Metodología sobre Comparaciones indirectas

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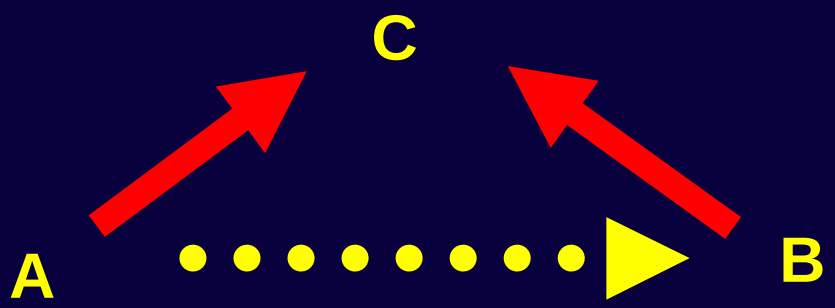
1. ¿Qué son las Comparaciones Indirectas?
2. Niveles de complejidad
3. Puntos clave
4. Validez
5. Herramientas
6. Conclusiones

1. ¿Qué son las comparaciones indirectas?

- **Los ECA frente a placebo son suficientes para obtener la aprobación de las agencias reguladoras**
- **No se dispone de ECAs frente al comparador de interés/referencia**
- **Métodos que permiten realizar una estimación indirecta entre 2 tratamientos frente a un comparador común**



2. Niveles de complejidad

1. **Situación más simple: un solo ensayo de A vs B y B vs C que combinados proveen una estimación indirecta de A vs C.**

2. **Uno de los brazos o ambos son un metanálisis**

3. **Comparaciones múltiples entre distintos tratamientos**

3. Puntos clave

1. **Homogeneidad**
2. **Consistencia**
3. **Similaridad**

Homogeneidad/Heterogeneidad

1. **La heterogeneidad es la variabilidad entre los resultados de los estudios en un metanálisis o en los brazos que conforman la CI**

2. **Es la variabilidad en el resultado medido en cada estudio con respecto al resultado global promedio (variabilidad estadística y no clínica)**

3. **Se cuantifica a partir de:**
   1. **Q de Cochrane (desviaciones cuadráticas ponderadas) Valor similar a la P**
   2. **Test I^2 (proporción de la variación de cada estudio respecto a la variación total). Valores: 25%, 50%, 75% heterogeneidad baja, moderada y alta correspondientemente.**

Measuring inconsistency in meta−analyses Julian P T Higgins, Simon G Thompson, Jonathan J Deeks, and Douglas G Altman BMJ, Sep 2003; 327: 557 − 560
Quantifying heterogeneity in a meta−analysis. Higgins JPT, Thompson SG. *Stat Med* 2002; 21: 1539−58.

Consistencia

1. Si se dispone de evidencia directa e indirecta, la consistencia es la determinación de que ambos resultados se dirigen en el mismo sentido

2. En el caso en que exista inconsistencia debe investigarse el motivo
    1. Falta de validez interna en los estudios
    2. Heterogeneidad elevada
    3. Sesgos o factores de confusión

3. Algunos autores indican que en los estudios indirectos se obtienen resultados mas cercanos a la realidad

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previous

Adjusted indirect comparison may be less biased than direct comparison for evaluating new pharmaceutical interventions

F. Song[ab], I. Harvey[a], R. Lilford[c]

Accepted 5 June 2007, published online 29 November 2007.

Abstract

Objective

To investigate discrepancies between direct comparison and adjusted indirect comparison in meta-analyses of new versus conventional pharmaceutical interventions.

Study Design and Setting

Results of direct comparison were compared with results of adjusted indirect comparison in three meta-analyses of new versus conventional drugs. The three case studies are (1) bupropion versus nicotine replacement therapy for smoking cessation, (2) risperidone versus haloperidol for schizophrenia, and (3) fluoxetine versus imipramine for depressive disorders.

Results

In all the three cases, effects of new drugs estimated by head-to-head trials tend to be greater than that by adjusted indirect comparisons. The observed discrepancies could not be satisfactorily explained by the play of chance or by bias and heterogeneity in adjusted indirect comparison. This observation, along with analysis of possible systematic bias in the direct comparisons, suggested that the indirect method might have produced less biased results. Simulations found that adjusted indirect comparison may counterbalance bias under certain circumstances.

Conclusion

Adjusted indirect comparison could be used to cross-examine the validity and applicability of results from head-to-head randomized trials. The hypothesis that adjusted indirect comparison may provide less biased results than head-to-head randomized trials needs to be investigated by further research.

Keywords: Adjusted indirect comparison, Head-to-head comparison, Bias, Meta-analysis, Clinical trials, Pharmaceutical intervention

Song F, Harvey I, Lilford R. J. Clin. Epidemiol 2008; 61: 455-463

Similaridad

1. **Grado de certeza en que el efecto del tratamiento en un brazo (de la CI) debería poderse generalizar a los pacientes del otro brazo**

2. **Ello implica "similaridad" en características:**
   1. **Pacientes**
      1. **Edad, sexo, severidad de la enfermedad, comorbilidades, medicación coexistente, …**
   2. **Metodológicas**
      1. **Tiempo de respuesta, duración del tratamiento, dosis de fármaco, tiempo de seguimiento, perdidas,….**

"Si los pacientes en ambos brazos no son similares la diferencia (o igualdad) detectada a través de la CI puede ser debidas precisamente a ello"

"Similaridad en subgrupos de pacientes"

4. Validez de CI

BMJ Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses

Fujian Song, Douglas G Altman, Anne-Marie Glenny and Jonathan J Deeks

BMJ 2003;326:472
doi:10.1136/bmj.326.7387.472

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Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses

Fujian Song, Douglas G Altman, Anne-Marie Glenny, Jonathan J Deeks

Abstract

Objective To determine the validity of adjusted indirect comparisons by using data from published meta-analyses of randomised trials.

Design Direct comparison of different interventions in randomised trials and adjusted indirect comparison in which two interventions were compared through their relative effect versus a common comparator. The discrepancy between the direct and adjusted indirect comparison was measured by the difference between the two estimates.

Data sources Database of abstracts of reviews of effectiveness (1994-8), the Cochrane database of systematic reviews, Medline, and references of

Well designed randomised controlled trials generally provide the most valid evidence of relative efficacy of competing interventions and minimise the possibility of selection bias.[1] However, many competing interventions have not been compared directly (head to head) in randomised trials. Even when different interventions have been directly compared in randomised trial(s) such direct evidence is often limited and insufficient.

As the results of placebo controlled trials are often sufficient to acquire the regulatory approval of new drugs, pharmaceutical companies may not be motivated to support trials that compare new drugs with existing active treatments. Lack of evidence from direct

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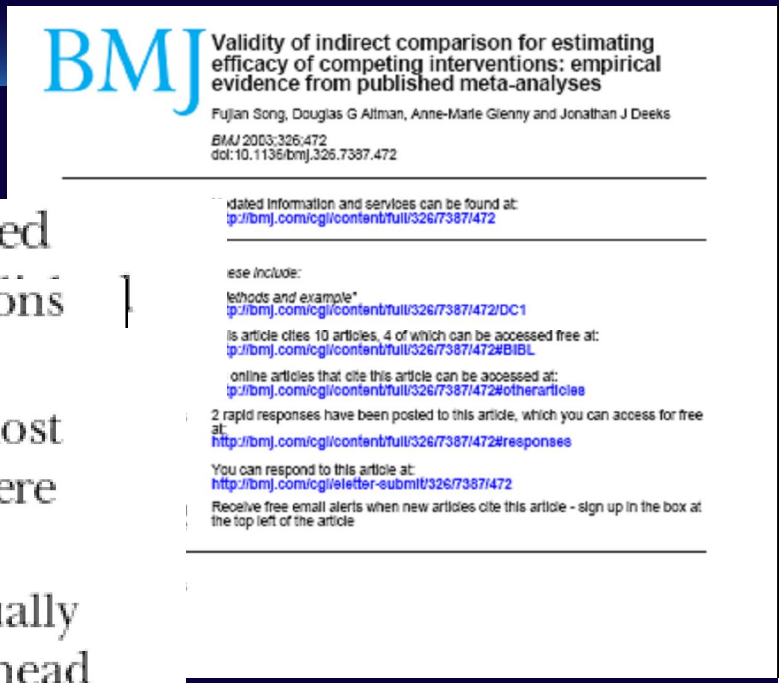
Jonathan J Deeks *senior medical*



BMJ

Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses

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Objective To determine the validity of adjusted

Design Direct comparison of different interventions

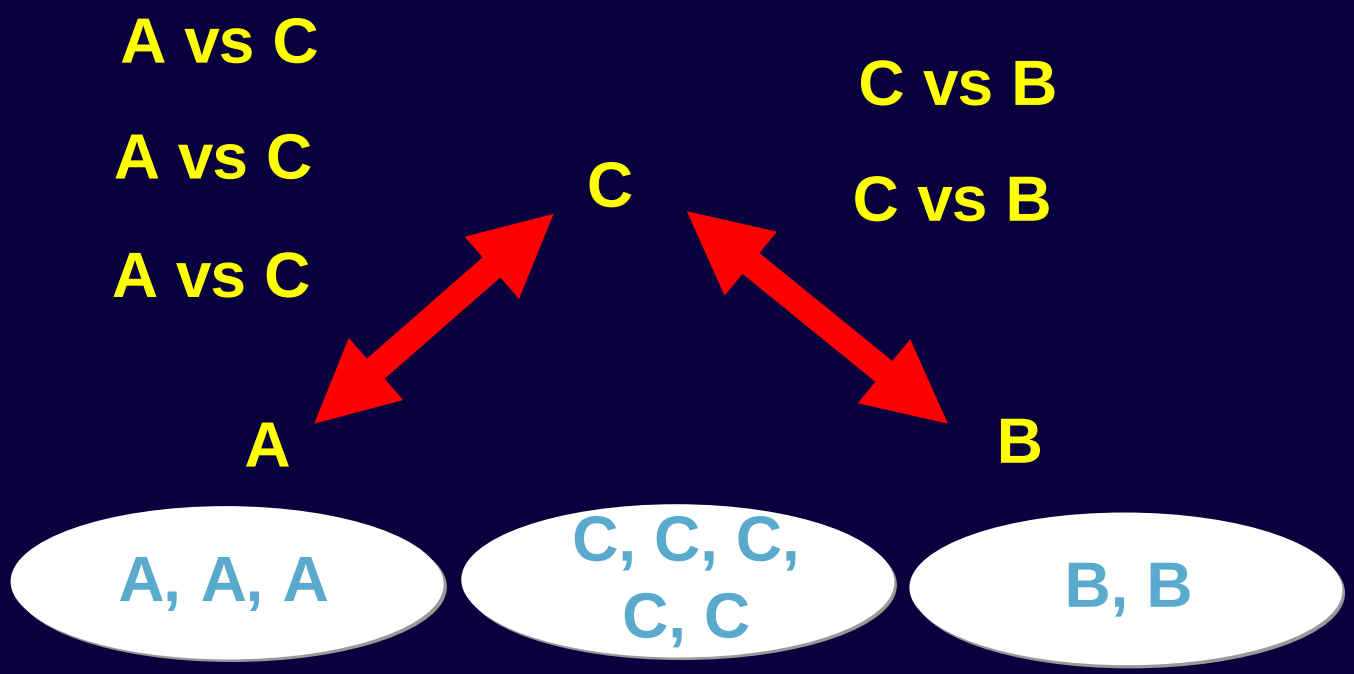
Results 44 published meta-analyses (from 28 systematic reviews) provided sufficient data. In most cases, results of adjusted indirect comparisons were not significantly different from those of direct

Conclusions Adjusted indirect comparisons usually but not always agree with the results of head to head randomised trials. When there is no or insufficient direct evidence from randomised trials, the adjusted indirect comparison may provide useful or supplementary information on the relative efficacy of competing interventions. The validity of the adjusted indirect comparisons depends on the internal validity and similarity of the included trials.

5. Herramientas disponibles

1. **CI naive**
2. **CI no ajustadas o informales**
3. **CI ajustadas**

CI naive

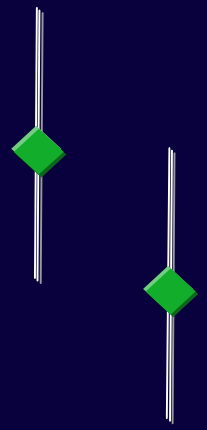


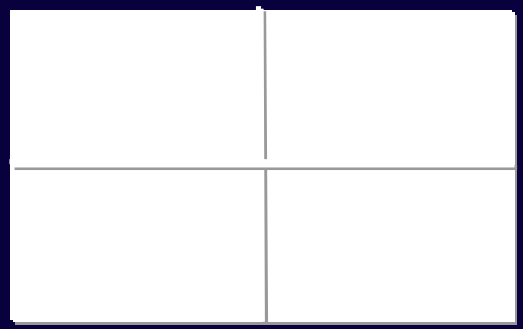
- Los resultados de los brazos individuales de distintos ensayos se comparan como si pertenecieran al mismo ensayo
- Ofrece una evidencia equivalente a un estudio observacional y debería ser evitado.

CI no ajustadas

- Los resultados de los brazos individuales de distintos ensayos se comparan a partir de sus IC

Los resultados de un solapamiento son consistentes con el test estadístico tradicional?





Daniel Smith
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California Department of Health Services

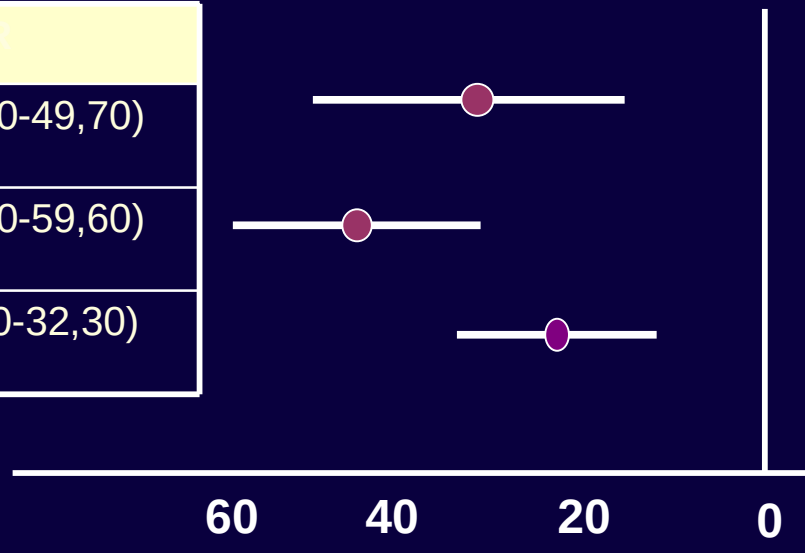
26th Annual Institute on Research and Statistics
March, 2005

CI no ajustadas

Ej: Anti-TNF en artritis reumatoide

- **Poblaciones comparables, misma indicación**
- **Respuesta del comparador en cada ensayo similar (IC95% superponibles)**
- **Comparación resultados (superposición IC95%)**

	RAR
Etanercept+MTX (Weimblatl 1999)	35,65 (21,60-49,70)
Adalimunab+MTX (ARMADA)	45,70 (31,80-59,60)
Infliximab +MTX (Maini 1999)	21,70(11,20-32,30)



Anti-TNF en artritis reumatoide

Scandinavian Journal of Rheumatology 2007; 36, (6): 411 - 417

The number needed to treat for adalimumab, etanercept, and infliximab based on ACR50 response in three randomized controlled trials on established rheumatoid arthritis: a systematic literature review

Authors: L. E. Kristensen [a]; R. Christensen [b]; H. Bliddal [b]; P. Geborek [a]; B. Danneskiold-Samsøe [b]; T. Saxne [a]

Affiliations: [a] Department of Rheumatology, Lund University Hospital, Lund, Sweden
[b] The Parker Institute, Musculoskeletal Statistics Unit, Frederiksberg Hospital, Frederiksberg, Denmark

Objective: To compare the efficacy of adalimumab, etanercept, and infliximab in patients with established rheumatoid arthritis (RA) taking concomitant methotrexate (MTX) by calculating the number needed to treat (NNT) using three different methods.

Methods: A systematic literature search of the Cochrane Library, MEDLINE, and EMBASE was conducted from inception to 30 June 2006. Two pairs of investigators, a Danish and a Swedish pair, independently conducted a structured literature review. The reviewers selected any published randomized, double-blind, MTX controlled study of adalimumab, etanercept, and infliximab, presenting the American College of Rheumatology 50% response (ACR50) after 12 months in RA patients with a mean disease duration of at least 5 years. The two review groups independently extracted the estimates necessary to calculate the NNT.

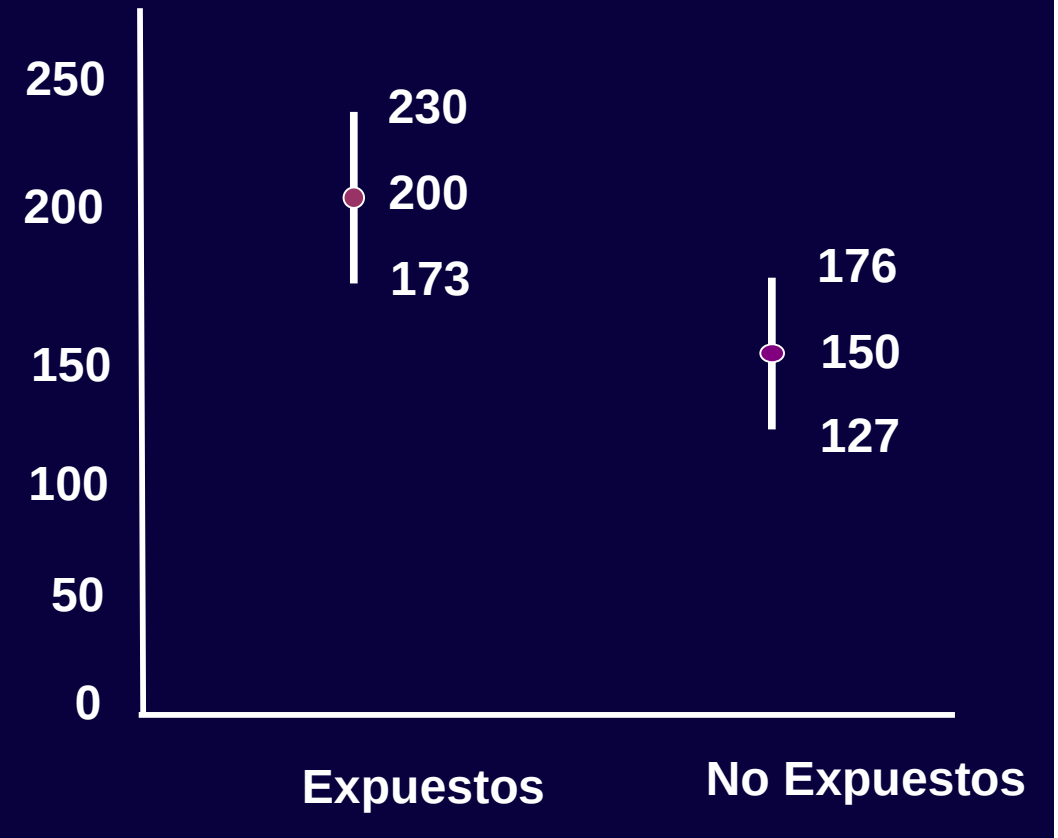
Results: The reviewers consistently selected the same three randomized, controlled trials (RCTs), one for each of the drugs, and extracted equal data for the number of patients completing the 12-month intervention, and the corresponding number of ACR50 responding patients after therapy. Some baseline differences were noted: patients in the etanercept trial had a shorter disease duration and did not receive MTX prior to inclusion; patients in the adalimumab study had lower Health Assessment Questionnaire (HAQ) scores. The calculated NNTs varied slightly depending on the method used. The fully adjusted NNTs (95% confidence intervals) for adalimumab, etanercept, infliximab standard dosage and infliximab double dosage were 4 (3-6), 4 (3-6), 8 (4-66), and 4 (3-11) patients, respectively.

Conclusion: This study indicates equal efficacy of the three anti-tumour necrosis factor (TNF) therapies.

	Expuestos	No Expuestos
Casos	200	150
Personas-año	100.000	100.000

$\chi^2 = 7.14$
P value = 0.0075

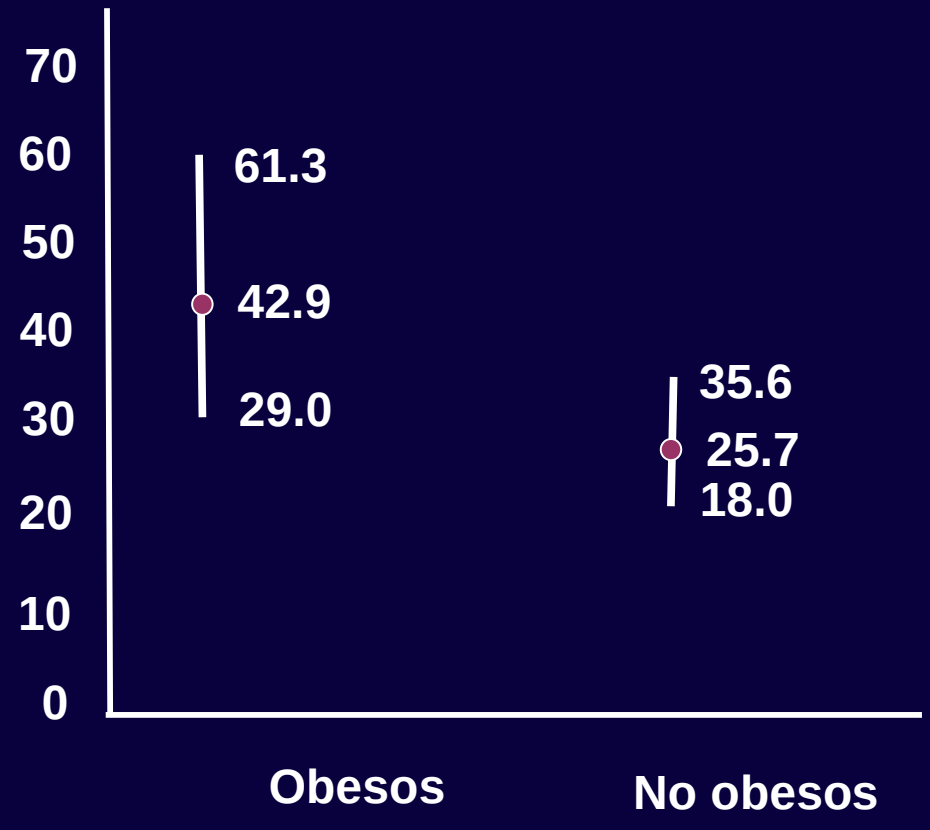
RR=1.33
95% CL: 1.08-1.65



	Obesos	No obesos
Mortalidad	30	36
Personas-año	699	1.399

$\chi^2 = 4.38$
P value = 0.036

RR=1.67
95% CL: 1.03-2.71



El problema es…

- Los IC son demasiado amplios
- Cada IC se calcula usando los datos correspondientes a cada brazo
- La comparación de dos IC no es un test estadístico

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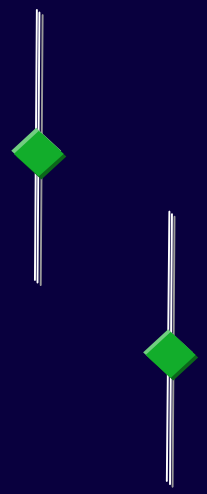
26th Annual Institute on Research and Statistics
March, 2005

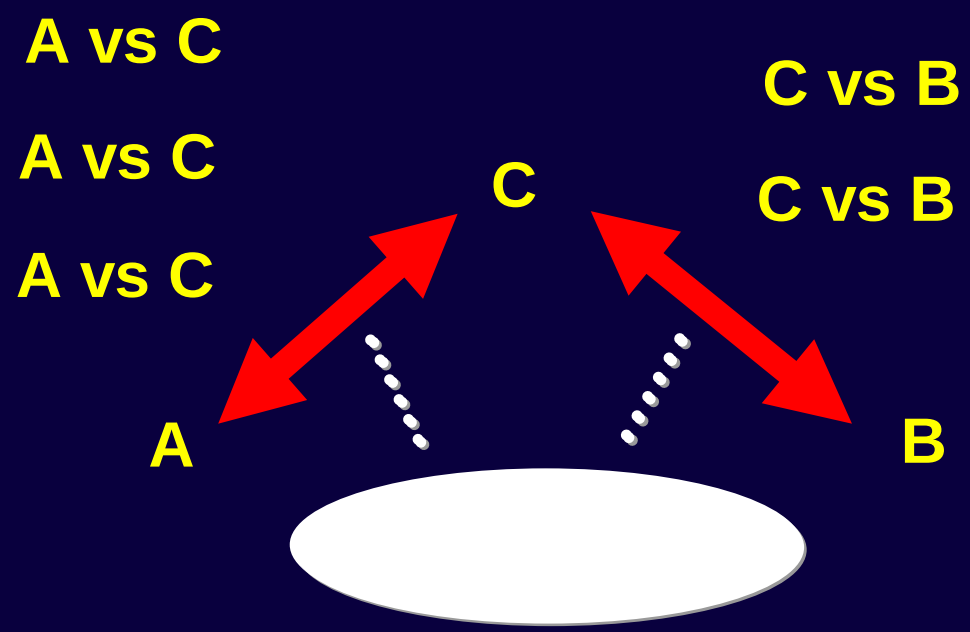
CI no ajustadas: cuidado con los IC!!

Porcentaje de solapamiento del IC					
0%	5%	10%	15%	20%	25%
0.0056	0.0085	0.0126	0.0185	0.0266	0.0376
Valor de P					



Los IC pueden solapar hasta un 29% y ser diferentes estadísticamente!!!

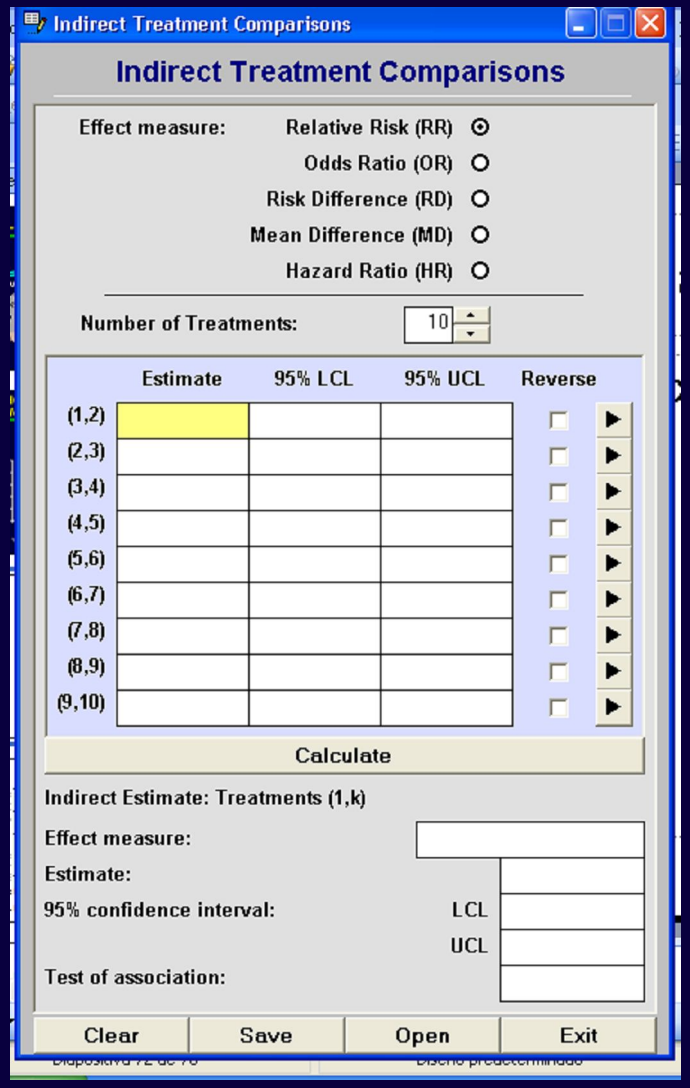
CI ajustadas



- Los medidas de estimación indirecta: odds ratio, riesgo relativo, hazard ratio, diferencia de riesgo y diferencia media así como los tests de asociación se obtienen a partir de simples reglas algebráicas
- $\ln(OR')_{AB} = \ln(OR)_{AC} - \ln(OR)_{BC}$
- $SE\ \ln(OR')_{AB} = \sqrt{SE\ \ln(OR)_{AC}^2 - SE\ \ln(OR)_{BC}^2}$

(Bucher et al J Clin Epidemiol 1997)

CI ajustadas: Calculadora ITC



Canadian Agency for Drugs and Technologies in Health

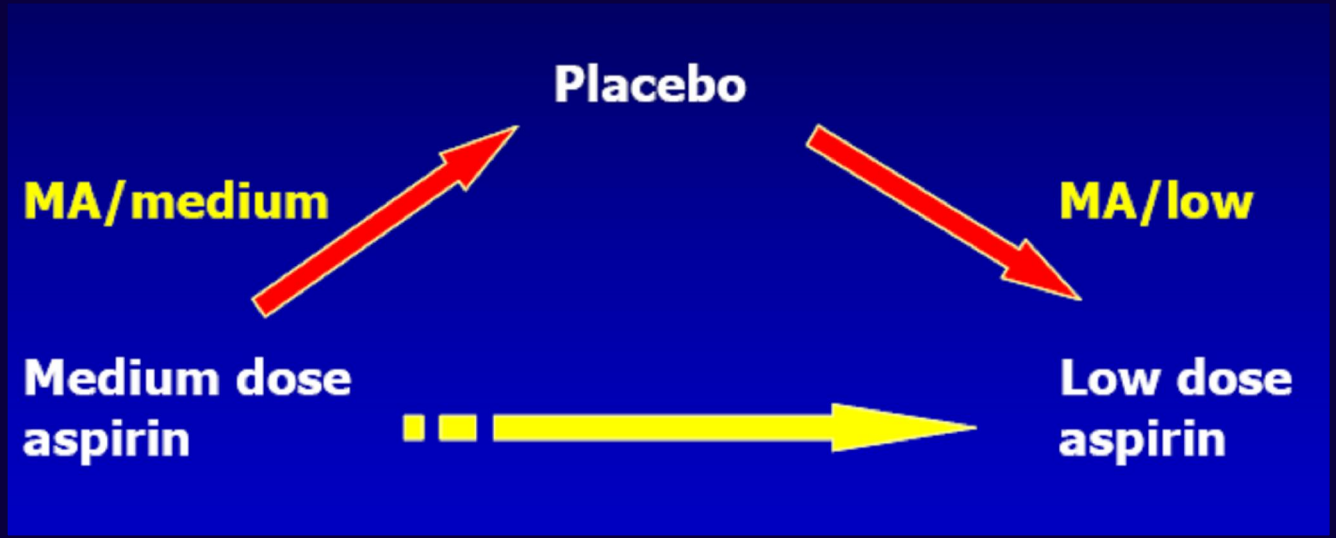
http://www.cadth.ca

Comparaciones indirectas

Cirugía coronaria by pass: Dosis altas frente a dosis bajas de aspirina

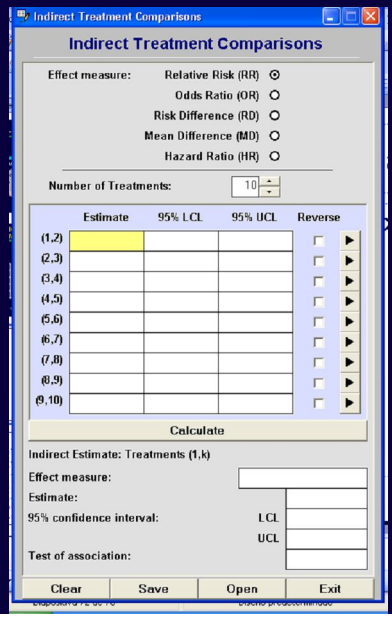
- Tres metanálisis sobre ensayos realizados desde 1979 a 1993 establecieron los efectos beneficiosos de aspirina tras cirugía coronaria
- Sin embargo no se tuvo en cuenta la dosis de aspirina usada (rango: 75 mg a 325mg) y se asumió equivalencia terapéutica
- Basándonos en estos resultados la dosis de 75-150 mg se prescribió mayoritariamente, a pesar de que no hubo nunca una comparación frente a la dosis de 300-325 mg

Comparaciones indirectas

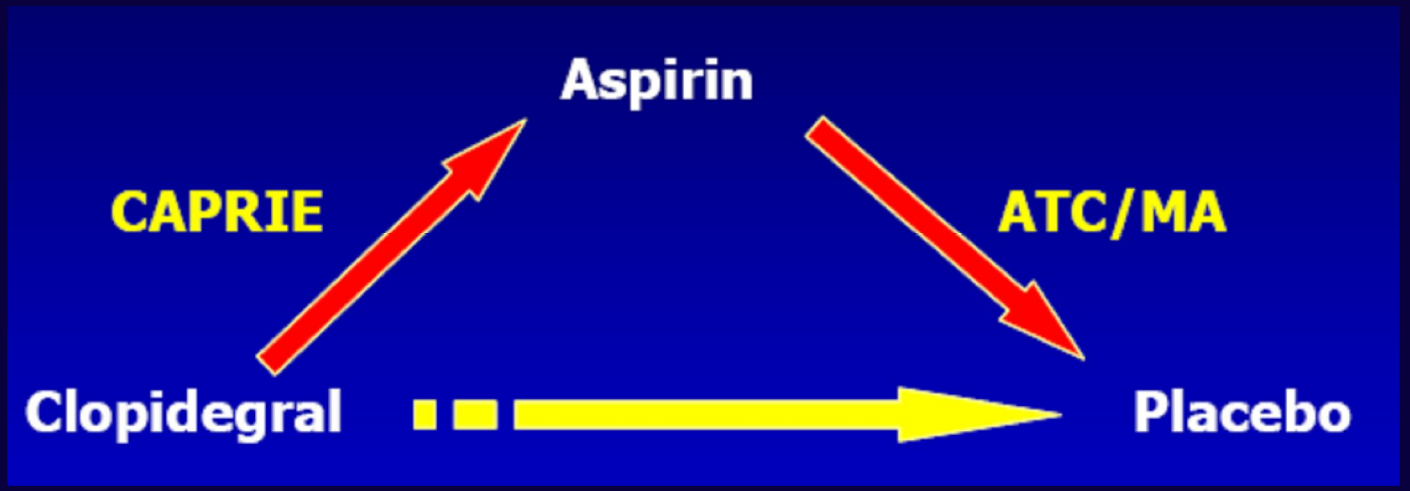


Comparison	RR (95% CI)
Medium dose aspirin vs Placebo	0.55 (0.41, 0.73)
Low dose aspirin vs Placebo	0.74 (0.60, 0.91)

Medium dose aspirin vs Low dose aspirin	0.74 (0.52, 1.06)



Comparaciones indirectas



composite outcome (stroke, myocardial infarction or vascular death)

Comparison	OR (95% CI)
Clopidogrel vs Aspirin	0.90 (0.82, 0.99)
Aspirin vs Placebo	0.78 (0.74, 0.82)
Clopidogrel vs Placebo	0.70 (0.63, 0.78)

Evidencia de equivalencia terapéutica

¿Qué evidencia de equivalencia nos dan estos ensayos? ¿es la misma para todos?

Estudios Equivalencia

Estudios No-Inferioridad

Estudios de superioridad sin significación

Estudios de superioridad sin relevancia

Distintos estudios frente al mismo comparador

Distintos estudios frente a diferentes comparadores

Estudios observacionales

Comparaciones indirectas

Niveles de Evidencia		
Evidencia	1	ECAs directos de equivalencia y de No-inferioridad
Estimación	2	ECAs directos de superioridad sin relevancia clínica
	3	ECAs directos de superioridad sin significación estadística
	4	ECAs indirectos. Comparación indirecta frente comparador común
	5	ECAs indirectos. Comparación indirecta frente comparadores diferentes
		Estudios observacionales
Soporte		Revisiones, GPC, recomendaciones, opinión expertos, juicio clínico

Evidencia de equivalencia terapéutica

- **Ejemplos**

Nivel de Evidencia	1	2	3	4	5
Tenecteplase/Alteplase (infarto agudo de miocardio)	1				
Darbopoetina/Eritropoyetina (anemia por IRC)	2				
Peginterferón alfa 2a/alfa 2b (VHC g1)				2	
Azitromicina/Claritromicina (infección respiratoria)		1		1	
Fondaparinux/Enoxaparina (profilaxis tromboembolismo)			4		
Darbepoetina/Eritropoyetina (anemia por quimioterapia)				2	
Pegfilgrastim/Filgrastim (neutropenia)	2				
Ganciclovir/Valganciclovir (prevención inf. CMV trasplante)	1				
Adalimumab/Etanercept (artritis reumatoide adulto)				3	
Escitalopram/Citalopram (Depresión Mayor)	1	1	1		
Doxo liposomal / Doxo liposomal pegilada (cáncer de mama metastásico)					2
Emtricitabina/Lamivudina (Infección HIV)	2				

Evidencia de equivalencia terapéutica

- **Ejemplos**

	Grado de evidencia
Tenecteplase/Alteplase (infarto agudo de miocardio)	**Muy elevado**
Darbopoetina/Eritropoyetina (anemia por IRC)	**Muy elevado**
Peginterferón alfa 2a/alfa 2b (VHC g1)	**Moderado**
Azitromicina/Claritromicina (infección respiratoria)	**Elevado**
Fondaparinux/Enoxaparina (profilaxis tromboembolismo)	**Elevado**
Darbepoetina/Eritropoyetina (anemia por quimioterapia)	**Moderado**
Pegfilgrastim/Filgrastim (neutropenia)	**Muy elevado**
Ganciclovir/Valganciclovir (prevención inf. CMV trasplante)	**Muy elevado**
Adalimumab/Etanercept (artritis reumatoide adulto)	**Moderado**
Escitalopram/Citalopram (Depresión Mayor)	**Muy elevado**
Doxo liposomal / Doxo liposomal pegilada (cáncer de mama metastásico)	**Bajo**
Emtricitabina/Lamivudina (Infección HIV)	**Muy elevado**

Ensayos diferentes frente a un tercer comparador común

Anti-TNF-α

Table 1 Characteristics of patients enrolled in placebo controlled, double blind, randomised controlled trials of the addition of tumour necrosis factor α blocking agents to methotrexate in patients with active rheumatoid arthritis

First author	Ther age	RF(+) (%)
Weinblatt [21]	Etan	86
Maini [19]	Infli	81
Weinblatt [22]	Ada	NS
Keystone [23]	Ada	79

NS, not stated; RF, rhe
*Combined treatment
10 mg/kg every 8 we
†Treatment group that

Table 2 Adjusted indirect comparisons of the efficacy of TNFα blocking agents in placebo controlled, randomised, double blind trials in patients with active rheumatoid arthritis with an incomplete response to methotrexate

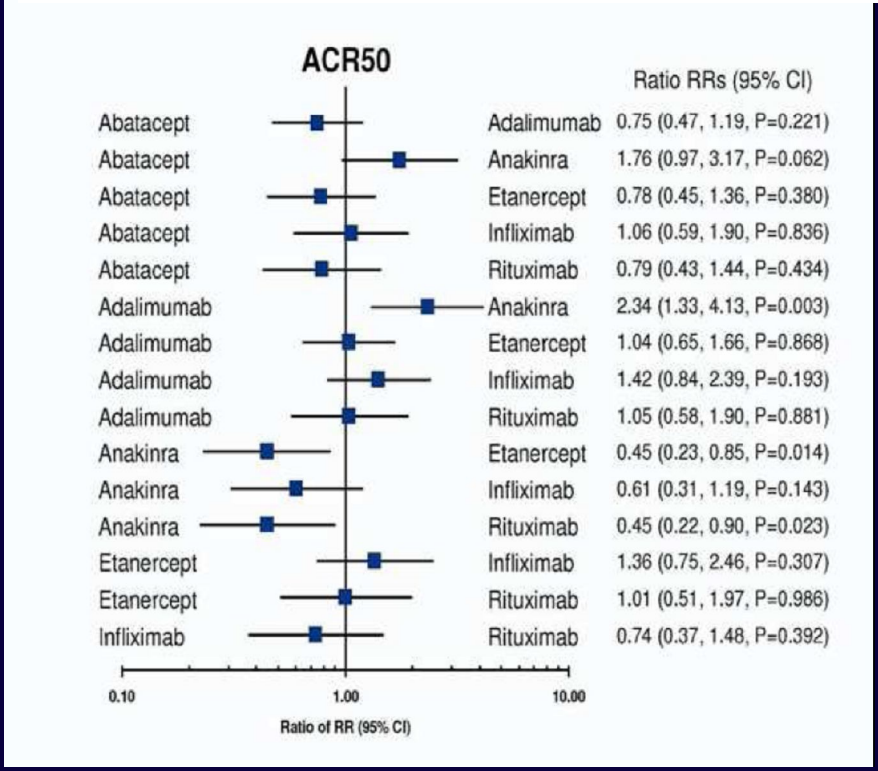
	Relative risk (95% CI)	
Comparison	ACR 20	ACR 50
Etanercept *v* adalimumab	1.10 (0.57 to 2.12)	2.60 (0.35 to 19.0)
Infliximab *v* adalimumab	1.07 (0.66 to 1.73)	1.35 (0.47 to 3.85)
Etanercept *v* infliximab	1.03 (0.49 to 2.18)	1.92 (0.22 to 17.0)

ACR, American College of Rheumatology; CI, confidence intervals.

weeks,

Biologics for rheumatoid arthritis: an overview of Cochrane reviews (Review)

Singh JA, Christensen R, Wells GA, Suarez-Almazo
Tanjong Ghogomu E,



DISCUSSION

Summary of main results

This is the first overview of Cochrane systematic reviews of biologic DMARDs for RA. We included updated reviews of six biologic DMARDs, including abatacept, adalimumab, anakinra, etanercept, infliximab and rituximab in recommended approved doses only.

Five of the six biologics were statistically significantly better than placebo in achieving ACR50, the main efficacy variable, as opposed to anakinra which was no different than placebo. The likelihood of achieving ACR50 varied with different biologic DMARDs. On the nominal level, all biologics had similar efficacy for ACR50 in indirect comparisons; it was evident that anakinra was half as efficacious as adalimumab, etanercept, and rituximab. This is an important observation, in the absence of direct comparisons of these biologic DMARDs in RCTs. While we noted that different types of patient populations were treated with different biologic DMARDs, with some biologics being used more in patients with longer disease duration and more DMARD failures than others, we are also aware of the limitations of such analyses, even when they were pre-specified. Most RCTs reported mean duration of RA (used for defining early, established and late RA), which may lead to ecological fallacy. Additionally, while these definitions of RA duration may not be universally accepted, these were perhaps the only clinically acceptable definitions available to us from the published literature available in existing Cochrane

Ensayos diferentes frente a un tercer comparador común

Estatinas

Are sta
trials o
cardiov

Zheng Zhou, M

Backgroun
undetermined.
Methods U
on published ra
between 1980 (
cardiovascular c
Trials were grou
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trials (n = 2498
statistical assess
statistically signi
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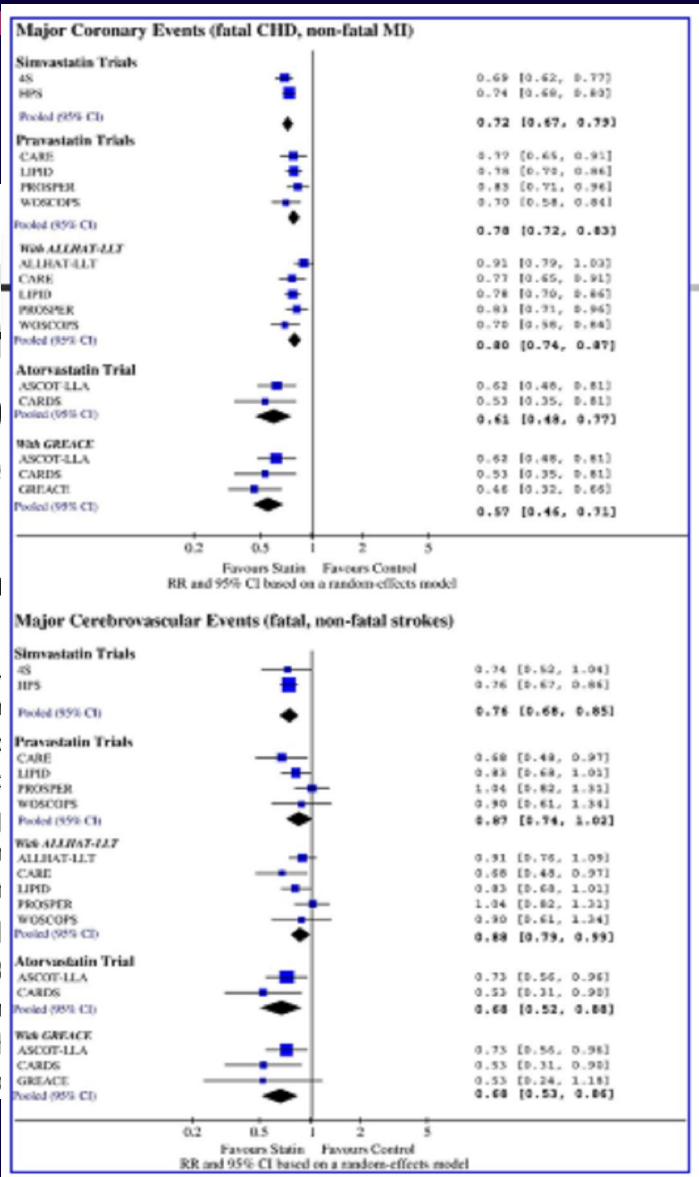
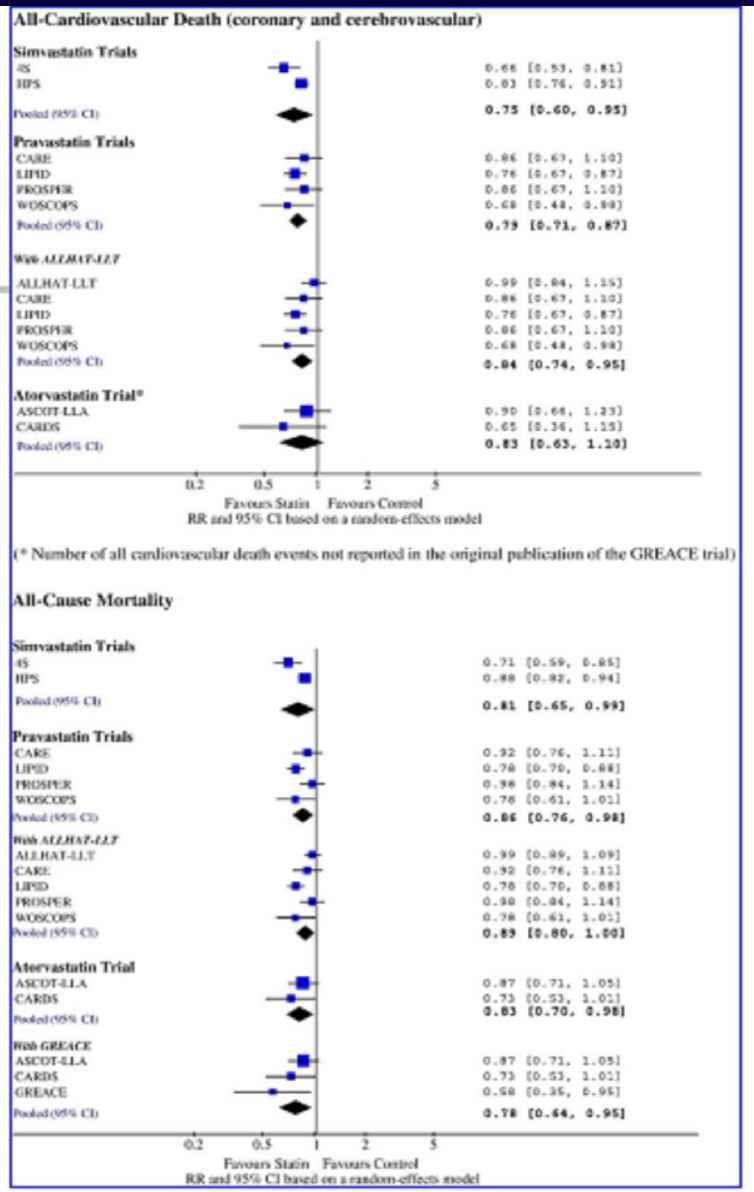




Ensayos diferentes frente a un tercer comparador común

Estatinas

Table II. Adjusted indirect comparisons between statins for different outcomes

	Point estimate of relative effect (95% CI)	P*
Major coronary events (fatal CHD and nonfatal MI)		
Simvastatin vs pravastatin	0.93 (0.84-1.03)	.18
Atorvastatin vs simvastatin	0.84 (0.66-1.08)	.18
Atorvastatin vs pravastatin	0.79 (0.61-1.02)	.06
Major cerebrovascular events (fatal, nonfatal stroke)		
Simvastatin vs pravastatin	0.87 (0.71-1.07)	.18
Atorvastatin vs simvastatin	0.90 (0.68-1.20)	.47
Atorvastatin vs pravastatin	0.78 (0.57-1.07)	.12
All-cardiovascular death (coronary and cerebrovascular)		
Simvastatin vs pravastatin	0.96 (0.75-1.23)	.73
Atorvastatin vs simvastatin	1.10 (0.77-1.58)	.61
Atorvastatin vs pravastatin	1.05 (0.78-1.42)	.74
All-cause death		
Simvastatin vs pravastatin	0.93 (0.73-1.19)	.57
Atorvastatin vs simvastatin	1.03 (0.79-1.35)	.82
Atorvastatin vs pravastatin	0.96 (0.78-1.18)	.71

Conclusion Evidence from published statin randomized placebo-controlled trials suggests that pravastatin, simvastatin, and atorvastatin, when used at their standard dosages, show no statistically significant difference in their effect on long-term cardiovascular prevention. (Am Heart J 2006;151:273-81.)

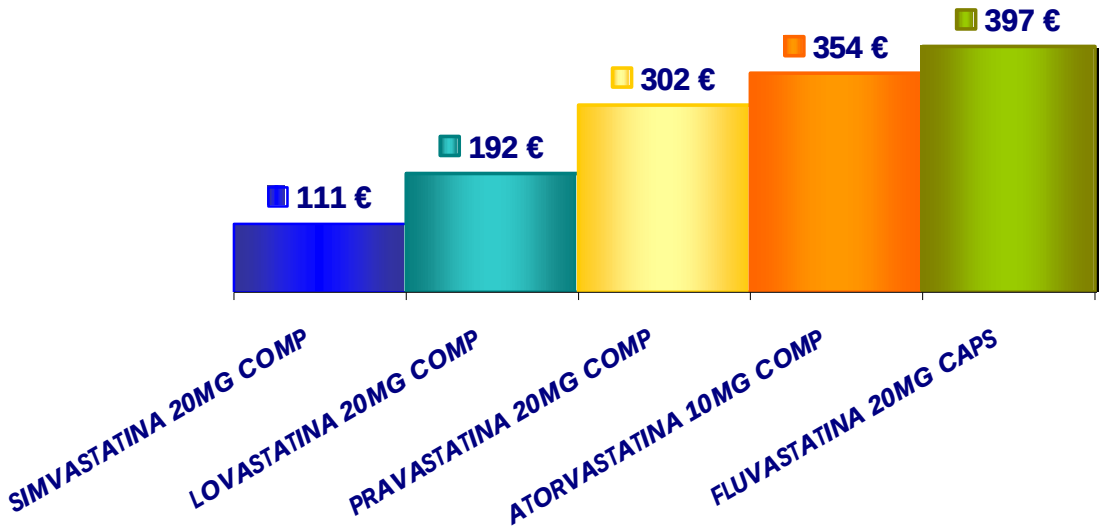
Implicaciones en gestión económica:

	DDD 2006	Gasto 2006
Atorvastatina	10.433.024	6.389.912 €
Pravastatina	2.048.802	1.865.710 €
Fluvastatina	2.101.666	1.186.668 €

Ejemplo estatinas

Si el 50% DDD de estas estatinas hubiesen sido SIMVASTATINA

Importe por paciente y año (datos 2006)



Ahorro anual BALEARES

2.755.794 €

6. Conclusiones

… las comparaciones indirectas permiten aportar evidencia en aquellos casos en los que las comparativas directas son no existentes

… la similaridad en la población analizada es una característica fundamental y necesaria en las CI

… la CI naives e informales no son suficientes para establecer conclusiones válidas

…las CI permiten estrategias en las políticas de selección de medicamentos con importantes repercusiones en gestión económica