Ensayos de superioridad, no inferioridad y equivalencia. Secuencialidad

Dr. Pere Ventayol

Concepto de EQUIVALENTE TERAPÉUTICO

Fármaco diferente en su estructura química del original, pero del que se espera un efecto terapéutico y un perfil de efectos adversos similares cuando se administra a un paciente a dosis equivalentes

- Medicamentos equivalentes NO son **moléculas** iguales
- Medicamentos equivalentes NO son distintas **marcas comerciales** de un mismo fármaco (EFG-marcas de fantasía)
- Equivalencia terapéutica NO significa **bioequivalencia**

El ECA: paradigma para demostrar eficacia

30.4.2004 ES Diario Oficial de la Unión Europea

I

(Actos cuya publicación es una condición para su aplicabilidad)

REGLAMENTO (CE) Nº 726/2004 DEL PARLAMENT

de 31 de marzo de 200

por el que se establecen procedimientos comunitarios para medicamentos de uso humano y veterinario y por el que se mentos

(13) En interés de la salud pública, las una autorización en el marco del lizado deben adoptarse a partir objetivos sobre la calidad, la segu medicamento de que se trate, excl sideración económica o de otro ti darse a los Estados miembros la p excepcional, de prohibir la utilizac medicamentos de uso humano q principios de orden público o definidos objetivamente. Además,

(34) Los Estados miembros han desarrollado una evaluación de la eficacia relativa de los medicamentos con objeto de situar los nuevos medicamentos respecto a los ya existentes, en la misma clase terapéutica. De igual modo, en sus Conclusiones sobre medicamentos y salud pública [1], adoptadas el 29 de junio de 2000 el Consejo subrayó la importancia de la identificación de medicamentos con un destacado valor terapéutico añadido. No obstante, no debe efectuarse este tipo de evaluación en el procedimiento de concesión de la autorización de comercialización, en el que deben primar los criterios fundamentales. Conviene a este respecto prever la posibilidad de recabar información sobre los métodos empleados por los Estados miembros para determinar el beneficio terapéutico aportado por cada nuevo medicamento.

¿Cuándo se asume la equivalencia terapéutica?

La diferencia está en un margen clínicamente irrelevante

δ

¿Siempre hay que demostrar mayor eficacia?

Ser mejor no siempre es demostrar mayor eficacia

Disponible	Ningún tratamiento	Otros tratamientos	Mejor tratamiento
Objetivo	Eficacia	Mejoría en eficacia/seguridad	Igualdad en eficacia y mejoría en otros aspectos
Comparador	Placebo	Otro tratamiento	Gold standard
Ensayos	Superioridad	Superioridad	Equivalencia/ No-inferioridad

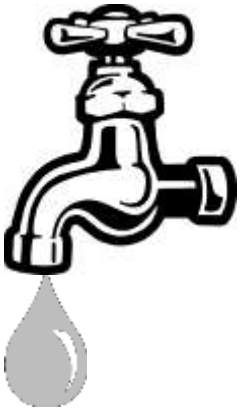
¿Para qué realizar ensayos de moléculas con eficacia similar?

¿Para qué realizar ensayos de moléculas con eficacia similar?

- Mayor seguridad
- Mayor comodidad, menor duración, facilitar adherencia, reducir coste
- Eficacia
  - Tratamientos alternativos o segundas líneas
  - Éticamente no es aceptable utilizar placebo

Estrategia de análisis

Estrategia de análisis



Objetivo: CV <400 a las 48 semanas

Randomizados
N=100

Datos disponibles a 48 semanas
N=75

Datos no disponibles a 48 semanas
N=25

CV<400
N=65

CV>400
N=10

CV<400
N=11

CV>400
N=14

Análisis PP
87% (65/75)

ITT (ultima observación)
76% (65+11/100)

ITT (perdidas=F)
65% (65/100)

Dilución de la respuesta: ¿Cuál es la verdadera?

Ejemplo:

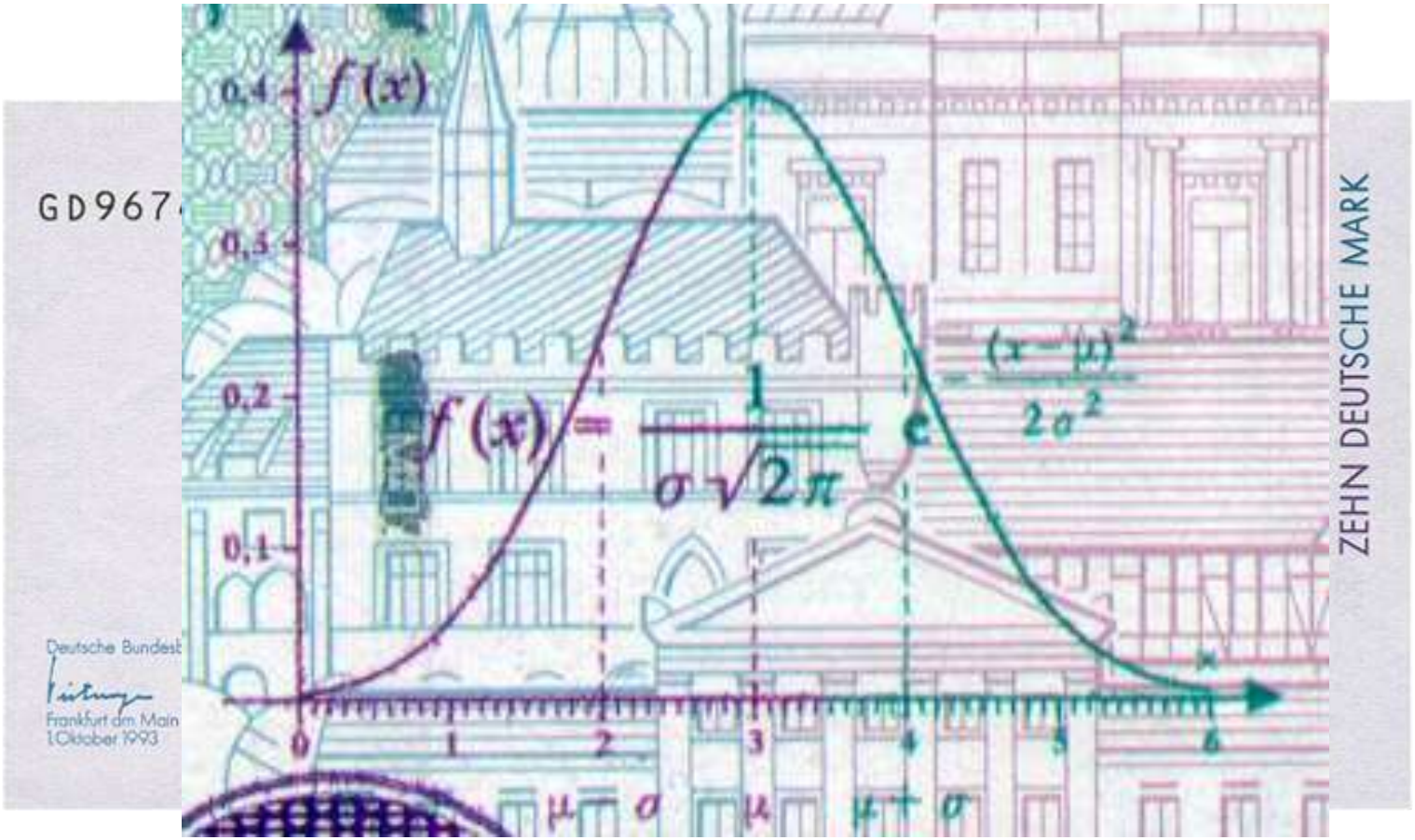
La empresa GIN-Lirios tiene como referencia un GIN, que hasta la fecha es el mejor del mercado

- Caso A. Necesito demostrar que mi GIN es muy parecido al mejor del mercado (equivalencia)

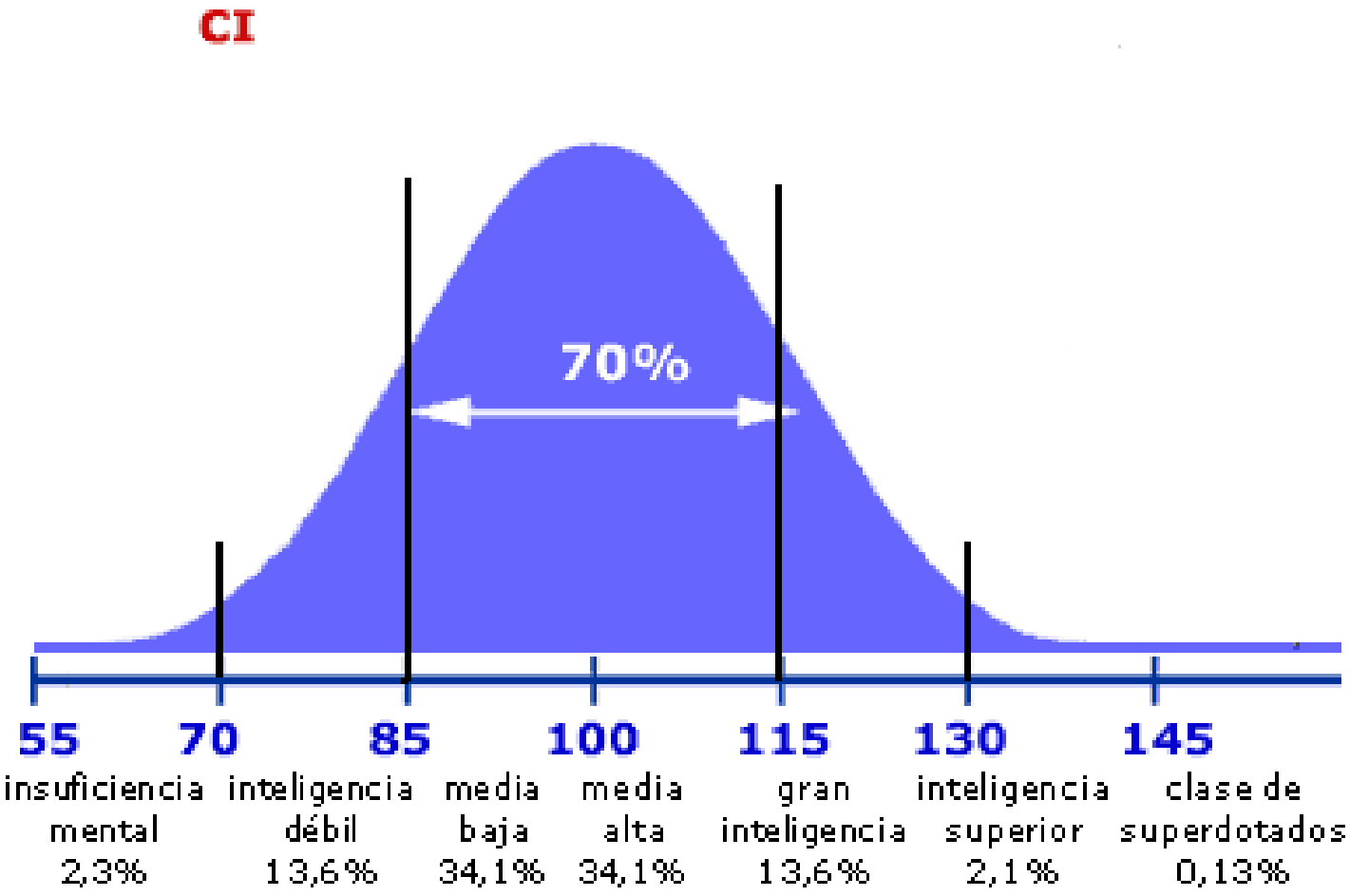
- Caso B: necesito demostrar que mi GIN es superior al de referencia (superioridad)

el revés….

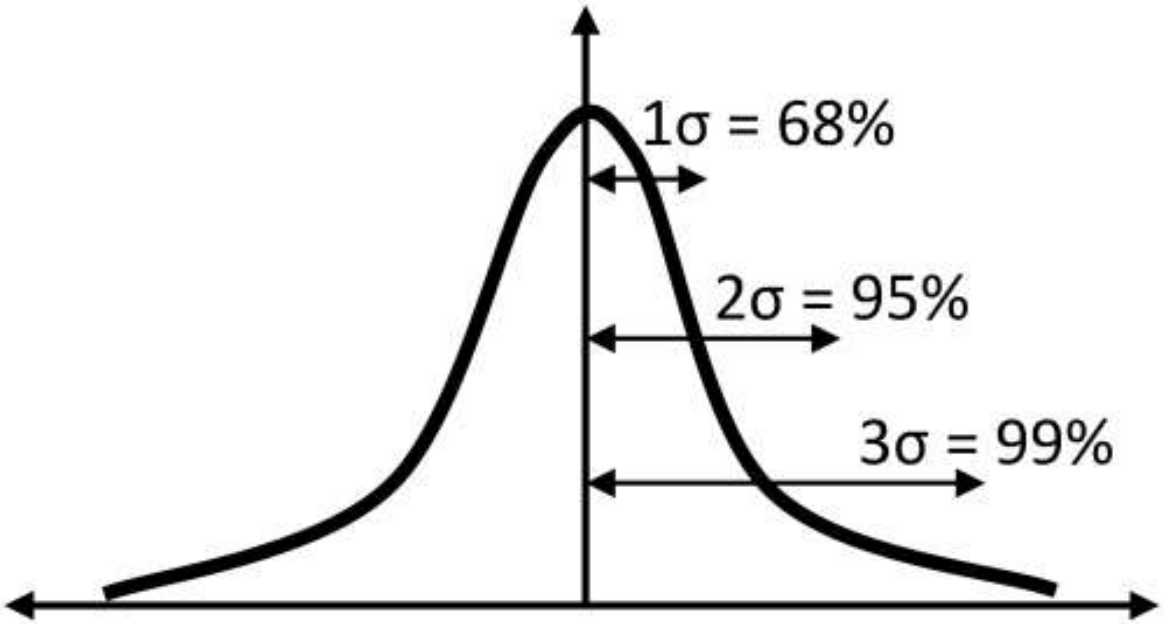
Si fueramos alemanes….

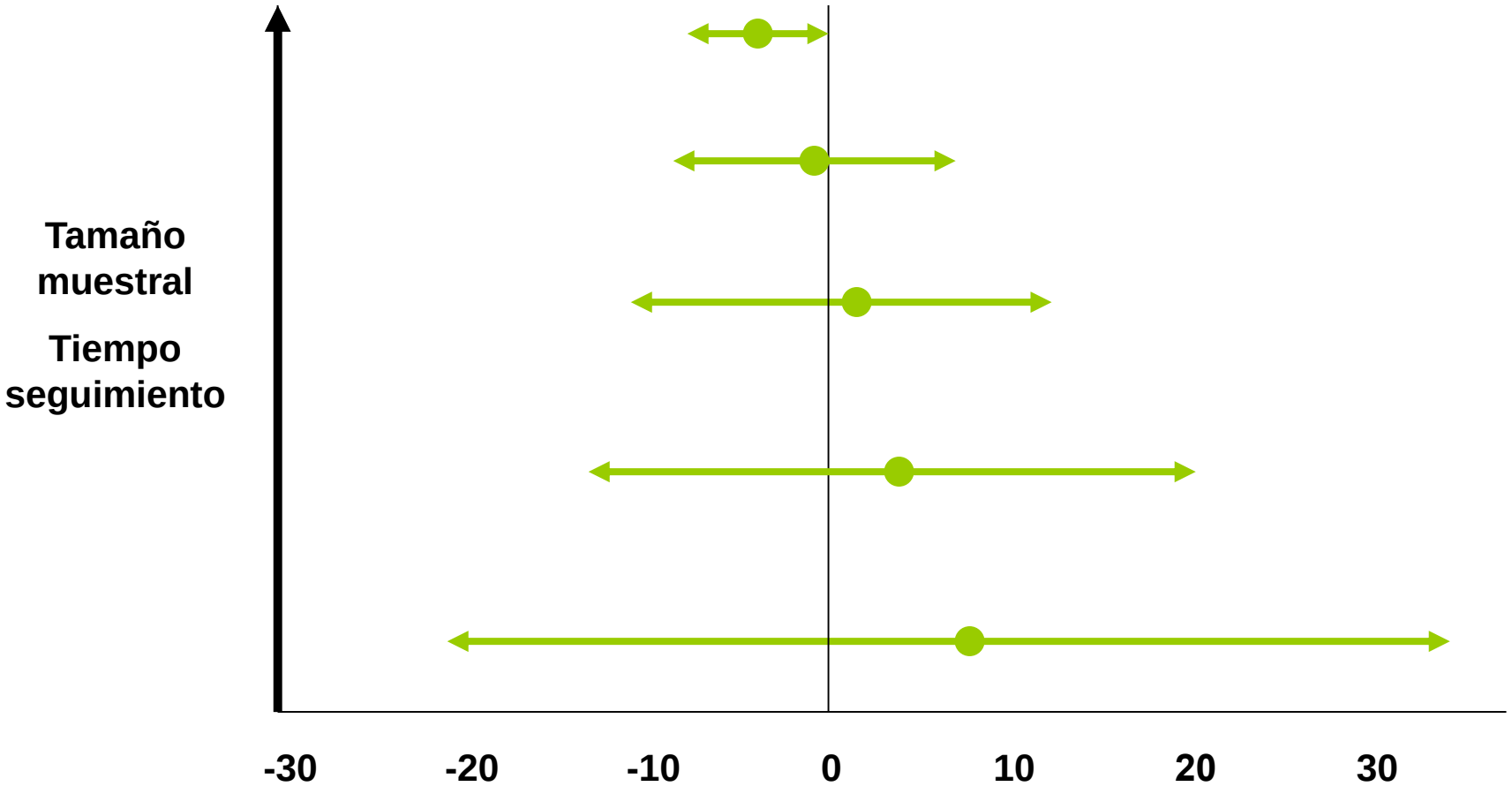


Gauss y el IC…..


CI
70%
55
70
85
100
115
130
145
insuficiencia mental 2,3%
inteligencia débil 13,6%
media baja 34,1%
media alta 34,1%
gran inteligencia 13,6%
inteligencia superior 2,1%
clase de superdotados 0,13%

Gauss y el IC…..




Tamaño muestral
Tiempo seguimiento
-30
-20
-10
0
10
20
30

…y la lectura….

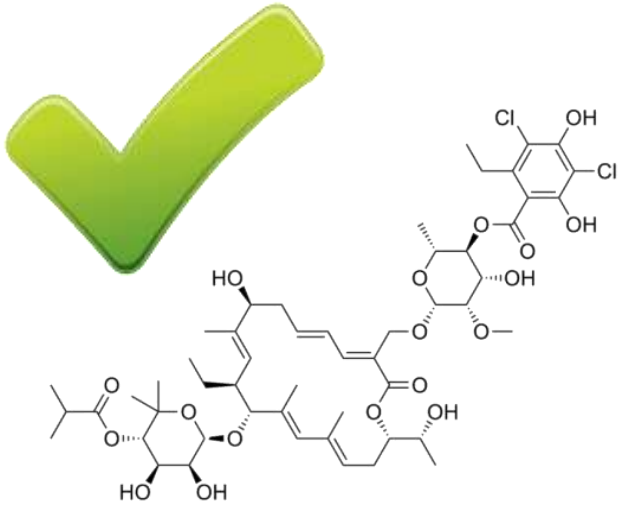
Ejemplo fidaxomicina:

1.Variable absoluta o relativa?

2. Lectura positiva o negativa?

Recaída

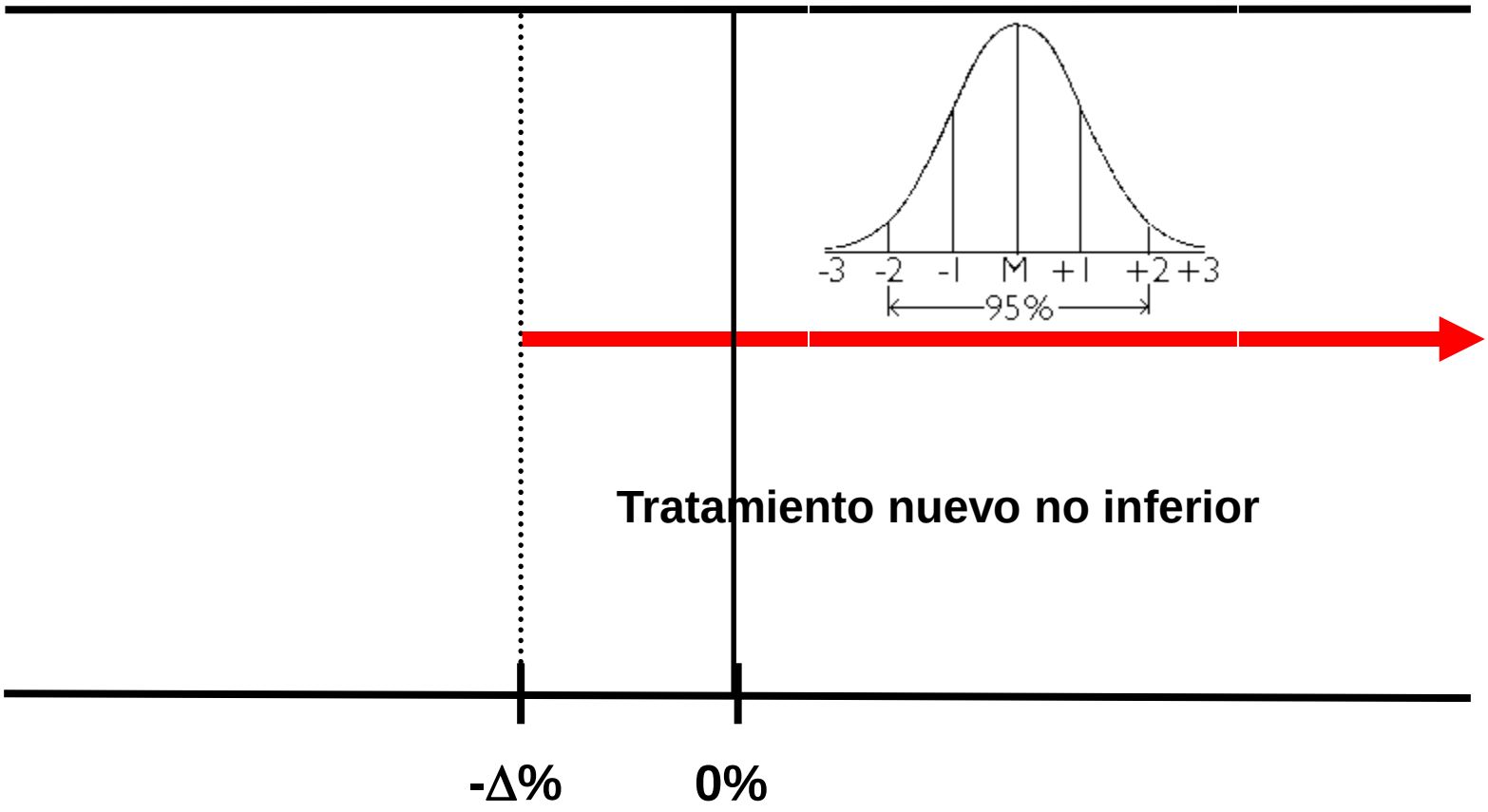
Curación



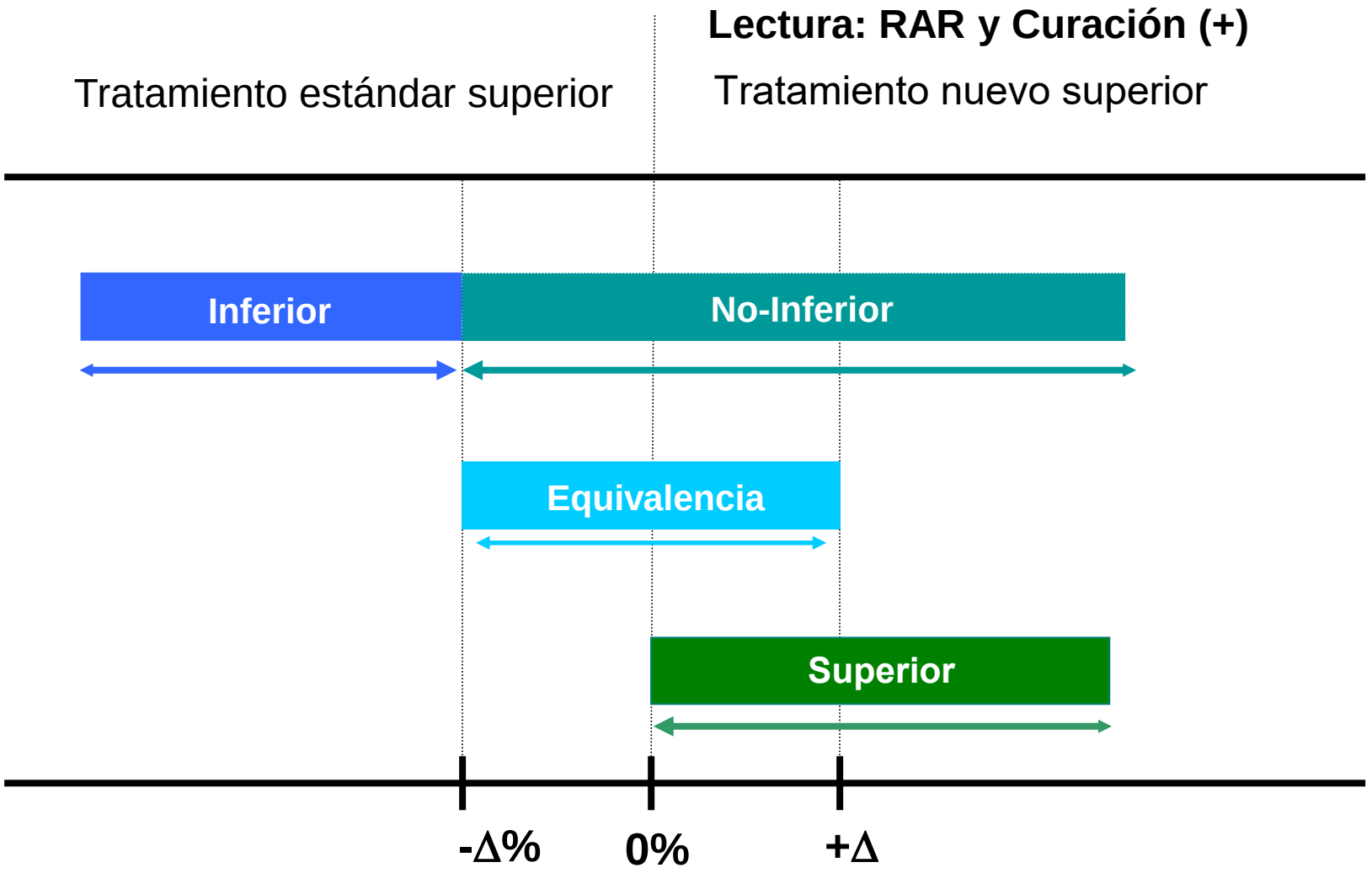
I need your atention
PLEASE

Gauss y la lectura

Lectura: RAR y Curación (+)

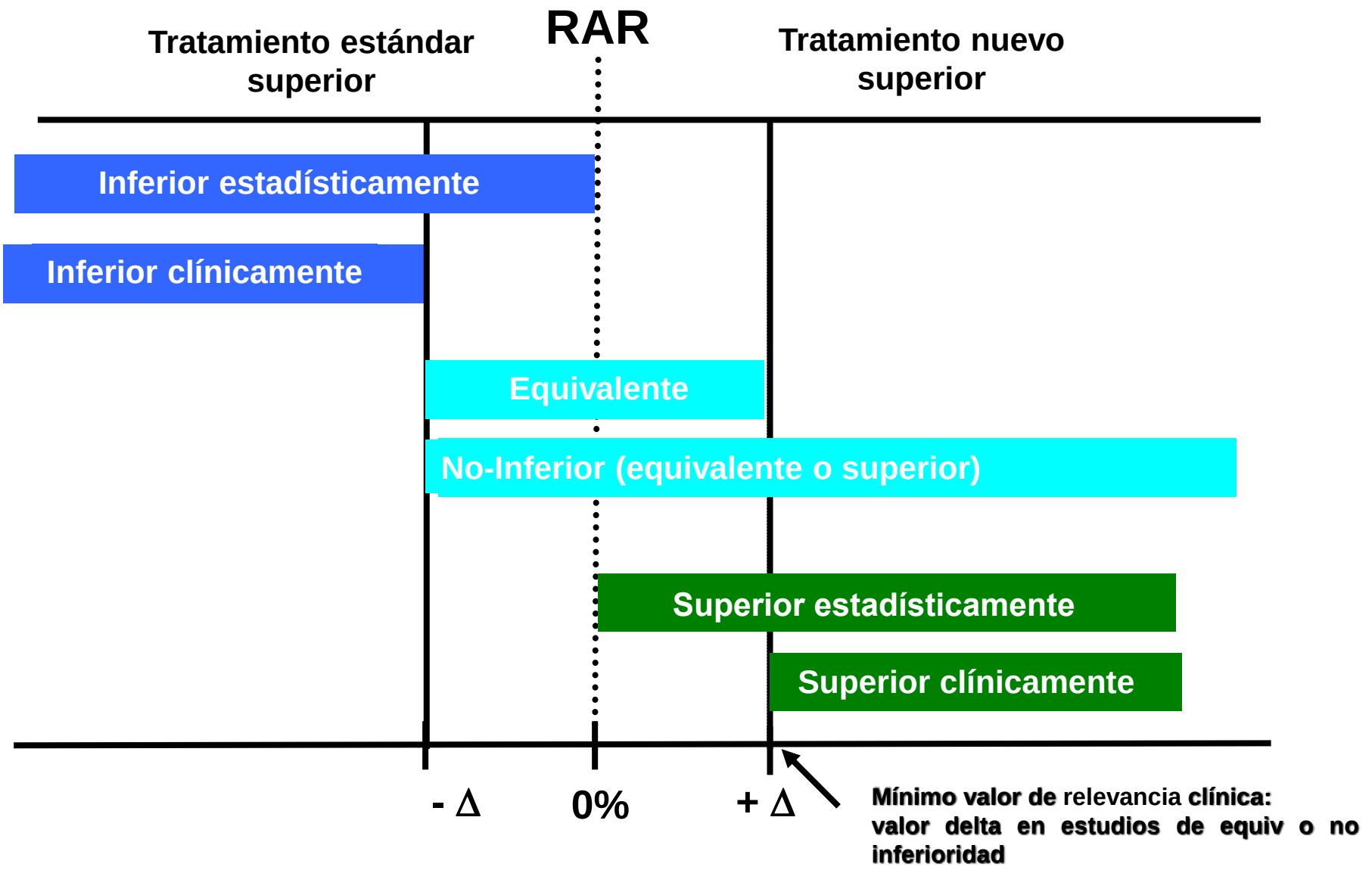


La lectura clínica y la estadística



Lectura: RAR y Curación (+)

La lectura clínica y la estadística



¿Cuánta diferencia es irrelevante?

¿Cuánta diferencia es irrelevante?

Requiere juicio clínico, debate y consenso

Ejemplo: El antirretroviral “A” produce un 70% de cargas virales indetectables a las 48 semanas. Opiniones de los clínicos de que valor de RAR consideran relevante para concluir que el tratamiento B es mejor.

Lugar	Delta
Barcelona	6%
Valencia	5%
Zaragoza	5%
Málaga	5%
Madrid	10%
S. Sebastian	5%
Sevilla	10%

La clave: el valor delta

Delta no deriva
de una regla matemática,
se basa en el razonamiento clínico
y características estudio

- Máxima diferencia entre los tratamientos que vamos a considerar clínicamente irrelevante
- Es un intervalo definido entre dos límites: Δ y $-\Delta$
- Se establece al inicio del estudio
- Elección complicada: valor distinto para cada tipo de fármacos →
  - requiere debate, consenso clínico y aprobación de las agencias reguladoras
- Las directrices de FDA y EMA orientan pero no especifican un valor predefinido

Valores utilizados

- FDA 1992 Comité Asesor Cardio Renal
  - recomendó la mitad del efecto del tratamiento estándar como margen de no inferioridad para nuevos **trombolíticos**

- FDA Oct 2002: Guidance for Industry **Antirretrovirales**
  - 10-12% (RAR) del % pacientes con carga viral indetectable

- FDA **Antiinfecciosos**
  - Delta modulable según la tasa de respuesta

¿Cuánta diferencia es irrelevante?

- Por orden de preferencia:
  - Valor delta establecido por agencias evaluadoras (EMA / FDA).
  - Propuesto por paneles de expertos, preferiblemente independientes.
  - Utilizado en EC de equivalencia / no inferioridad.
  - Valor de referencia utilizado para el cálculo de muestra:
    - Utilizado en EC con comparador activo.
    - Utilizado para el cálculo de muestra utilizado en EC frente a placebo.
  - Fracción de resultado de un fármaco frente a placebo → se ha empleado el 50% (discutible, justificar)

Ejemplo dabigatran

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

RESULTS

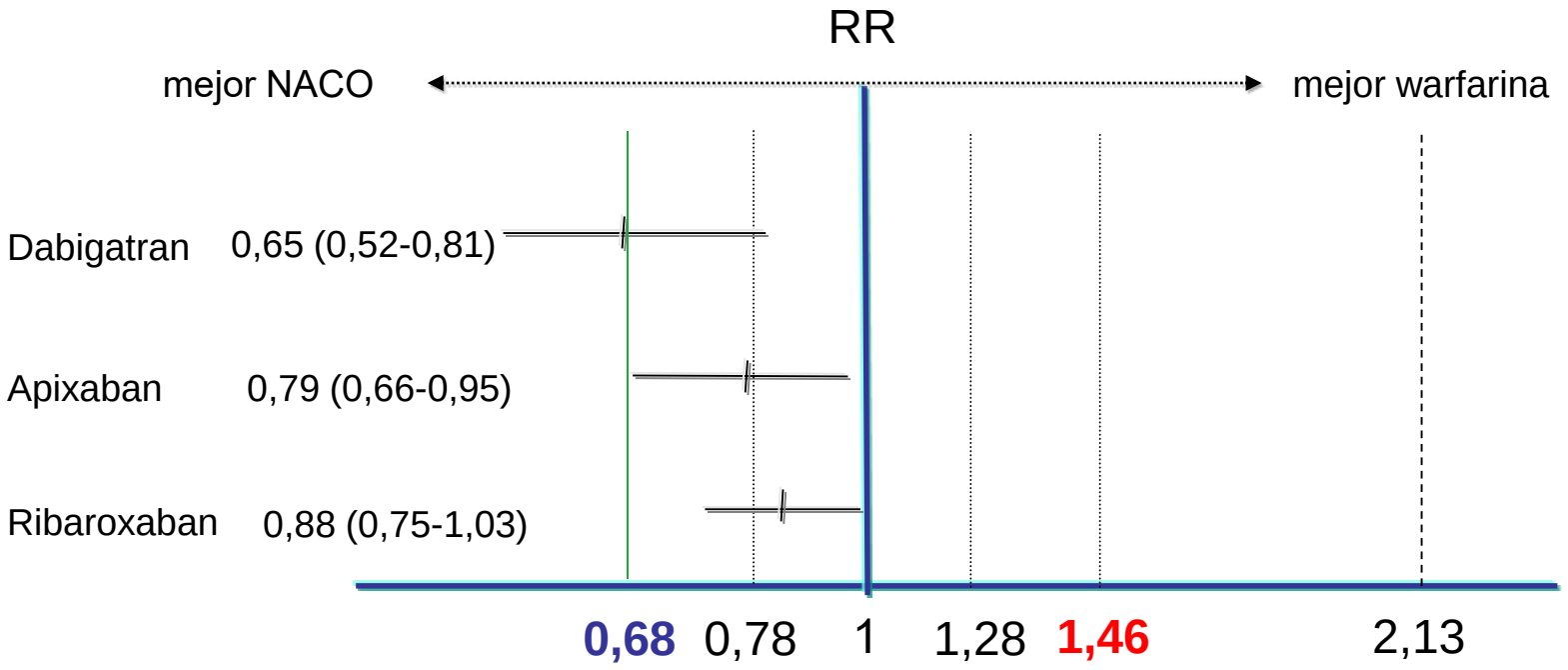
Rates of the primary outcome were 1.69% per year in the warfarin group, as compared with 1.53% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.91; 95% confidence interval [CI], 0.74 to 1.11; P<0.001 for noninferiority) and 1.11% per year in the group that received 150 mg of dabigatran (relative risk, 0.66; 95% CI, 0.53 to 0.82; P<0.001 for superiority). The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group receiving 110 mg of dabigatran (P=0.003) and 3.11% per year in the group receiving 150 mg of dabigatran (P=0.31). The rate of hemorrhagic stroke was 0.38% per year in the warfarin group, as compared with 0.12% per year with 110 mg of dabigatran (P<0.001) and 0.10% per year with 150 mg of dabigatran (P<0.001). The mortality rate was 4.13% per year in the warfarin group, as compared with 3.75% per year with 110 mg of dabigatran (P=0.13) and 3.64% per year with 150 mg of dabigatran (P=0.051).

rates of stroke and systemic embolism but similar rates of major hemorrhage. (ClinicalTrials.gov number, NCT00262600.)

N Engl J Med 2009;361:1139-51.

Consideraciones sobre el valor delta

Lectura: RR
Variable: Ictus y embolismo sistémico (-)



Secuencialidad:
¿Es posible cambiar de objetivo?

Once noninferiority is evident, it is acceptable to then assess whether the new treatment appears superior to the reference treatment, using an appropriate test or CI (ie, not just the point estimate), preferably defined a priori and with an ITT analysis.[22,28,43]

It is inappropriate to claim noninferiority post hoc from a superiority trial unless clearly related to a predefined margin of equivalence. That is, both superiority and noninferiority hypotheses need explicit specification in the trial protocol.[44] It is, however, always

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JAMA. 2006;295:1152-1160

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 27 July 2005
Doc. Ref. EMEA/CPMP/EWP/2158/99

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE CHOICE OF THE NON-INFERIORITY MARGIN

DRAFT AGREED BY THE EFFICACY WORKING PARTY	December 1999 – January 2004
ADOPTION BY COMMITTEE FOR RELEASE FOR CONSULTATION	February 2004
END OF CONSULTATION (DEADLINE FOR COMMENTS)	May 2004
AGREED BY WORKING PARTY	June 2004
ADOPTION BY COMMITTEE	July 2005
DATE FOR COMING INTO EFFECT	January 2006

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fidaxomicin versus Vancomycin for

Thomas J. Loui
Karl Wel
Sherwood Gorba

BACKGROUND

Clostridium difficile in
morbidity and mort
metronidazole; how
compared the effica
ing *C. difficile* infecti

RESULTS

A total of 629 patients were enrolled, of whom 548 (87.1%) could be evaluated for the per-protocol analysis. The rates of clinical cure with fidaxomicin were noninferior to those with vancomycin in both the modified intention-to-treat analysis (88.2% with fidaxomicin and 85.8% with vancomycin) and the per-protocol analysis (92.1% and 89.8%, respectively). Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection, in both the modified intention-to-treat analysis (15.4% vs. 25.3%, P=0.005) and the per-protocol analysis (13.3% vs. 24.0%, P=0.004). The lower rate of recurrence was seen in patients with non–North American Pulsed Field type 1 strains. The adverse-event profile was similar for the two therapies.

CONCLUSIONS

The rates of clinical cure after treatment with fidaxomicin were noninferior to those after treatment with vancomycin. Fidaxomicin was associated with a significantly lower rate of recurrence of *C. difficile* infection associated with non–North American Pulsed Field type 1 strains. (Funded by Optimer Pharmaceuticals; ClinicalTrials.gov number, NCT00314951.)

Variable principal: curación clínica

Tabla 5. Resultados de la variable primaria: curación clínica

Estudio Referencia	Tipo de Estudio	Tiempo de Seguimiento	n	Tipo de Análisis	Resultado FDX 200mg	Resultado VA 125mg	RAR IC 95%	p	NNT (IC95%)
Louie TJ 2011	ECA No inferioridad (Δ=-10%)	28 días	548	PP	92,1% (244/265) IC95% (88,1 a 94,8)	89.8% (254/283) IC95% (85,6 a 92,8)	2,3 (-7,1 a 2,5)	NS	-
			596	ITTm	88.2% (253/287) IC95% (83,8 a 91,4)	85.8% (265/309) IC95% (81,4 a 89,2)	2,4 (-3 a 7,8)	NS	-
Cornely OA 2012	ECA No inferioridad (Δ=-10%)	28 días	451	PP	91.7% (198/216) IC95% (87,1 a 94,7)	90.6% (213/235) IC95% (86,1 a 93,8)	1,1 (-4,3 a 6,3)	NS	-
			509	ITTm	87.7% (221/252) IC95% : 83,0 a 91,2	86.8% (223/257) IC95% : 82,0 a 90,4	0,9 (-4,9 a 6,7)	NS	-

Variable secundaria: recurrencia

Table 27: Summary of CDI Recurrence Rates in the Phase 3 Studies

	101.1.C.003			101.1.C.004			Pooled 003 and 004		
	Fidaxo-micin n/N (%)	Vanco-mycin n/N (%)	Difference 95% CI n/N (%)	Fidaxo-micin n/N (%)	Vanco-mycin n/N (%)	Difference 95% CI n/N (%)	Fidaxo-micin n/N (%)	Vanco-mycin n/N (%)	Difference 95% CI n/N (%)
mITT population	39/253 (15.4)	67/265 (25.3)	-9.9	28/221 (12.7)	60/223 (26.9)	-14.2	67/474 (14.14)	127/488 (26.02)	-11.89
95% CI	(11.5, 20.4)	(20.4, 30.9)	(-16.6, -2.9)	(8.9, 17.8)	(21.5, 33.1)	(-21.4, -6.8)	(11.22, 17.65)	(22.25 30.19)	(-16.83, -6.84)
P-value			0.005			<0.001			<0.001
PP population	28/211 (13.3)	53/221 (24.0)	-10.7	23/180 (12.8)	46/182 (25.3)	-12.5	51/391 (13.04)	99/403 (24.57)	-11.52
95% CI	(9.3, 18.6)	(18.8, 30.1)	(-17.9, -3.3)	(8.6, 18.5)	(19.5, 32.1)	(-20.3, -4.4)	(9.99, 16.85)	(20.53, 29.10)	(-16.83, -6.09)
P-value			0.004			0.002			<0.001

Variable secundaria: curación global

Table 28: Summary of Global Cure Rates in the Phase 3 Studies

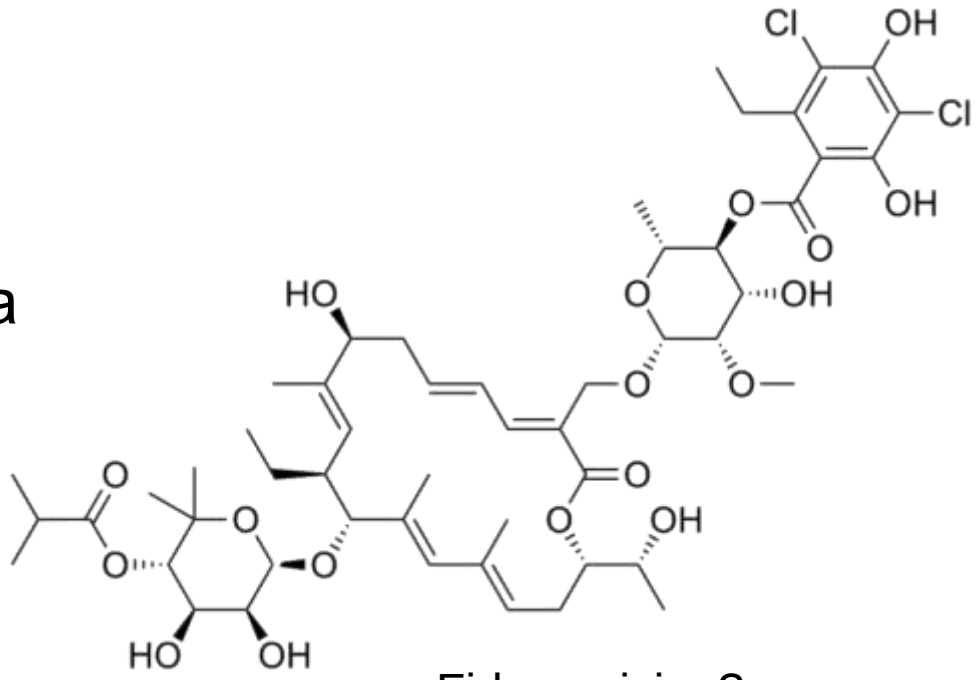
	101.1.C.003			101.1.C.004			Pooled 003 and 004		
	Fidaxo-micin n/N (%)	Vanco-mycin n/N (%)	Difference 95% CI[1]	Fidaxo-micin n/N (%)	Vanco-mycin n/N (%)	Difference 95% CI[1]	Fidaxo-micin n/N (%)	Vanco-mycin n/N (%)	Difference 95% CI[1]
mITT population 95% CI[2] P-value	214/287 (74.6) (69.2, 79.3)	198/309 (64.1) (58.6, 69.2)	10.5 (3.1, 17.7) 0.006[3]	193/252 (76.6) (71.0, 81.4)	163/257 (63.4) (57.4, 69.1)	13.2 (5.2, 20.9) 0.001[4]	407/539 (75.51) (71.62, 79.02)	361/566 (63.78) (59.66, 67.71)	11.73 (6.32, 17.04) <0.001[4]
PP population 95% CI[2] P-value	206/265 (77.7) (72.3, 82.3)	190/283 (67.1) (61.5, 72.3)	10.6 (3.1, 17.9) 0.006[3]	172/216 (79.6) (73.7, 84.5)	154/235 (65.5) (59.2, 71.3)	14.1 (5.9, 22.1) <0.001[4]	378/481 (78.59) (74.61, 82.09)	344/518 (66.41) (62.15, 70.42)	12.18 (6.66, 17.59) <0.001[4]

[1] 2-sided 95% CI around the difference (fidaxomicin minus vancomycin) in global cure rates.
[2] 2-sided 95% point estimate CI surrounding the global cure rate.
[3] 2-tailed z-Test for two population proportions based on the normality assumption.
[4] p-value from Chi-square test of difference in global cure rates between fidaxomicin and vancomycin.

Note: The global cure rate was defined as the percentage of patients who achieved cure and did not have a recurrence at any time up to the post-study visit.

Ensayos Fidaxomicina

- ensayos primero de no inferioridad
- y después…
  - superior
    - estadísticamente
    - variable secundaria
  - más seguro
  - mejor posología



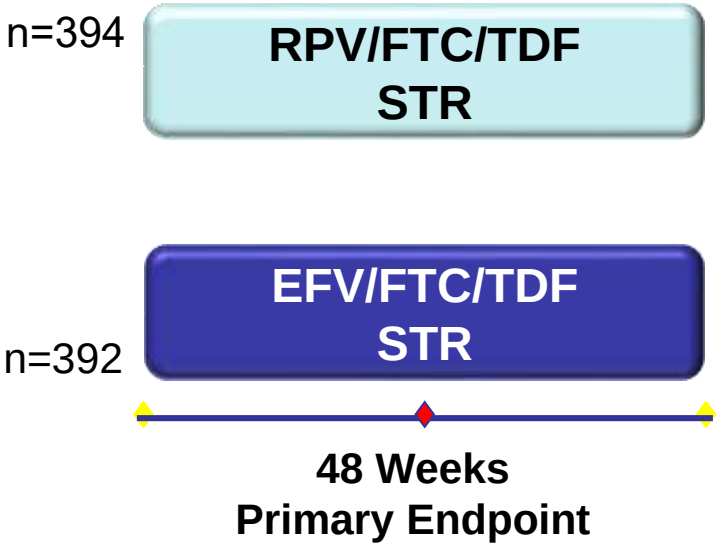
Fidaxomicina?

Study Design STaR

Multicenter, international, randomized, open-label, Phase 3b, 96-week study

ARV-naive
HIV-1 RNA >2500 c/mL
Sensitivity to EFV, FTC, RPV, TDF
(N=786)

Stratified by HIV RNA (≤ or >100,000 c/mL)



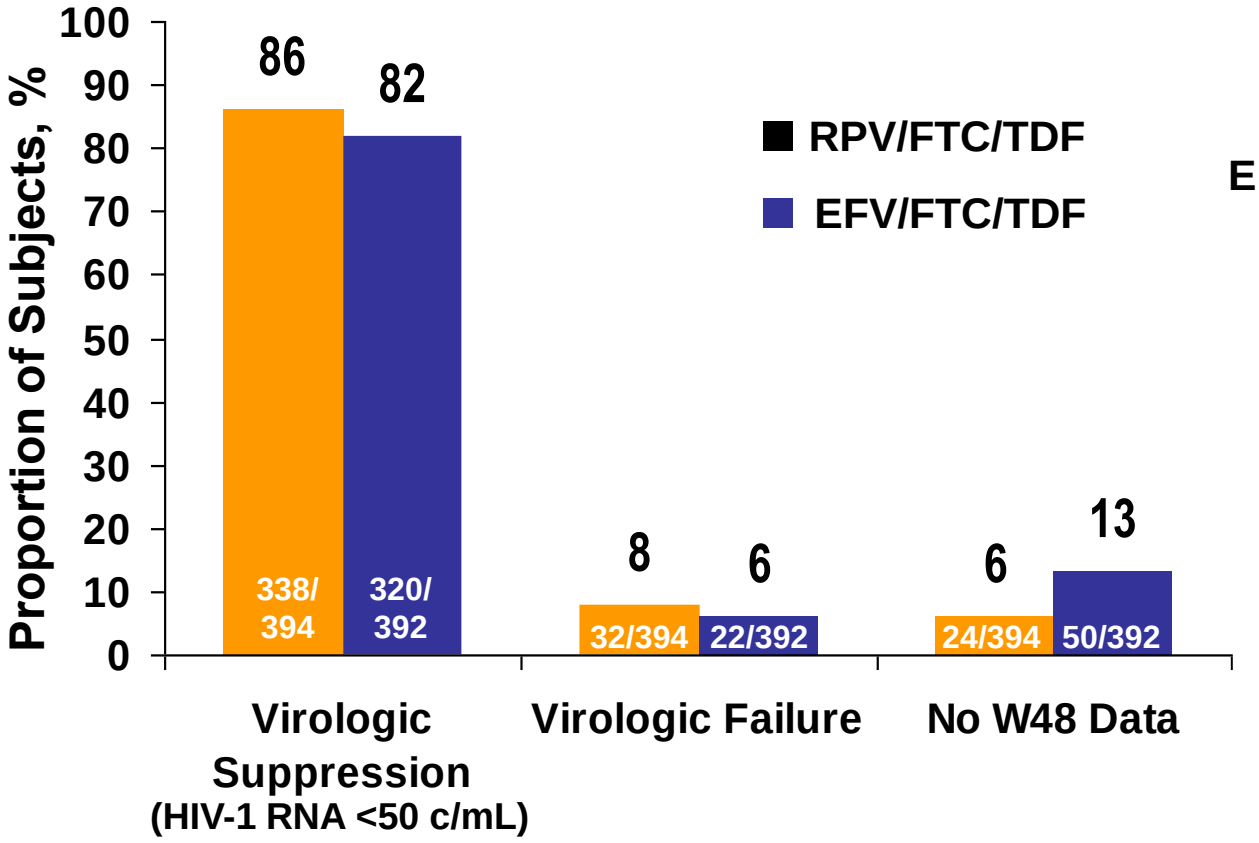
Primary endpoint: **Efficacy of the 2 STRs by proportion with HIV-1 RNA <50 c/mL at Week 48 (FDA Snapshot analysis); non-inferiority margin of 12%**

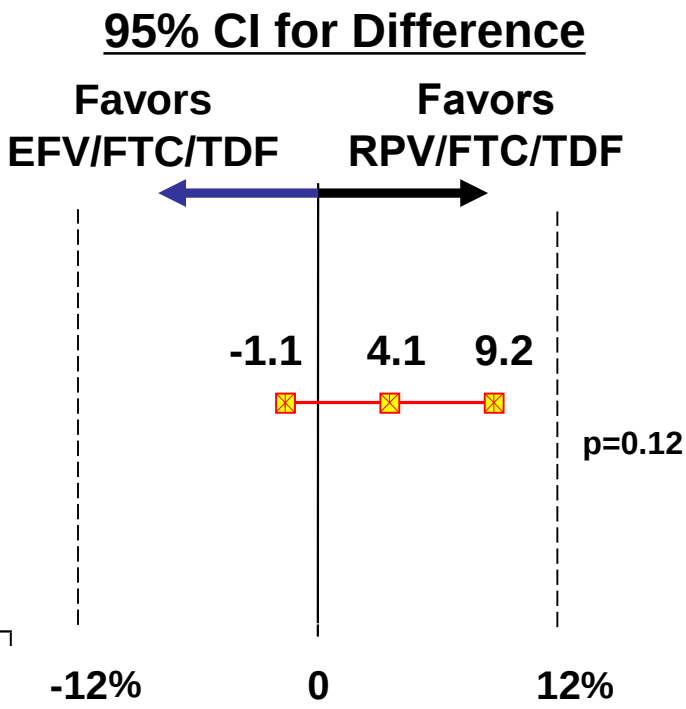
Secondary endpoints: **Safety and efficacy of the 2 STRs by proportion with HIV-1 RNA <50 c/mL at Week 96 (FDA Snapshot analysis)**
Change in CD4 cell count at Weeks 48 and 96
Genotype/phenotype resistance at time of virologic failure

STaR

Virologic Suppression and CD4 Change at Week 48 FDA Snapshot Analysis – ITT Population

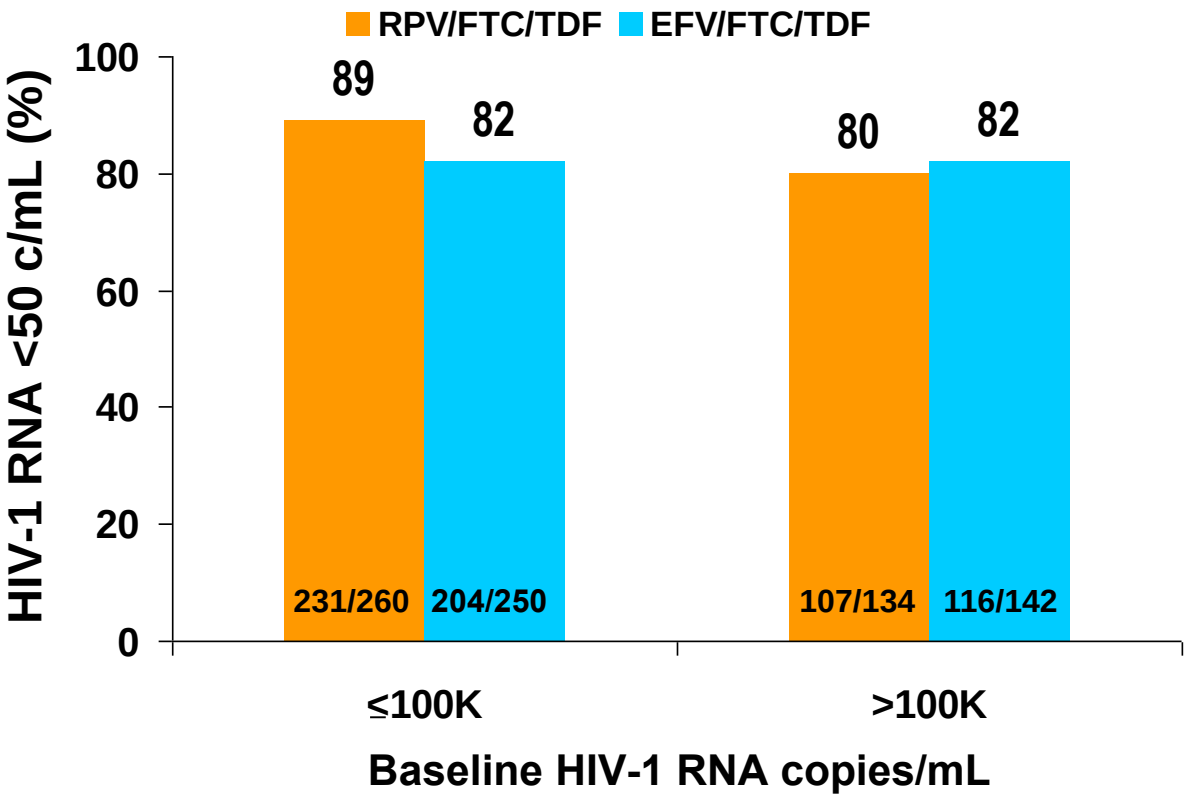
RPV/FTC/TDF is non-inferior to EFV/FTC/TDF

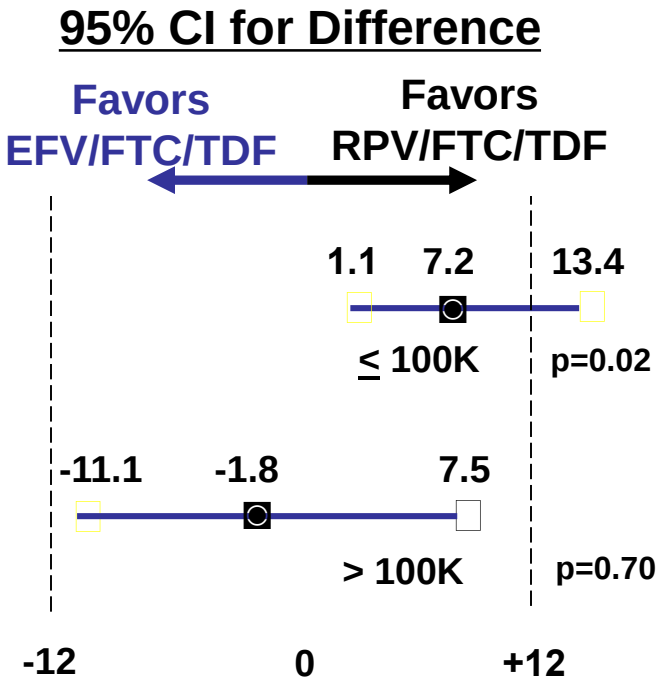




CD4 count change (cells/mm^3): RPV/FTC/TDF +200 vs EFV/FTC/TDF +191 (p=0.34)

Virologic Suppression at Week 48 FDA Snapshot Analysis by Baseline HIV-1 RNA Stratified by 100,000 c/mL





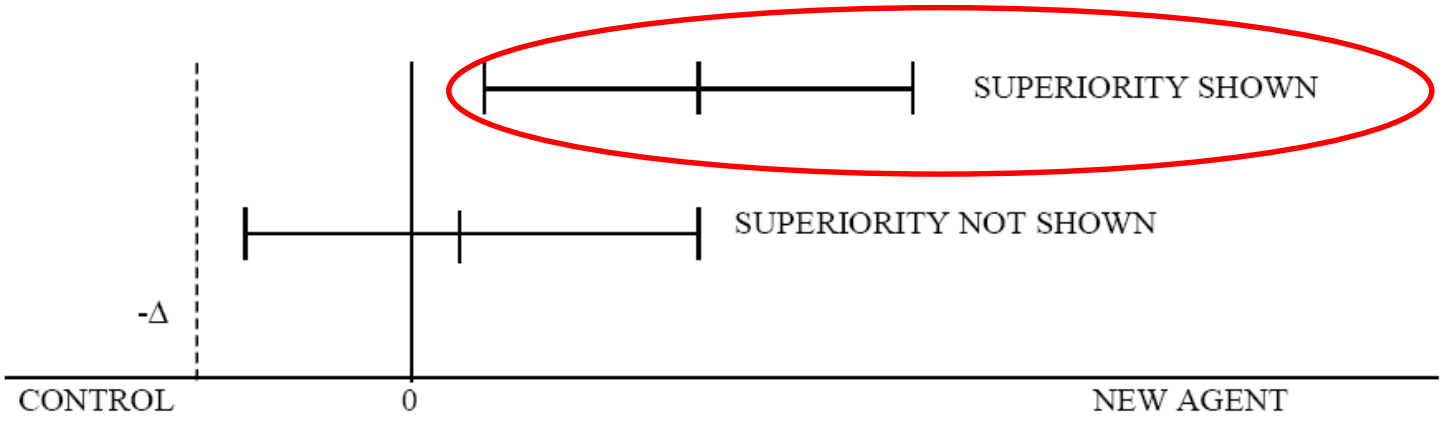
RPV/FTC/TDF compared to EFV/FTC/TDF
Superior for subjects with baseline HIV-1 RNA ≤100,000 c/mL
Non-inferior for subjects with baseline HIV-1 RNA >100,000 c/mL

IV. SWITCHING THE OBJECTIVE OF THE COMPARISON

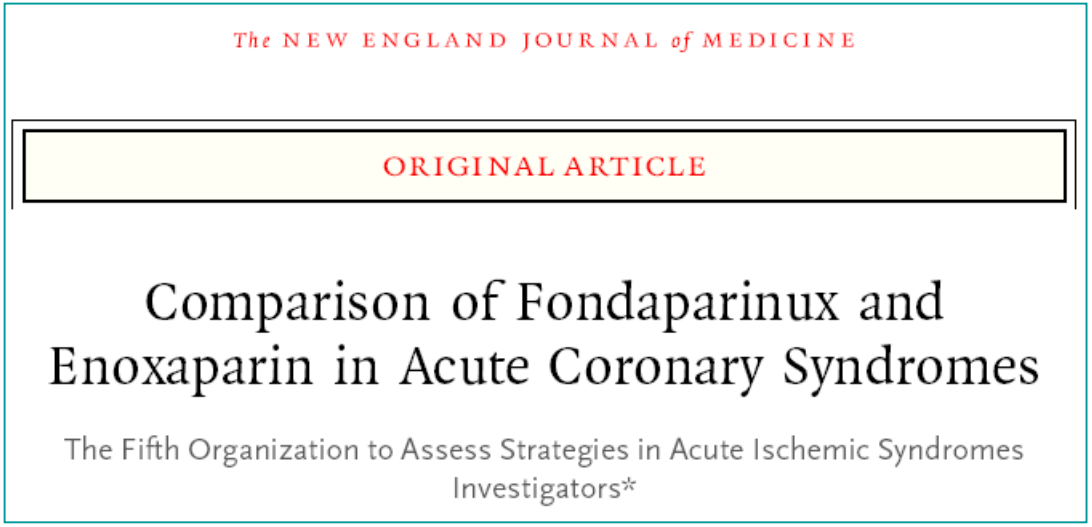
The only switching which is likely to have any practical relevance is switching between superiority and non-inferiority. The place of equivalence trials is so specific that they stand alone.

IV.1 Interpreting a non-inferiority trial as a superiority trial

If the 95% confidence interval for the treatment effect not only lies entirely above $-\Delta$ but also above zero then there is evidence of superiority in terms of statistical significance at the 5% level ($p<0.05$). See Figure 4. In this case it is acceptable to calculate the p-value associated with a test of superiority and to evaluate whether this is sufficiently small to reject convincingly the hypothesis of no difference. There is no multiplicity argument that affects this interpretation because, in statistical terms, it corresponds to a simple closed test procedure. Usually this demonstration of a benefit is sufficient on its own, provided the safety profiles of the new agent and the comparator are similar. When there is an increase in adverse events, however, it is important to estimate the size of the effect to evaluate whether it is sufficient in clinical terms to outweigh the adverse effects.



Secuencialidad: Ensayos mixtos, objetivos mixtos



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

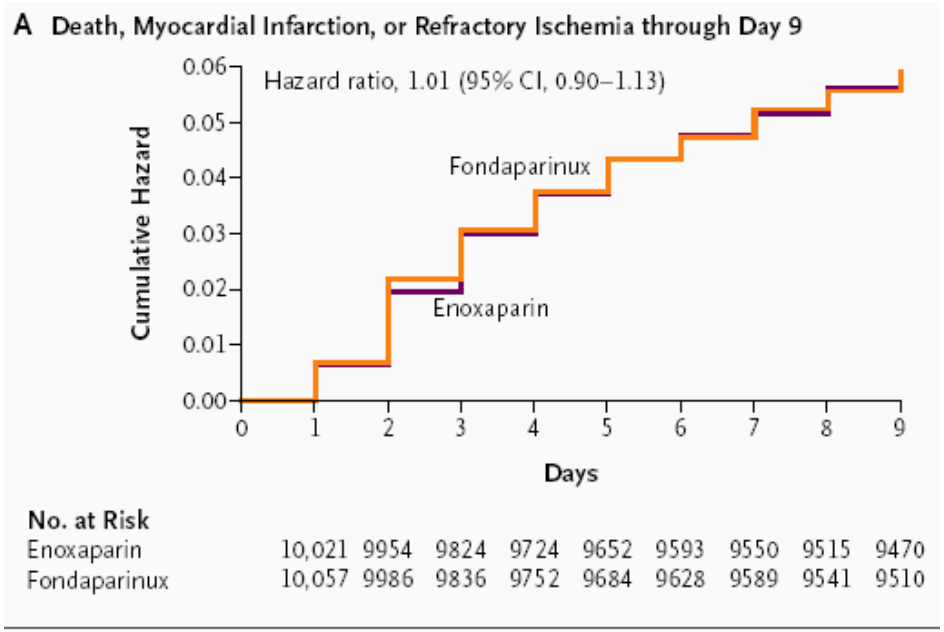
Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes

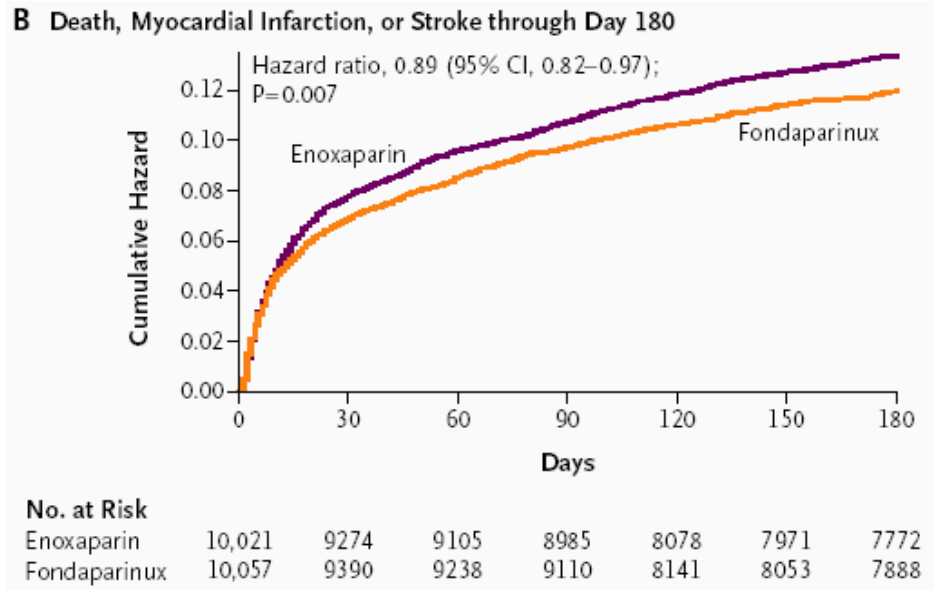
The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators*

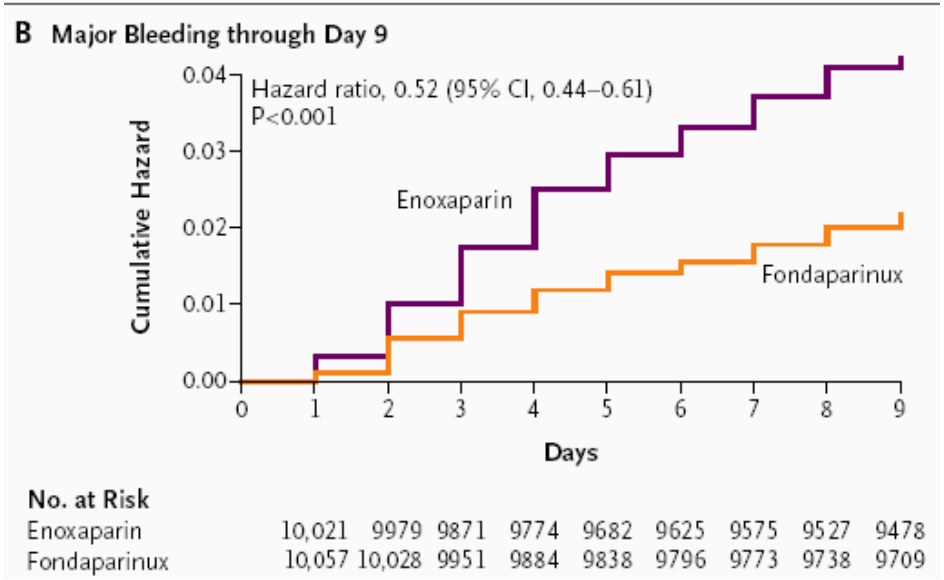
N Engl J Med 2006;354. 24 March.
Oasis 5: Fondaparinux vs Enoxaparina en Síndromes Coronarios Adudos.

Variable principal eficacia: muerte, infarto miocardio, isquemia refractaria
Variable principal seguridad: hemorragia mayor
Objetivo: demostrar la no-inferioridad de FON al 9º día con superioridad en seguridad

Margen No-inferioridad: 1.185 RR







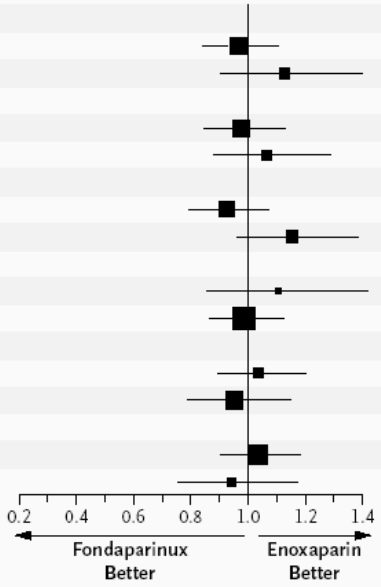
Eficacia:
5,8 frente 5,7

Hazard Ratio 1,01 (0.90-1.13)

Seguridad: 2,2% frente 4,1%
Hazard Ratio 0,52 (0,44 a 0,61)

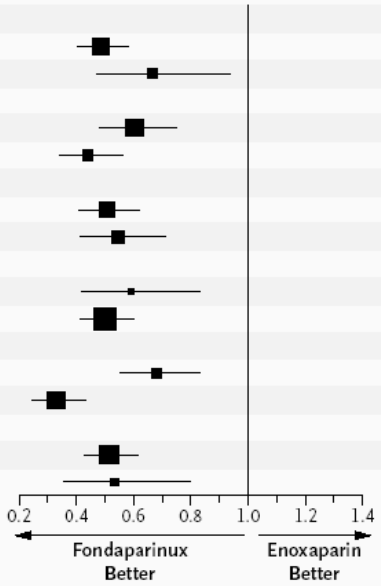
A Primary Efficacy at 9 Days

Characteristic	No. of Patients	Percentage of Patients with Event		Interaction P Value
		Enoxaparin	Fondaparinux	
Age				
≥65 yr	12,261	6.8	6.6	
<65 yr	7,814	4.0	4.4	0.25
Sex				
Male	12,379	6.0	5.8	
Female	7,699	5.3	5.7	0.48
Creatinine				
At or above median	11,124	6.4	5.9	
Less than median	8,871	4.9	5.6	0.07
Heparin at randomization				
Yes	3,566	6.5	7.1	
No	16,512	5.6	5.5	0.43
Revascularization in 9 days				
Yes	7,372	9.6	9.9	
No	12,706	3.5	3.3	0.47
Catheterization laboratory in center				
Yes	14,028	5.9	6.0	
No	6,050	5.4	5.1	0.48

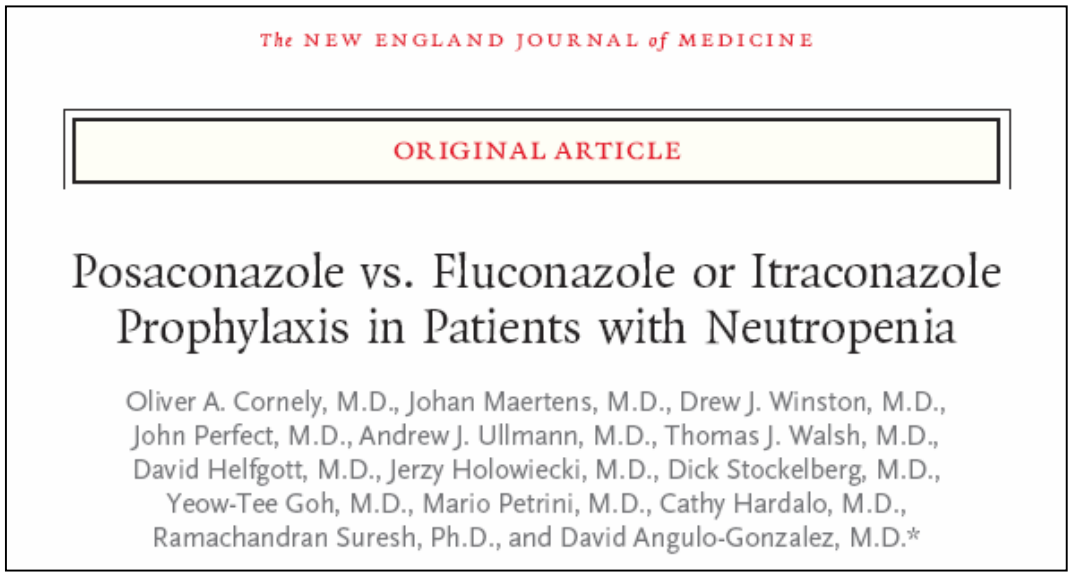


B Major Bleeding at 9 Days

Characteristic	No. of Patients	Percentage of Patients with Event		Interaction P Value
		Enoxaparin	Fondaparinux	
Age				
≥65 yr	12,261	5.5	2.7	
<65 yr	7,814	2.1	1.4	0.11
Sex				
Male	12,379	3.3	2.0	
Female	7,699	5.5	2.5	0.07
Creatinine				
At or above median	11,124	4.7	2.4	
Less than median	8,871	3.4	1.9	0.71
Heparin at randomization				
Yes	3,566	5.0	3.0	
No	16,512	4.0	2.0	0.35
Revascularization in 9 days				
Yes	7,372	6.0	4.2	
No	12,706	3.0	1.0	<0.001
Catheterization laboratory in center				
Yes	14,028	5.0	2.6	
No	6,050	2.3	1.2	0.88



Objetivos secuenciales



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia

Oliver A. Cornely, M.D., Johan Maertens, M.D., Drew J. Winston, M.D., John Perfect, M.D., Andrew J. Ullmann, M.D., Thomas J. Walsh, M.D., David Helfgott, M.D., Jerzy Holowiecki, M.D., Dick Stockelberg, M.D., Yeow-Tee Goh, M.D., Mario Petrini, M.D., Cathy Hardalo, M.D., Ramachandran Suresh, Ph.D., and David Angulo-Gonzalez, M.D.*

N Engl J Med 2007;356:348-59. 25 January.
Posaconazol vs Fluconazol o Itraconazol en profilaxis infección fúngica en paciente neutropénico.

Variable principal eficacia: incidencia infección fúngica invasora

<u>Objetivo secuencial (en dos fases)</u>:

1. Demostrar la No-inferioridad de Posaconazol (Δ=4%)

↓ si se demuestra

2. Demostrar la superioridad de Posaconazol


Ya, exactly.

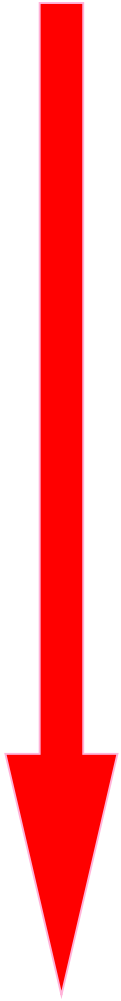
Consideración

Con el mismo criterio con el que se demuestra no inferioridad podemos demostrar equivalencia terapéutica

Aprendemos desde la diferencia

Niveles de equivalencia

Niveles de evidencia de equivalencia

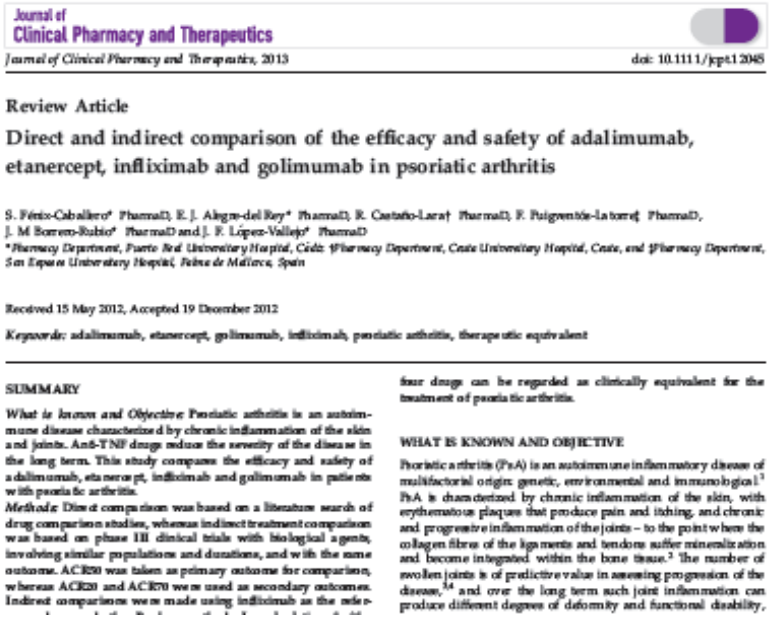


- ✓Ensayos comparativos directos de equivalencia o no inferioridad
- ✓Ensayos comparativos directos de superioridad, con resultados sin relevancia clínica
- ✓Ensayos comparativos directos de superioridad, con diferencias sin significación estadística
- ✓Ensayos de superioridad de los dos fármacos evaluados frente a un tercer comparador común
- ✓Juicio clínico, opinión de expertos, recomendaciones, guías clínicas

Implicaciones de la equivalencia

Implicación de la equivalencia

1. PIT
2. ATE
3. Económica
   - Estudios de minimización de costes
   - Concursos y Subastas públicas



Journal of Clinical Pharmacy and Therapeutics

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Review Article

Direct and indirect comparison of the efficacy and safety of adalimumab, etanercept, infliximab and golimumab in psoriatic arthritis

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Keywords: adalimumab, etanercept, golimumab, infliximab, psoriatic arthritis, therapeutic equivalent

SUMMARY

What is known and Objective: Psoriatic arthritis is an autoimmune disease characterized by chronic inflammation of the skin and joints. Anti-TNF drugs reduce the severity of the disease in the long term. This study compares the efficacy and safety of adalimumab, etanercept, infliximab and golimumab in patients with psoriatic arthritis.

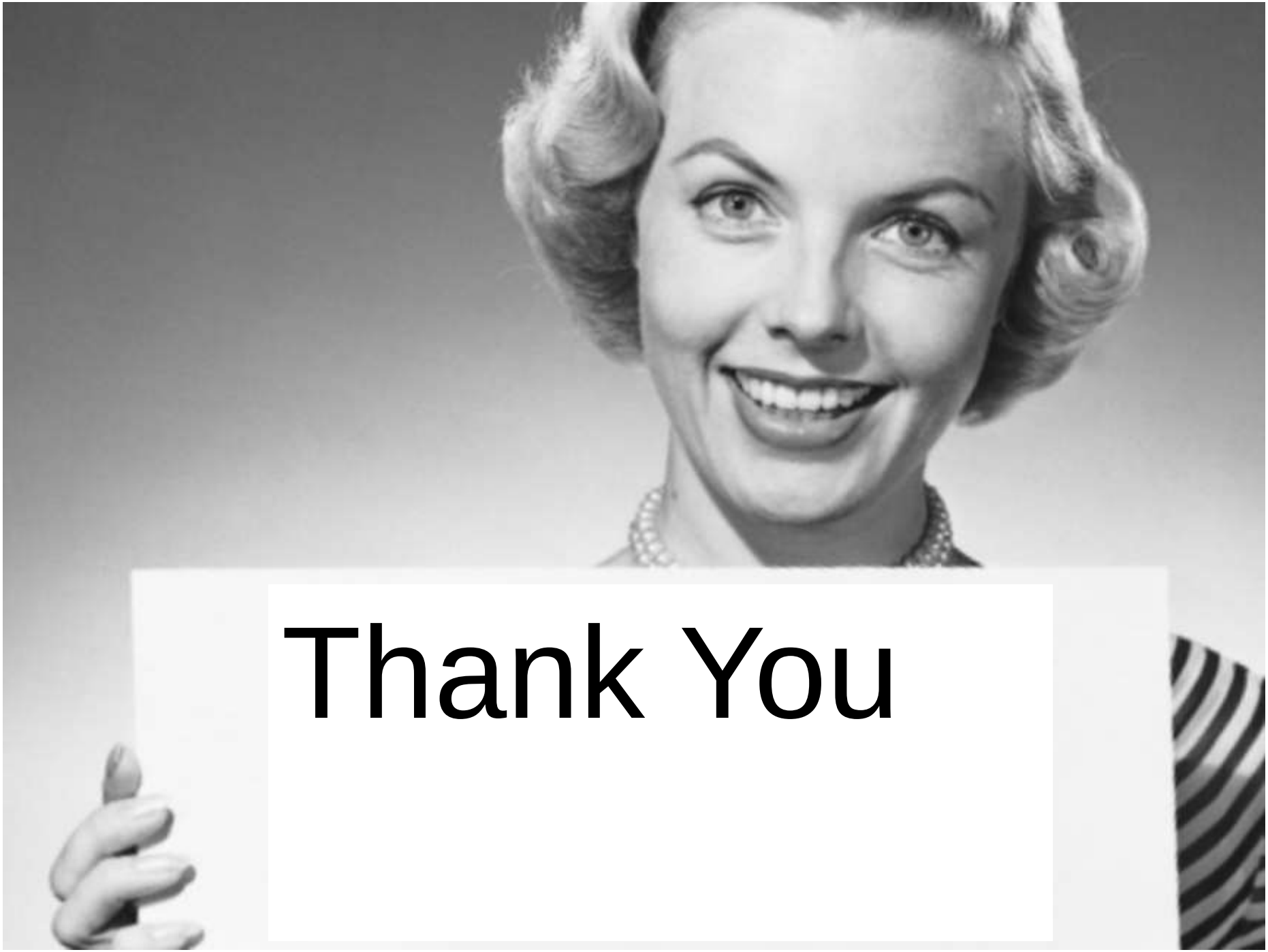
Methods: Direct comparison was based on a literature search of drug comparison studies, whereas indirect treatment comparison was based on phase III clinical trials with biological agents, involving similar populations and durations, and with the same outcome. ACR20 was taken as primary outcome for comparison, whereas ACR50 and ACR70 were used as secondary outcomes. Indirect comparisons were made using infliximab as the refe-

four drugs can be regarded as clinically equivalent for the treatment of psoriatic arthritis.

WHAT IS KNOWN AND OBJECTIVE

Psoriatic arthritis (PsA) is an autoimmune inflammatory disease of multifactorial origin: genetic, environmental and immunological.[1] PsA is characterized by chronic inflammation of the skin, with erythematous plaques that produce pain and itching, and chronic and progressive inflammation of the joints – to the point where the collagen fibres of the ligaments and tendons suffer mineralization and become integrated within the bone tissue.[2] The number of swollen joints is of predictive value in assessing progression of the disease,[3,4] and over the long term such joint inflammation can produce different degrees of deformity and functional disability,


La diferencia es relativa: orienta el valor δ
δ depende de consenso y debate clínico
Establecer equivalencia terapéutica tiene implicaciones prácticas muy importantes
THM


Thank You