



## Análisis de estudios clínicos: integración y ejemplos

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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](http://www.pubmed.com))
  - 347741 resultados de búsqueda (al 3 abril a las 11 PM)
- Google
- Google scholar ([scholar.google.com](http://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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## EL CASO DE LOS INHIBIDORES DE DPP-4: LA PROMESA DE LAS INCRETINAS?

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| Characteristic                                    | Sitagliptin 100 mg<br>0.4 + metformin<br>(N = 588) |  | Glipizide + metformin<br>(N = 584) |                                      |
|---|--|--|------------------------------------|--------------------------------------|
|   |  |  |                                    |                                      |
| Age (years)                                       | 56.8 (9.3)   |  | 56.6 (9.8)                         |                                      |
| Sex, n (%)  |  |  |                                    |                                      |
| Male  | 336 (57.1)   |  | 358 (61.3)                         |                                      |
| Female  | 252 (42.9)   |  | 226 (38.7)                         |                                      |
| Race, n (%)                                       |  |  |                                    |                                      |
| Caucasian   | 432 (73.5)   |  | 434 (74.3)                         |                                      |
| Black   | 41 (7.0)   |  | 35 (6.0)                           |                                      |
| Hispanic  | 43 (7.3)   |  | 46 (7.9)                           |                                      |
| Asian   | 50 (8.6)   |  | 49 (8.4)                           |                                      |
| Other   | 22 (3.7)   |  | 20 (3.4)                           |                                      |
| Body weight (kg)                                  | 89.5 (17.4)  |  | 89.7 (17.5)                        |                                      |
| Body mass index (kg/m <sup>2</sup> )              | 31.2 (6.0)   |  | 31.3 (5.2)                         |                                      |
| Duration of diabetes mellitus (years)             | 6.5 (6.1)  |  | 6.2 (5.4)                          |                                      |
| Use of OHA at screening, n (%)                    |  |  |                                    |                                      |
| Dual therapy                                      | 177 (30.1)   |  | 159 (27.2)                         |                                      |
| Monotherapy                                       | 386 (65.6)   |  | 397 (68.0)                         |                                      |
| Absence   | 25 (4.3)   |  | 28 (4.8)                           |                                      |
| HbA <sub>1c</sub> , % (range)                     | 7.7 (0.9) (6.1–11.0)                               |  | 7.6 (0.9) (5.8–10.5)               |                                      |
| HbA <sub>1c</sub> distribution at baseline, n (%) |  |  |                                    |                                      |
| HbA <sub>1c</sub> < 8%                            | 375 (64.0)   |  | 381 (65.5)                         |                                      |
| HbA <sub>1c</sub> ≥ 8 to <9%                      | 151 (25.8)   |  | 141 (24.2)                         |                                      |
| HbA <sub>1c</sub> ≥ 9%                            | 60 (10.2)  |  | 60 (10.3)                          |                                      |
| FPG (mmol/l)                                      | 9.2 (2.3)  |  | 9.1 (2.3)                          |                                      |
|   |  |  |                                    | Nauk MA. Diab Obes Metab. 2007;9:194 |

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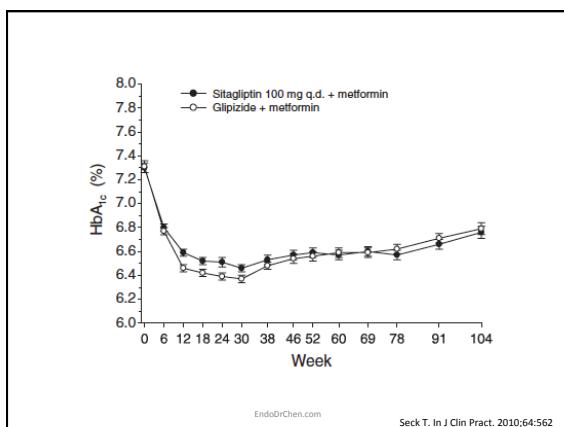
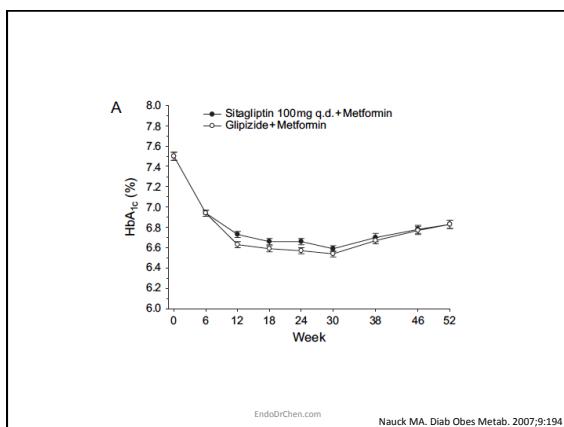
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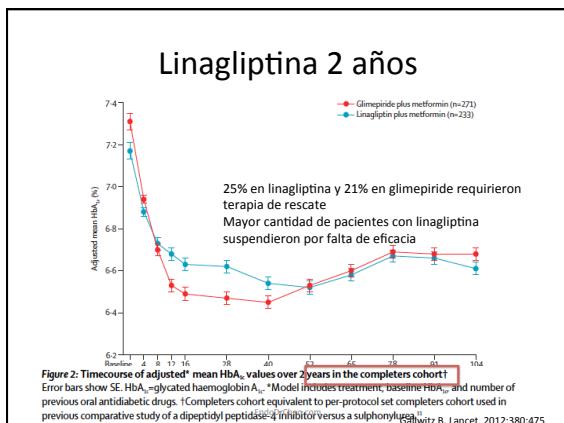
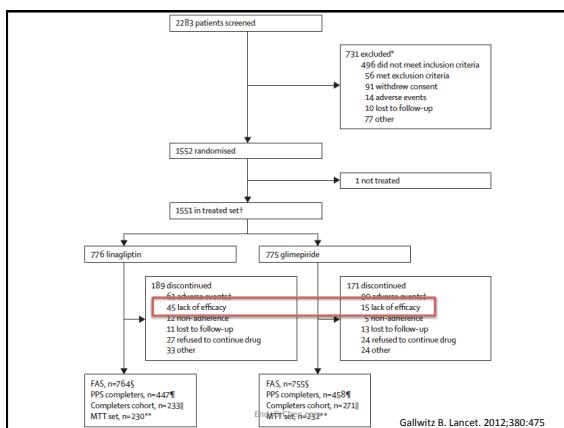
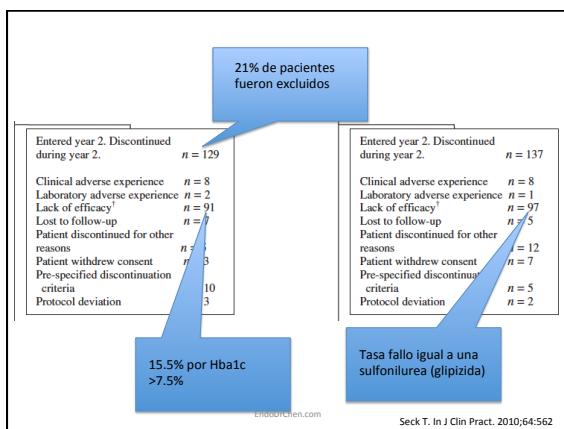


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|   | Linagliptin   | Glimepiride   | Difference (linagliptin-glimepiride) |            |         |
|---|---------------|---------------|--------------------------------------|------------|---------|
|   |               |               | Adjusted* mean (SE %)                | CI         | p value |
| <b>HbA<sub>1c</sub> in full analysis set (LOCF)</b> |               |               |                                      |            |         |
| n   | 764           | 755           | ..                                   | ..         | ..      |
| Mean at baseline (SE, %)                            | 7.69% (0.03)  | 7.69% (0.03)  | ..                                   | ..         | ..      |
| Change from baseline                                |               |               |                                      |            |         |
| Mean (SE, %)  | -0.21% (0.03) | -0.41% (0.03) | ..                                   | ..         | ..      |
| Adjusted* mean (SE, %)                              | -0.16% (0.03) | -0.36% (0.03) | 0.20% (0.05)                         | 0.09-0.30† | 0.0004‡ |
| <b>HbA<sub>1c</sub> in PPS completers (OC)</b>      |               |               |                                      |            |         |
| n   | 477           | 458           | ..                                   | ..         | ..      |
| Mean at baseline (SE, %)                            | 7.43% (0.04)  | 7.53% (0.04)  | ..                                   | ..         | ..      |
| Change from baseline                                |               |               |                                      |            |         |
| Mean (SE, %)  | -0.37% (0.04) | -0.61% (0.04) | ..                                   | ..         | ..      |
| Adjusted* mean (SE, %)                              | -0.35% (0.04) | -0.53% (0.04) | 0.17% (0.05)                         | 0.07-0.28† | 0.0001‡ |
| <b>HbA<sub>1c</sub> in the completers cohort</b>    |               |               |                                      |            |         |
| n   | 233           | 271           | ..                                   | ..         | ..      |
| Mean at baseline (SE, %)                            | 7.17% (0.04)  | 7.31% (0.04)  | ..                                   | ..         | ..      |
| Change from baseline                                |               |               |                                      |            |         |
| Adjusted* mean (SE, %)                              | -0.56% (0.03) | -0.63% (0.03) | 0.08% (0.04)                         | 0.00-0.15§ | 0.0468¶ |

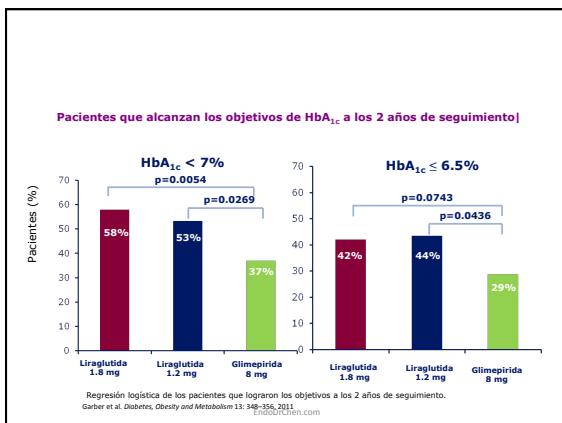
HbA<sub>1c</sub>=glycated haemoglobin A<sub>1c</sub>. LOCF=last observation carried forward. PPS=per-protocol set. OC=observed cases.  
\*Model includes treatment, baseline HbA<sub>1c</sub>, and number of previous oral antidiabetic drugs. †97.5% CI. ‡p<0.0125, one-sided. §95% CI. ¶p<0.05, two-sided.

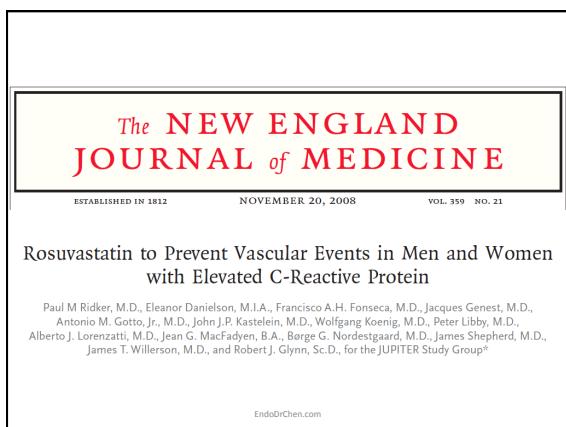
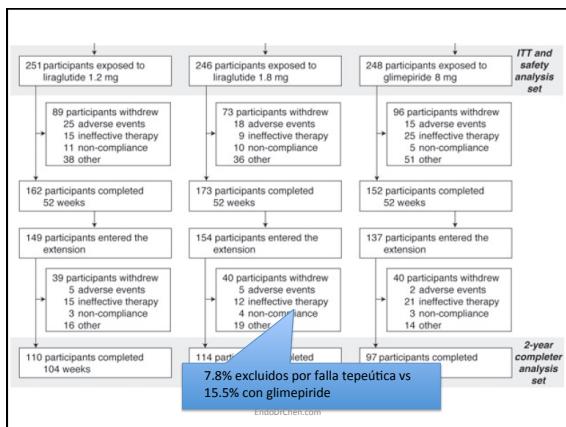
EndoDrChen.com Gallwitz B. Lancet. 2012;380:475

## Sostenibilidad control

- Preservación de células beta demostrado en modelos animales con análogos de GLP-1
- Los niveles de GLP-1 alcanzados con inhibidores de DPP-4 probablemente no sean suficientes para alterar la historia natural de la enfermedad
- No tenemos evidencia que comparado con SU tengamos mejor sostenibilidad del control a largo plazo

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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 Goto\*, 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  
Ridker et al NEJM 2008  
Primary Objectives

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,<sup>17,18</sup> 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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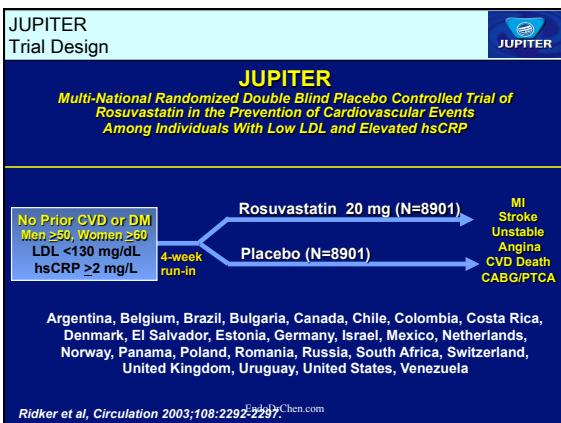
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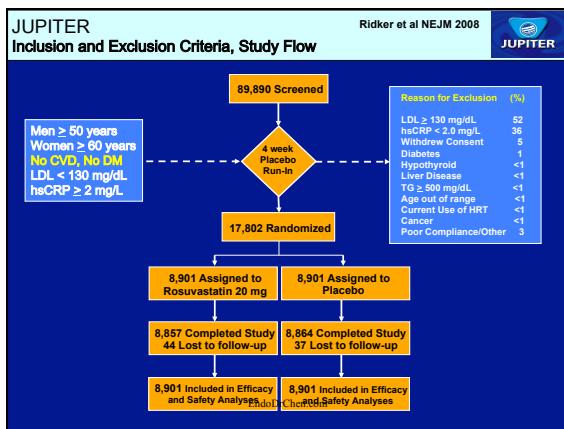
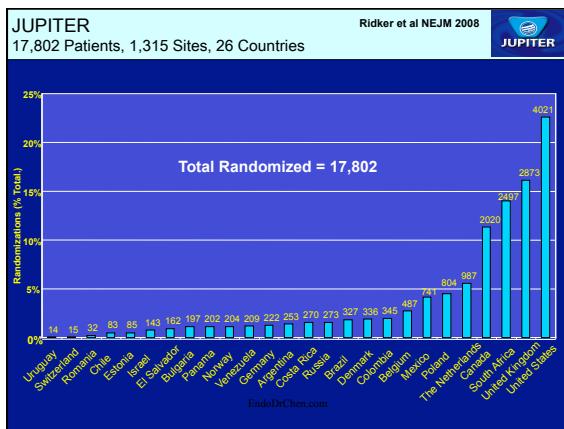
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Exclusion criteria were previous or current use of lipid-lowering therapy, current use of post-menopausal hormone-replacement therapy, evidence of hepatic dysfunction (an alanine aminotransferase level that was more than twice the upper limit of the normal range), a creatinine 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  $\mu$ 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

the successful completion of the study. Because a core scientific hypothesis of the trial concerned the role of underlying low-grade inflammation as evidenced by elevated high-sensitivity C-reactive protein levels, patients with inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease were excluded, as were patients taking immunosuppressive agents such as cyclosporine, tacrolimus, azathioprine, or long-term oral glucocorticoids.





**JUPITER**  
Baseline Clinical Characteristics  
Ridker et al NEJM 2008

|                           | Rosuvastatin<br>(N = 8901) | Placebo<br>(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)          |

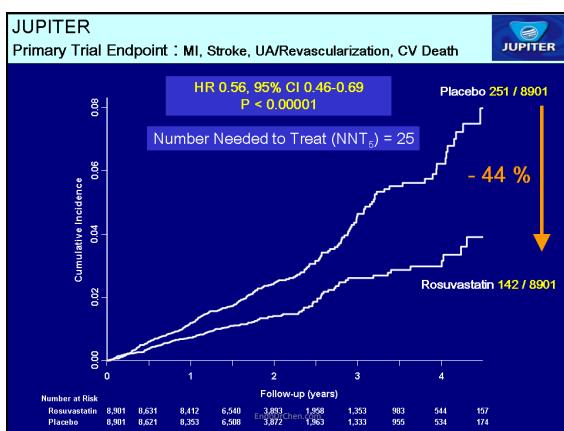
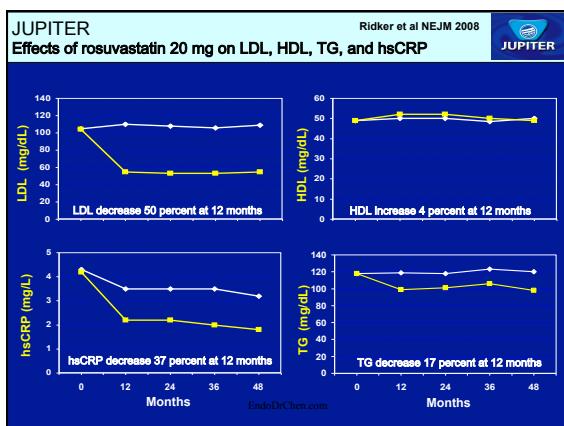
All values are median (interquartile range) or N (%)

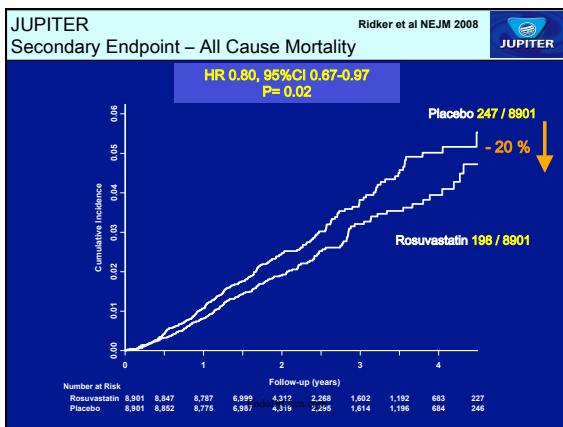
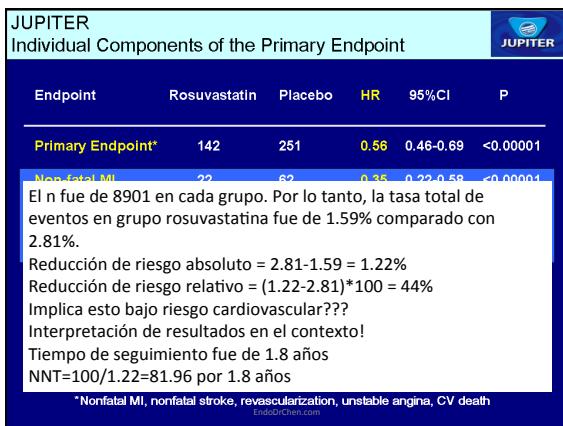
**JUPITER** Ridker et al NEJM 2008  
Baseline Blood Levels (median, interquartile range)

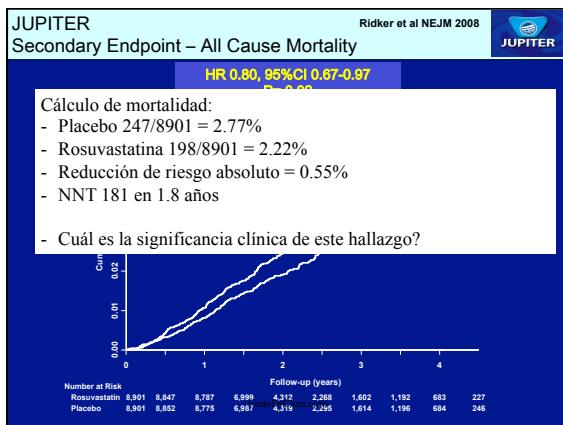


|                          | Rosuvastatin<br>(N = 8901) | Placebo<br>(n = 8901) |
|--------------------------|----------------------------|-----------------------|
| hsCRP, mg/L              | 4.2 (2.8 - 7.1)            | 4.3 (2.8 - 7.2)       |
| LDL, mg/dL               | 108 (94 - 119)             | 108 (94 - 119)        |
| HDL, mg/dL               | 49 (40 - 60)               | 49 (40 - 60)          |
| Triglycerides, mg/L      | 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 ]



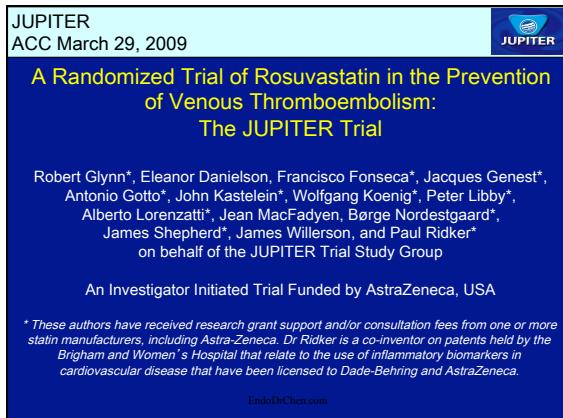


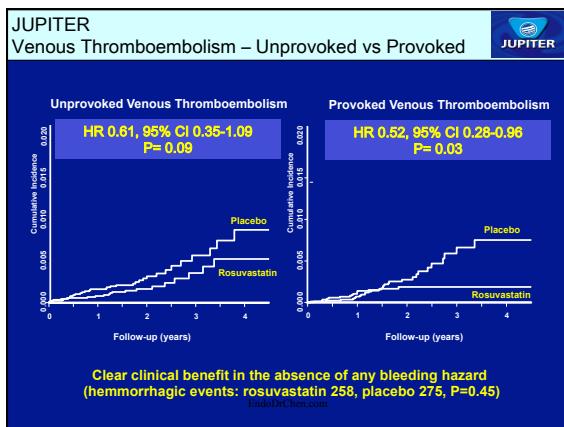
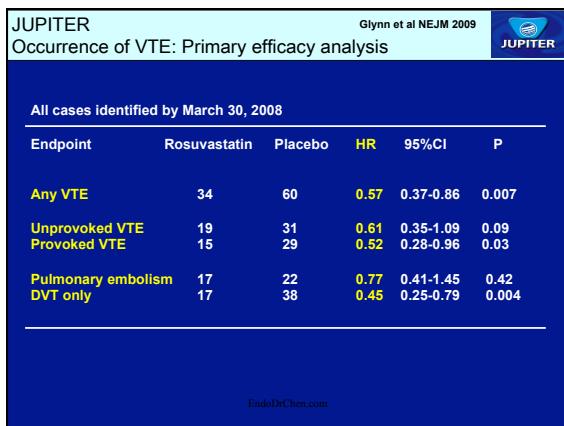
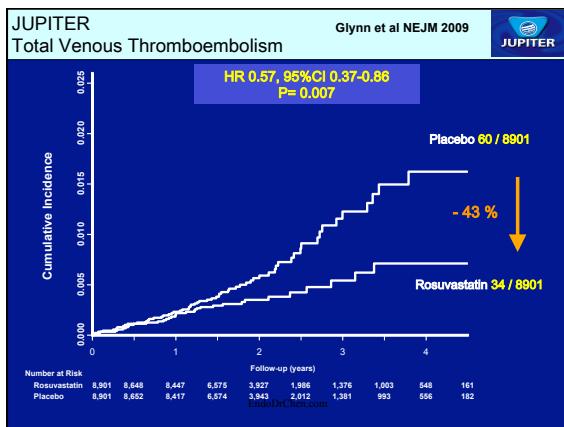


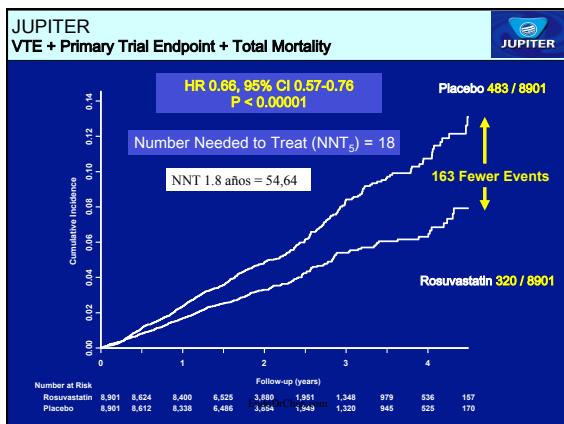
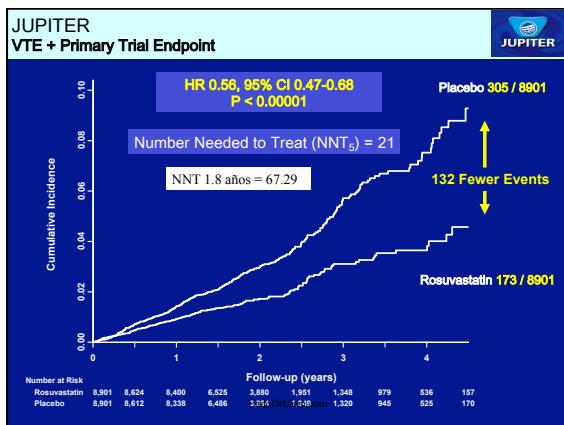
### Estudios principales

| Ensayo             | Fármaco              | Población  | Años de seguimiento | Reducción del punto final primario                        | Reducción de mortalidad total     |
|--------------------|----------------------|--|---------------------|---|-----------------------------------|
| AFCAPS/<br>TEXCAPS | Lovastatina 20-40 mg | Hombres 45-74 años<br>Mujeres 55-73 años<br>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<br>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 >350 mg/dl, más 3 factores adicionales | 3.3 años            | 36% IAM no fatal y EAC fatal                              | 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**  
VTE in JUPITER: Conclusions

**JUPITER**

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

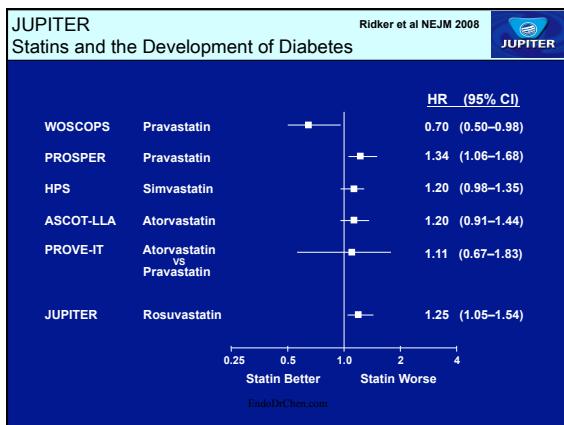
A Randomized Trial of Rosuvastatin in the Prevention of Venous Thromboembolism

Robert J. Glynn, Sc.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. 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 Paul M. Ridker, M.D.  
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JUPITER  
Ridker et al NEJM 2008  
Adverse Events and Measured Safety Parameters

| Event   | Rosuvastatin     | Placebo          | P    |
|---|------------------|------------------|------|
| <b>Any SAE</b>                                  | 1,352 (15.2)     | 1,337 (15.5)     | 0.60 |
| <b>Muscle weakness</b>                          | 1,421 (16.0)     | 1,375 (15.4)     | 0.34 |
| <b>Myopathy</b>                                 | 10 (0.1)         | 9 (0.1)          | 0.82 |
| <b>Rhabdomyolysis</b>                           | 1 (0.01)*        | 0 (0.0)          | --   |
| <b>Incident Cancer</b>                          | 298 (3.4)        | 314 (3.5)        | 0.51 |
| <b>Cancer Deaths</b>                            | 35 (0.4)         | 58 (0.7)         | 0.02 |
| <b>Hemorrhagic stroke</b>                       | 6 (0.1)          | 9 (0.1)          | 0.44 |
| <b>GFR (ml/min/1.73m<sup>2</sup> at 12 mth)</b> | 66.8 (59.1-76.5) | 66.6 (58.8-76.2) | 0.02 |
| <b>ALT &gt; 3xULN</b>                           | 23 (0.3)         | 17 (0.2)         | 0.34 |
| <b>Fasting glucose (24 mth)</b>                 | 98 (91-107)      | 98 (90-106)      | 0.12 |
| <b>HbA1c (%) at 24 mth)</b>                     | 5.9 (5.7-6.1)    | 5.8 (5.6-6.1)    | 0.01 |
| <b>Glucosuria (12 mth)</b>                      | 36 (0.5)         | 32 (0.4)         | 0.64 |
| <b>Incident Diabetes**</b>                      | 270 (3.0)        | 216 (2.4)        | 0.01 |

\*Occurred after trial completion, trauma induced. All values are median (interquartile range) or N (%)  
\*\*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

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**LOS ANÁLISIS POST HOC PUEDEN SERVIR DE ALGO?**

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**JUPITER**

- Factores de riesgo:
  - Síndrome metabólico
  - IMC > 30 kg/m<sup>2</sup>
  - 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

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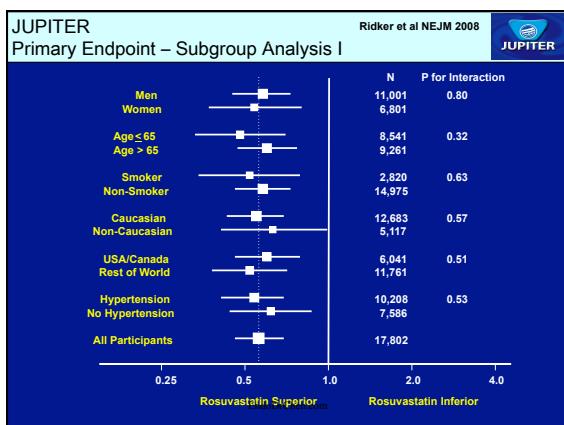
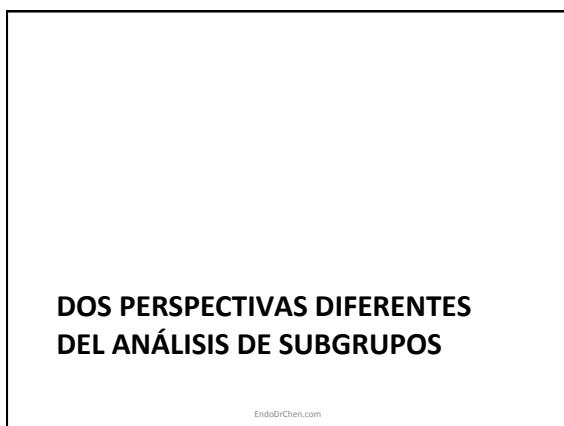
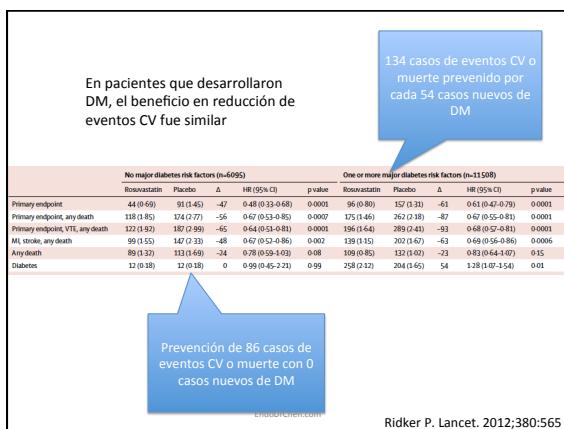
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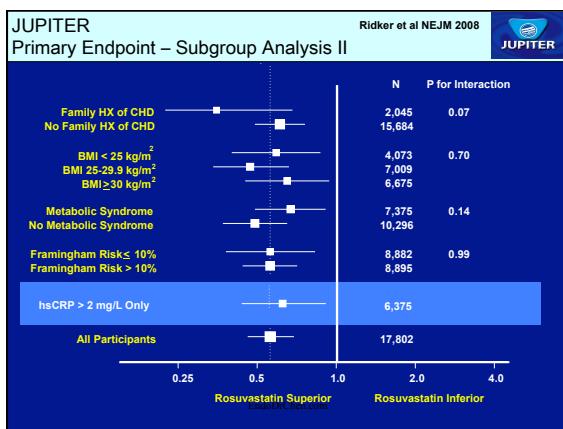


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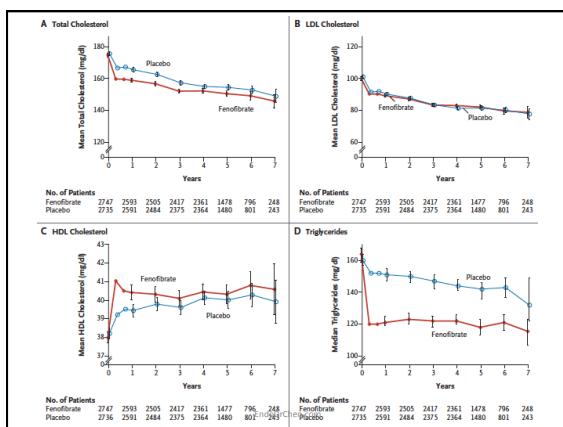
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

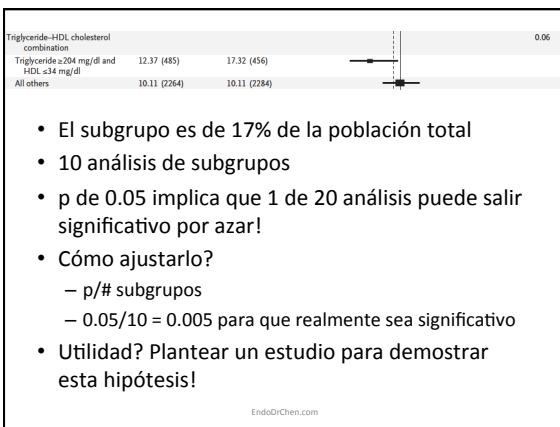
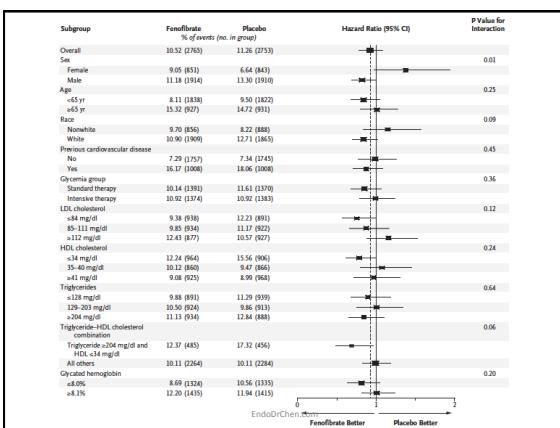
The ACCORD Study Group\*

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| Outcome  | Fenofibrate<br>(N=2765) | Placbo<br>(N=2753) | Hazard Ratio<br>(95% CI) | P Value |                        |
|--|-------------------------|--------------------|--------------------------|---------|------------------------|
|  | no. of events           | rate/yr            | no. of events            | rate/yr |                        |
| Primary outcome (major fatal or nonfatal cardiovascular event)                         | 291                     | 2.24               | 310                      | 2.41    | 0.92 (0.79-1.05) 0.32* |
| Secondary outcomes   |                         |                    |                          |         |                        |
| Primary outcome plus revascularization or hospitalization for congestive heart failure | 641                     | 5.35               | 667                      | 5.64    | 0.94 (0.85-1.05) 0.30  |
| Major coronary disease event†  | 332                     | 2.58               | 353                      | 2.79    | 0.92 (0.79-1.07) 0.26  |
| Nonfatal myocardial infarction   | 173                     | 1.32               | 186                      | 1.44    | 0.91 (0.74-1.12) 0.39  |
| Stroke   |                         |                    |                          |         |                        |
| Any  | 51                      | 0.38               | 48                       | 0.36    | 1.05 (0.71-1.56) 0.80  |
| Nonfatal   | 47                      | 0.35               | 40                       | 0.30    | 1.17 (0.76-1.78) 0.48  |
| Death  |                         |                    |                          |         |                        |
| From any cause   | 203                     | 1.47               | 221                      | 1.61    | 0.91 (0.75-1.10) 0.33* |
| From cardiovascular cause  | 99                      | 0.72               | 114                      | 0.83    | 0.86 (0.66-1.12) 0.26  |
| Fatal or nonfatal congestive heart failure   | 120                     | 0.90               | 143                      | 1.09    | 0.82 (0.65-1.05) 0.10  |

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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

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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

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**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.

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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 lorcasérin 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 lorcasérin,<sup>14</sup> 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 lorcasérin 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

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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 lorcasérin use at week 52, by means of last-observation-carried-forward analysis.

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

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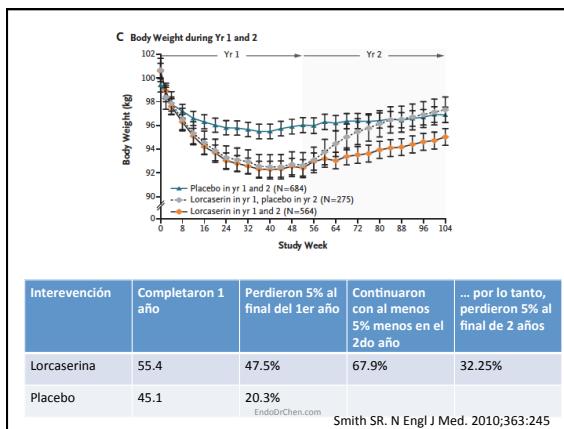
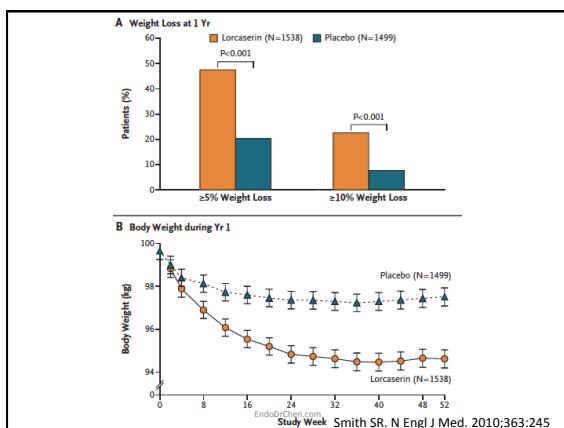
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**PATIENTS AND STUDY COMPLETION**

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 discontinuation are shown in the Supplementary Appendix.

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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.<sup>11,28</sup> Lorcaserin caused no significant increase, relative to placebo, in the incidence of FDA-defined valvulopathy,<sup>5</sup> a finding that supports the hypothesis that valvulopathy is not associated with activation of the 5-HT<sub>2c</sub> 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?**

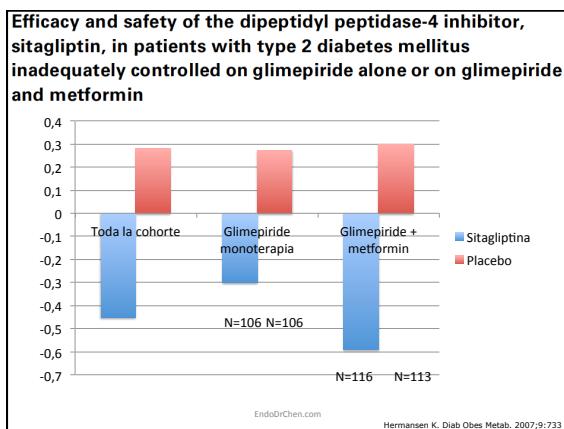
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**Metanálisis: eficacia luego de  
metformin más SU**

| <b>Hemoglobin A<sub>1c</sub> change from baseline (%)</b> |   |                               |                           |
|---|---|-------------------------------|---------------------------|
| Treatment (compared with placebo + Met + SU)              | Studies   | Direct estimate, WMD (95% CI) | MTC estimate MD (95% CrI) |
| Basal insulin + Met + SU                                  | 2 <sup>34,48</sup>  | -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 <sup>34,35</sup>  | -1.16 (-1.36 to -0.96)        | -0.96 (-1.35 to -0.59)    |
| DPP-4 + Met + SU  | 1 <sup>31</sup>   | -0.89 (-1.11 to -0.66)        | -0.89 (-1.51 to -0.26)    |
| AG inhibitor + Met + SU                                   | 3 <sup>32,34,36</sup>   | -0.43 (-0.72 to -0.14)        | -0.46 (-0.96 to 0.03)     |
| GLP-1 + Met + SU  | 2 <sup>34,48</sup>  | -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                               | 21 RCTs <sup>33,37,38,30,32-35,38,40-44,48,50,51,53-55,57</sup> |                               |                           |
| meta-analysis   |   |                               |                           |

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



**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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