



Análisis de estudios clínicos: integración y ejemplos

Dr. Chih Hao Chen Ku, FACE
Servicio de Endocrinología, Hospital San Juan de Dios
Departamento de Farmacología y Toxicología Clínica,
Universidad de Costa Rica

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Conflictos de interés

- He recibido honorarios por conferencias, advisory board y/o investigación clínica de:
 - Astra Zeneca
 - Abbott Nutrición
 - Novartis Pharma Logistics Inc
 - Novartis Oncology
 - Novo Nordisk
 - Merck Sharp & Dohme
 - Roche
 - Glaxo SmithKline
 - Sanofi Aventis
 - Boehringer
 - Organon

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Objetivos

- Ejemplos en estudios publicados relevantes
 - Diseño
 - Poder estudio
 - Interpretación de resultados

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Introducción

- Llega a la consulta por primera vez un paciente diabético de 40 años quien recién se le diagnosticó.
- Yo quiero investigar cuál es la mejor estrategia de tratamiento en un paciente que está haciendo el debut.
- Dónde busco la información?

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Búsqueda de información

- Medline (www.pubmed.com)
 - 340072 resultados de búsqueda (al 5 diciembre a las 7 AM)
- Google
- Google scholar (scholar.google.com)
- Wikipedia!

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Revistas (ranking al 2013)

Rank	Journal	Impact Factor
1	NEW ENGL J MED	51.658
2	LANCET	39.06
3	JAMA-J AM MED ASSOC	29.978
4	BRIT MED J	17.215
5	PLOS MED	15.253
6	ANN INTERN MED	13.976
7	BMC MED	6.679
8	CAN MED ASSOC J	6.465
9	J INTERN MED	6.455
10	MAYO CLIN PROC	5.79
11	COCHRANE DB SYST REV	5.703
12	ANN MED	5.094
13	AM J MED	4.768
14	ANN FAM MED	4.613
15	AMYLOID	4.436
16	BRIT MED BULL	4.363
17	MEDICINE	4.233
18	AM J PREV MED	3.945
19	DTSCH ARZTEBL INT	3.542
20	PREV MED	3.496

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Análisis de un artículo científico

- Qué tengo que fijarme en un artículo científico?
 - Autores y conflictos de interés
 - Tipo de estudio
 - Objetivo: este aspecto es fundamental
 - Criterios de selección
 - Resultados
 - Aplicabilidad al mundo real

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

NOVEMBER 20, 2008

VOL. 359 NO. 21

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

Paul M Ridker, M.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Robert J. Glynn, Sc.D., for the JUPITER Study Group*

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JUPITER
AHA November 9, 2008



A Randomized Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among 17,802 Apparently Healthy Men and Women With Elevated Levels of C-Reactive Protein (hsCRP): The JUPITER Trial

Paul Ridker*, Eleanor Danielson, Francisco Fonseca*, Jacques Genest*, Antonio Gotto*, John Kastelein*, Wolfgang Koenig*, Peter Libby*, Alberto Lorenzatti*, Jean MacFadyen, Børge Nordestgaard*, James Shepherd*, James Willerson, and Robert Glynn*
on behalf of the JUPITER Trial Study Group

An Investigator Initiated Trial Funded by AstraZeneca, USA

* These authors have received research grant support and/or consultation fees from one or more statin manufacturers, including Astra-Zeneca. Dr Ridker is a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease that have been licensed to Dade-Behring and AstraZeneca.

JUPITER
Primary Objectives

Ridker et al NEJM 2008

**Justification for the Use of statins in Prevention:
an Intervention Trial Evaluating Rosuvastatin**

To investigate whether rosuvastatin 20 mg compared to placebo would decrease the rate of first major cardiovascular events among apparently healthy men and women with LDL < 130 mg/dL (3.36 mmol/L) who are nonetheless at increased vascular risk on the basis of an enhanced inflammatory response, as determined by hsCRP \geq 2 mg/L.

To enroll large numbers of women and individuals of Black or Hispanic ethnicity, groups for whom little data on primary prevention with statin therapy exists.

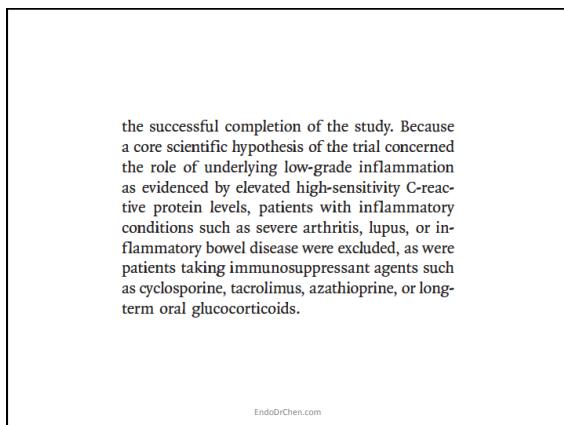
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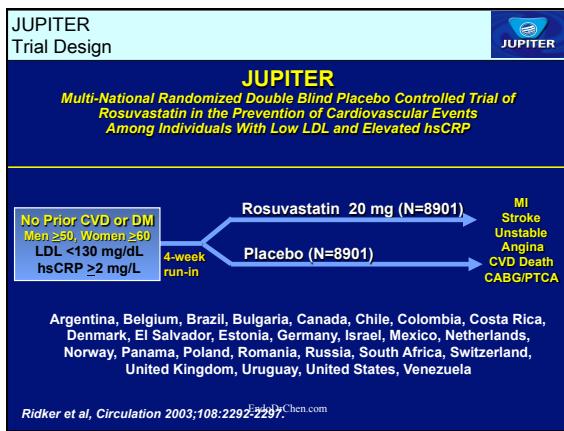
Ojo, usualmente nadie lo revisa...
algunos aspectos relevantes!

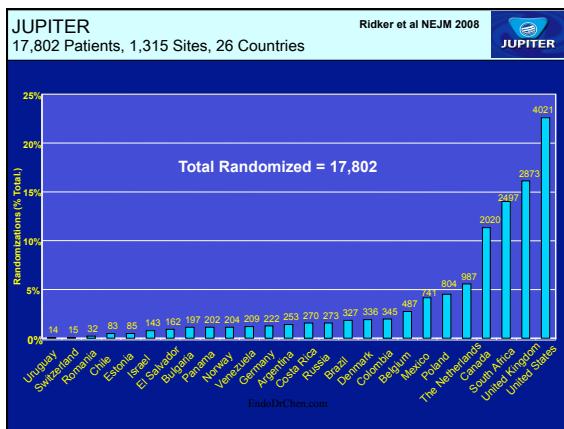
As described in detail elsewhere,^{17,18} men 50 years of age or older and women 60 years of age or older were eligible for the trial if they did not have a history of cardiovascular disease and if, at the initial screening visit, they had an LDL cholesterol level of less than 130 mg per deciliter (3.4 mmol per liter) and a high-sensitivity C-reactive protein level of 2.0 mg per liter or more. Other requirements for inclusion were a willingness to participate for the duration of the trial, provision of written informed consent, and a triglyceride level of less than 500 mg per deciliter (5.6 mmol per liter).

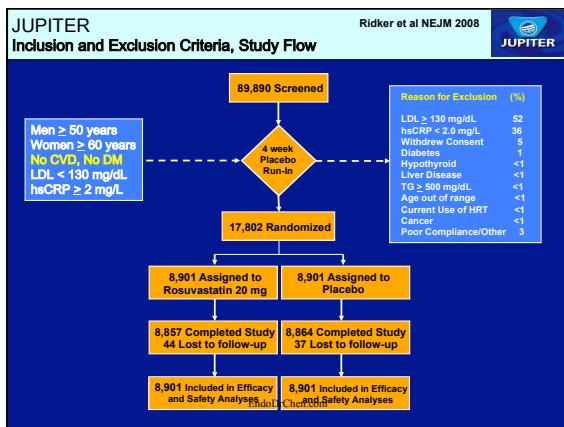
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Exclusion criteria were previous or current use of lipid-lowering therapy, current use of postmenopausal hormone-replacement therapy, evidence of hepatic dysfunction (an alanine aminotransferase level that was more than twice the upper limit of the normal range), a creatine kinase level that was more than three times the upper limit of the normal range, a creatinine level that was higher than 2.0 mg per deciliter (176.8 μ mol per liter), diabetes, uncontrolled hypertension (systolic blood pressure $>$ 190 mm Hg or diastolic blood pressure $>$ 100 mm Hg), cancer within 5 years before enrollment (with the exception of basal-cell or squamous-cell carcinoma of the skin), uncontrolled hypothyroidism (a thyroid-stimulating hormone level that was more than 1.5 times the upper limit of the normal range), and a recent history of alcohol or drug abuse or another medical condition that might compromise safety or the successful completion of the study. Because









JUPITER
Baseline Clinical Characteristics

Ridker et al NEJM 2008

	Rosuvastatin (N = 8901)	Placebo (n = 8901)
Age, years (IQR)	66.0 (60.0-71.0)	66.0 (60.0-71.0)
Female, N (%)	3,426 (38.5)	3,375 (37.9)
Ethnicity, N (%)		
Caucasian	6,358 (71.4)	6,325 (71.1)
Black	1,100 (12.4)	1,124 (12.6)
Hispanic	1,121 (12.6)	1,140 (12.8)
Blood pressure, mm (IQR)		
Systolic	134 (124-145)	134 (124-145)
Diastolic	80 (75-87)	80 (75-87)
Smoker, N (%)	1,400 (15.7)	1,420 (16.0)
Family History, N (%)	997 (11.2)	1,048 (11.8)
Metabolic Syndrome, N (%)	3,652 (41.0)	3,723 (41.8)
Aspirin Use, N (%)	1,481 (16.6)	1,477 (16.6)

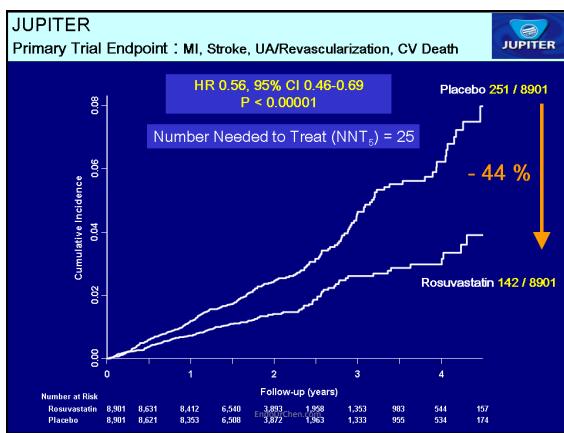
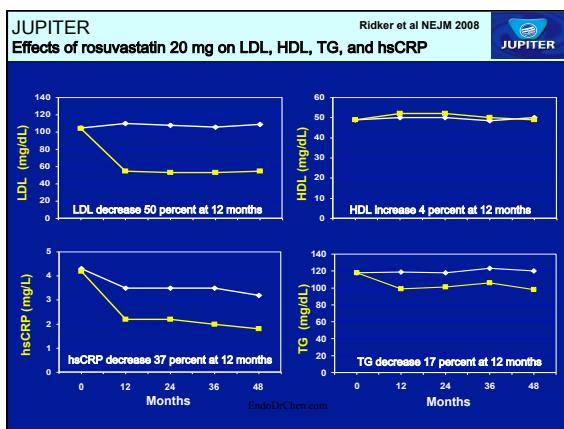
All values are median (interquartile range) or N (%)

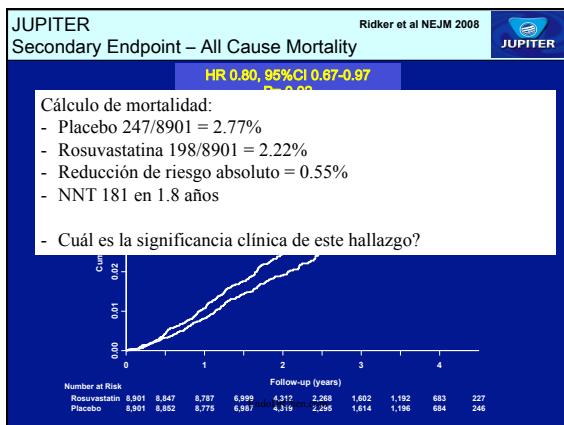
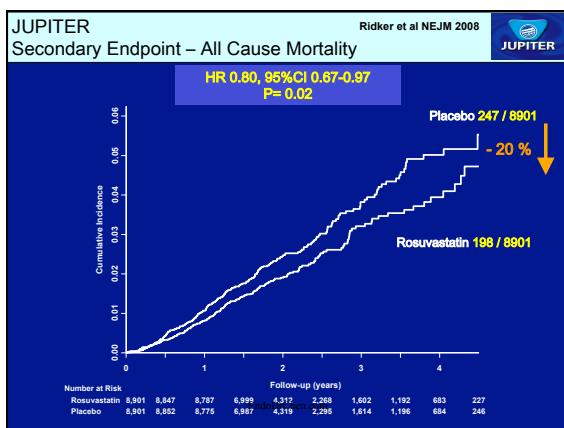
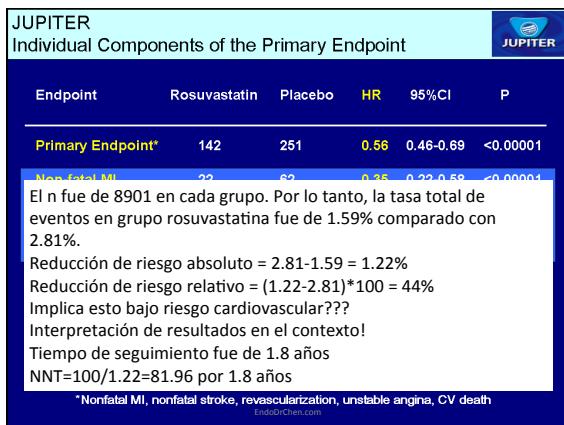
JUPITER
Baseline Blood Levels (median, interquartile range)

Ridker et al NEJM 2008

	Rosuvastatin (N = 8901)	Placebo (n = 8901)
hsCRP, mg/L	4.2 (2.8 - 7.1)	4.3 (2.8 - 7.2)
LDL, mg/dL	108 (94 - 119)	108 (94 - 119)
HDL, mg/dL	49 (40 - 60)	49 (40 - 60)
Triglycerides, mg/dL	118 (85 - 169)	118 (86 - 169)
Total Cholesterol, mg/dL	186 (168 - 200)	185 (169 - 199)
Glucose, mg/dL	94 (87 - 102)	94 (88 - 102)
HbA1c, %	5.7 (5.4 - 5.9)	5.7 (5.5 - 5.9)

All values are median (interquartile range). [Mean LDL = 104 mg/dL]





Estudios principales					
Ensayo	Fármaco	Población	Años de seguimiento	Reducción del punto final primario	Reducción de mortalidad total
AFCAPS/ TEXCAPS	Lovastatina 20-40 mg	Hombres 45-74 años Mujeres 55-73 años LDL 130-190 mg/dl	5.2 años	37% en IAM fatal o no fatal, AI, o muerte súbita cardíaca	No diferencia en mortalidad total
WOSCOPS	Pravastatina 40 mg	Hombres 45-64 años LDL >155 mg/dl	4.9 años	31% en IAM no fatal y muerte por EAC	22% p=0.051
ASCOT	Atorvastatina 10 mg	Hombres y mujeres 40-79 años, HTA, CT <250 mg/dl, más 3 factores adicionales	3.3 años	36% IAM no fatal y EAC fatal ¹	13% NS p=0.14

1. Downs JR. JAMA. 1998;279(20):1615-1622.
 2. Shepherd J. N Engl J Med. 1995;333(20):1301-7
 3. Sever PS. Lancet. 2003;361:1149-1158
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JUPITER
 ACC March 29, 2009



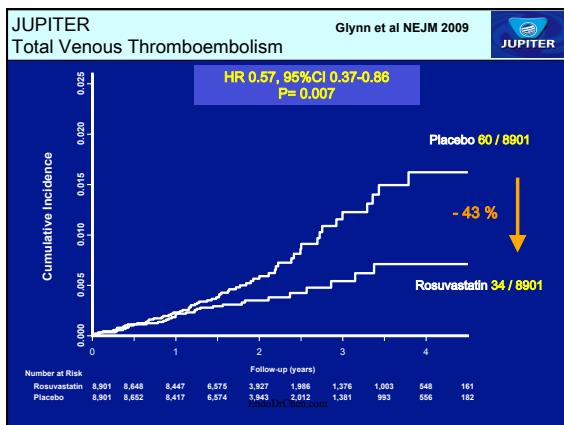
**A Randomized Trial of Rosuvastatin in the Prevention of Venous Thromboembolism:
 The JUPITER Trial**

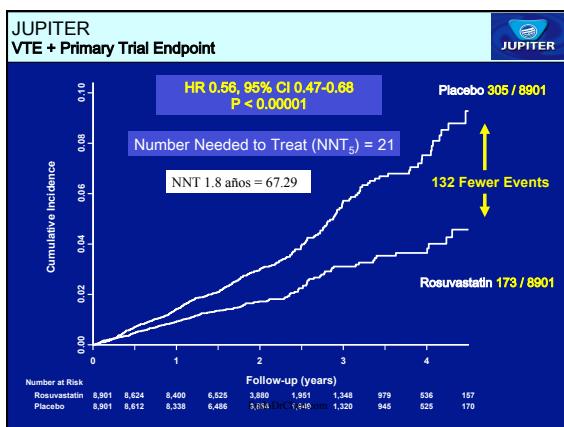
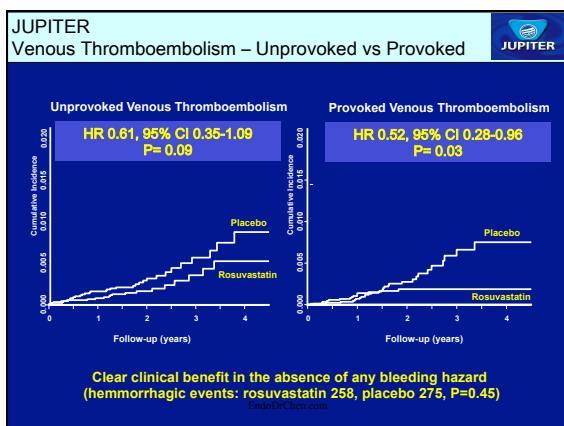
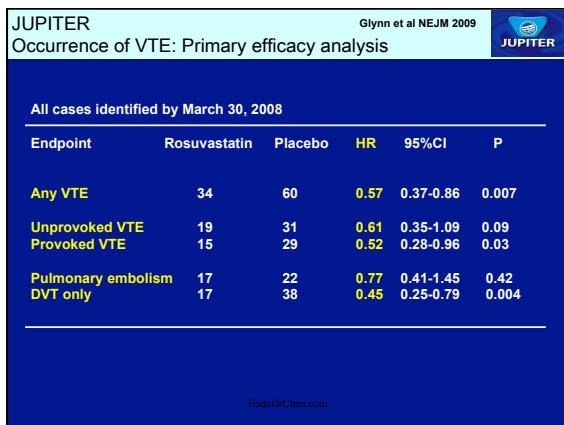
Robert Glynn*, Eleanor Danielson, Francisco Fonseca†, Jacques Genest*, Antonio Gotto*, John Kastelein*, Wolfgang Koenig*, Peter Libby*, Alberto Lorenzatti*, Jean MacFadyen, Børge Nordestgaard*, James Shepherd*, James Willerson, and Paul Ridker*
 on behalf of the JUPITER Trial Study Group

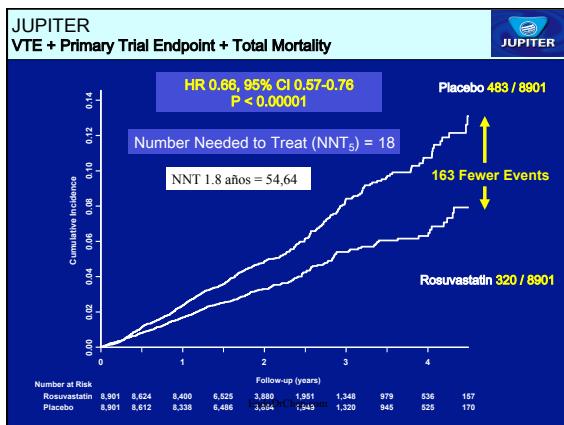
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JUPITER
VTE in JUPITER: Conclusions

VTE is a serious event that occurred about as often as MI and stroke in the JUPITER study

Rosuvastatin was associated with a significant 43 percent reduction in risk of VTE with no increase in bleeding.

This benefit was comparable in magnitude and independent of the effect on arterial events

Widening the treatment target to include prevention of VTE and death in addition to arterial thrombosis increases the estimated benefit of statin use

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JUPITER
VTE detailed results

Posted at NEJM.org

The NEW ENGLAND JOURNAL of MEDICINE

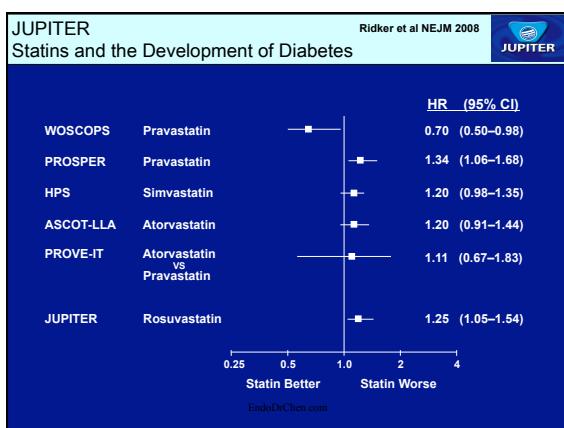
ORIGINAL ARTICLE

A Randomized Trial of Rosuvastatin in the Prevention of Venous Thromboembolism

Robert J. Glynn, Sc.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Goto, Jr., M.D., John P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Borge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Paul M. Ridker, M.D.
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JUPITER Adverse Events and Measured Safety Parameters			
Event	Rosuvastatin	Placebo	P
Any SAE	1,352 (15.2)	1,337 (15.5)	0.60
Muscle weakness	1,421 (16.0)	1,375 (15.4)	0.34
Myopathy	10 (0.1)	9 (0.1)	0.82
Rhabdomyolysis	1 (0.01)*	0 (0.0)	--
Incident Cancer	298 (3.4)	314 (3.5)	0.51
Cancer Deaths	35 (0.4)	58 (0.7)	0.02
Hemorrhagic stroke	6 (0.1)	9 (0.1)	0.44
GFR (ml/min/1.73m² at 12 mth)	66.8 (59.1-76.5)	66.6 (58.8-76.2)	0.02
ALT > 3xULN	23 (0.3)	17 (0.2)	0.34
Fasting glucose (24 mth)	98 (91-107)	98 (90-106)	0.12
HbA1c (%) at 24 mth	5.9 (5.7-6.1)	5.8 (5.6-6.1)	0.01
Glucosuria (12 mth)	36 (0.5)	32 (0.4)	0.64
Incident Diabetes**	270 (3.0)	216 (2.4)	0.01

*Occurred after trial completion, trauma induced.
**Physician reported



Por qué es importante revisar la “letra menuda”?

- Definición de casos nuevos de diabetes en JUPITER:
 - Reporte de diagnóstico por parte del paciente
 - Inicio de terapia antidiabética
- NO hay medición rutinaria de glicemia ni CTG
- Sí hay medición de Hba1c

LOS ANÁLISIS POST HOC PUEDEN SERVIR DE ALGO?

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JUPITER

- Factores de riesgo:
 - Síndrome metabólico
 - IMC > 30 kg/m²
 - Alteración de glicemia en ayunas
 - Hba1c > 6%
- Uso de rosuvastatina
 - Aceleró el desarrollo de DM por 5.4 semanas

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Ridker P. Lancet. 2012;380:565

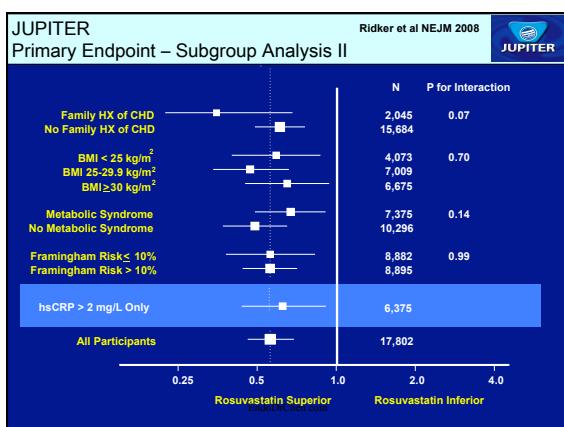
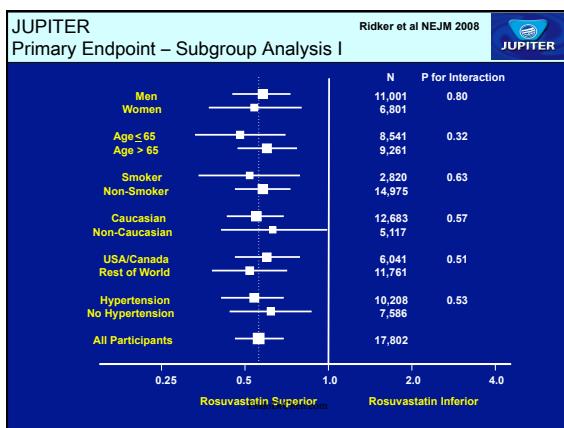
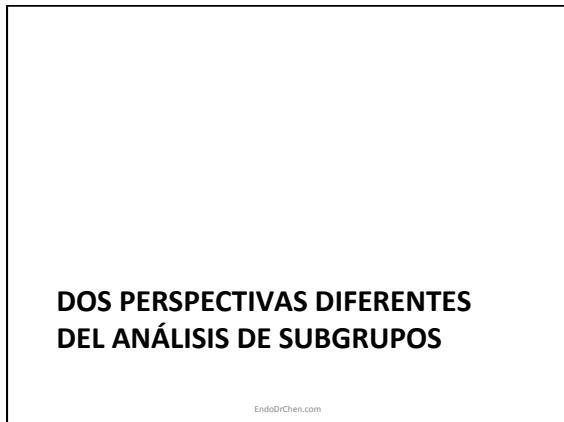
En pacientes que desarrollaron DM, el beneficio en reducción de eventos CV fue similar

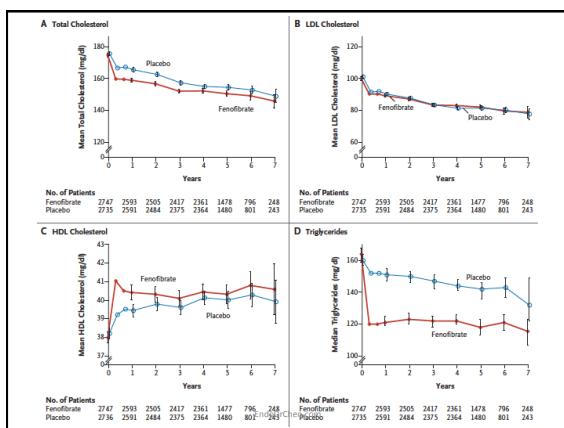
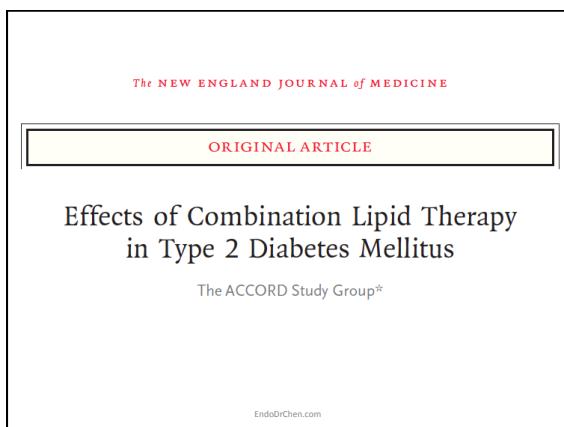
134 casos de eventos CV o muerte preventido por cada 54 casos nuevos de DM

No major diabetes risk factors (n=695)			One or more major diabetes risk factors (n=1158)							
Rosuvastatin	Placebo	Δ	Rosuvastatin	Placebo	Δ					
HR (95% CI)		p value	HR (95% CI)		p value					
Primary endpoint	44 (0.69)	91 (0.45)	-47	0.48 (0.33-0.68)	0.0001	96 (0.80)	157 (1.33)	-61	0.61 (0.47-0.79)	0.0001
Primary endpoint, any death	118 (1.65)	212 (1.26)	-94	0.50 (0.33-0.68)	0.0001	127 (1.46)	262 (1.46)	-135	0.58 (0.45-0.71)	0.0001
Primary endpoint, VTE, any death	122 (1.73)	187 (1.89)	-65	0.54 (0.33-0.81)	0.0001	186 (1.61)	282 (1.41)	-93	0.58 (0.57-0.81)	0.0001
MI, stroke, any death	99 (1.53)	147 (1.33)	-48	0.47 (0.3-0.86)	0.0002	130 (1.15)	202 (1.67)	-73	0.49 (0.5-0.96)	0.0006
Any death	88 (1.32)	113 (1.69)	-24	0.78 (0.58-1.03)	0.008	109 (0.82)	132 (1.02)	-23	0.82 (0.64-1.07)	0.15
Diabetes	12 (0.18)	12 (0.18)	0	0.99 (0.45-2.23)	0.99	258 (2.12)	204 (1.65)	54	1.28 (0.07-1.54)	0.01

Previsión de 86 casos de eventos CV o muerte con 0 casos nuevos de DM

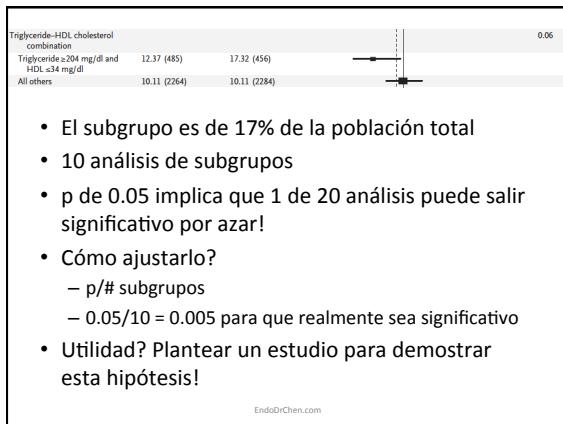
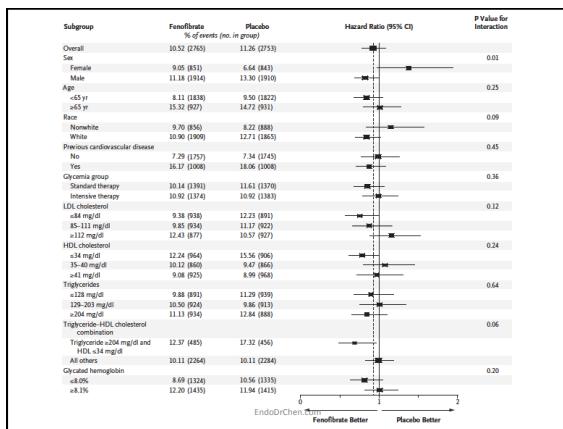
Ridker P. Lancet. 2012;380:565





Outcome	Fenofibrate (N = 2765)	Placebo (N = 2753)	Hazard Ratio (95% CI)	P Value
no. of events				
Primary outcome (major fatal or nonfatal cardiovascular event)	291	224	310	2.41
rate/yr				
Secondary outcomes				
Primary outcome plus revascularization or hospitalization for congestive heart failure	641	535	667	5.64
Major coronary disease event†	332	2.58	353	2.79
Nonfatal myocardial infarction	173	1.32	186	1.44
Stroke				
Any	51	0.38	48	0.36
Nonfatal	47	0.35	40	0.30
Death				
From any cause	203	1.47	221	1.61
From cardiovascular cause	99	0.72	114	0.83
Fatal or nonfatal congestive heart failure	120	0.90	143	1.09
0.92 (0.83-1.08)			0.32*	
0.30				
0.26				
0.39				
0.80				
0.48				
0.33*				
0.26				
0.10				

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EL RETO DE LOS ESTUDIOS DE OBESIDAD

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ORIGINAL ARTICLE

Multicenter, Placebo-Controlled Trial of Lorcaserin for Weight Management

Steven R. Smith, M.D., Neil J. Weissman, M.D., Christen M. Anderson, M.D., Ph.D., Matilde Sanchez, Ph.D., Emil Chuang, M.D., Scott Stubbe, M.B.A., Harold Bays, M.D., William R. Shanahan, M.D., and the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group

ABSTRACT

EndoDrChen.com Smith SR. N Engl J Med. 2010;363:245

The present report describes the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trial, a 2-year, randomized, placebo-controlled, double-blind clinical trial designed to evaluate the efficacy and safety, including safety regarding cardiac valves, of lorcaserin used for weight management.

EndoDrChen.com Smith SR. N Engl J Med. 2010;363:245

PATIENTS

Eligibility criteria included an age of 18 to 65 years and a BMI (the weight in kilograms divided by the square of the height in meters) of 30 to 45 or of 27 to 45 with at least 1 coexisting condition (hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, or sleep apnea). Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix (available at NEJM.org). Key exclusion criteria included moderate or more severe mitral regurgitation or mild or more severe aortic regurgitation (i.e., valvulopathy, as defined by the Food and Drug Administration [FDA]), diabetes mellitus, a systolic blood pressure exceeding 140 mm Hg or a diastolic blood pressure exceeding 90 mm Hg, depression or other major psychiatric disease within 2 years before randomization that necessitated treatment with prescription medication, and pregnancy or lactation.

EndoDrChen.com Smith SR. N Engl J Med. 2010;363:245

The echocardiographic safety end point — the proportion of patients in whom FDA-defined valvulopathy had developed by week 52 — was the primary determinant of sample size. A noninferiority analysis was used to establish that the rate of FDA-defined valvulopathy among patients treated with lorcaserin was no worse than the rate among patients in the placebo group. On the basis of the results of a 3-month phase 2 study of lorcaserin,¹⁴ we estimated that the proportion of patients in the placebo group in whom FDA-defined valvulopathy would develop was approximately 5% per year. On the basis of a noninferiority margin of -0.025 (equivalent to a relative risk of valvulopathy with lorcaserin of 1.5), a rate in the placebo group of 5%, and a one-sided test at the 5% level of significance, we calculated that the total sample size required to provide 80% power was 1879 patients (approximately 940 patients in each of the two study groups). The analysis was performed on data from a modified intention-to-treat population — all patients with a screening echocardiogram and at least one post-baseline echocardiogram — with last-observation-carried-forward imputation. Assuming a dropout rate as high as 40%, 3182 patients were randomly assigned to a study group. Smith SR. N Engl J Med. 2010;363:245

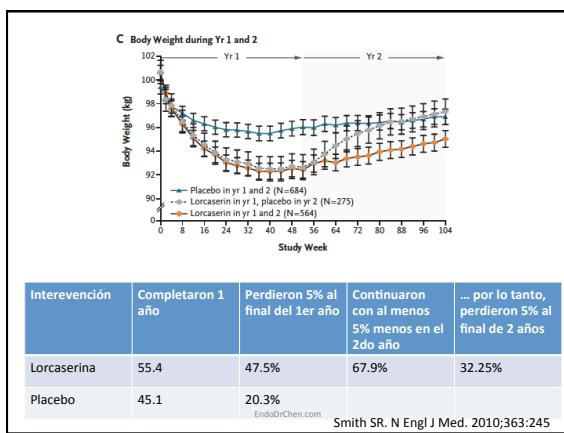
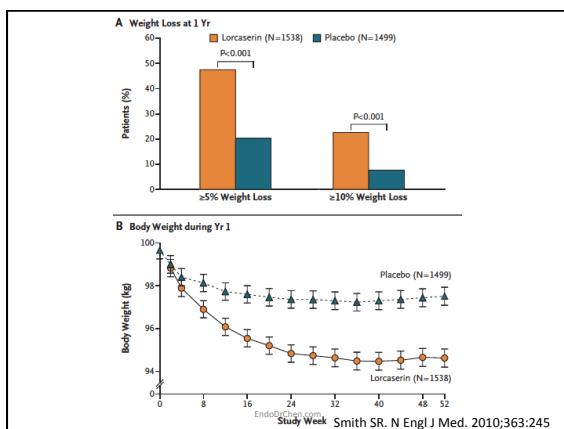
At week 52, a total of 2472 patients had undergone echocardiography at both the screening visit and at least one subsequent visit, and the observed rate of FDA-defined valvulopathy in the placebo group was 2.3%. Hence, our data provide a statistical power of 60% to rule out a relative risk of 1.5 of valvulopathy having developed with lorcaserin use at week 52, by means of last-observation-carried-forward analysis.

EndoDrChen.com
Smith SR. N Engl J Med. 2010;363:245

PATIENTS AND STUDY COMPLETION

In the trial, 3182 patients were randomly assigned to receive one of the two study drugs; the two groups had similar baseline characteristics (Table 1). The rates of completion of year 1 of the study were 55.4% in the lorcaserin group and 45.1% in the placebo group, and 7.1% and 6.7% of patients, respectively, discontinued the study because of adverse events (see the figure in the Supplementary Appendix). More patients in the lorcaserin group than in the placebo group withdrew from the study owing to headache (2.0% vs. 0.8%) and dizziness (0.8% vs. 0.1%). The overall rate of completion of year 2 of the study was 72.6% of patients who completed year 1, with a slightly higher rate of discontinuation among patients who received placebo in both years (27.3%) than among patients who received lorcaserin in both years (25.7%). The rates and reasons for discon-

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Smith SR. N Engl J Med. 2010;363:245



At year 1, FDA-defined valvulopathy had developed in 2.3% of patients in the placebo group and 2.7% of patients in the lorcaserin group ($P=0.70$) (relative risk with lorcaserin, 1.1; 95% confidence interval, 0.69 to 1.85). At year 2, the rate of valvulopathy was 2.7% in the placebo group and 2.6% among patients who received lorcaserin during year 1 and year 2 (Fig. 2A).

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lopathy.^{11,28} Lorcaserin caused no significant increase, relative to placebo, in the incidence of FDA-defined valvulopathy,⁵ a finding that supports the hypothesis that valvulopathy is not associated with activation of the 5-HT_{2c} receptor. When the

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LIMITANTES DE METANÁLISIS

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... LOS METANÁLISIS VUELVEN A
COMETER LOS ERRORES DE LOS
ESTUDIOS UNA SEGUNDA VEZ!

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USO DE INHIBIDORES DE DPP-4 EN TERCERA LÍNEA DE TRATAMIENTO?

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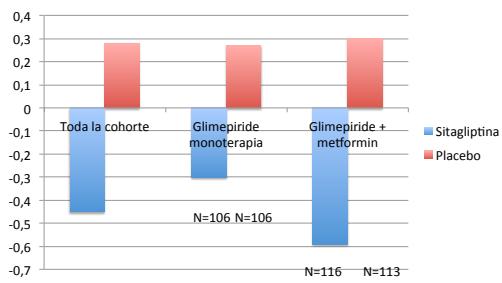
Metanálisis: eficacia luego de metformin más SU

Hemoglobin A _{1c} change from baseline (%)			
Treatment (compared with placebo + Met + SU)	Studies	Direct estimate, WMD (95% CI)	MTC estimate MD (95% CrI)
Basal insulin + Met + SU	2 ¹⁴⁸	-1.22 (-2.33 to -0.10)	-1.17 (-1.57 to -0.81)
Biphasic insulin + Met + SU	NA	NA	-1.10 (-1.59 to -0.67)
TZD + Met + SU	2 ^{13,31}	-1.16 (-1.36 to -0.96)	-0.96 (-1.35 to -0.59)
DPP-4 + Met + SU	1 ³¹	-0.89 (-1.11 to -0.66)	-0.89 (-1.51 to -0.26)
AG inhibitor + Met + SU	3 ^{32,34,35}	-0.43 (-0.72 to -0.14)	-0.46 (-0.96 to 0.03)
GLP-1 + Met + SU	2 ^{36,48}	-0.96 (-1.14 to -0.89)	-1.06 (-1.45 to -0.69)
IAsp + Met + SU	NA	NA	-1.01 (-1.71 to -0.35)
Meglitinide + Met + SU	NA	NA	-0.18 (-2.08 to 1.71)
No. of RCTs included in MTC meta-analysis	21 RCTs ^{13,27,28,30,32-35,38,40-44,48,56,51,53-55,57}		

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McIntosh B. Open Medicine. 2012;6(2):e62

Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin



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Hermannsen K. Diab Obes Metab. 2007;9:733

**POR LO TANTO, EL METANÁLISIS ES
TAN BUENO COMO LOS ESTUDIOS
ESCOGIDOS**

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Conclusiones

- Se debe leer con cuidado los artículos científicos
- La publicación en una revista reconocida no garantiza la calidad de la publicación
- Precaución con llegar a falsas conclusiones sobre todo aquellos basados en análisis de subgrupos

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Preguntas...
chenku2409@gmail.Com
EndoDrChen.Com

EndoDrChen.com
