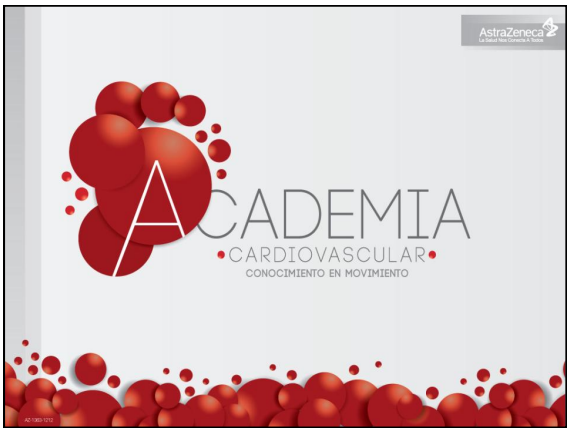

Abordaje práctico de la dislipidemia

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Servicio de Endocrinología, Hospital San Juan de Dios
Departamento de Farmacología y Toxicología Clínica,
Universidad de Costa Rica

Caso clínico

- Masculino de 43 años, con IMC 27 kg/m2. Se le realiza un perfil de lípidos por control.
- Laboratorios muestran:
  - Glicemia 102 mg/dl
  - Colesterol total 190 mg/dl
  - HDL 32 mg/dl
  - Triglicéridos 347 mg/dl
  - LDL 88.6 mg/dl

Pregunta

- Cuál es el riesgo para la salud de este paciente por su dislipidemia?

1. Infarto miocardio?
2. Pancreatitis?
3. Diabetes mellitus?
4. Ictus?

Pregunta #2

- Cuál debe ser el manejo inicial en este paciente?

1. Modificación de estilos de vida?
2. Fibratos?
3. Estatinas?
4. Ezetimibe/estatinas?

Pregunta #3

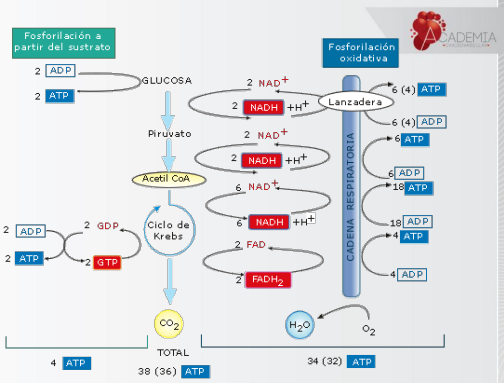
- Cuál es la recomendación de estilos de vida específico para esta situación?

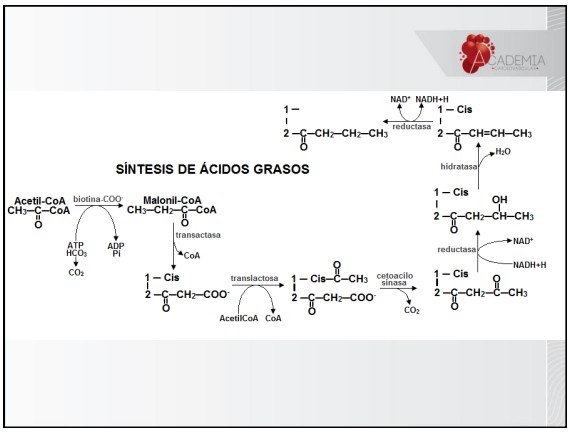
1. Aumentar ejercicio
2. Eliminar azúcares refinados
3. Aumentar consumo de alcohol
4. Eliminar grasas y frituras

Agenda

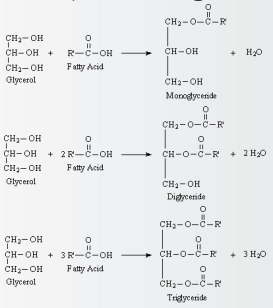
- Manejo de hipertrigliceridemia
  - Cómo hacer modificaciones de estilos de vida?
- Manejo de dislipidemia mixta
  - Tratamiento por cuánto?
  - Con qué?

HIPERTRIGLICERIDEMIA

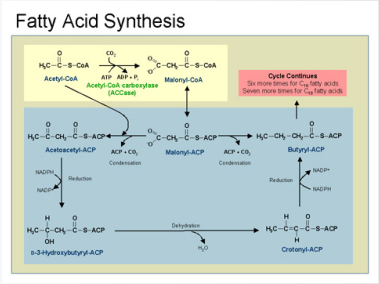


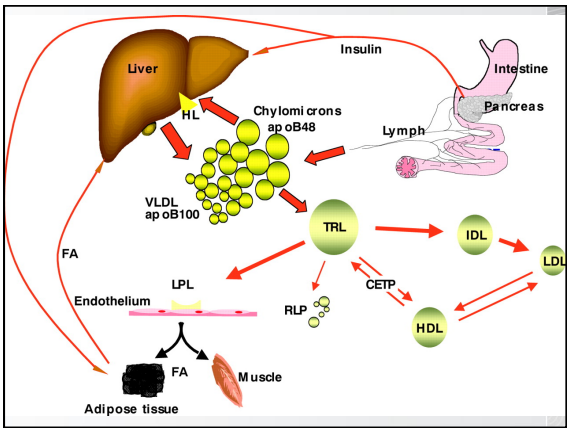


Ensamblaje en triglicéridos



Síntesis de triglicéridos





Introducción

- Hipertrigliceridemia (mayor a 1000 mg/dl) se ha observado entre 12 y 38% de pacientes con pancreatitis
- Pocos estudios controlados
- Al parecer niveles muy altos aumentan el RR 4.0
- Pancreatitis de otras causas pueden cursar con hipertrigliceridemia moderada

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

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

Nueva clasificación

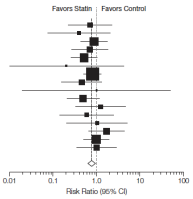
NCEP ATP III (3)			The Endocrine Society 2010[a]		
Normal	<150 mg/dl	<1.7 mmol/liter	Normal	<150 mg/dl	<1.7 mmol/liter
Borderline-high triglycerides	150–199 mg/dl	1.7–2.3 mmol/liter	Mild hypertriglyceridemia	150–199 mg/dl	1.7–2.3 mmol/liter
High triglycerides	200–499 mg/dl	2.3–5.6 mmol/liter	Moderate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

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

INTERVENCIÓN FARMACOLÓGICA

Estatinas

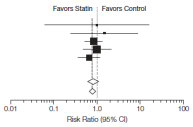
Source	Statin Cases	Statin Total	Control Cases	Control Total	Weight, %	Risk Ratio (95% CI)
Placebo- and standard care-controlled						
4S,[16] 1994	5	2223	7	2221	2.60	0.71 (0.23-2.25)
WOSCOPS,[17] 1995	2	3302	5	3293	1.28	0.40 (0.08-2.06)
CARE,[18] 1996	15	2081	17	2078	7.07	0.88 (0.44-1.77)
AFCAPS/TexCAPS,[19] 1998	7	3304	10	3301	3.67	0.70 (0.27-1.84)
LIPID,[20] 1998	12	4512	23	4502	7.02	0.52 (0.26-1.05)
GISSI Prevenzione,[21] 2000	0	2138	2	2133	0.37	0.20 (0.01-4.16)
HPS,[22] 2002	33	10269	41	10267	16.29	0.80 (0.51-1.27)
PROSPER,[23] 2002	5	2891	11	2913	3.07	0.46 (0.16-1.32)
GREACE,[24] 2002	0	800	0	800	0.22	1.00 (0.02-50.49)
ASCOT-LLA,[25] 2003	8	5168	16	5137	4.76	0.50 (0.21-1.16)
CARDS,[26] 2004	5	1428	4	1410	1.98	1.23 (0.33-4.61)
ASPEN,[27] 2006	3	1211	5	1199	1.67	0.59 (0.14-2.49)
MEGA,[28] 2006	3	3866	3	3966	1.34	1.03 (0.21-5.09)
CORONA,[29] 2007	12	2514	7	2497	3.94	1.70 (0.67-4.33)
JUPITER,[30] 2008	17	8901	17	8901	7.58	1.00 (0.51-1.96)
GISSI-HF,[31] 2008	7	2285	7	2289	3.12	1.00 (0.35-2.86)
Subtotal: $I^2 = 0.0\%$, $P = .87$					65.98	0.77 (0.62-0.97)



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

Dosis estatinas

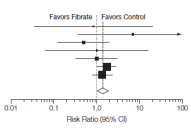
Source	Statin Cases	Statin Total	Control Cases	Control Total	Weight, %	Risk Ratio (95% CI)
Intensive vs moderate dose						
PROVE-IT TIMI 22,[32] 2004	1	2099	1	2063	0.45	0.98 (0.06-15.72)
A to Z,[33] 2004	3	2265	2	2234		1.48 (0.25-8.86)
TNT,[34] 2005	33	4995	40	5006	16.05	0.83 (0.52-1.31)
IDEAL,[35] 2005	14	4439	14	4449	6.24	1.00 (0.48-2.10)
SEARCH,[36] 2010	19	6031	29	6033	10.22	0.66 (0.37-1.17)
Subtotal: $I^2 = 0.0\%$, $P = .86$					34.02	0.82 (0.59-1.12)
Overall: $I^2 = 0.0\%$, $P = .96$					100.00	0.79 (0.65-0.95)



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

Fibratos

Source	Fibrate Cases	Fibrate Total	Control Cases	Control Total	Weight, %	Risk Ratio (95% CI)
CORONARY Drug Project,[37] 1975	0	1103	1	2789	1.11	0.84 (0.03-20.71)
WHO-COOR[38] 1978	3	5331	0	5296	1.29	6.95 (0.35-134.99)
HHS,[40] 1987	3	2362	6	2347	5.89	0.50 (0.12-1.99)
VA-HIT,[41] 1999	1	1264	1	1267	1.47	1.00 (0.06-16.04)
BIP,[42] 2000	6	1548	6	1542	8.82	1.00 (0.32-3.10)
FIELD,[77] 2005	40	4895	23	4900	42.83	1.74 (1.04-2.91)
ACCORD Lipid,[43] 2010	31	2765	23	2753	38.59	1.34 (0.78-2.31)
Overall: $I^2 = 0.0\%$, $P = .61$					100.00	1.39 (1.00-1.95)



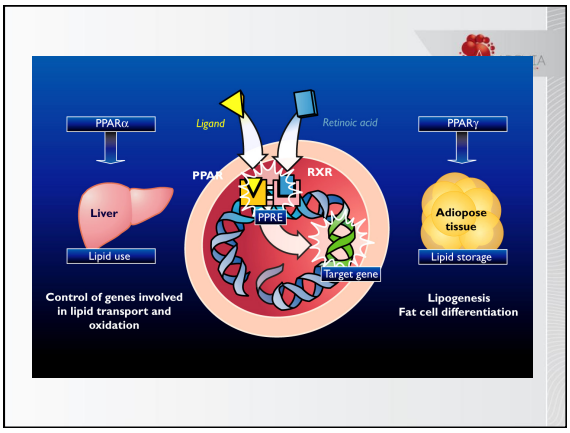
NNH 1 en 935

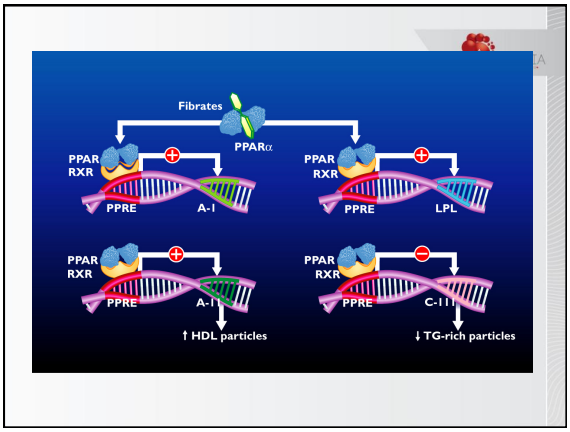
Preiss D. JAMA. 2012;308(8):804

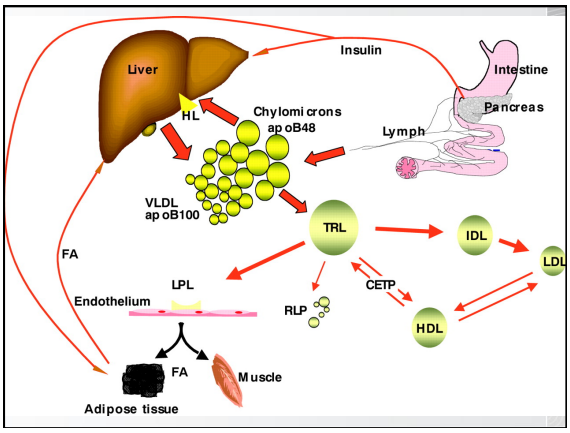
Fibratos y pancreatitis

- 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

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


PPARα
Ligand
Retinoic acid
PPARγ
PPAR
RXR
Liver
PPRE
Adiopose tissue
Lipid use
Target gene
Lipid storage
Control of genes involved in lipid transport and oxidation
Lipogenesis
Fat cell differentiation

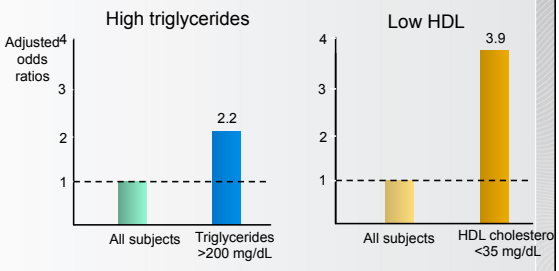

Fibrates
PPARα
PPAR
RXR
PPRE
A-I
LPL
A-II
C-III
↑ HDL particles
↓ TG-rich particles


Liver
Insulin
Intestine
Pancreas
HL
Chylomicrons
apoB48
Lymph
VLDL
apoB100
TRL
IDL
LDL
FA
LPL
Endothelium
RLP
CETP
HDL
FA
Muscle
Adipose tissue

QUÉ HAY SOBRE EL IMPACTO CARDIOVASCULAR?

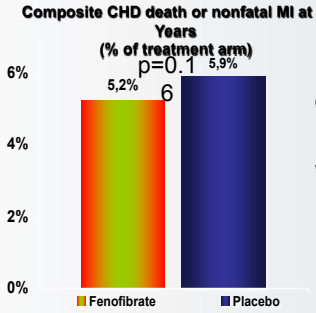
Triglycerides and HDL Cholesterol Predict CV Mortality in Type 2 Diabetes

313 Patients Followed for 7 Years



Laakso M et al. *Circulation*. 1993;88(part 1):1421-1430

FIELD: Primary Endpoint



- The primary composite endpoint of CHD death or non-fatal MI was not significantly lower in the fenofibrate group compared to the placebo group.

AHA 2005

Accord lipidos - resultados

Outcome	Fenofibrate (N=2765)		Placebo (N=2753)		Hazard Ratio (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 (0.79–1.08)	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

The Accord Study Group N Engl J Med. 2010

Y QUÉ TAL GEMFIBROZIL?

Helsinky Heart Study

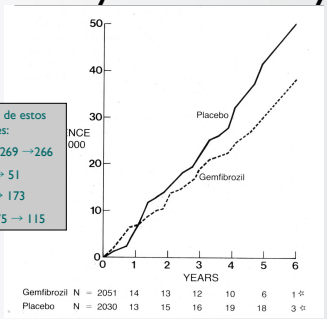
Perfil de lípidos de estos pacientes:

Colesterol total 269 →266

HDL 47 → 51

LDL 189 → 173

Triglicéridos 175 → 115



Heikki M. N Engl J Med. 1987;317:1237

VAHIT

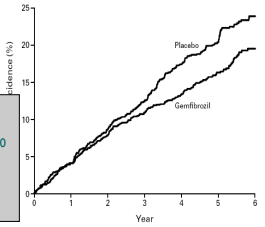
Perfil de lípidos de estos pacientes:

Colesterol total 177 →170

HDL 32 → 34

LDL 113 → 113

Triglicéridos 166 → 113



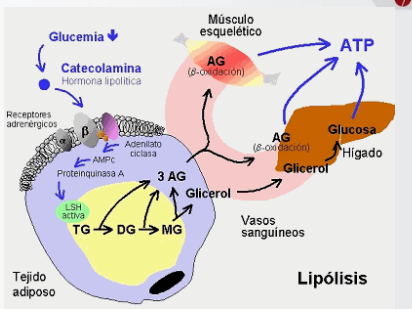
No. at Risk

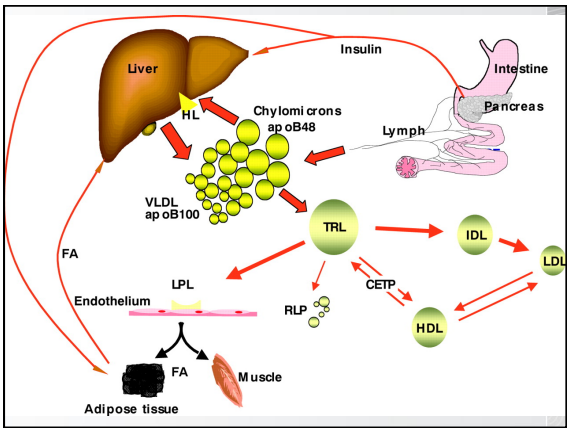
Placebo	1267	1200	1118	1040	962	666	466
Gemfibrozil	1264	1201	1128	1067	1005	706	498

Figure 2. Kaplan–Meier Estimates of the Incidence of Death from Coronary Heart Disease and Nonfatal Myocardial Infarction in the Gemfibrozil and Placebo Groups.
The relative risk reduction was 22 percent (P=0.006), as derived from a Cox model.

Bloomfield H. N Engl J Med. 1999;341:410

HIPERTRIGLICERIDEMIA COMO MARCADOR DE RIESGO DE DM





Variable	Hazard Ratio (95% CI)					P Value for Trend	P Value for Interaction
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
Body-mass index†							
<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	
Triglyceride level							
<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	
Family history							
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	

Tirosh A. N Engl J Med. 2005;353:1454

Caso #2

- Femenina de 65 años, portadora de hipertensión arterial y tabaquista. Consulta para control y se encuentra con el siguiente perfil de lípidos:
  - Colesterol total 225 mg/dl
  - HDL 38 mg/dl
  - Triglicéridos 196 mg/dl
  - LDL 147.8 mg/dl

Pregunta

- Cuál es la meta de LDL?

1. <160 mg/dl
2. <130 mg/dl
3. <100 mg/dl
4. <70 mg/dl

Pregunta

- Cuál es la primera intervención que se le debe hacer?

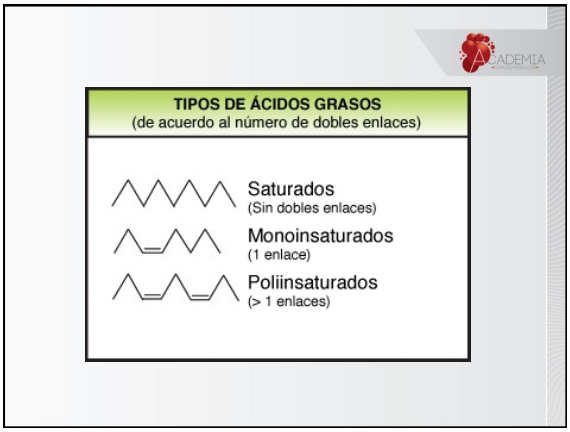
1. Modificar estilos de vida
2. Estatinas
3. Fibratos
4. Ezetimibre/estatina

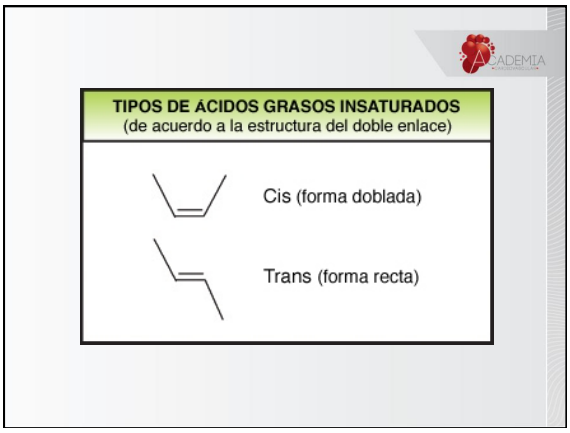
Pregunta

- Cuál es la modificación de estilo de vida que se debe recomendar?

1. Aumentar ejercicio
2. Dieta SIN grasas
3. Dieta mediterránea
4. Aumentar fibra y reducir grasas saturadas

Fisiopatología

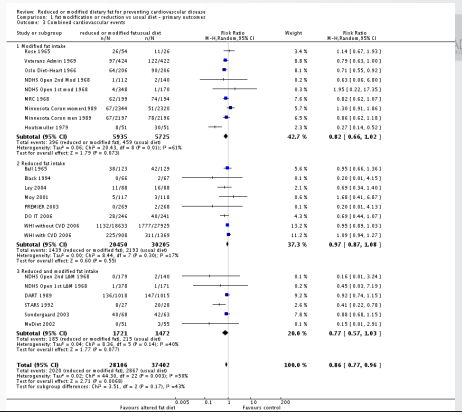




Grasas trans

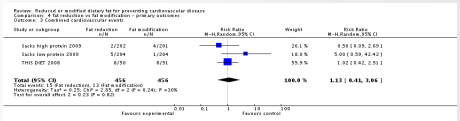
- Originado de ácidos grasos insaturados
- Aceites vegetales parcialmente hidrogenados que se convierten fácilmente a sólidos
- Usados en productos procesados y repostería

EVENTOS CARDIOVASCULARES



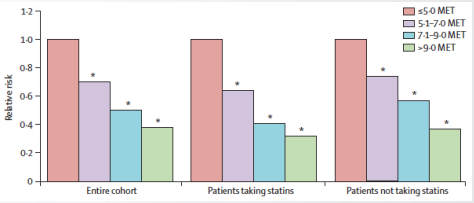
REDUCIR GRASAS O SUSTITUIR GRASAS?

Eventos cardiovasculares



Hooper L. Coch Dat Syst Rev. 2012;3:may 12

Interacción entre estatina y condición física



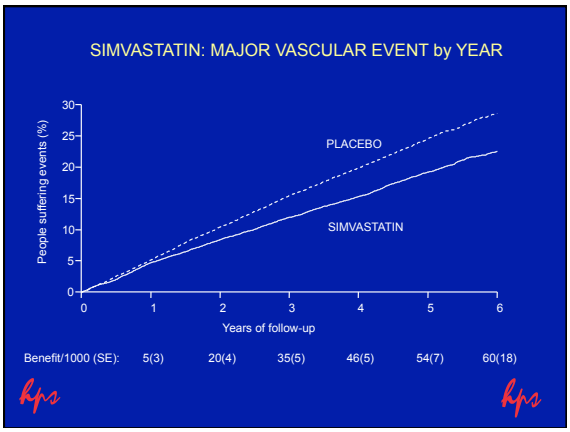
Fokkinos PF. Lancet. 2012. Online nov 28.

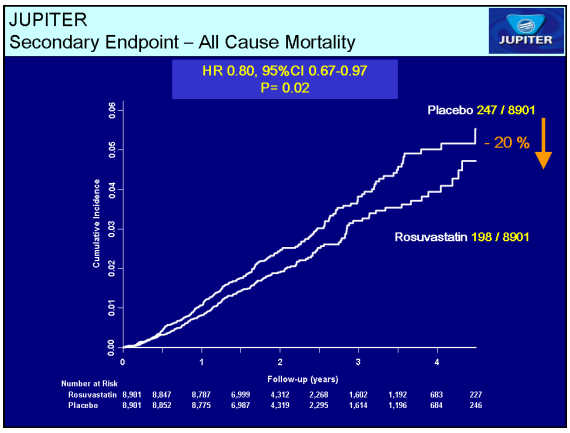
Interacción entre condición física y estatina

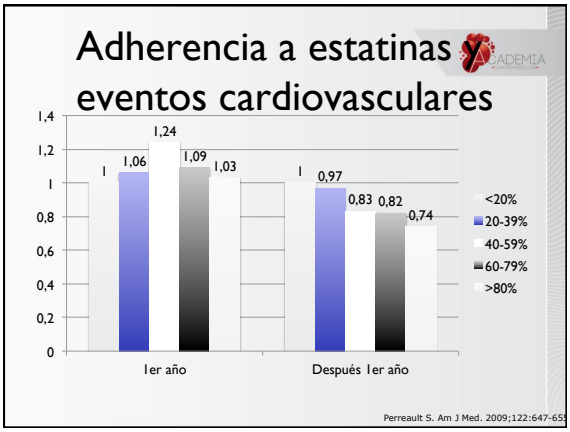
	Deaths (n; %)	Unadjusted HR	Age-adjusted HR	Fully adjusted HR*	p value†
Least fit, statins (n=1060)	389 (37%)	1	1	1	..
Least fit, no statins (n=1024)	531 (52%)	1·22 (1·07–1·39)	1·22 (1·07–1·38)	1·35 (1·17–1·54)	<0·0001
Moderately fit, statins (n=1573)	329 (21%)	0·57 (0·49–0·66)	0·64 (0·56–0·75)	0·65 (0·56–0·75)	<0·0001
Moderately fit, no statins (n=1154)	397 (34%)	0·81 (0·70–0·93)	0·89 (0·77–1·02)	1·02 (0·88–1·12)	0·81
Fit, statins (n=1705)	173 (10%)	0·28 (0·23–0·33)	0·40 (0·33–0·48)	0·41 (0·34–0·49)	<0·0001
Fit, no statins (n=1335)	270 (20%)	0·50 (0·43–0·58)	0·69 (0·59–0·81)	0·81 (0·69–0·96)	0·01
Highly fit, statins (n=694)	39 (6%)	0·16 (0·12–0·22)	0·27 (0·19–0·38)	0·30 (0·21–0·41)	<0·0001
Highly fit, no statins (n=1498)	190 (13%)	0·27 (0·22–0·32)	0·42 (0·35–0·51)	0·53 (0·44–0·65)	<0·0001

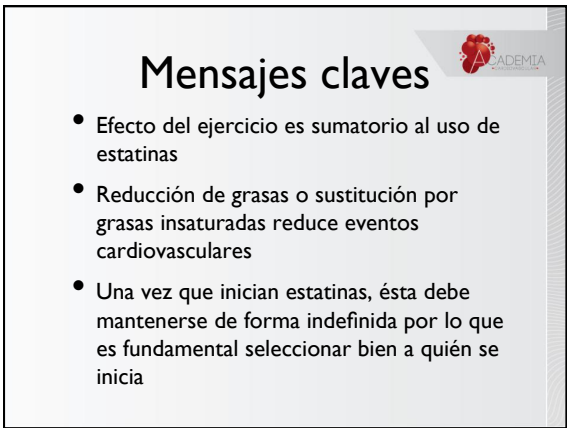
Fokkinos PF. Lancet. 2012. Online nov 28.

ES EL EFECTO HIPOLIPEMIANTE O ES LA ESTABILIZACIÓN DE LA PLACA?




JUPITER
Secondary Endpoint – All Cause Mortality
JUPITER
HR 0.80, 95%CI 0.67-0.97
P= 0.02
Placebo 247 / 8901
- 20 %
Rosuvastatin 198 / 8901
Cumulative Incidence
0.00
0.01
0.02
0.03
0.04
0.05
0.06
0
1
2
3
4
Follow-up (years)
Number at Risk
Rosuvastatin 8,901 8,847 8,787 6,999 4,312 2,268 1,602 1,192 683 227
Placebo 8,901 8,852 8,775 6,987 4,319 2,295 1,614 1,196 684 246


Adherencia a estatinas y eventos cardiovasculares
ACADEMIA
1,4
1,2
1
0,8
0,6
0,4
0,2
0
1
1,06
1,24
1,09
1,03
1
0,97
0,83
0,82
0,74
<20%
20-39%
40-59%
60-79%
>80%
1er año
Después 1er año
Perreault S. Am J Med. 2009;122:647-65


Mensajes claves
ACADEMIA
• Efecto del ejercicio es sumatorio al uso de estatinas
• Reducción de grasas o sustitución por grasas insaturadas reduce eventos cardiovasculares
• Una vez que inician estatinas, ésta debe mantenerse de forma indefinida por lo que es fundamental seleccionar bien a quién se inicia

Conclusiones

- Objetivo del tratamiento de hipertrigliceridemia es reducción de pancreatitis
- Aumento de HDL con gemfibrozil reduce eventos cardiovasculares, no así la reducción de triglicéridos como tal
- Dislipidemia mixta se debe manejar farmacológicamente con estatinas y no con fibratos como primera línea

Preguntas…
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