



## Perlas en el manejo de dislipidemias

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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

- Implicaciones y manejo de hipertrigliceridemia/dislipidemia mixta
- Cuánto tiempo se deben usar las estatinas?
- Cómo minimizar el riesgo de efectos adversos?
- Modificación de estilos de vida basado en la evidencia
- Cuándo tamizar en niños?

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## HIPERTRIGLICERIDEMIA/ DISLIPIDEMIA MIXTA

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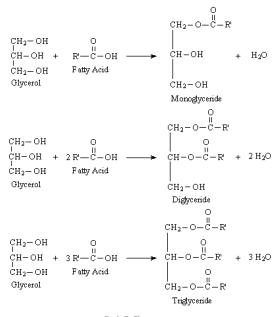


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### Ensamblaje en triglicéridos



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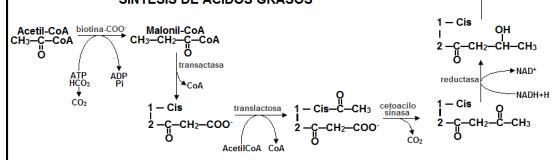


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### SÍNTESIS DE ÁCIDOS GRASOS



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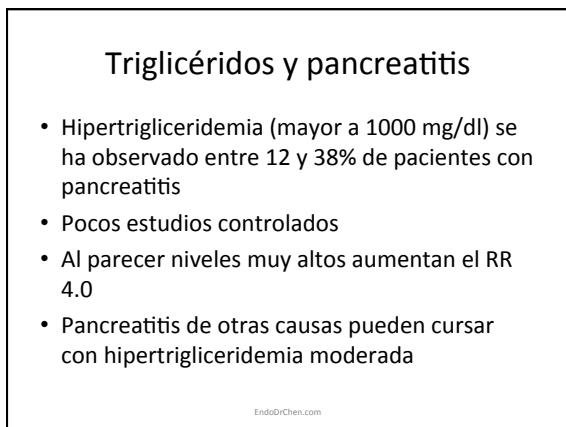
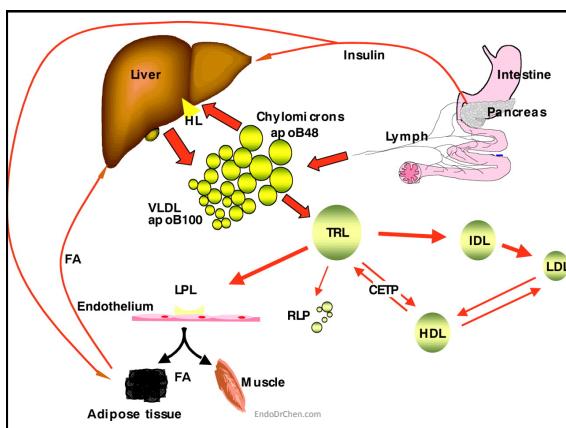
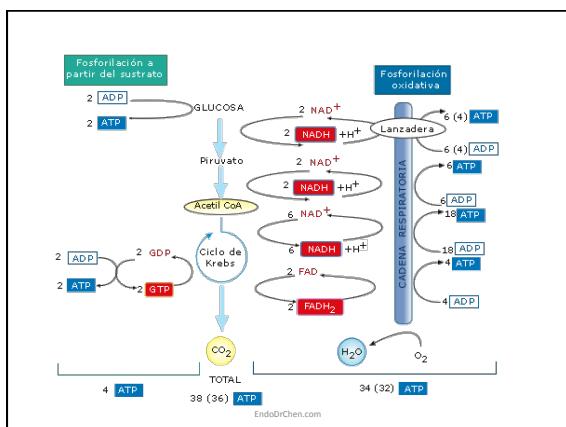
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## Mecanismos

- Mediado por quilomicrones
- Alteración del flujo capilar que lleva a isquemia en lecho pancreático
- Liberación de lipasa aumenta ácidos grasos libres que son proinflamatorios

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Gan SI. World J Gastroenterol. 2006;12(44):7197

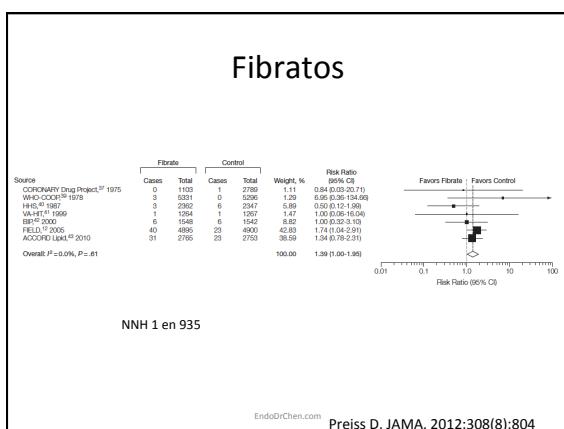
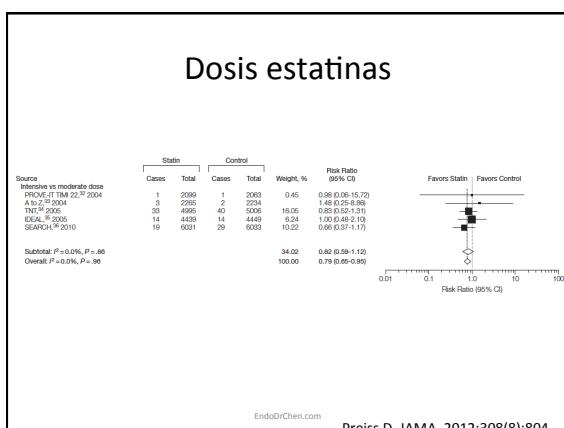
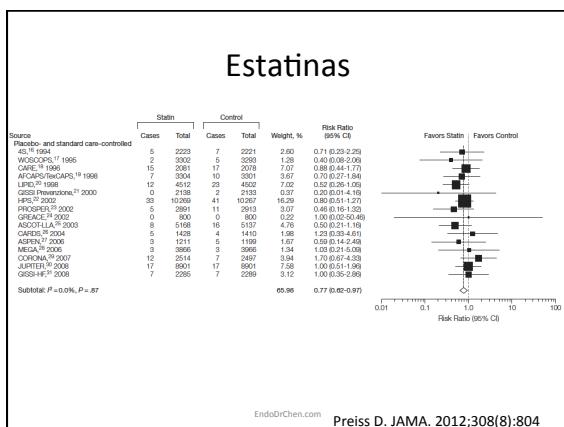
## Nueva clasificación

	NCEP ATP III (3)		The Endocrine Society 2010*	
Normal	<150 mg/dl	<1.7 mmol/liter	Normal	<150 mg/dl
Borderline-high triglycerides	150–199 mg/dl	1.7–2.3 mmol/liter	Mild hypertriglyceridemia	<1.7 mmol/liter
High triglycerides	200–499 mg/dl	2.3–5.6 mmol/liter	Moderate hypertriglyceridemia	150–199 mg/dl
Very high triglycerides	≥500 mg/dl	≥5.6 mmol/liter	Severe hypertriglyceridemia	200–999 mg/dl
				2.3–11.2 mmol/liter
				1000–1999 mg/dl
				11.2–22.4 mmol/liter
			Very severe hypertriglyceridemia	≥2000 mg/dl
				≥22.4 mmol/liter

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Berglund L. J Clin Endocrinol Metab. 2012;97:2969

## INTERVENCIÓN FARMACOLÓGICA

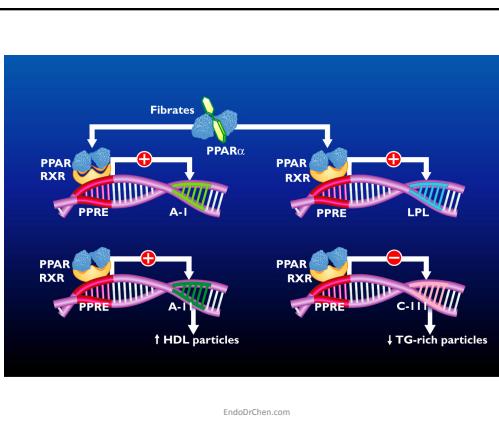
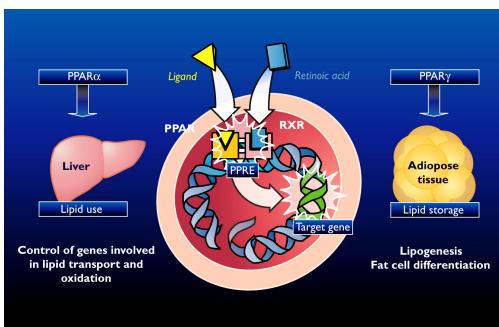
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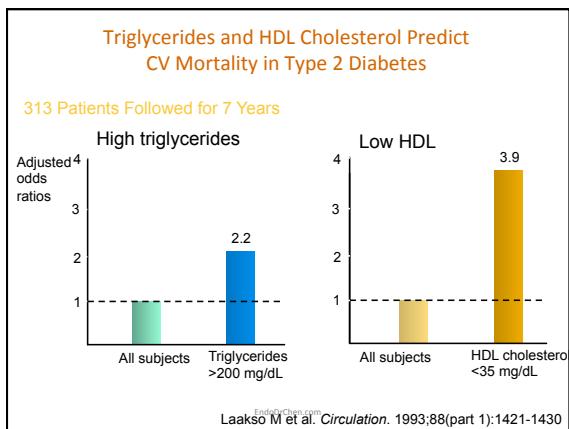
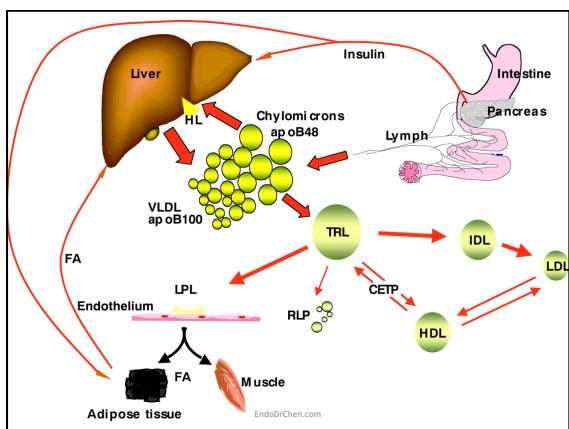


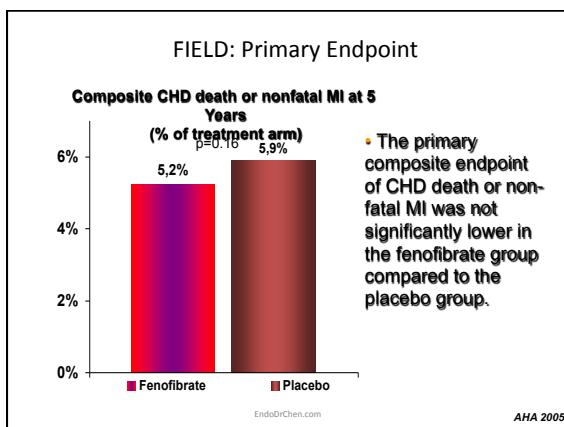
## Fibratos y pancreatitis

- Clofibrato aumentaba el riesgo de colelitiasis
- Los fibratos nuevos tienen menor riesgo
- Aumentan la concentración de colesterol en la bilis
- No hay ensayos clínicos para triglicéridos mayores a 500 mg/dl

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Preiss D. JAMA. 2012;308(8):804





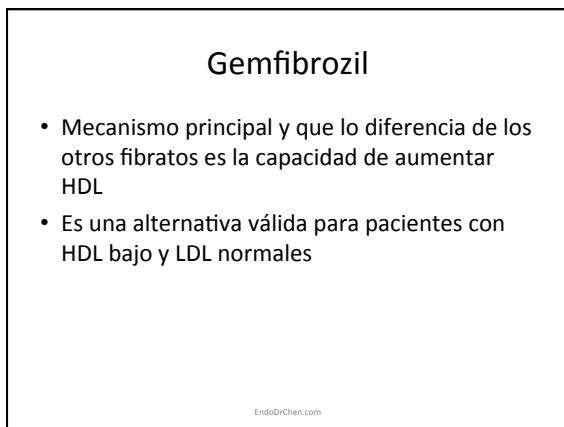
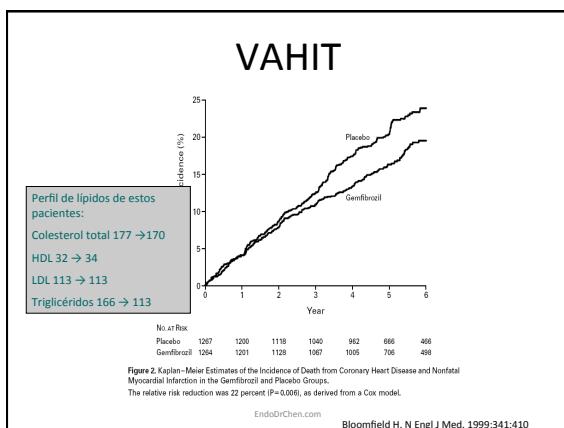
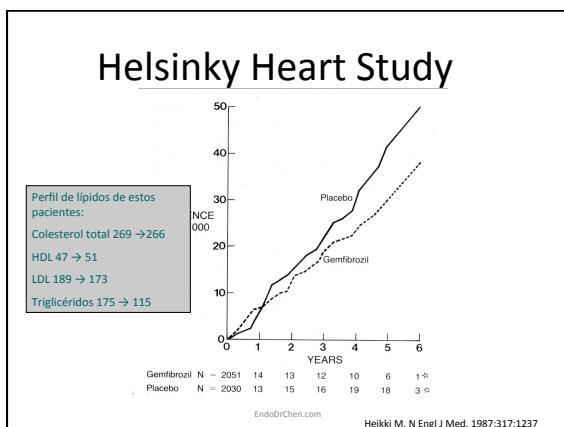


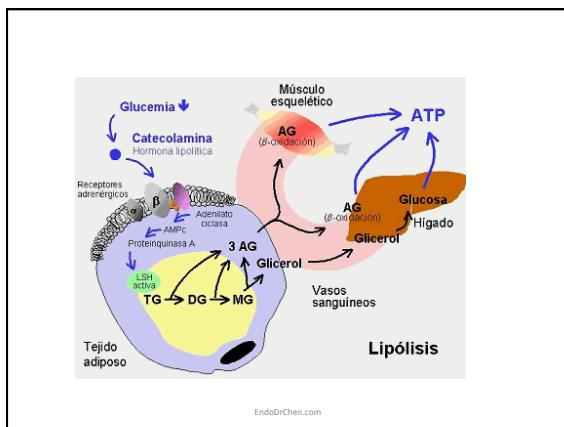
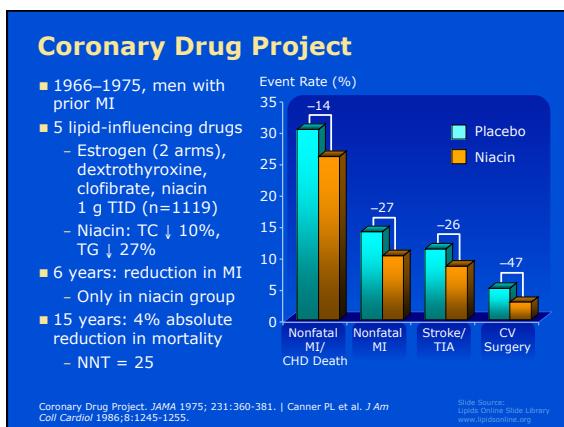
**Accord lipidos - resultados**

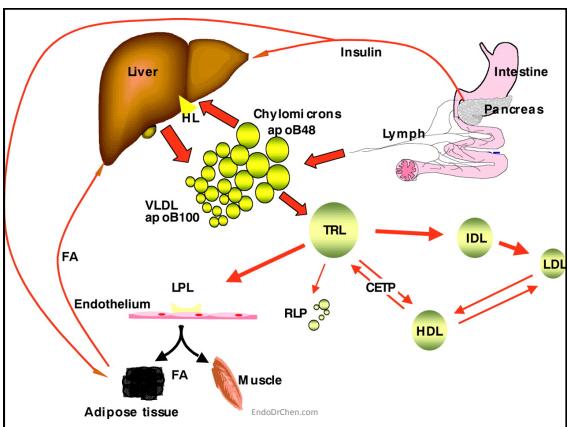
Outcome	Fenofibrate (N=2765)	Placebo (N=2753)	Hazard Ratio (95% CI)	P Value
Primary outcome (major fatal or nonfatal cardiovascular event)	291	2.24	310	2.41 0.92 (0.79-1.08) 0.32*
<b>Secondary outcomes</b>				
Primary outcome plus revascularization or hospitalization for congestive heart failure	641	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
<b>Stroke</b>				
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
<b>Death</b>				
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 (0.65-1.06) 0.10

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The Accord Study Group N Engl J Med. 2010



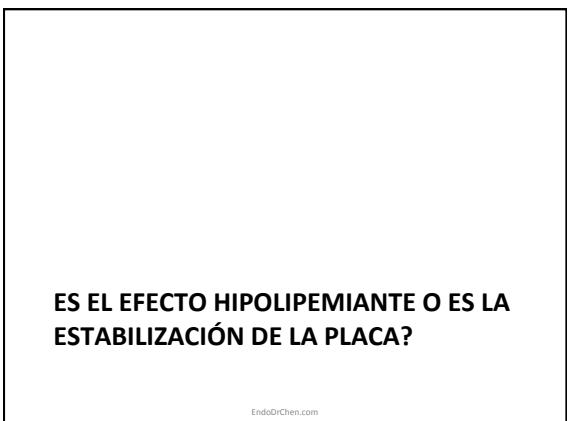


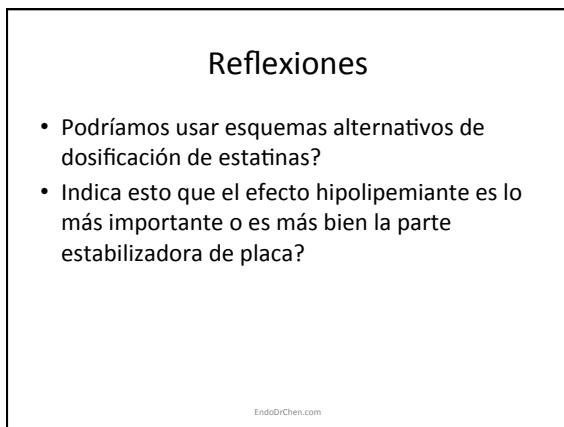
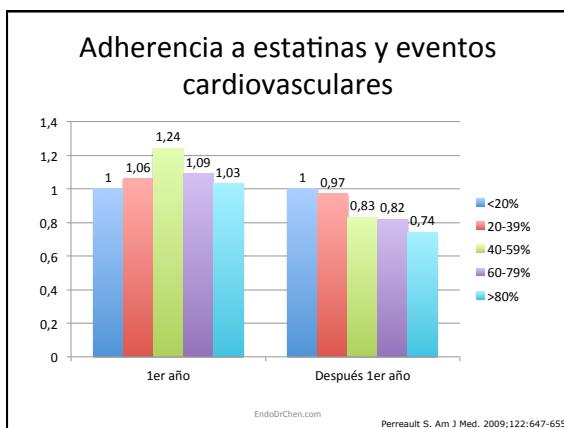
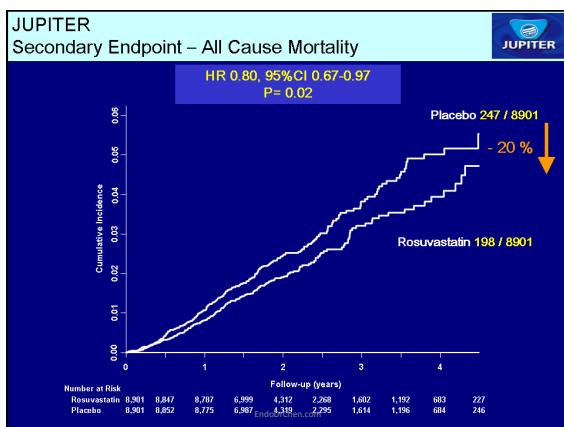




Variable	Hazard Ratio (95% CI)					P Value for Trend	P Value for Interaction
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
<b>Body-mass index†</b>							
<25	1	1.48 (0.52–4.23)	1.64 (0.54–5.29)	1.71 (0.73–6.42)	1.73 (0.79–6.60)	<0.001	0.03
≥25	1	1.36 (0.86–2.15)	1.66 (1.02–2.68)	2.44 (1.43–4.16)	3.78 (1.95–7.35)	<0.001	
<b>Triglyceride level</b>							
<150 mg/dl	1	1.21 (0.63–2.29)	1.50 (0.76–2.97)	2.43 (1.14–5.23)	2.73 (1.28–6.67)	<0.001	0.87
≥150 mg/dl	1	1.41 (0.80–2.49)	1.90 (1.03–3.51)	2.37 (1.25–4.50)	3.24 (1.48–7.10)	<0.001	
<b>Family history</b>							
Negative	1	1.24 (0.66–2.35)	1.50 (0.78–2.87)	3.77 (1.62–8.77)	6.49 (2.25–18.86)	<0.001	0.37
Positive	1	1.96 (0.77–5.02)	2.51 (0.88–7.19)	2.57 (0.94–6.99)	4.58 (1.58–13.33)	<0.001	

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**CÓMO MINIMIZAR RIESGO DE EFECTOS ADVERSOS?**

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**For Consumers**

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**FDA: Limit Use of 80 mg Simvastatin**

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More on Safe Use

The Food and Drug Administration is recommending that use of drugs containing 80 mg of simvastatin—the highest approved dose of the popular cholesterol-lowering drug—is sharply curtailed because of the risk of muscle injury.

FDA says this dose should only be used by patients who have been taking it for 12 months or more and still need it.

"Our overall goal is to get doctors to not start patients on 80 mg of simvastatin," says Amy Egan, M.D., deputy director of FDA's Division of Metabolism and Endocrinology Products.

And if health care professionals find that patients now taking 40 mg of simvastatin are having trouble with their cholesterol, FDA is advising them to choose a different statin rather than raising the simvastatin dose to 80 mg, says Amy Egan, M.D., deputy director for safety in the FDA division.

All statins, despite their proven benefit in lowering the risk of heart attacks and strokes, carry some risk of an injury called rhabdomyolysis, which can lead to kidney damage or even death.

But the risk is greater for patients who take the 80 mg doses of simvastatin, especially in the first year of treatment. Colman says the muscle damage is often caused by interactions with other medications. And some people are genetically predisposed towards simvastatin-related myopathy, he says.

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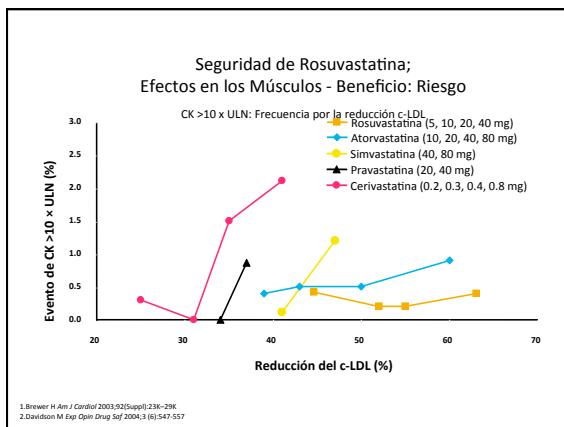
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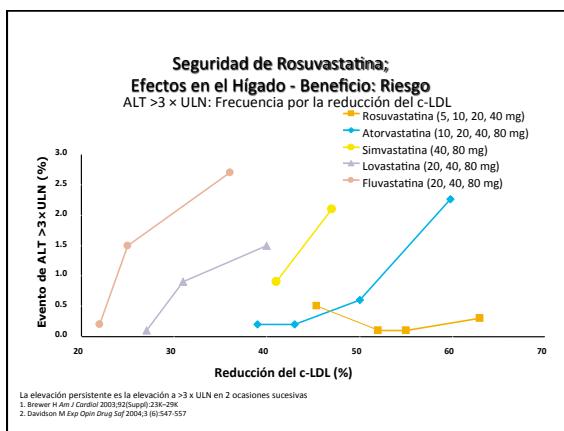
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**Drugs**

Home Drugs Drug Safety and Availability

**Drug Safety and Availability**

- Drug Alerts and Statements
- Importing Prescription Drugs
- Medication Guides
- Drug Safety Communications
- Drug Shortages
- Postmarket Drug Safety Information for Patients and Providers
- Information by Drug Class
- Medication Errors
- FDA Drug Safety Newsletter
- Drug Safety Podcasts
- Safe Use Initiative
- Drug Recalls
- Drug Integrity and Supply Chain Security

**FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs**

**Facts about statins**

- A class of prescription drugs used together with diet and exercise to reduce blood levels of low-density lipoprotein (LDL) cholesterol ("bad cholesterol").
- Marketed as single-dose products, extended-release products, or combinations (Lipitor, fluvastatin, Mevacor (lovastatin), Atorv (lovastatin extended-release), Livalo (pravastatin sodium), Simvastatin, Zocor (rosuvastatin), and Zocor (simvastatin)).
- Also marketed as combination products, including Lipitor/atorvastatin, Crestor (rosuvastatin extended-release), Simcor (simvastatin/niacin extended-release), and Vytorin (simvastatin/ezetimibe).

**Safety Announcement**

[2-28-2012] The U.S. Food and Drug Administration (FDA) has approved important safety label changes for the class of cholesterol-lowering drugs known as statins. These changes were made to provide the public with more information about the risks and effective use of statins and are based on FDA's comprehensive review of the statin class of drugs (see Data Summary below). The changes include the following:

**Monitoring Liver Enzymes**

Labels have been changed to remove the need for routine periodic monitoring of liver enzymes in patients taking statins. The labels now recommend that liver enzyme tests should be performed before starting statin therapy and at least once a year thereafter. It is also recommended that serious liver injury with statins is rare and unpredictable in individual patients, and that routine periodic monitoring of liver enzymes does not appear to be effective in detecting or preventing serious liver injury.

**Adverse Event Information**

Information about the potential for generally non-serious and reversible cognitive side effects (memory loss, confusion, etc.) and reports of increased blood sugar and glycosylated hemoglobin (HbA1c) levels has been added to the labels. FDA believes that the cardiovascular benefits of statins outweigh these small increased risks.

**Drug Interactions**

The drug interaction section has been extensively updated with new contraindications (situations when the drug should not be used) and dose limitations when it is taken with certain medicines that can

**Resources for You**

- FDA Announces safety changes in labeling for some cholesterol-lowering drugs
- Infographic about Cholesterol and Statins (PDF - 2.5MB)

**Infographic About Cholesterol and Statins**

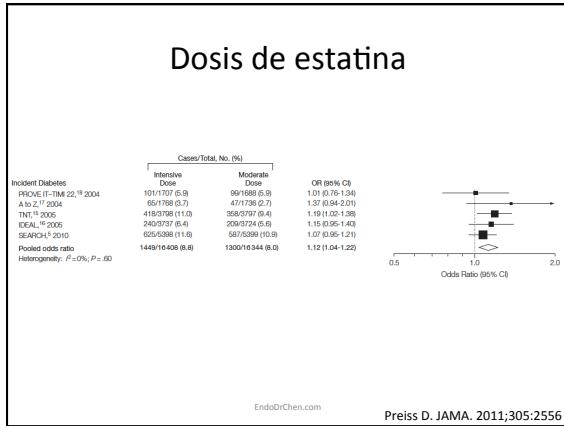
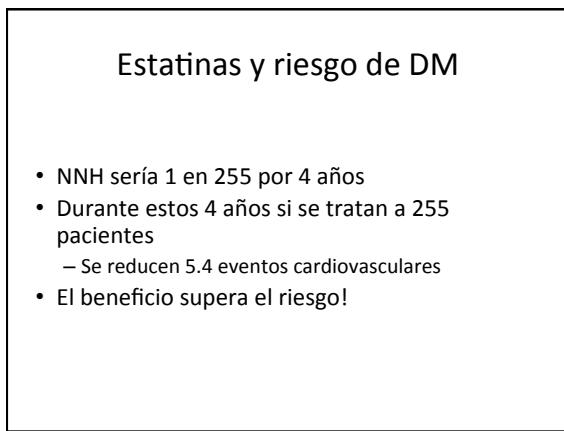
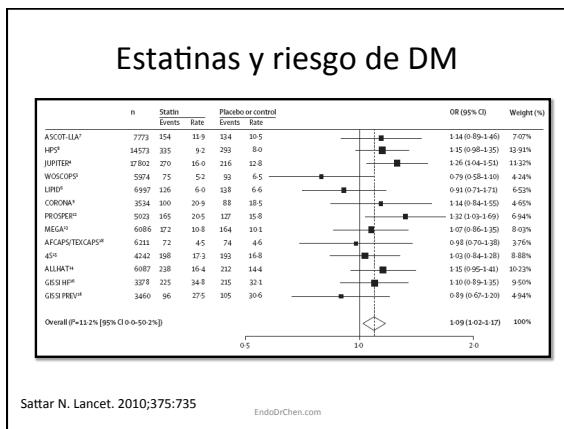
**Cholesterol Overview**

**Statins**

## Deterioro cognitivo

- Demostrado en estudios observacionales, no en RCT
- 50% se produce en los primeros 2 meses de uso, 50% revierte al suspenderlo
- Datos preliminares parecen indicar que aquellos menos lipofílicos dan menos problemas (pravastatina y rosuvastatina)
- Una posible alternativa es pasar de estatina lipofílica a hidrofílica

1. Rojas-Fernandez CH. Ann Pharmacother. 2012;46:549  
2. Wagstaff LR. Pharmacotherapy. 2003;23:871



## 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

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=6995)			One or more major diabetes risk factors (n=11508)						
	Rosuvastatin	Placebo	Δ	HR (95% CI)	p value	Rosuvastatin	Placebo	Δ	HR (95% CI)	p value
Primary endpoint	44 (9.69)	91 (14.45)	-47	0.48 (0.33-0.68)	0.0001	96 (8.80)	152 (13.31)	-56	0.61 (0.47-0.79)	0.0001
Primary endpoint, any death	119 (1.85)	174 (2.77)	-56	0.67 (0.53-0.85)	0.0007	175 (1.46)	262 (2.18)	-87	0.67 (0.55-0.81)	0.0001
Primary endpoint, VTE, any death	127 (1.97)	187 (2.99)	-65	0.64 (0.51-0.81)	0.0001	196 (1.64)	289 (2.41)	-93	0.68 (0.57-0.81)	0.0001
MI, stroke, any death	99 (1.55)	147 (2.33)	-48	0.67 (0.53-0.86)	0.002	139 (1.15)	202 (1.67)	-63	0.69 (0.56-0.86)	0.0006
Any death	89 (1.37)	133 (1.69)	-44	0.78 (0.59-1.03)	0.08	109 (0.85)	132 (1.02)	-23	0.83 (0.64-1.07)	0.15
Diabetes	12 (0.18)	12 (0.18)	0	0.99 (0.45-2.21)	0.99	258 (2.12)	204 (1.65)	54	1.28 (1.07-1.54)	0.01

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

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Ridker P. Lancet. 2012;380:565

## Estatinas y lesiones osteomusculares

- RR 1.19 para todas las enfermedades musculoesqueléticas
- RR 1.13 para lesiones y enfermedades relacionadas
- RR 1.09 dolor musculoesquelético asociado a medicamentos

EndoDrChen.com Mansi I. JAMA Intern Med. Online June 3 2013

## Diferencias farmacocinéticas

Características	Atorvastina	Lovastatina	Simvastatina	Pravastatina	Fluvastatina	Rosuvastatina
Biodisponibilidad	12%	<5%	<5%	17%	24%	20%
Eliminación urinaria	<2%	10%	13%	20%	5%	10%
Eliminación Fecal	98%	83%	60%	70%	90%	90%
Unión a proteinas	>90%	>95%	95%	50%	98%	88%
Sustrato CYP	CYP3A4	CYP3A4	CYP3A4	Sulfatación	CYP2C9	CYP2C9
Lipofiliaidad	Lipofílico	Lipofílico	Lipofílico	Hidrofílico	Hidrofílico	Hidrofílico

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## Riesgo de interacciones

- Inhibidores CYP3A4
  - Fluconazol, itraconazol, ketoconazol
  - Eritromicina, claritromicina
  - Omeprazole, lanzoprazole
  - Bloqueadores de canales de calcio
  - Fluoxetina, venlafaxina, paroxetina
  - Ciclosporina, tacrolimus
  - Jugo de toronja
- Inhibidores CYP2C9:
  - amiodarona

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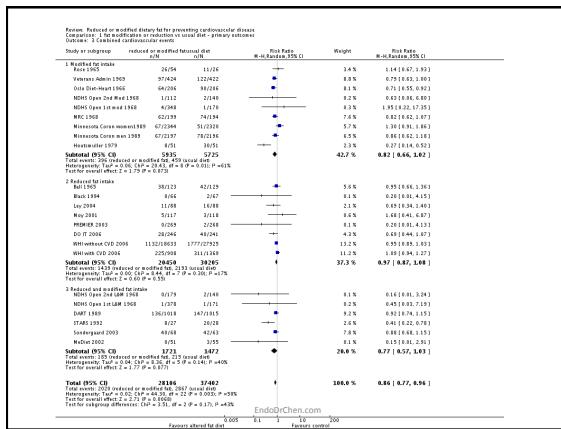
## MODIFICACIÓN DE ESTILOS DE VIDA BASADO EN EVIDENCIA

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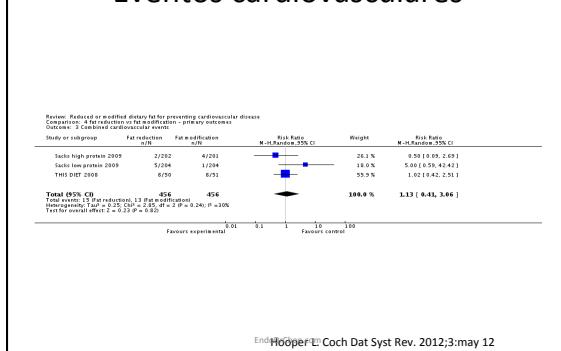
## Recomendaciones

- Las intervenciones que funcionan según las guías:
  - Fibra
  - Esteroles vegetales
  - Grasas saturadas
  - Reducir colesterol de la dieta

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## Eventos cardiovasculares



PREDIMED

- Hombres 55-80 años
  - Mujeres 60-80 años
  - DM ó 3 factores de riesgo:
    - Tabaquismo
    - HTA
    - LDL alto
    - HDL bajo
    - Sobre peso u obesidad
    - Historia de enfermedad coronaria prematura

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Est. J. B. N.E. U.M. 4. 2012

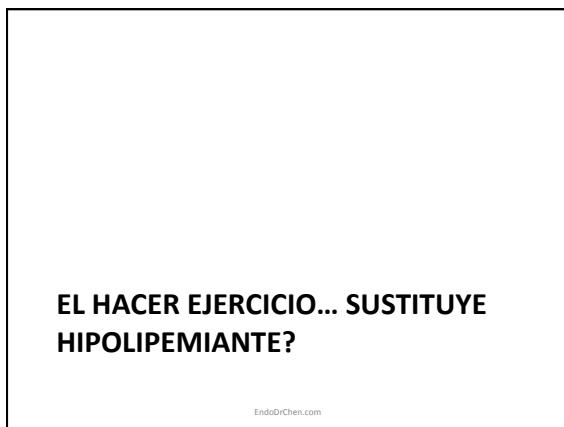
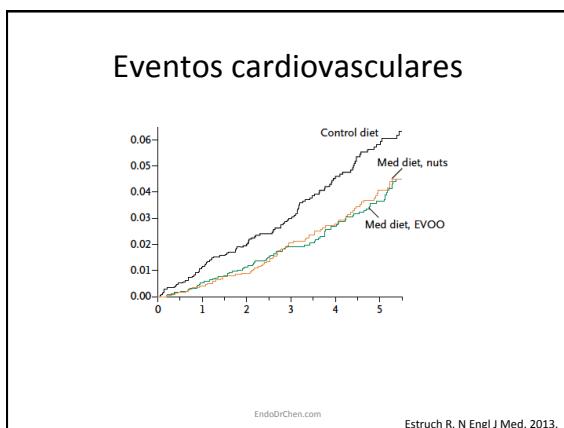
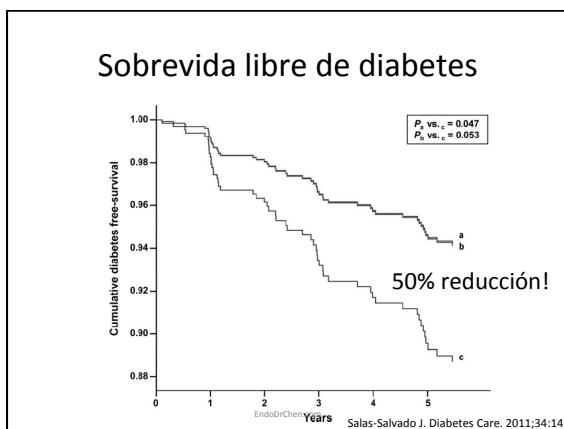
Mediterranean diet	
Recommended	
Olive oil*	≥4 tbsps/day
Tree nuts and peanuts†	≥3 servings/wk
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Fish (especially fatty fish), seafood	≥3 servings/wk
Legumes	≥3 servings/wk
Sofrito‡	≥2 servings/wk
White meat	Instead of red meat
Wine with meals (optionally, only for habitual drinkers)	≥7 glasses/wk
Discouraged	
Soda drinks	<1 drink/day
Commercial bakery goods, sweets, and pastries§	<3 servings/wk
Spread fats	<1 serving/day
Red and processed meats	<1 serving/day

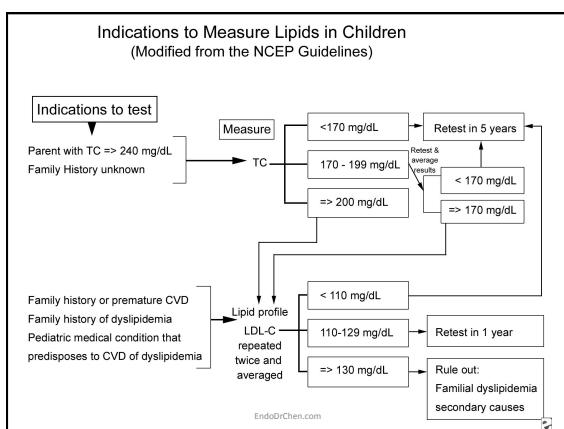
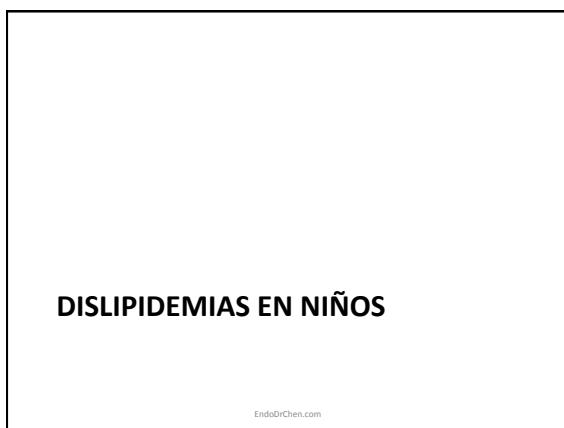
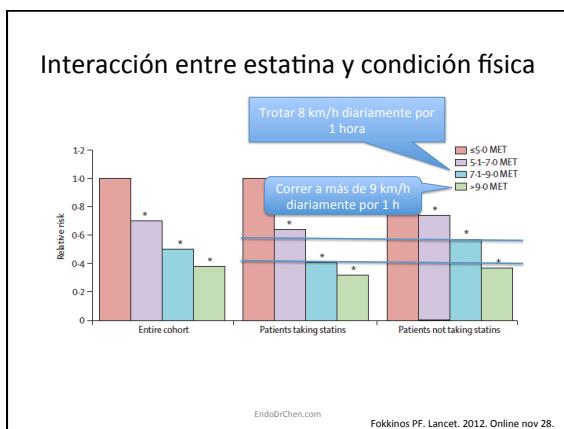
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1 serving, 1/2 cup

Low-fat diet (control)	
<b>Recommended</b>	
Low-fat dairy products	≥3 servings/day
Bread, potatoes, pasta, rice	≥3 servings/day
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/wk
Lean fish and seafood	≥3 servings/wk
<b>Discouraged</b>	
Vegetable oils (including olive oil)	≤2 tbsp/day
Commercial bakery goods, sweets, and pastries§	≤1 serving/wk
Nuts and fried snacks	≤1 serving /wk
Red and processed fatty meats	≤1 serving/wk
Visible fat in meats and soups¶	Always remove
Fatty fish, seafood canned in oil	≤1 serving/wk
Spread fats	≤1 serving/wk
Sofrito§	≤2 servings/wk

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### Condiciones médicas predisponentes

- Obesidad (>30% sobre peso ideal)
- Inactividad física
- Diabetes
- HDL bajo
- Enfermedad renal
- Enfermedad hepática
- Hipotiroidismo o Cushing
- Fármacos que inducen dislipidemias (inhibidores de proteasas, inmunosupresores, esteroides)

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### consideraciones

- Niveles de triglicéridos ajustados por edad
- No podemos aplicar el nivel de adultos
- Indicación de tratamiento indicado por riesgo y sobre todo para hipercolesterolemias familiares
- Las estatinas son teratogénicas

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### Conclusiones

- Hipertrigliceridemia tiene implicación para pancreatitis y riesgo de DM, pero la intervención farmacológica no ha reducido riesgo de eventos CV
- Adherencia es fundamental para que haya beneficio a largo plazo
- Perfil de seguridad es diferente según cada estatina
- Modificación de estilos de vida y dieta mediterránea

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