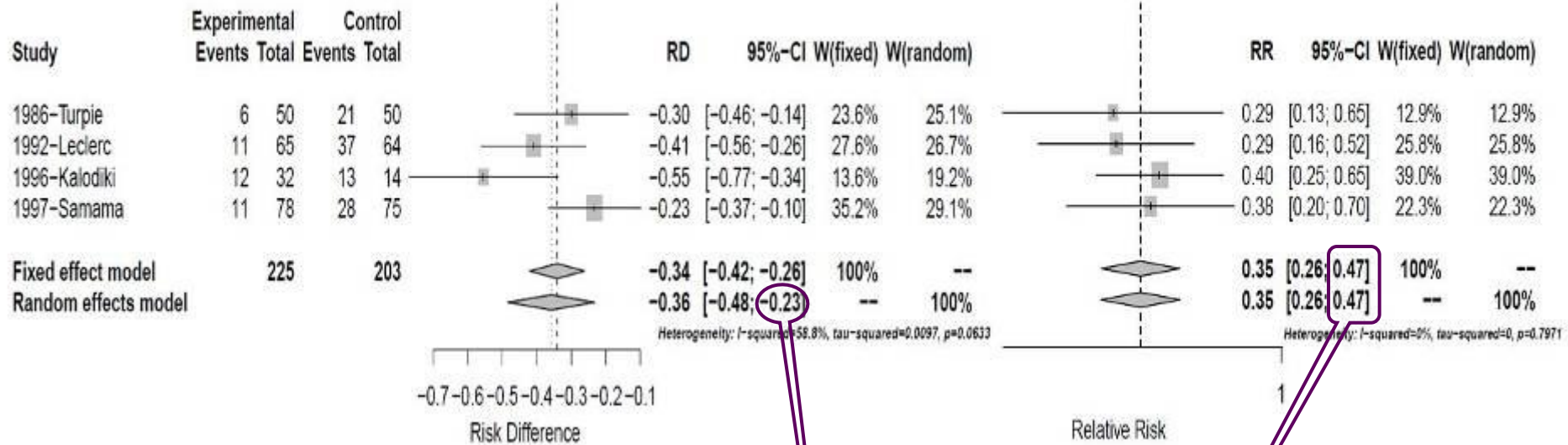
*(2 trials were published in 2 different publications, 1 trial was published in 3 different publications)*

**4 placebo-controlled trials before year 2000**

# Results – Placebo–controlled trials

Name of author	Date of publication	Duration of therapy (days)	Dosage of enoxaparin	Mean age of subjects	Female subjects (%)
Turpie, et.al	Oct-86	14	30 mg bid	67	52
Leclerc, et.al	Jan-92	14	30 mg bid	69	60
Kalodiki, et.al	Jun-96	8 - 12	40 mg qd	67	65
Samama, et.al	Jan-97	10 ± 2	40 mg qd	69	42
Fuji, et.al (1)	Jun-08	14	20 mg qd, 20 mg bid, 40 mg qd	62	88
Fuji, et.al (2)	Jun-08	14	20 mg qd, 20 mg bid, 40 mg qd	70	84

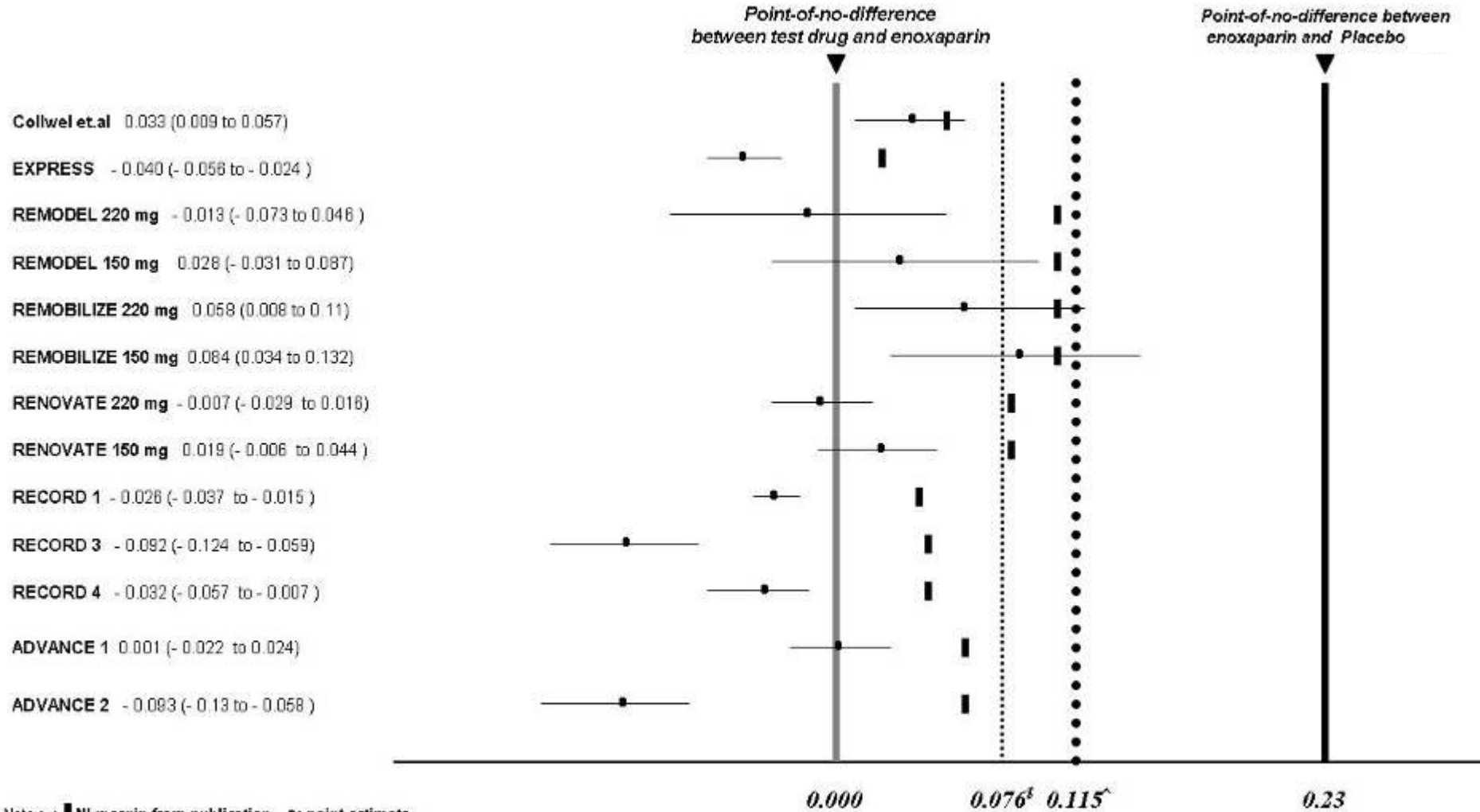
# Determining reference NI margin



Preserved-effects	RD	RR
	Random-effects model M1 = -0.23	M1 = 0.47 Method 3
50%	0.115	1.46
67%	0.076	1.28

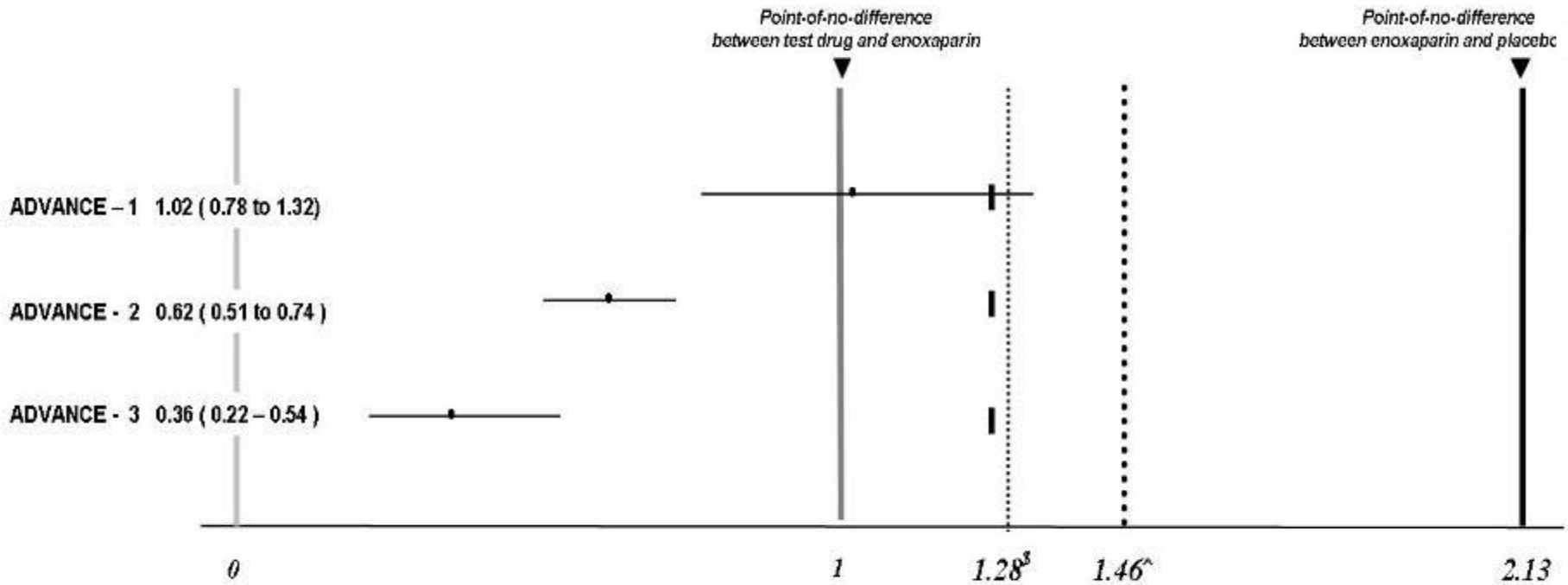


# Plot of NI trials results on reference NI margin (RD)



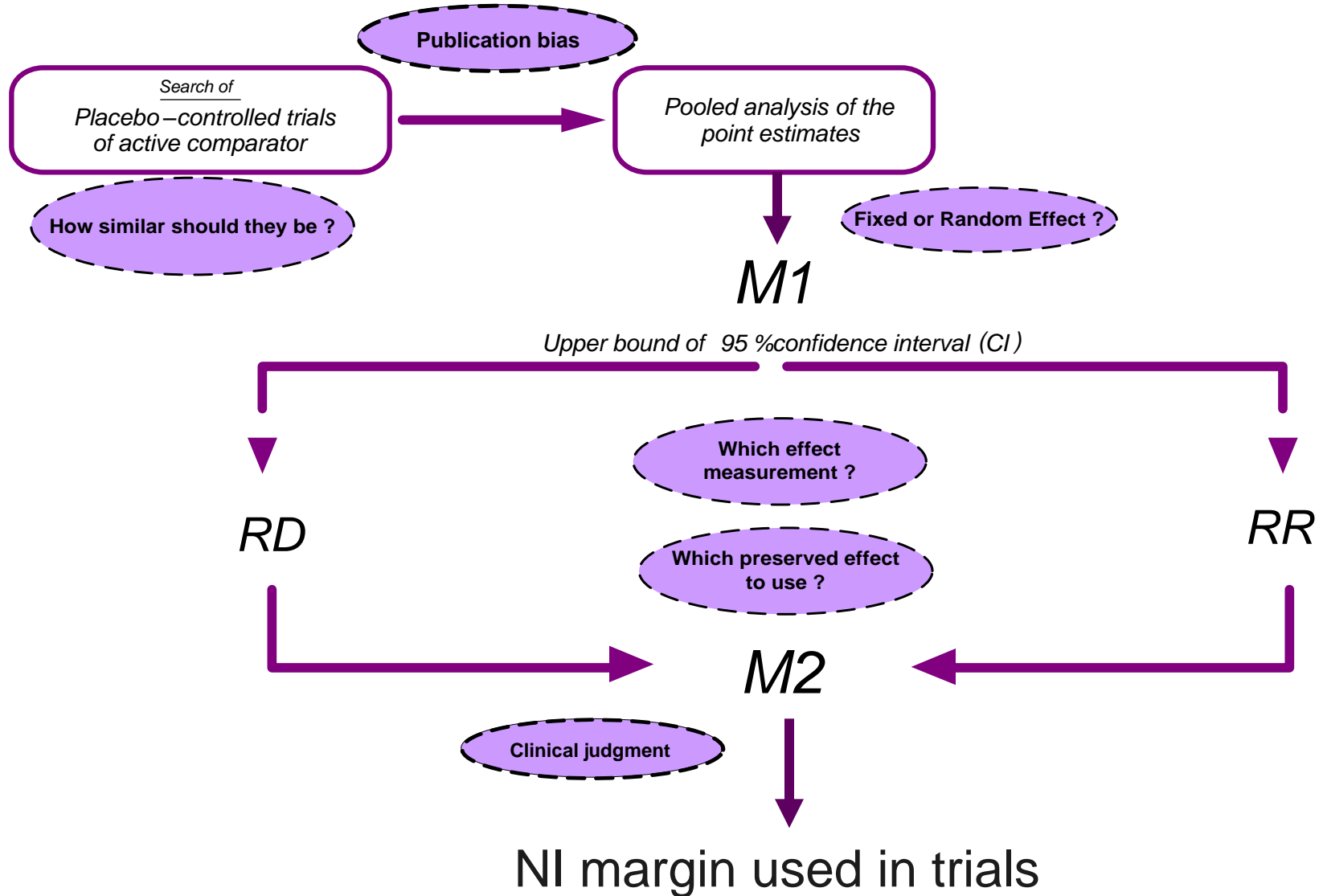
Note : ■ NI margin from publication, ● : point estimate,  
 ‡ : M2 based on 67 % preserved effect, ^ : M2 based on 50 % preserved effect

# Plot of NI trials results reference NI margin (RR)

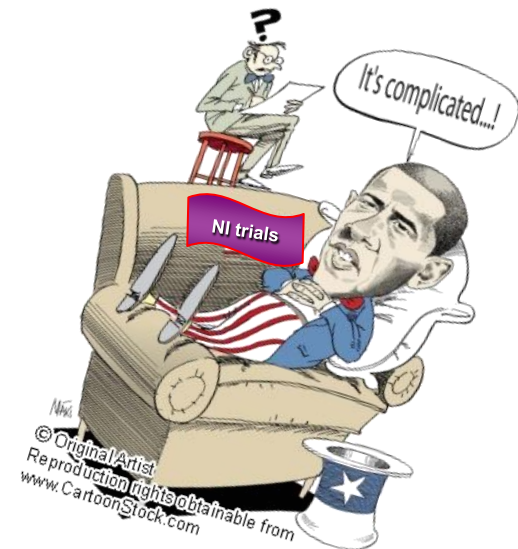


Note : ■ NI margin from publication, ● : point estimate,  
S : M2 based on 67 % preserved effect, A : M2 based on 50% preserved effect

# Challenges in determining a NI margin



- Determination of NI margin is still intricate
- Although a same comparator was used, a variation in NI margins among NI RCTs of oral anticoagulants for prophylaxis of VTE after orthopedic surgery exists
- Using different NI margins could lead to different conclusions.



# Thank you

Escher is project T6-202 of the Dutch Top Institute Pharma



Partners in Escher:



# Formula for reference margin calculation

\*

- for the RD

$$(1 - \text{preserved-effects}) * -(M1)$$

- for the RR:

- preserved-effects of the control effect vs. placebo:

$$1 / (M1 + ((1-M1) * \text{preserved-effects}))$$

- preserved-effects of the increased risk of placebo vs. active comparator:

$$1 + (((1 / M1) - 1) * (1 - \text{preserved-effects}))$$

- preserved-effects of the increased risk of placebo vs. active comparator after log transformation:

$$e^{\ln(1/M1) * (1 - \text{preserved-effects})} \quad \text{or}$$

$$(1/M1)^{(1 - \text{preserved-effects})}$$