Sciences Economiques et Sociales de la Santé
& Traitement de l'Information Médicale

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Les comparaisons indirectes des essais thérapeutiques et les méta-analyses en réseau

octobre 2018

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Les comparaisons indirectes des essais thérapeutiques et les méta-analyses en réseau

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ORIGINAL ARTICLE

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

This article was published on September 25, 2015, at NEJM.org.

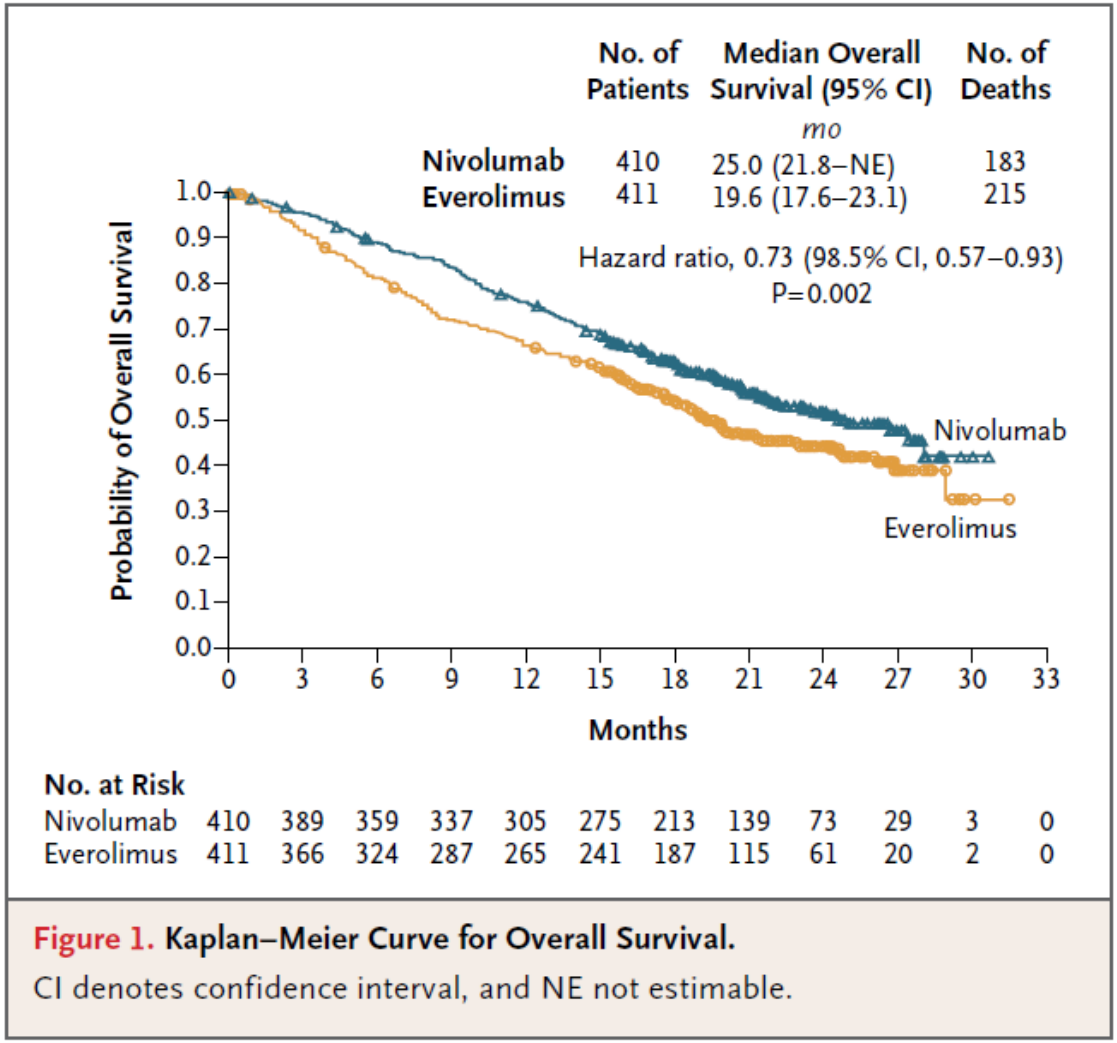
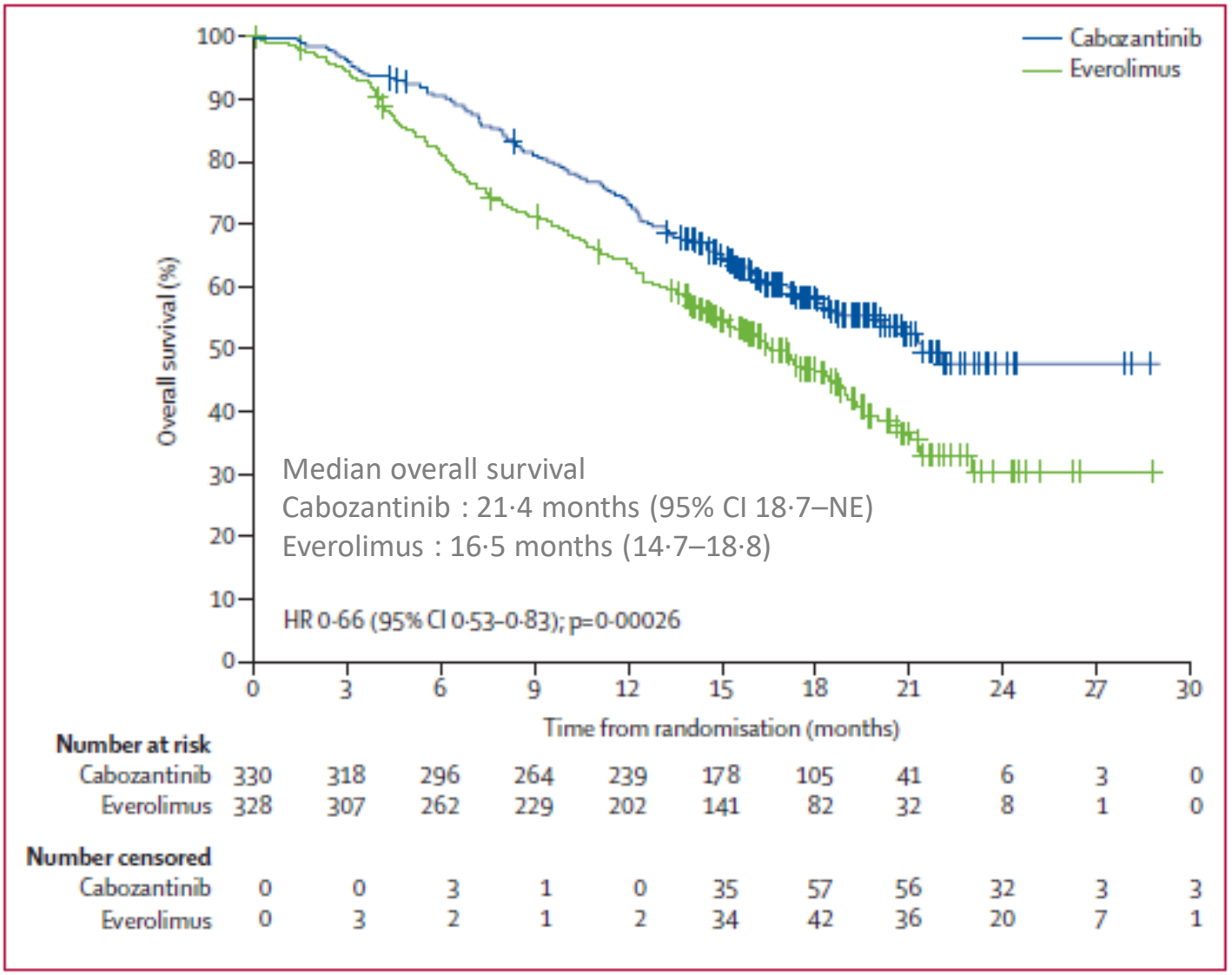


Figure 1. Kaplan–Meier Curve for Overall Survival.

CI denotes confidence interval, and NE not estimable.

Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial

Lancet Oncol 2016; 17: 917–27



- Comparaison indirecte, méta-analyse en réseau
  - Comparer A versus B
  - Alors qu'aucun essai ne compare directement A vs B
  - En faisant une comparaison indirecte à partir des essais A vs PBO et B vs PBO

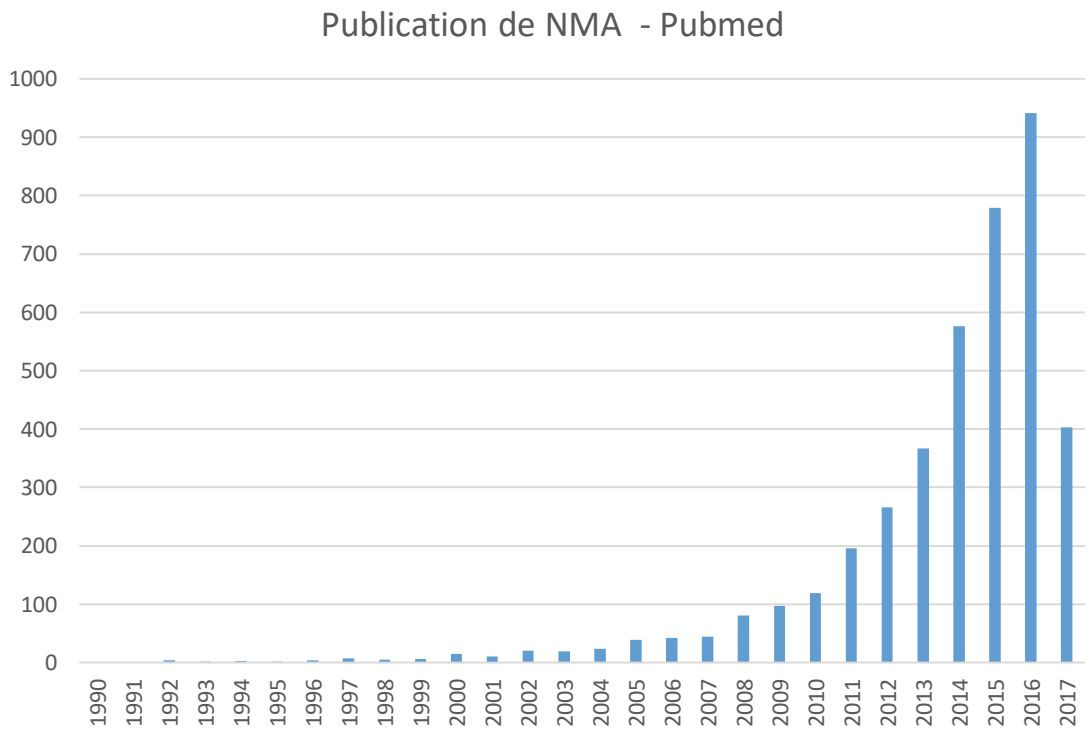
- Méta-analyse classique
  - Faire la synthèse des résultats des comparaisons effectuées dans les études
  - 3 essais comparant A vs PBO -> synthèse
  - 2 essais comparant B vs A -> synthèse

Méta-analyse en réseau

- Nombreux synonymes
  - Méta-analyse en réseau
  - Méta-analyse multitraitement
  - « Comparaisons indirectes »

- Approche visant à faire simultanément la synthèse concernant plusieurs traitements de la même « condition clinique »
  - Synthèse des comparaisons effectuées dans les essais
  - Extrapolation des comparaisons non disponibles par un processus de « comparaison indirecte »
- Efficacité et safety relative d'un traitement par rapport aux autres
  - Dossier d'accès au marché

Technique connaissant un succès grandissant

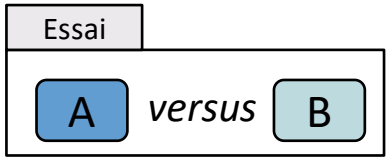


LES COMPARAISONS INDIRECTES

Objectif des comparaisons indirectes

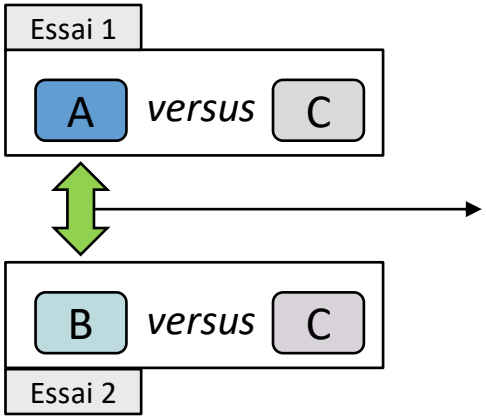
- Comparer A et B
  - En l'absence d'essai de comparaison directe A vs B
  - À partir d'essais du type
    - A versus Control et B versus Control

Comparaison directe



HR 0.80 IC 95% [0.70,0.90]

Comparaison indirecte

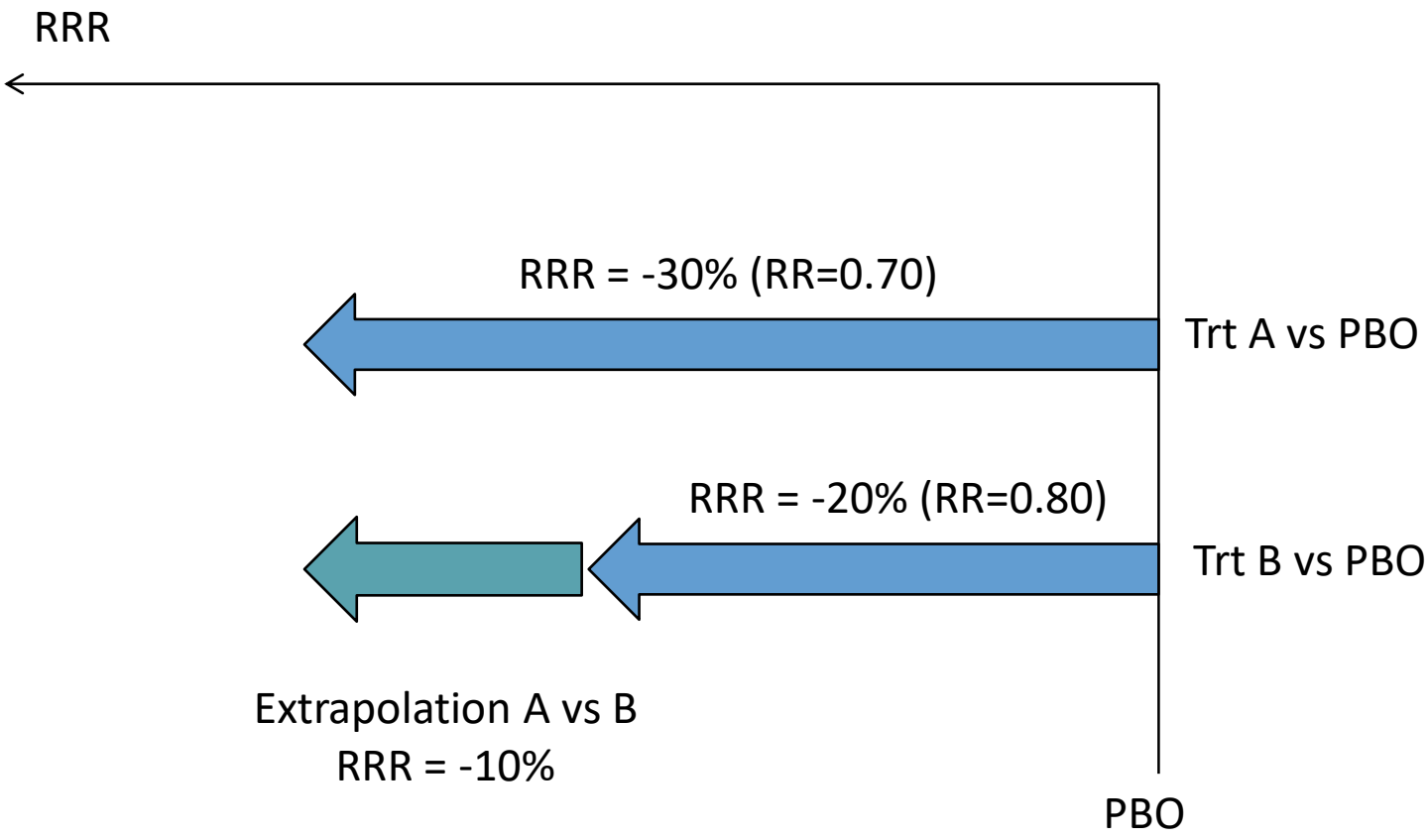


HR 0.80 IC 95% [0.70,0.90]

Comparaisons directes

- Rarement faites
- Difficultés
  - Double aveugle (formes différentes, fabricants différents)
  - Nombre de sujets nécessaires important
  - difficultés propres aux essais vs traitement actif
- Réticence des sponsors

Principe de l'extrapolation



$$d_{AB} = d_{AP} - d_{BP}$$

Hypothèse de transitivité

Calculs

- Pour les risque ratios, hazard ratios et les odds ratios

$$RR_{B/A} = \frac{RR_{B/pbo}}{RR_{A/pbo}}$$

$$\text{var log}(RR_{B/A}) = \text{var log}(RR_{B/pbo}) + \text{var log}(RR_{A/pbo})$$

- Pour les différences (risques, moyennes)
  - $d_{B/A} = d_{B/PBO} - d_{A/PBO}$

HYPOTHÈSE DE TRANSITIVITÉ

Hyp. de transitivité (Échangeabilité des effets)

- Les traitements peuvent être échangés entre les essais sans changer les résultats

- Exemple : apixaban versus rivaroxaban dans la FA
  - Apixaban versus warfarin
    - ARISTOTLE
    - RR = 0.79
  - Rivaroxaban versus warfarin
    - ROCKET
    - RR = 0.91

- Hypothèse d'échangeabilité
  - Apixaban dans ROCKET -> RR = 0.79
  - Rivaroxaban dans ARRISTOTLE -> RR = 0.91

Hypothèse de transitivité

- Hypothèse fondamentale des comparaisons indirectes
- Intestable
- Mais on peut évaluer sa plausibilité
  - Par le raisonnement
  - Par analyse de sensibilité
  - Par ajustement

- En moyenne sur les essais du même traitement

Modificateurs de l'effet

A Primary Efficacy Outcome: Stroke and Systemic Embolism

Subgroup	No. of Patients	Apixaban	Warfarin	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events (%/yr)			
All patients	18,201	212 (1.27)	265 (1.60)		
Prior use of warfarin or other vitamin K antagonist					0.39
Yes	10,401	102 (1.1)	138 (1.5)		
No	7,800	110 (1.5)	127 (1.8)		
Age					0.12
<65 yr	5,471	51 (1.0)	44 (0.9)		
65 to <75 yr	7,052	82 (1.3)	112 (1.7)		
≥75 yr	5,678	79 (1.6)	109 (2.2)		
Sex					0.60
Male	11,785	132 (1.2)	160 (1.5)		
Female	6,416	80 (1.4)	105 (1.8)		
$CHADS_2$ score					0.45
1	6,183	44 (0.7)	51 (0.9)		
2	6,516	74 (1.2)	82 (1.4)		
≥3	5,502	94 (1.9)	132 (2.8)		

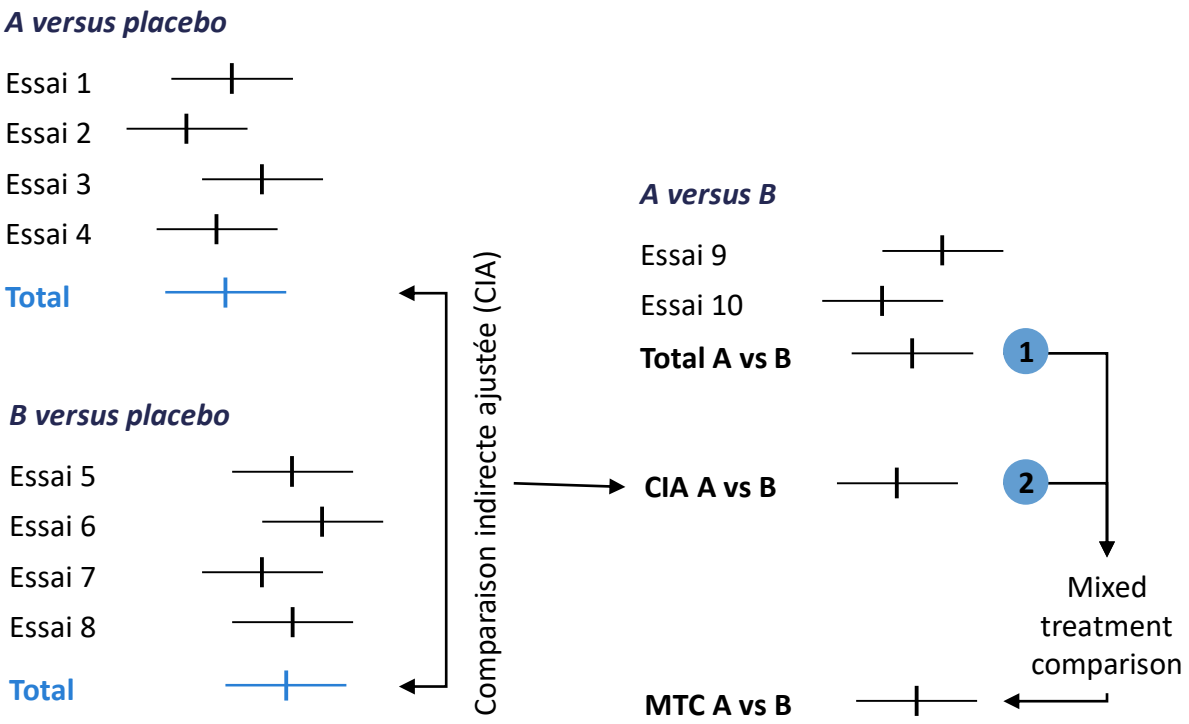
N Engl J Med 2011 (PMID: 21870978)

Justification de la plausibilité de la transitivité

- Recherche des modificateurs de l'effet (effect modifiers)
- Si il existe des modificateurs de l'effet
  - Les population doivent être identiques **en moyenne** entre les essais
- Si aucun modificateur de l'effet
  - Aucun problème si les populations sont différentes entre études

- Difficulté
  - Être certain de l'absence de modificateur de l'effet
    - Test d'interaction NS !
    - Modificateurs non mesurés

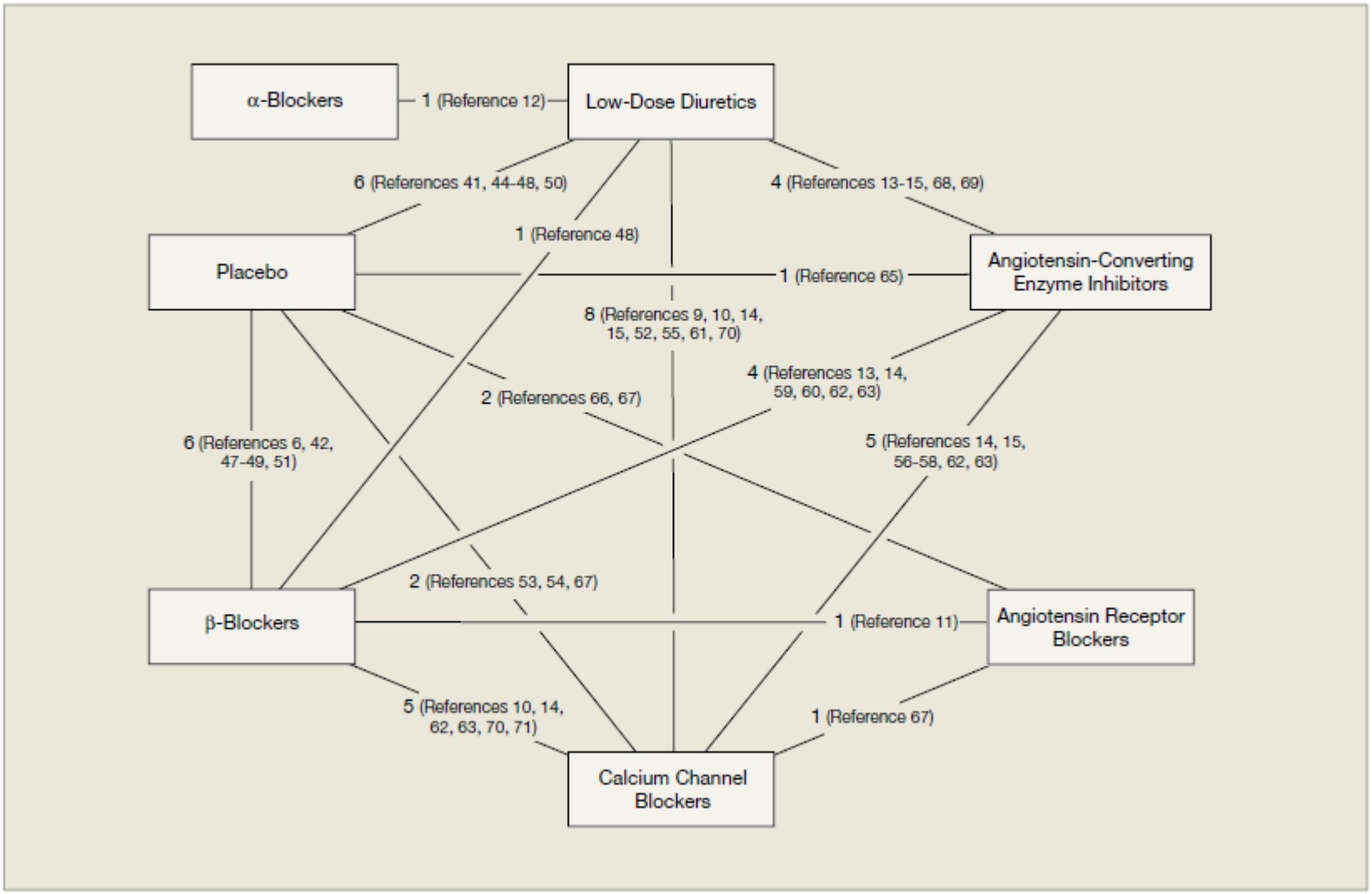
Quatre méta-analyses en une



MÉTA-ANALYSE EN RÉSEAU

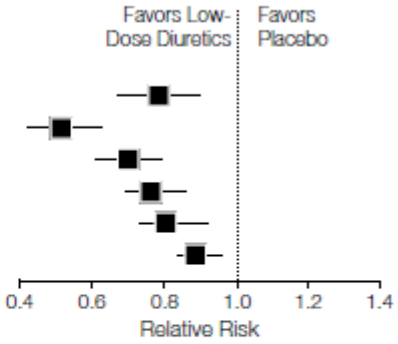
Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, Weiss NS.
Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis.
JAMA. 2003 May 21;289(19):2534-44.
PMID: 12759325

- OBJECTIVE: To summarize the available clinical trial evidence concerning the safety and efficacy of various antihypertensive therapies used as first-line agents and evaluated in terms of major cardiovascular disease end points and all-cause mortality


α-Blockers
1 (Reference 12)
Low-Dose Diuretics
6 (References 41, 44-48, 50)
4 (References 13-15, 68, 69)
1 (Reference 48)
Placebo
1 (Reference 65)
Angiotensin-Converting Enzyme Inhibitors
8 (References 9, 10, 14, 15, 52, 55, 61, 70)
4 (References 13, 14, 59, 60, 62, 63)
2 (References 66, 67)
6 (References 6, 42, 47-49, 51)
5 (References 14, 15, 56-58, 62, 63)
2 (References 53, 54, 67)
β-Blockers
1 (Reference 11)
Angiotensin Receptor Blockers
5 (References 10, 14, 62, 63, 70, 71)
1 (Reference 67)
Calcium Channel Blockers

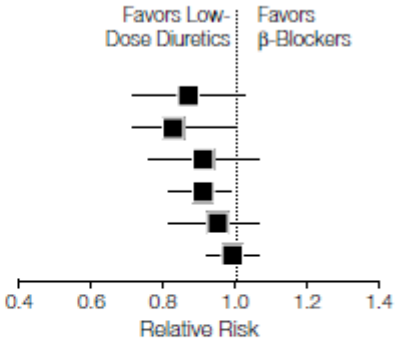
A Low-Dose Diuretics vs Placebo

Outcome	RR (95% CI)	*P* Value
CHD	0.79 (0.69-0.92)	.002
CHF	0.51 (0.42-0.62)	<.001
Stroke	0.71 (0.63-0.81)	<.001
CVD Events	0.76 (0.69-0.83)	<.001
CVD Mortality	0.81 (0.73-0.92)	.001
Total Mortality	0.90 (0.84-0.96)	.002



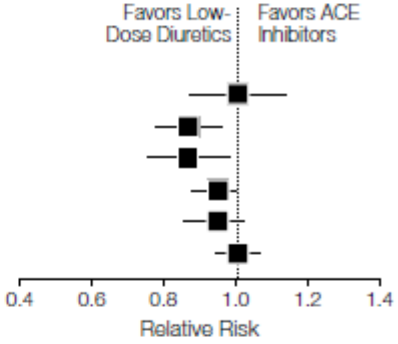
B Low-Dose Diuretics vs β-Blockers

RR (95% CI)	*P* Value
0.87 (0.74-1.03)	.10
0.83 (0.68-1.01)*	.07
0.90 (0.76-1.06)*	.20
0.89 (0.80-0.98)*	.02
0.93 (0.81-1.07)*	.34
0.99 (0.91-1.07)*	.73



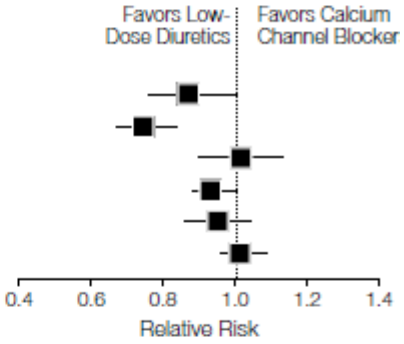
C Low-Dose Diuretics vs Angiotensin-Converting Enzyme (ACE) Inhibitors

Outcome	RR (95% CI)	*P* Value
CHD	1.00 (0.88-1.14)*	.99
CHF	0.88 (0.80-0.96)*	.01
Stroke	0.86 (0.77-0.97)*	.01
CVD Events	0.94 (0.89-1.00)*	.04
CVD Mortality	0.93 (0.85-1.02)*	.13
Total Mortality	1.00 (0.95-1.05)*	.86



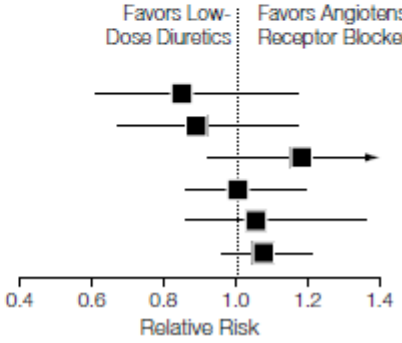
D Low-Dose Diuretics vs Calcium Channel Blockers

RR (95% CI)	*P* Value
0.89 (0.76-1.01)	.07
0.74 (0.67-0.81)*	<.001
1.02 (0.91-1.14)*	.74
0.94 (0.89-1.00)*	.045
0.95 (0.87-1.04)*	.29
1.03 (0.98-1.08)*	.30



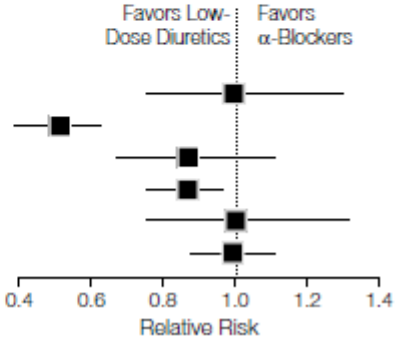
E Low-Dose Diuretics vs Angiotensin Receptor Blockers

Outcome	RR (95% CI)	*P* Value
CHD	0.83 (0.59-1.16)	.28
CHF	0.88 (0.66-1.16)*	.36
Stroke	1.20 (0.93-1.55)*	.16
CVD Events	1.00 (0.85-1.18)*	.98
CVD Mortality	1.07 (0.85-1.36)*	.55
Total Mortality	1.09 (0.96-1.22)*	.18

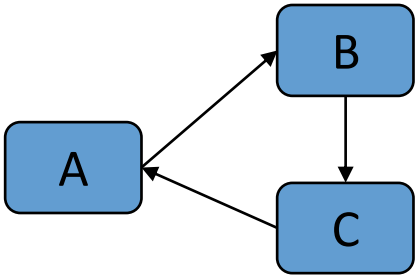


F Low-Dose Diuretics vs α-Blockers

RR (95% CI)	*P* Value
0.99 (0.75-1.31)	.97
0.51 (0.43-0.60)	<.001
0.85 (0.66-1.10)	.22
0.84 (0.75-0.93)	.001
1.00 (0.75-1.34)	>.99
0.98 (0.88-1.10)	.79



Méta-analyse en réseau – principe



- Méta-analyse en réseau
  - Estimation globalement et simultanément de toutes les comparaisons 2 à 2
  - A l'aide d'une modélisation globale du réseau
- Méthode de Bucher (pairwise comparisons)
  - Estimations les unes après les autres des comparaisons 2 à 2
  - À l'aide de MA classique

CLASSEMENT PROBABILISTE DES TRAITEMENTS

Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis

Andrea Cipriani, Corrado Barbui, Georgia Salanti, Jennifer Rendell, Rachel Brown, Sarah Stockton, Marianna Purgato, Loukia M Spineli, Guy M Goodwin, John R Geddes

Lancet 2011; 378: 1306–15
Published Online
August 17, 2011
DOI:10.1016/S0140-6736(11)60873-8

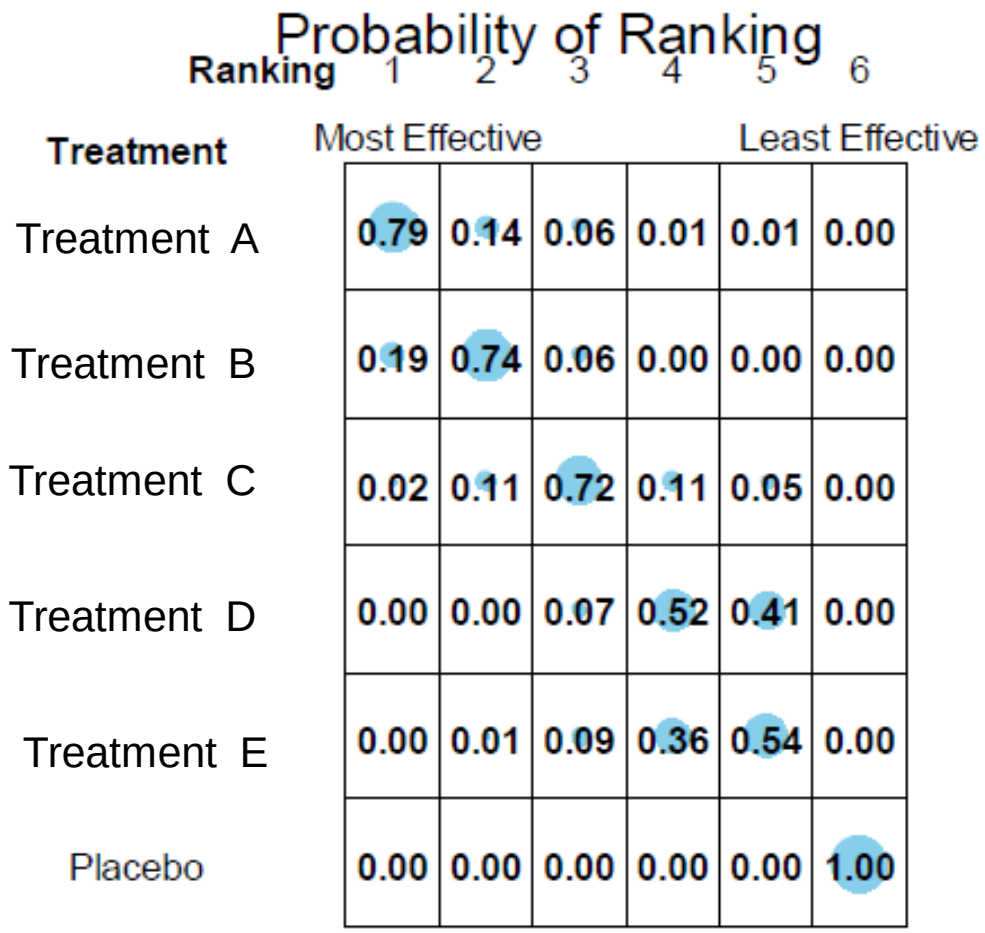
HAL	1·40 (0·93 to 2·11)	1·49 (1·03 to 2·15)	0·81 (0·53 to 1·22)	1·32 (0·85 to 2·06)	1·11 (0·75 to 1·66)	1·16 (0·63 to 2·14)	0·86 (0·46 to 1·60)	1·16 (0·73 to 1·86)	0·93 (0·59 to 1·49)	0·69 (0·36 to 1·36)	0·85 (0·62 to 1·15)	0·56 (0·34 to 0·93)	0·48 (0·16 to 1·44)
−0·06 (−0·22 to 0·11)	RIS	1·06 (0·72 to 1·56)	0·58 (0·37 to 0·88)	0·94 (0·60 to 1·47)	0·80 (0·51 to 1·25)	0·83 (0·44 to 1·57)	0·62 (0·33 to 1·16)	0·83 (0·51 to 1·34)	0·67 (0·41 to 1·10)	0·50 (0·25 to 0·98)	0·61 (0·44 to 0·83)	0·40 (0·24 to 0·68)	0·34 (0·11 to 1·03)
−0·12 (−0·28 to 0·02)	−0·07 (−0·22 to 0·08)	OLZ	0·54 (0·37 to 0·79)	0·88 (0·58 to 1·36)	0·75 (0·49 to 1·13)	0·78 (0·43 to 1·44)	0·58 (0·33 to 1·00)	0·78 (0·52 to 1·17)	0·63 (0·40 to 1·00)	0·47 (0·24 to 0·89)	0·57 (0·44 to 0·74)	0·38 (0·23 to 0·61)	0·32 (0·11 to 0·95)
−0·19 (−0·36 to −0·01)	−0·13 (−0·30 to 0·04)	−0·06 (−0·22 to 0·10)	LIT	1·63 (1·06 to 2·54)	1·38 (0·91 to 2·12)	1·44 (0·81 to 2·60)	1·07 (0·57 to 2·00)	1·44 (0·92 to 2·28)	1·15 (0·71 to 1·91)	0·86 (0·47 to 1·59)	1·05 (0·78 to 1·43)	0·70 (0·44 to 1·11)	0·60 (0·20 to 1·77)
−0·19 (−0·37 to −0·01)	−0·13 (−0·31 to 0·04)	−0·07 (−0·24 to 0·11)	−0·01 (−0·18 to 0·17)	QTP	0·85 (0·52 to 1·35)	0·88 (0·46 to 1·70)	0·66 (0·34 to 1·25)	0·88 (0·53 to 1·46)	0·71 (0·42 to 1·20)	0·53 (0·27 to 1·05)	0·64 (0·45 to 0·91)	0·43 (0·25 to 0·73)	0·36 (0·12 to 1·10)
−0·19 (−0·36 to −0·02)	−0·13 (−0·31 to 0·05)	−0·06 (−0·23 to 0·11)	−0·01 (−0·18 to 0·17)	0·00 (−0·19 to 0·20)	ARI	1·04 (0·55 to 1·98)	0·77 (0·41 to 1·47)	1·05 (0·64 to 1·70)	0·84 (0·51 to 1·39	0·62 (0·32 to 1·24)	0·76 (0·55 to 1·06)	0·50 (0·30 to 0·85)	0·43 (0·14 to 1·29)
−0·20 (−0·36 to −0·01)	−0·14 (−0·42 to 0·12)	−0·08 (−0·34 to 0·18)	−0·02 (−0·28 to 0·24)	−0·01 (−0·30 to 0·26)	−0·01 (−0·29 to 0·26)	CBZ	0·74 (0·34 to 1·62)	1·00 (0·52 to 1·91)	0·80 (0·41 to 1·59)	0·60 (0·27 to 1·33)	0·73 (0·42 to 1·28)	0·48 (0·25 to 0·96)	0·41 (0·13 to 1·37)
−0·26 (−0·52 to −0·01)	−0·20 (−0·46 to 0·05)	−0·14 (−0·36 to 0·10)	−0·08 (−0·41 to 0·27)	−0·07 (−0·34 to 0·20)	−0·07 (−0·34 to 0·20)	−0·06 (−0·39 to 0·28)	ASE	1·35 (0·71 to 2·58)	1·08 (0·56 to 2·14)	0·81 (0·36 to 1·83)	0·98 (0·57 to 1·72)	0·65 (0·33 to 1·30)	0·56 (0·17 to 1·82)
−0·36 (−0·56 to −0·15)	−0·30 (−0·50 to −0·10)	−0·23 (−0·40 to −0·06)	−0·10 (−0·41 to 0·23)	−0·17 (−0·38 to 0·05)	−0·17 (−0·38 to 0·05)	−0·15 (−0·44 to 0·13)	−0·10 (−0·37 to 0·18)	VAL	0·80 (0·47 to 1·37)	0·60 (0·30 to 1·20)	0·73 (0·51 to 1·05)	0·48 (0·28 to 0·83)	0·41 (0·13 to 1·25)
−0·36 (−0·56 to −0·15)	−0·31 (−0·51 to −0·10)	−0·24 (−0·43 to −0·03)	−0·15 (−0·44 to 0·16)	−0·17 (−0·39 to 0·05)	−0·18 (−0·39 to 0·04)	−0·16 (−0·45 to 0·14)	−0·10 (−0·39 to 0·18)	−0·01 (−0·24 to 0·23)	ZIP	0·75 (0·37 to 1·51)	0·91 (0·61 to 1·34)	0·61 (0·34 to 1·06)	0·52 (0·17 to 1·58)
−0·48 (−0·77 to −0·19)	−0·43 (−0·71 to −0·14)	−0·36 (−0·64 to −0·08)	−0·32 (−0·67 to 0·06)	−0·29 (−0·58 to 0·00)	−0·29 (−0·58 to 0·00)	−0·28 (−0·63 to 0·08)	−0·22 (−0·57 to 0·12)	−0·13 (−0·43 to 0·18)	−0·12 (−0·43 to 0·19)	LAM	1·22 (0·67 to 2·21)	0·81 (0·40 to 1·65)	0·69 (0·21 to 2·30)
−0·56 (−0·69 to −0·43)	−0·50 (−0·63 to −0·38)	−0·43 (−0·54 to −0·32)	−0·37 (−0·63 to −0·11)	−0·37 (−0·51 to −0·23)	−0·37 (−0·51 to −0·23)	−0·36 (−0·60 to −0·11)	−0·30 (−0·53 to −0·07)	−0·20 (−0·37 to −0·04)	−0·20 (−0·37 to −0·03)	−0·08 (−0·34 to 0·18)	PBO	0·66 (0·44 to 1·00)	0·57 (0·20 to 1·62)
−0·63 (−0·84 to −0·43)	−0·58 (−0·78 to −0·37)	−0·51 (−0·70 to −0·31)	−0·45 (−0·75 to −0·14)	−0·44 (−0·66 to −0·23)	−0·45 (−0·66 to −0·23)	−0·43 (−0·72 to −0·14)	−0·38 (−0·66 to −0·09)	−0·28 (−0·52 to −0·04)	−0·27 (−0·51 to −0·04)	−0·15 (−0·46 to 0·15)	−0·07 (−0·24 to 0·09)	TOP	0·85 (0·28 to 2·63)
−0·88 (−1·40 to −0·36)	−0·83 (−1·34 to −0·31)	−0·76 (−1·27 to −0·24)	−0·70 (−1·21 to −0·18)	−0·69 (−1·21 to −0·17)	−0·69 (−1·21 to −0·17)	−0·68 (−1·23 to −0·12)	−0·62 (−1·17 to −0·07)	−0·53 (−1·05 to 0·01)	−0·52 (−1·05 to 0·01)	−0·40 (−0·96 to 0·16)	−0·32 (−0·82 to 0·18)	−0·25 (−0·77 to 0·28)	GBT

Treatment Efficacy (SMD with 95% CrI) Dropout rate (OR with 95% CrI)

Figure 4: Efficacy and acceptability of all antimanic drugs according to multiple-treatments meta-analysis (primary outcomes)

Lancet. 2011 Oct 8;378(9799):1306-15. doi: 10.1016/S0140-6736(11)60873-8

Classement probabiliste des traitements



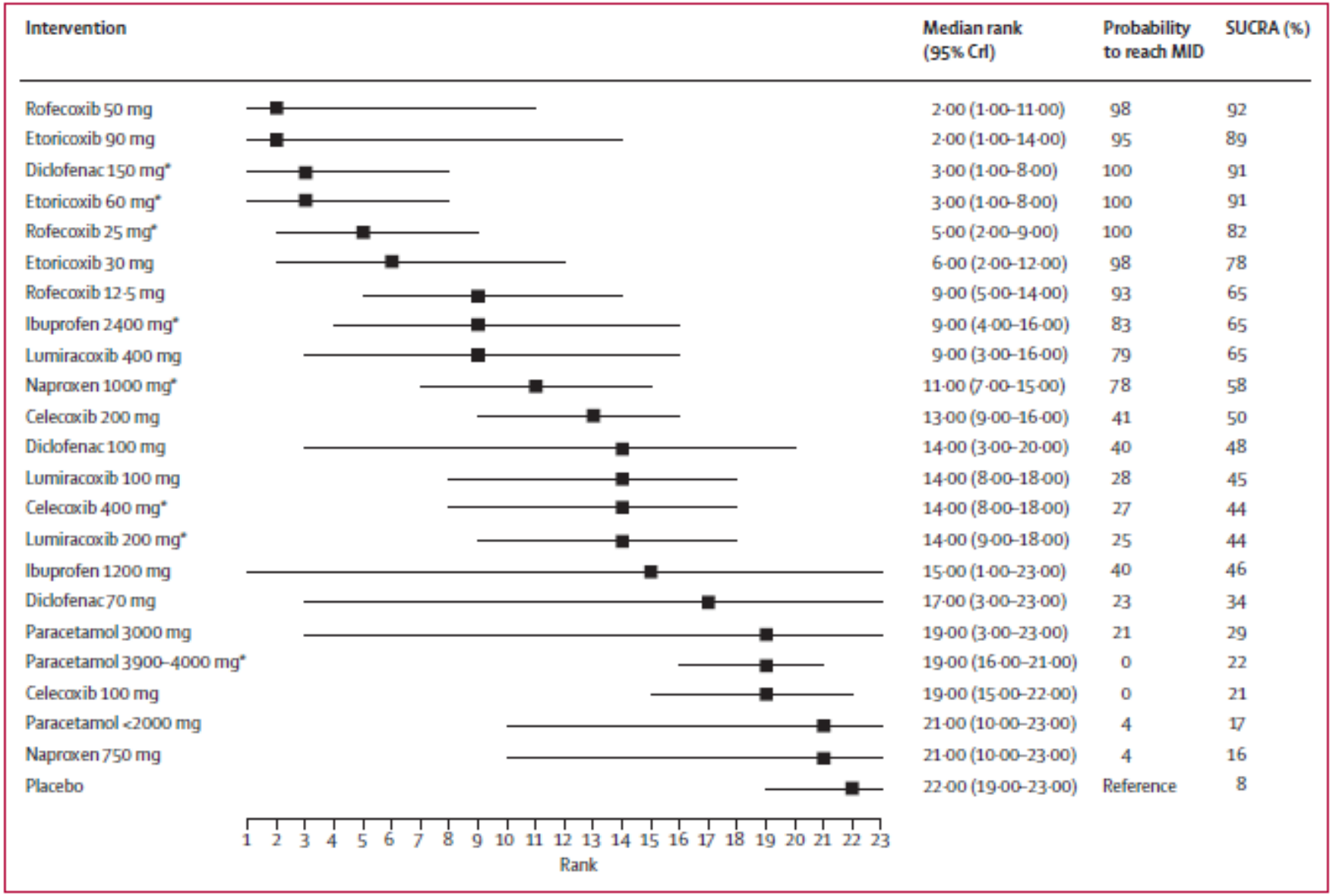


Figure 3: **Median rank, probability of reaching MID, and SUCRA values of competing interventions and daily doses**

MID=minumum clinically important difference. SUCRA=surface under the cumulative ranking curve. CrI=credibility interval. *Maximum daily dose

Da Costa Lancet. 2017 Jul 8;390(10090):e21-e33. doi: 10.1016/S0140-6736(17)31744-0