'12 HighLights

Aterosclerosis y lípidos

American Heart Association
Learn and Live

SCIENTIFIC SESSIONS 2012
EXHIBITS: NOVEMBER 4-6
SESSIONS: NOVEMBER 3-7
RESUSCITATION SCIENCE SYMPOSIUM: NOVEMBER 3-4

Highlights AHA 2012. Lípidos

- Recomendaciones:
  - cLDL es el objetivo
  - Las estatinas son el tratamiento de elección
  - Ezetimiba es el segundo fármaco a utilizar en ausencia de consecución de objetivos
- Efectos secundarios estatinas
- Ensayos clínicos/fármacos
  - Inhibidores de PCSK9
  - Dal-Outcomes
  - Subanálisis de AIM-High
  - Anacetrapib: mecanismo acción
- Metabolismo
  - HDL: Función vs concentración de cHDL
  - Lp(a): renacimiento de una lipoproteína aterogénica

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Discontinuación de estatinas

- Estudio USAGE (Dr. Cohen)
  - 37% pacientes discontinúan a corto plazo
    - >60% por efectos secundarios
    - 20%: coste medicación
  - 63% mantienen tramiento
    - 84% muy satisfechos del tratamiento
- Recomendaciones
  - **Pacientes**: deben conocer objetivos, costes y beneficios
  - **Médicos:** debemos explicar mejor efectos secundarios, estar alertas y no minimizarlos
  - **Sistema**: debe educar en prevención
  - **Nuevas tecnologías**: deben ayudar más cumplimiento: smart phones,…

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Efectos secundarios estatinas

- Mialgias, miositis
- Diabetes
- Cataratas: dudoso
- Cáncer: NO
- Problemas neurológicos: anecdótico
- Enzimas hepáticos: NO
  - No se recomienda la monitorización de transaminasas en el seguimiento
- Pueden ser una limitación para su utilización en sujetos de bajo riesgo

Mialgias y estatinas

- Frecuencia: 10-20%
- Estudio STOMPS
  - 9,4% atorvastatina
  - 4,6% placebo (también al reintentar placebo)
  - Elevación de CK media 21 u/L con estatina
- Características:
  - Simétricas, grandes músculos, inicio pronto al instaurar trtº, mejoría rápida tras suspensión, recurrencia con otra estatina, empeoran tras ejercicio físico
- Patogenia: ????
  - Disminución colesterol sarcolema, disminución de CoQ10, descenso de vit D, aumento de fitosteroles, miopatía inflamatoria,..

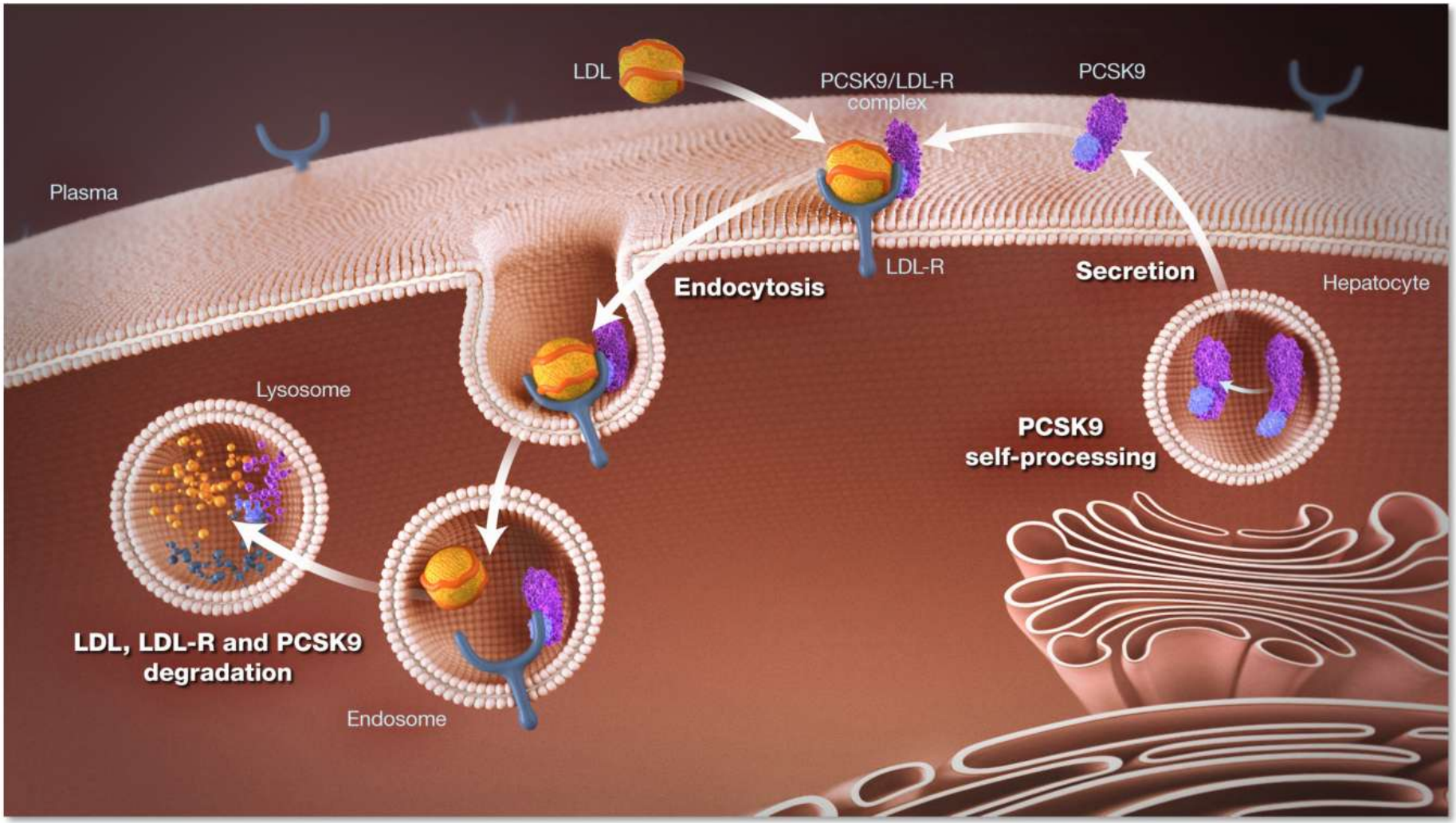
Mialgias y estatinas

- Recomendaciones
  - Descartar: hipotiroidismo, deficiencia de VitD, polimialgia reumática,
  - Reducir dosis o cambiar estatinas
  - Asociar Ezetimiba a dosis bajas de estatinas
  - Tónica (quinina) : calambres
  - Arroz rojo chino
  - Evitar tomas de fármaco con ejercicio intenso excepcional
  - CoQ10 (?)

Diabetes y estatinas

- Aumento del 9% diagnósticos de DM
- 1 caso por cada 255 sujetos tratados vs 9 eventos mayores cardiovasculares
- Factores de riesgo: aumento de glucosa, HbA1c, Tgs, IMC, edad.
- Patogenia: ?????????
  - Disminución sensibilidad insulina
    - Disminución de GLUT4 (?)
    - Disminución mitocondrias y su función (?)
- Los beneficios superan con creces al riesgo en sujetos de riesgo intermedio o alto

PCSK9 regula la expresión en la superficie celular del receptor LDL



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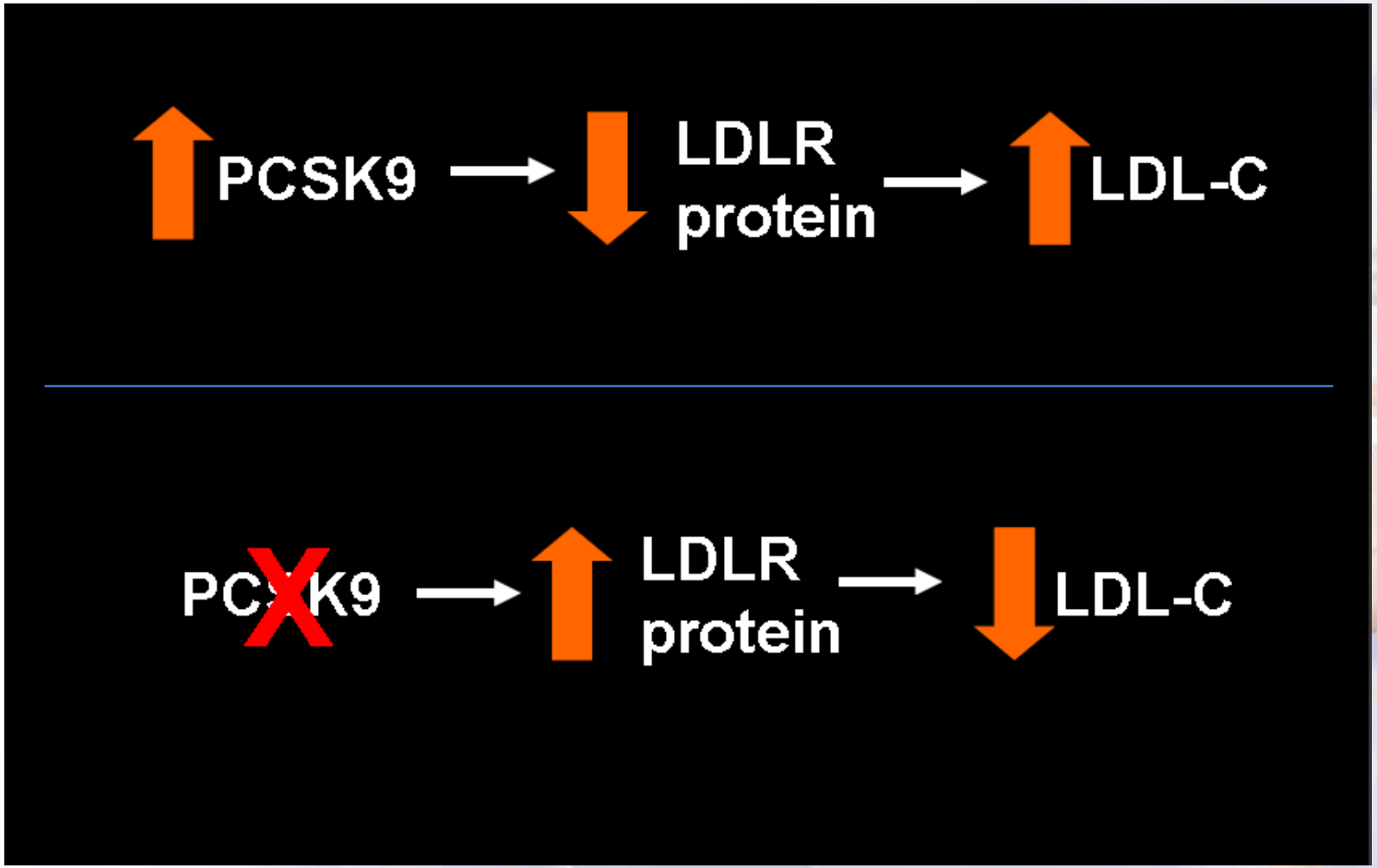
PCSK9 promueve la degradación del receptor LDL



Estudio RUTHERFORD

Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD): Results from a Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial

Frederick Raal[1], Rob Scott[2], Ransi Somaratne[2], Ian Bridges[3], Thomas Liu[2], Scott M. Wasserman[2], Evan A. Stein[4]

[1]Carbohydrate & Lipid Metabolism Research Unit, University of Witwatersrand, Johannesburg, South Africa; [2]Amgen Inc., Thousand Oaks, CA, USA; [3]Amgen Ltd., Uxbridge, UK; [4]Metabolic and Atherosclerosis Research Center, Cincinnati, OH, USA

November 5, 2012, Session: LBCT.04
American Heart Association Scientific Sessions, Los Angeles, CA

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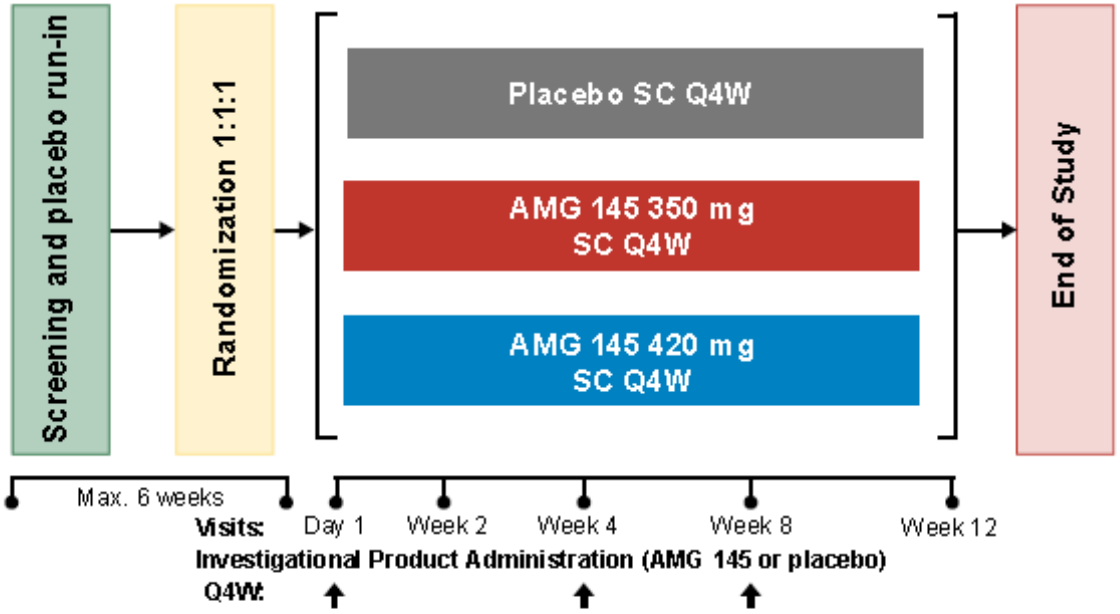
RUTHERFORD: Study Design



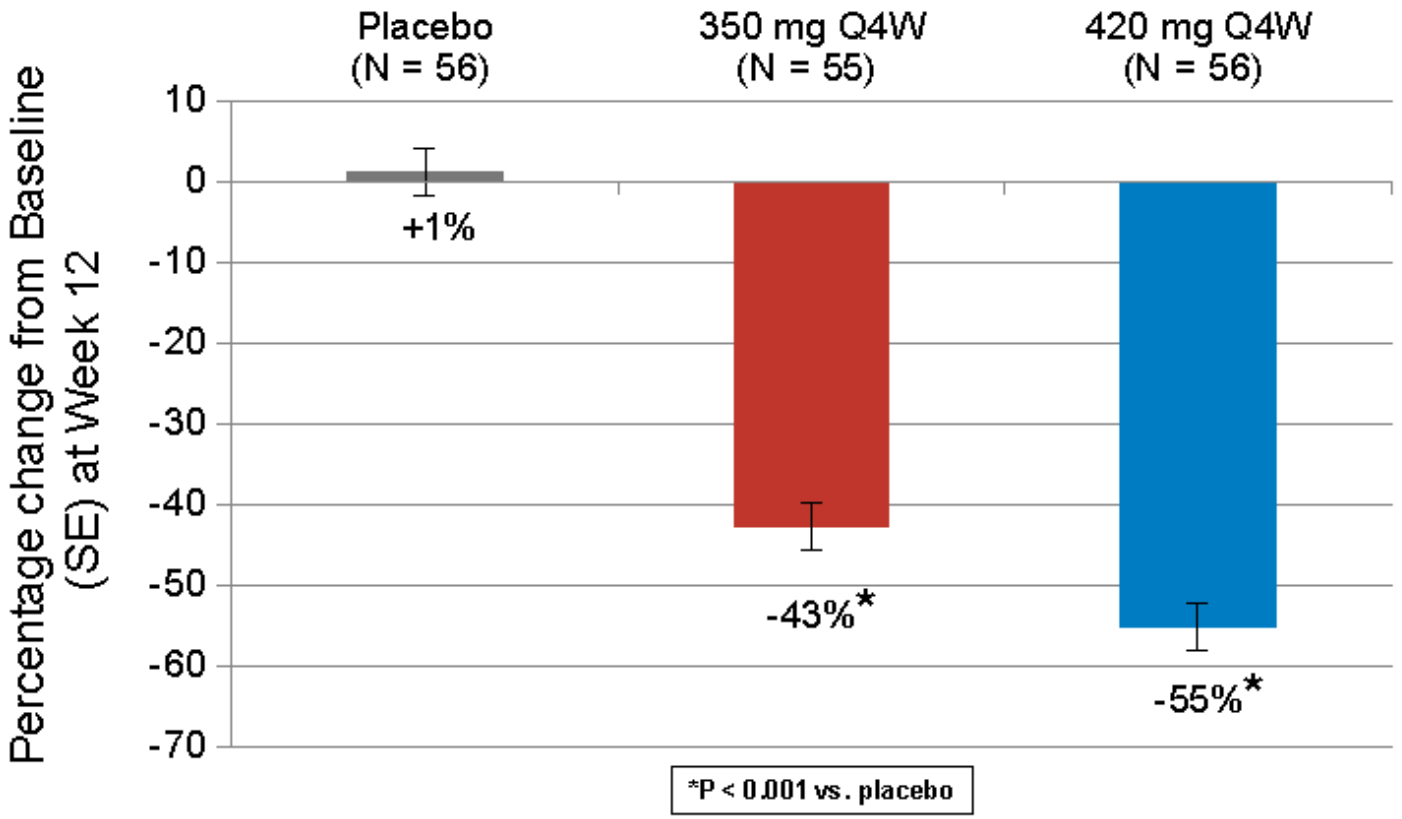
Q4W, every 4 weeks; SC, subcutaneous

Primary endpoint:
% change in LDL-C, *measured by ultracentrifugation*, from baseline at 12 weeks

Population

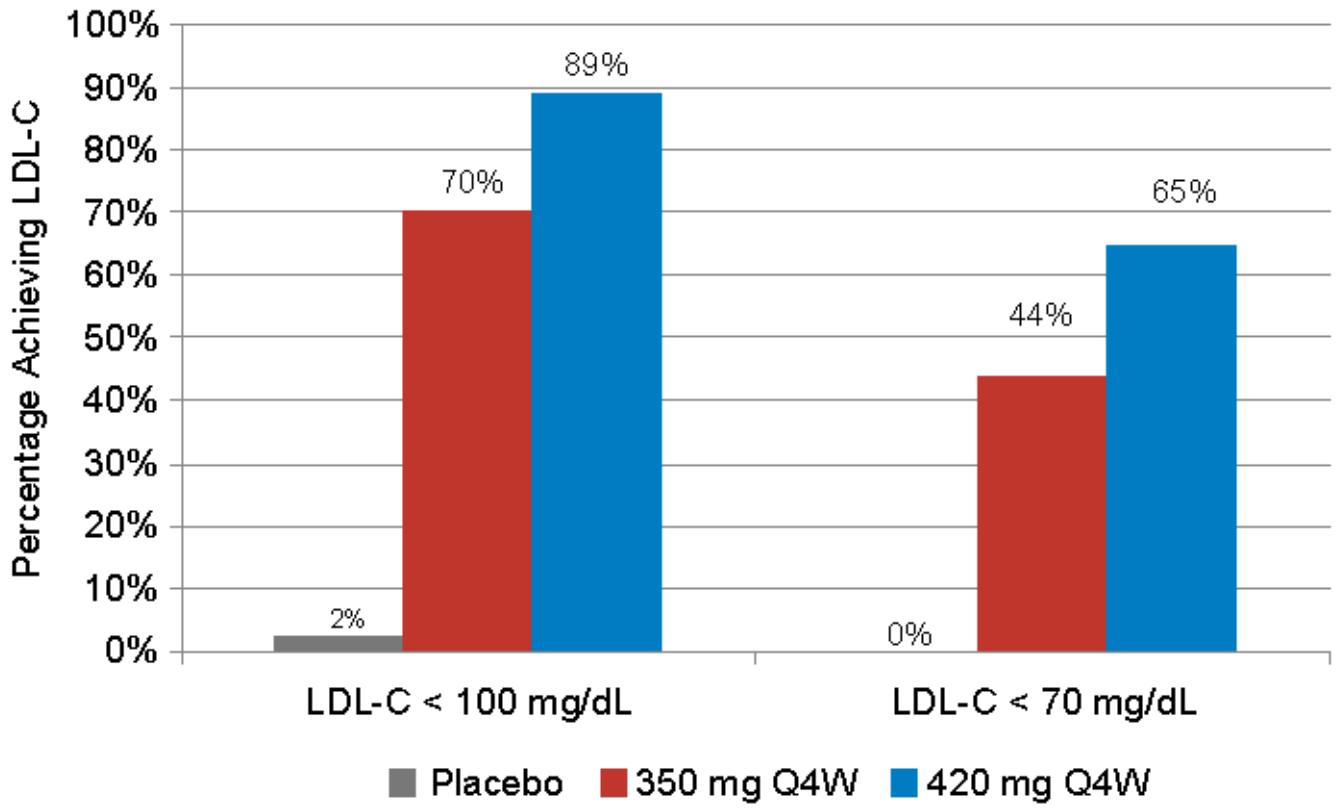
- 18–75 years, with a diagnosis of HeFH by Simon Broome criteria
- LDL-C ≥ 100 mg/dL and triglycerides ≤ 400 mg/dL
- At least 4 weeks of stable lipid-lowering therapy (eg, statin, ezetimibe, bile-acid sequestants, niacin)

RUTHERFORD: % Change in LDL-C, by UC, from Baseline to Week 12



Q4W, every 4 weeks; SE, standard error; UC, ultracentrifugation
LDL-C values at baseline and week 12 were measured using preparative UC.
Least Square Means are presented from the ANCOVA model including treatment and stratification factors as covariates.
Missing UC LDL-C values at week 12 were imputed using last observation carried forward and calculated LDL-C. A Hochberg adjustment was used to control the family wise error rate at ≤ 0.05.

RUTHERFORD: % of Patients Achieving LDL-C, by UC, Targets at Week 12



UC, ultracentrifugation

Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects (GAUSS): Interim Results from a Randomized, Double-blind, Placebo-controlled Study

- **Background:** Many patients experience muscle-related side effects to statins and cannot meet goal lipid levels with alternative methods. Plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) binds LDL receptors, therefore increasing levels of LDL-C in the blood. Phase 1 studies of a human monoclonal antibody to PCSK9, AMG145, have shown tolerance and effectiveness in lowering LDL-C.
- **Purpose:** To assess the effectiveness and safety of AMG145 in patients with muscle-related statin intolerance.
- **Methods:** During the 12-week, phase 2, randomized, double-blind, placebo- and ezetimibe-controlled study, 160 patients were randomized to one of 5 treatments: 280 mg, 350 mg, or 420 mg of AMG145, 420 mg AMG145 plus 10 mg ezetimibe, or placebo plus 10 mg ezetimibe administered subcutaneously every 4weeks. Primary endpoint was percent change in LDL-C levels from baseline to 12 weeks.
- **Results:** At week 12, mean percent decrease in LDL-C ranged from -67% in the 280 mg group to -110 in the 420 mg plus ezetimibe group compared with only -14% decrease in the placebo group. Four serious adverse events were reported among the AMG145 patients. Myalgia was the most common side effect reported.

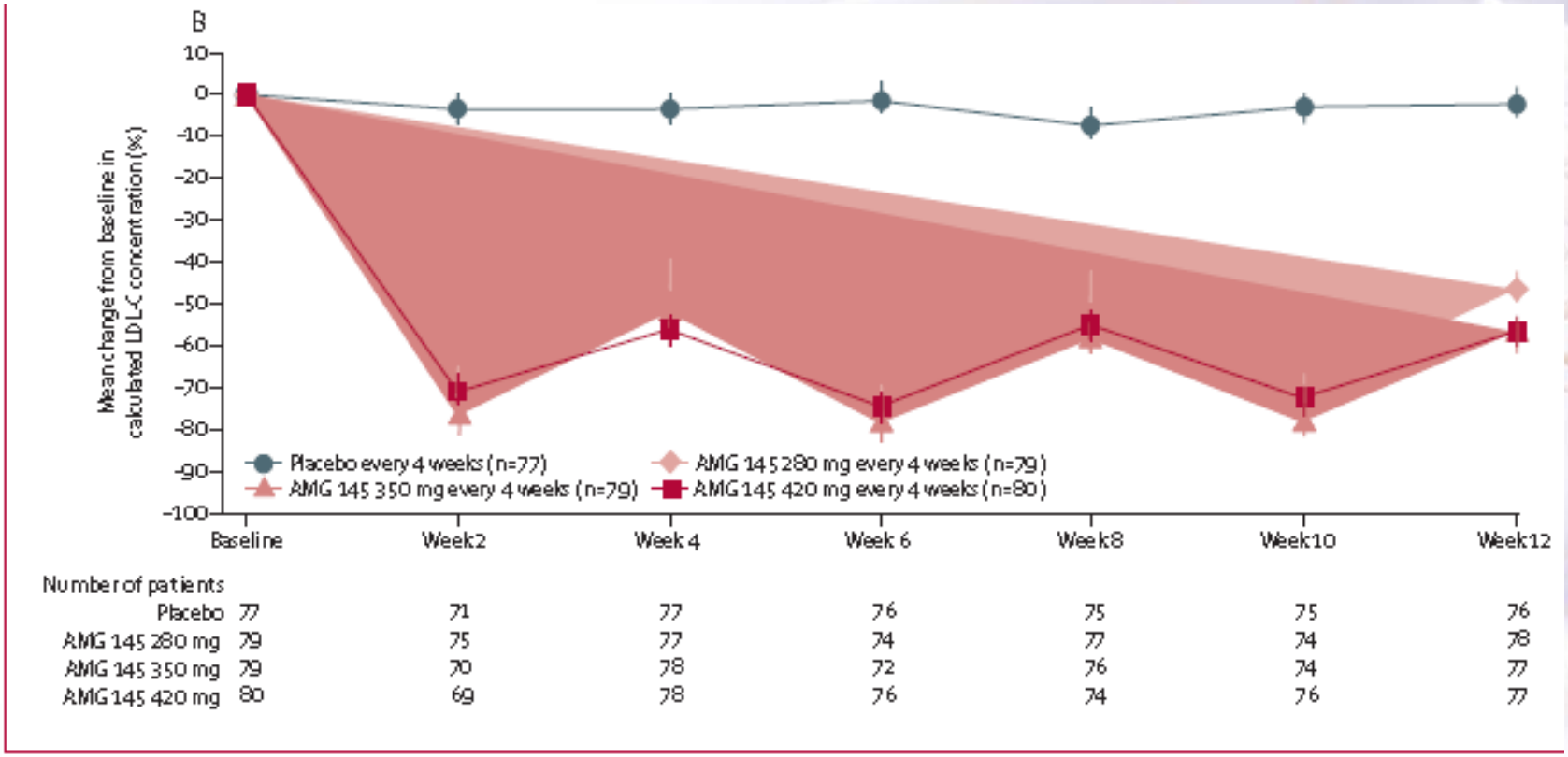
Percent of Patients Treated to LDL-C Goal at Week 12

Treatment	LDL-C < 100 mg/dL	LDL-C < 70 mg/dL
280 mg AMG145	47%	9%
350 mg AMG145	53%	17%
420 mg AMG145	61%	29%
420 mg AMG145 + ezetimibe	90%	62%
Placebo + ezetimibe	7%	0%

- **Conclusions:** Treatment with AMG145 displayed short-term tolerability and significant reduction in LDL-C levels.

Presented by: Sullivan D, AHA Scientific Sessions, Los Angeles

Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study



Number of patients							
Placebo	77	71	77	76	75	75	76
AMG 145 280 mg	79	75	77	74	77	74	78
AMG 145 350 mg	79	70	78	72	76	74	77
AMG 145 420 mg	80	69	78	76	74	76	77

Figure 3: Percentage change in calculated LDL-C concentration in 2 week intervals from baseline to week 12 in groups assigned to treatment every 2 weeks (A) and every 4 weeks (B)

www.thelancet.com **Published online November 6, 2012**

LAPLACE-TIMI 57. Consecución de objetivos lipídicos

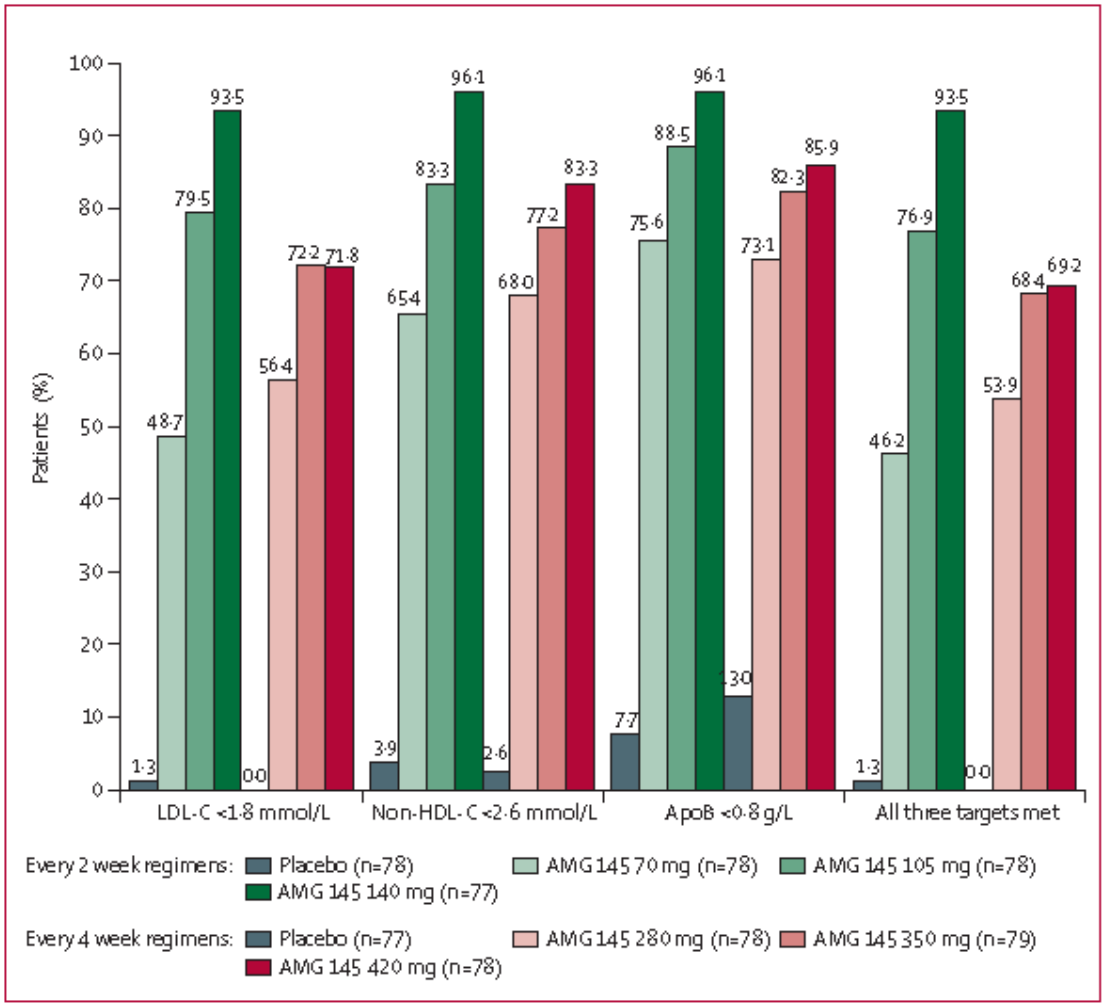


Figure 4: **Frequency of attainment of lipoprotein targets at week 12**

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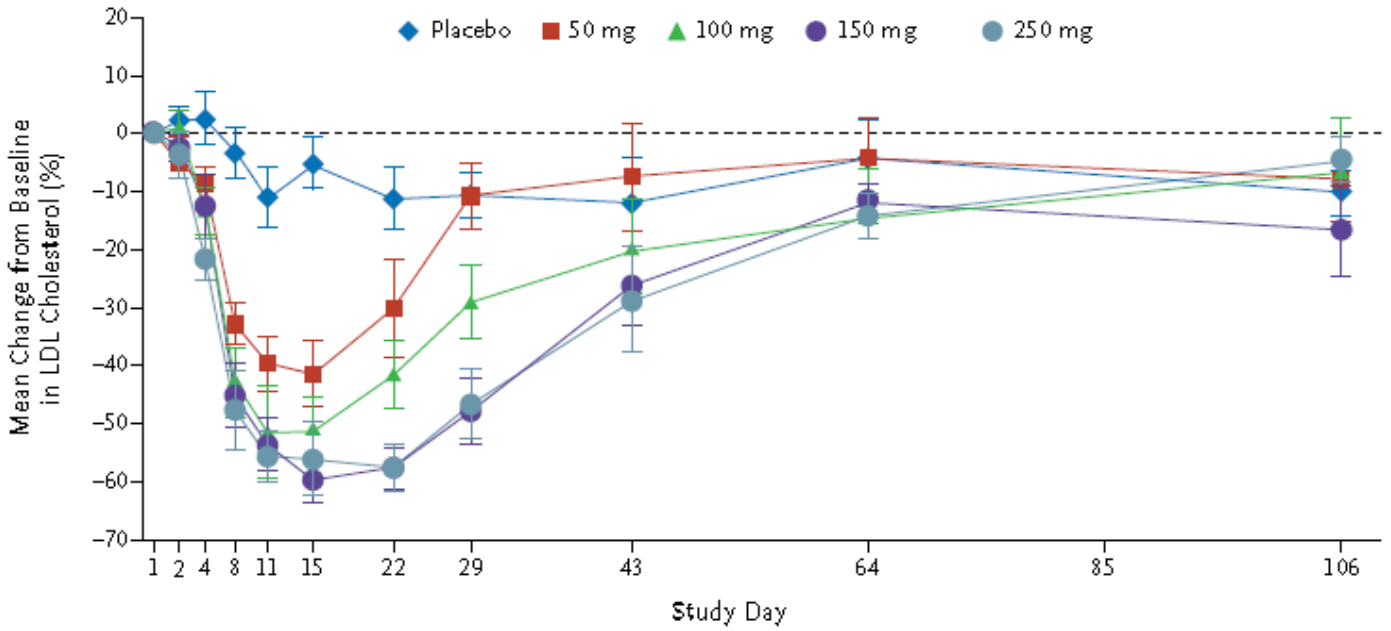
Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol **SAR 236**

B Subcutaneous Administration



No. at Risk											
Placebo	8	8	8	8	8	8	8	8	7	7	7
50 mg	6	6	6	6	6	6	6	6	5	6	5
100 mg	6	6	6	6	5	6	6	6	5	6	6
150 mg	6	6	5	5	5	5	5	5	5	4	5
250 mg	6	6	6	6	6	6	6	6	6	6	6

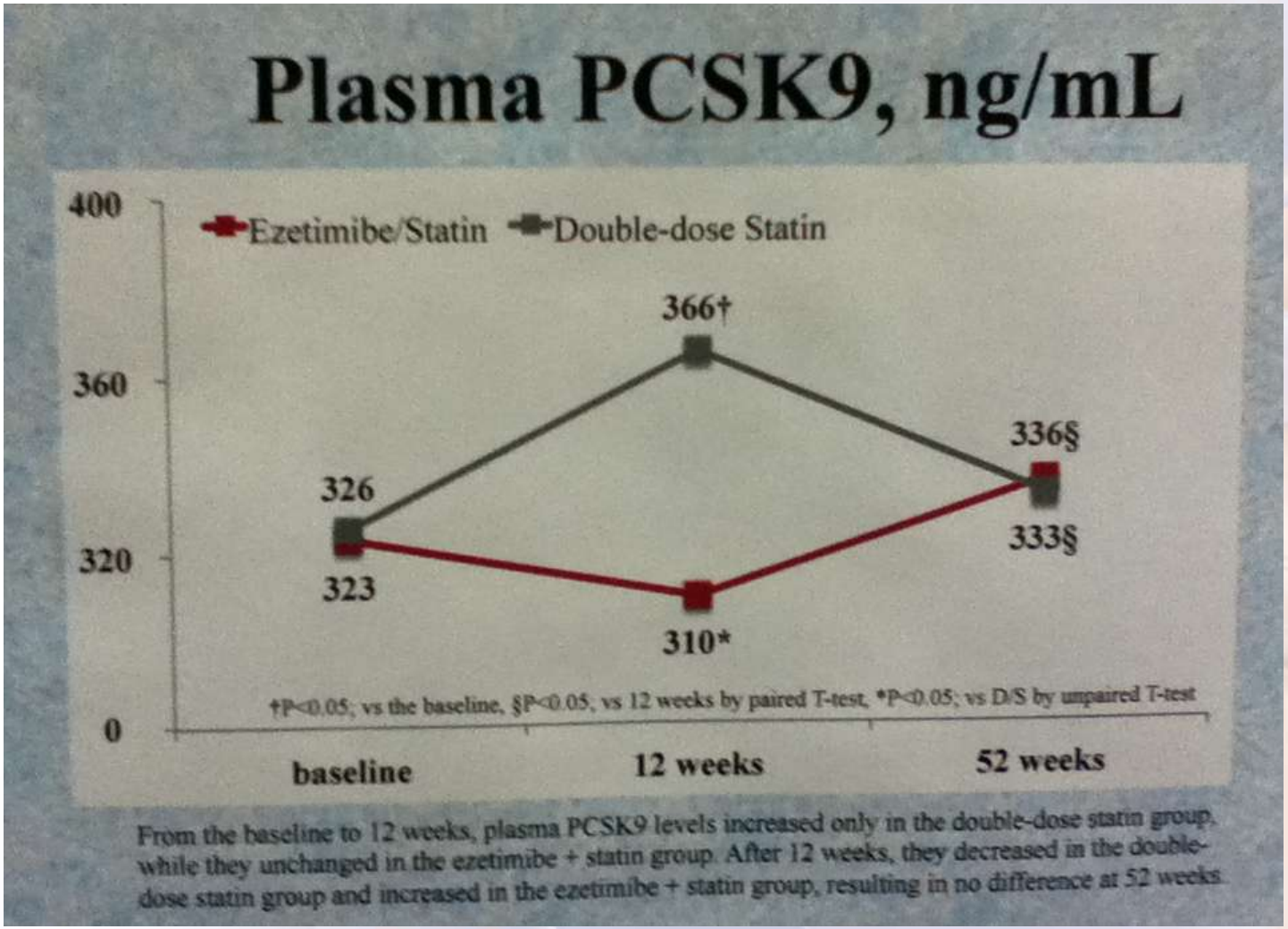
Figure 1. Mean Percent Change from Baseline in LDL Cholesterol Values among Healthy Volunteers in Single-Dose Studies.

Effects of 12 Weeks of Treatment with RN316 (PF-04950615), a Humanized IgG2Δa Monoclonal Antibody Binding Proprotein Convertase Subtilisin Kexin Type 9, in Hypercholesterolemic Subjects on High and Maximal Dose Statins

- **Background:** Proprotein convertase subtilisin kexin type 9 (PCSK9) binds to LDL-C receptors preventing LDL-C clearance, therefore increasing LDL-C levels in the blood. RN316, a humanized monoclonal antibody, binds to PCSK9 preventing down-regulation of the LDL-C receptors, which has been shown to improve LDL-C clearance, therefore reducing LDL-C levels.
- **Purpose:** To evaluate effects of RN316 on LDL-C levels in patients on high-to-maximal doses of atorvastatin, rosuvastatin or simvastatin.
- **Methods:** In this Phase 2, double-blind, randomized, placebo-controlled study, 135 patients already undergoing statin treatment were randomized to 1 of 5 treatment arms: placebo, 0.25 mg/kg, 1.0 mg/kg, 3.0 mg/kg, or 6.0 mg/kg of RN316 administered every 4 weeks for 12 weeks with an 8 week follow-up period.
- **Results:** LDL-C levels were significantly decreased with 3.0 and 6.0 mg/kg doses of RN316 in addition to high or maximal dosage statin treatment. Total cholesterol was also reduced and levels of HDL-C increased. No significant changes were observed in triglycerides across any of the 5 treatment arms. Very few drug-related adverse events were observed. Those that did occur were mild and resolved with no intervention. The effects on LDL-C persisted for 4 weeks post treatment.
- **Conclusions:** RN316 significantly lowered LDL-C in addition to high or maximal statin dosage and was generally safe and well tolerated.

Presented by: Gumbiner B, AHA Scientific Sessions, Los Angeles

Efecto de estatinas en monoterapia o en combinación con Ezetimiba en la concentración de PCSK9



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Effects of the Cholesteryl Ester Transfer Protein Inhibitor Dalcetrapib in Patients with Recent Acute Coronary Syndrome

Gregory G. Schwartz, MD PhD
VA Medical Center and University of Colorado School of Medicine, Denver, Colorado

On behalf of the **dal-OUTCOMES*** investigators

* Funded by F. Hoffmann-La Roche, Ltd.

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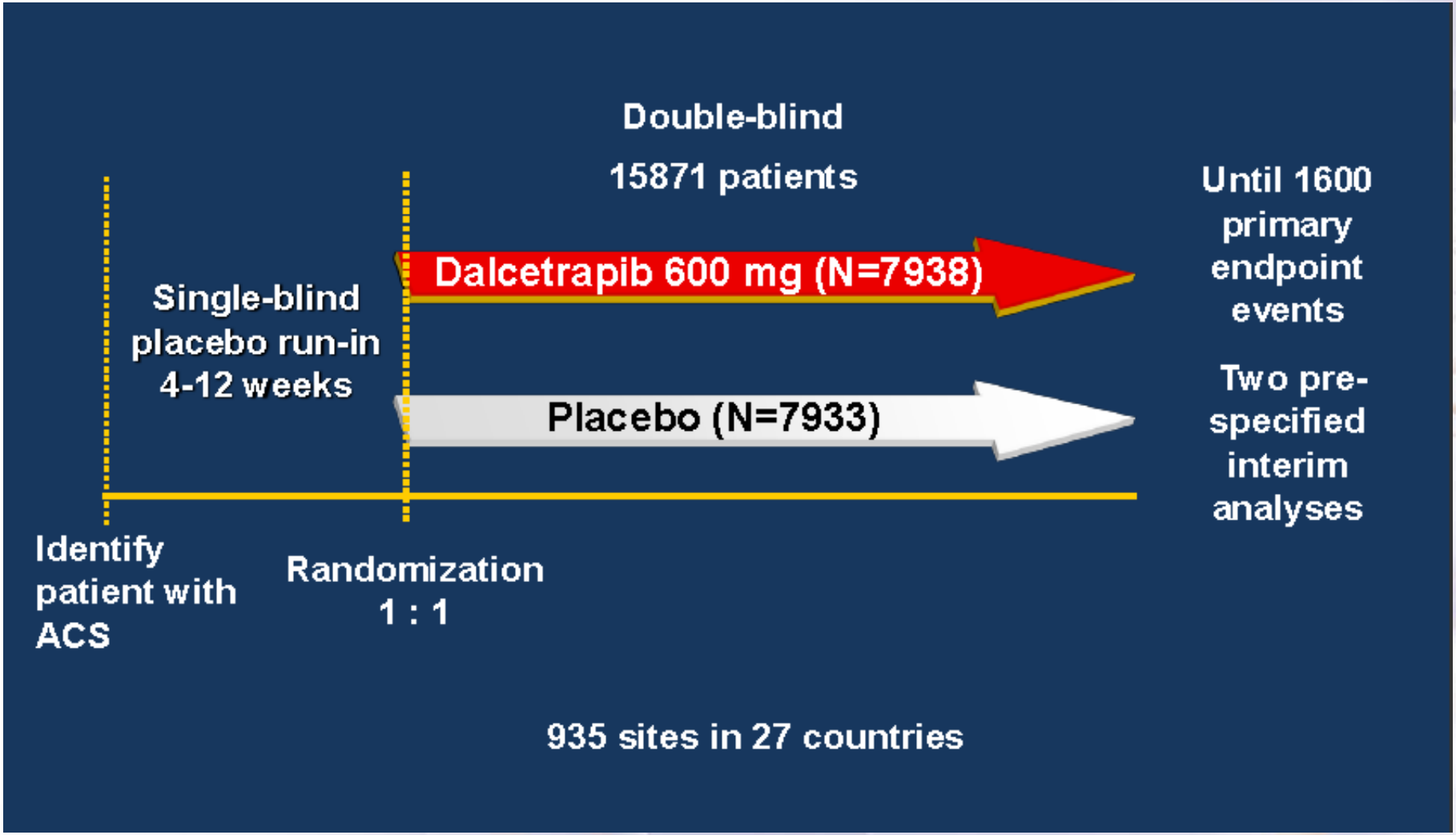
Dal-Outcomes. Diseño del estudio



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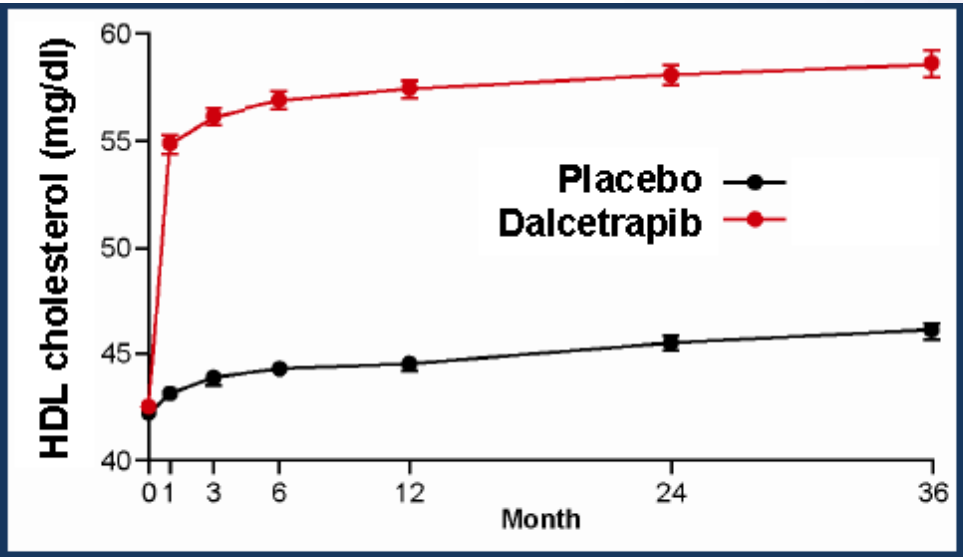
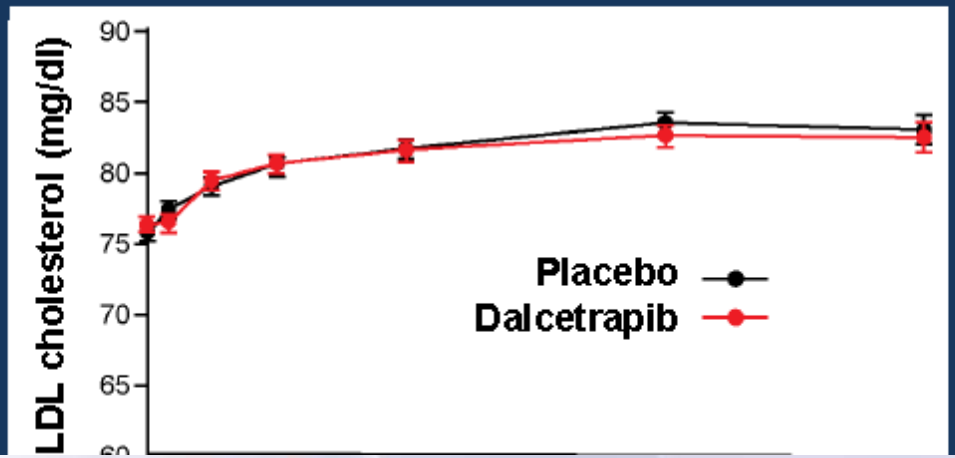
Efecto del tratamiento sobre cHDL y cLDL





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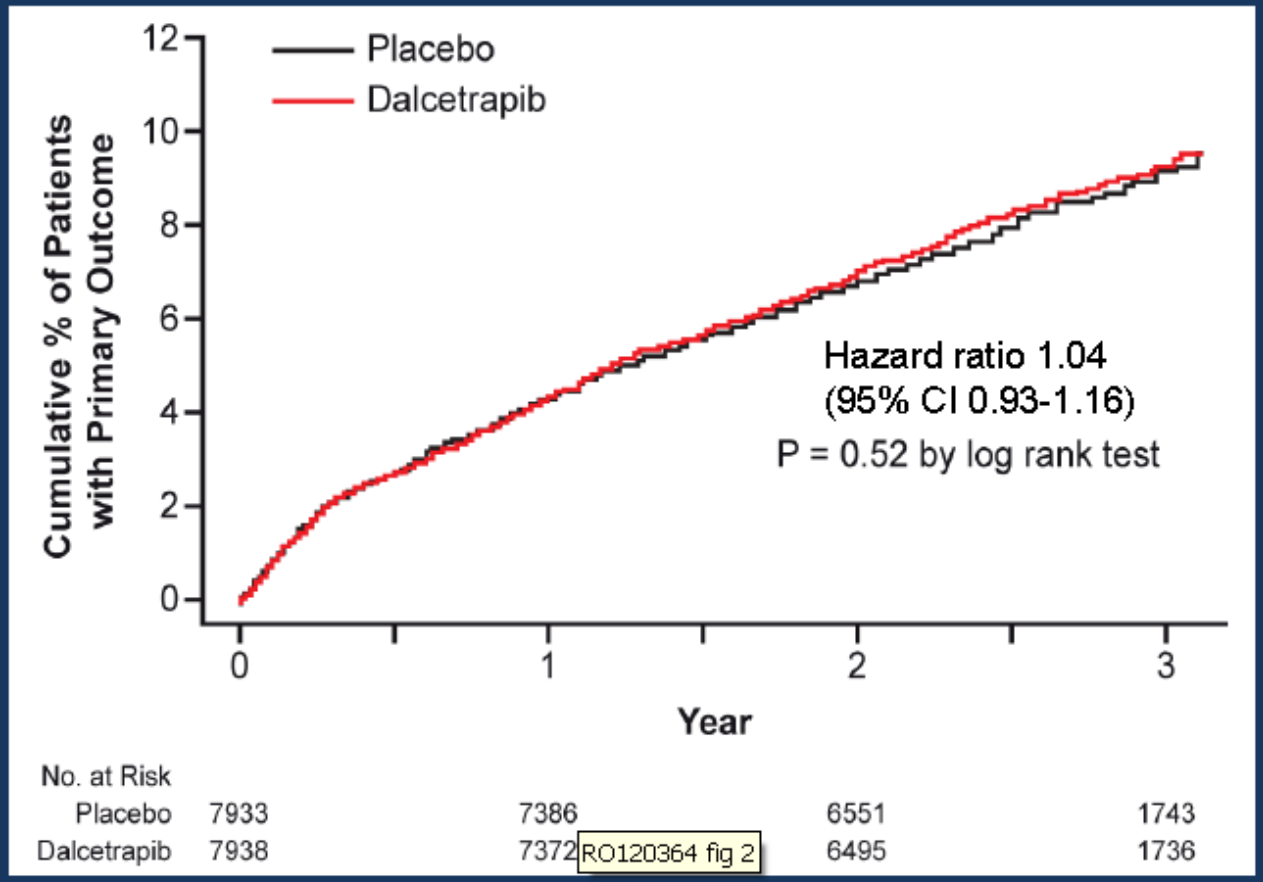
Dal-Outcomes.
Objetivo primario por grupos de intervención



* Coronary heart disease death, non-fatal MI, ischemic stroke, hospitalization for unstable angina, resuscitated cardiac arrest

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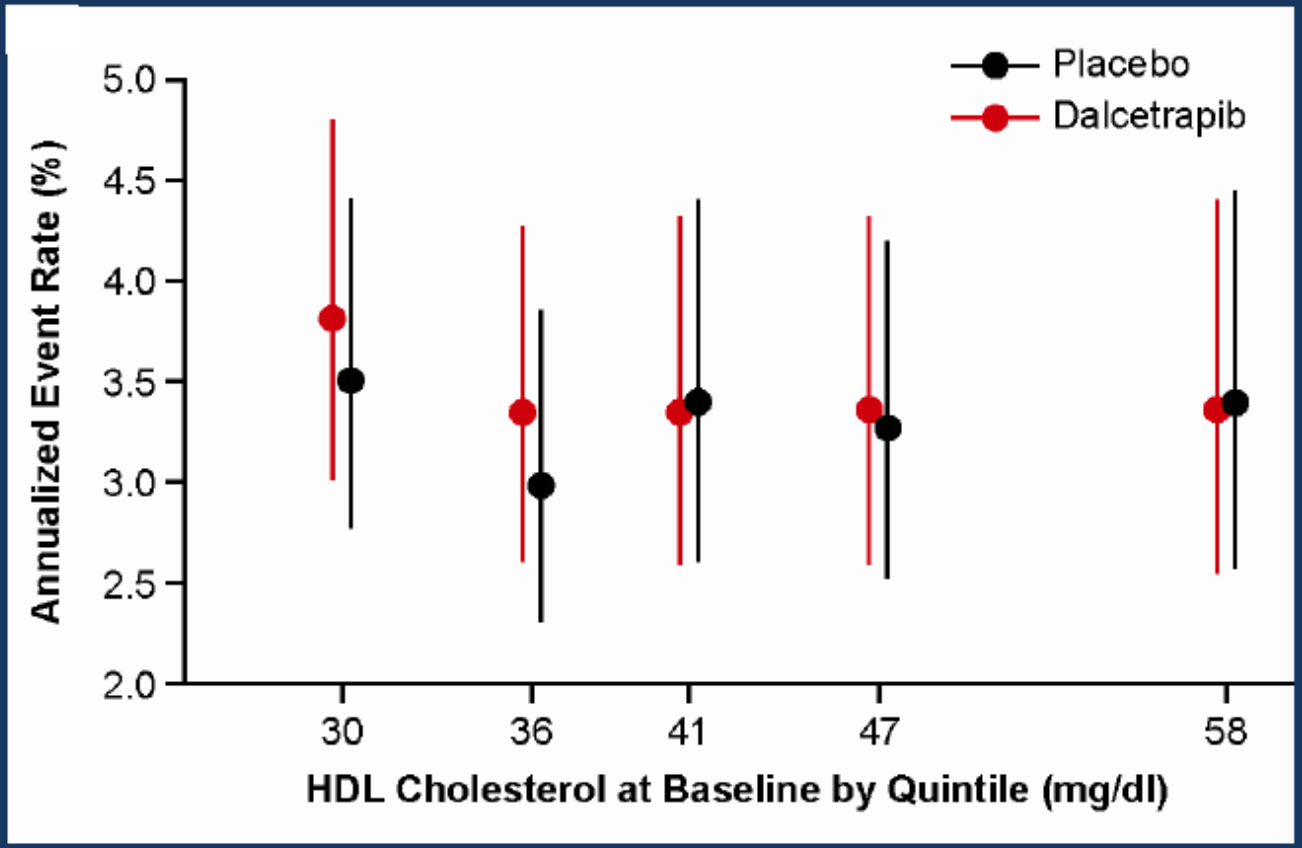
Why did dalcetrapib fail to reduce risk?

No association between baseline HDL-C (by quintiles) and risk of primary endpoint



Niacin Use in Patients with Low HDL-Cholesterol Receiving Intensive Statin Therapy

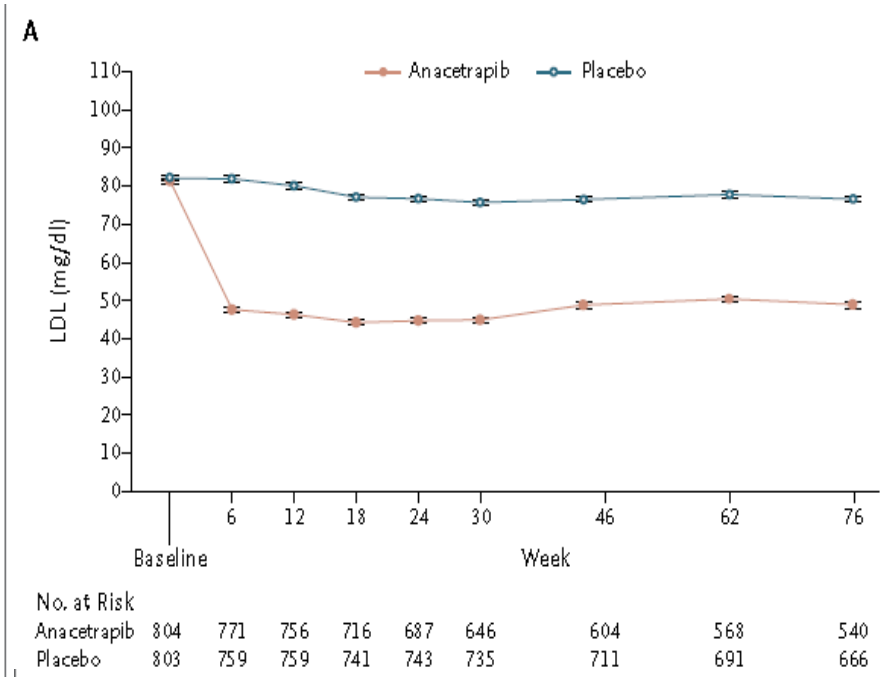
William E. Boden, MD, FACC, FAHA
Jeffrey Probstfield, MD, FACC, FAHA

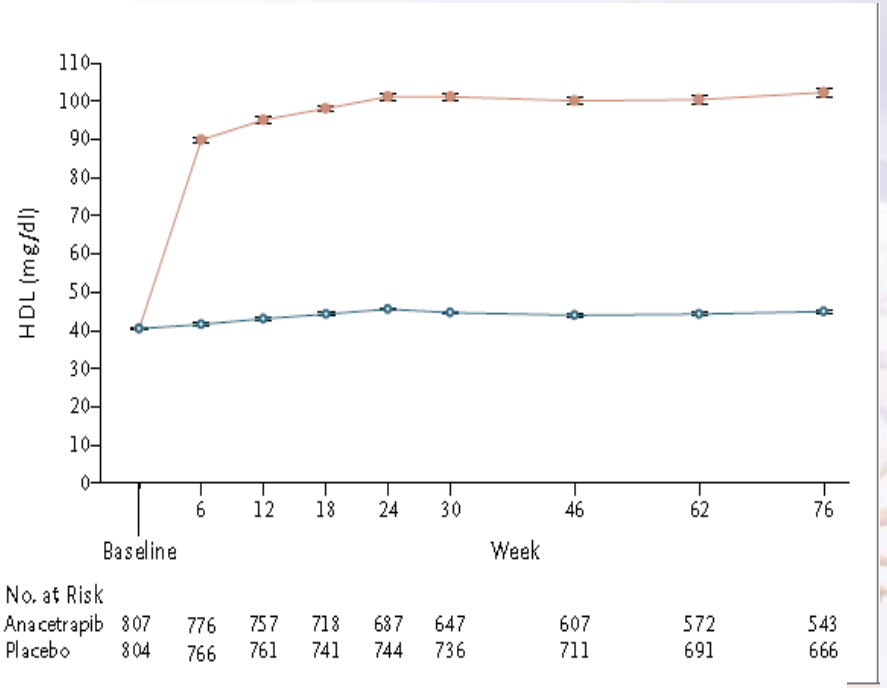
Co-Principal Investigators
on behalf of the AIM-HIGH Investigators

AIM-High. Subanálisis (Dr. Guyton)

- Lípidos al inicio
  - cLDL: No
  - Tgs: No
  - cHDL: No
  - TG≥ 200 mg/dL y cHDL < 33 mg/dL: reduccion del 37% (p=0,01). 13% de los sujetos (se habían excluiso sujetos con Tg > 400 mg/dL)
- Lípidos durante el ensayo
  - cHDL: No
  - C-No-HDL: Heterogeneidad significativa
    - HR 1,23 (p=0,02) en grupo placebo
    - HR 1,02 (NS) con niaspan
  - Sugiere que los beneficios del niaspan en ese subgrupo pueden no ser lípido-dependientes

ESTUDIO DEFINE. EFECTO DE ANACETRAPIB EN LIPIDOS PLASMÁTICOS





Variable	Baseline		Week 24			
	No. of Patients with Data	Level	No. of Patients with Data	Level	Change from Baseline	Change from Baseline beyond That with Placebo (95% CI)
						percent
Lipoprotein(a) — nmol/liter						
Placebo	768	25.9	765	29.6	0.5±32.9	
Anacetrapib	762	26.8	758	14.8	−23.8±50.5	−36.4 (−40.7 to −32.3)

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N Engl J Med 2010;363:2406-15.

Cambios lipídicos asociados con Anacetrapib

	VLDL	LDL	HDL	Lp(a)
Pool	↓	↓	↑	↓
FCR	↑	↑	↓	↔
SR	↔	↔	↔	↓

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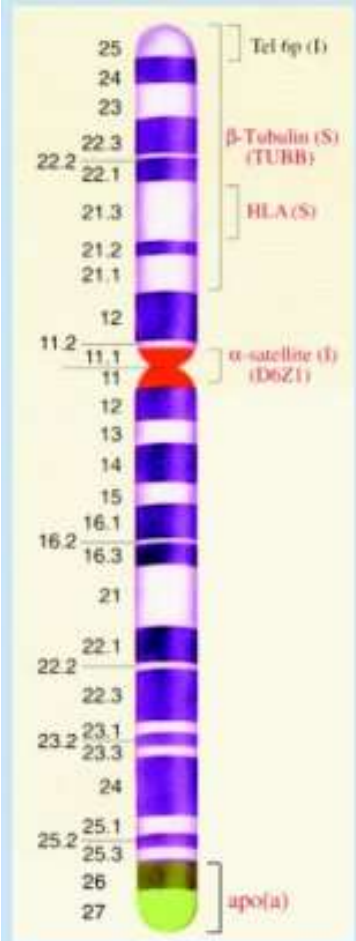
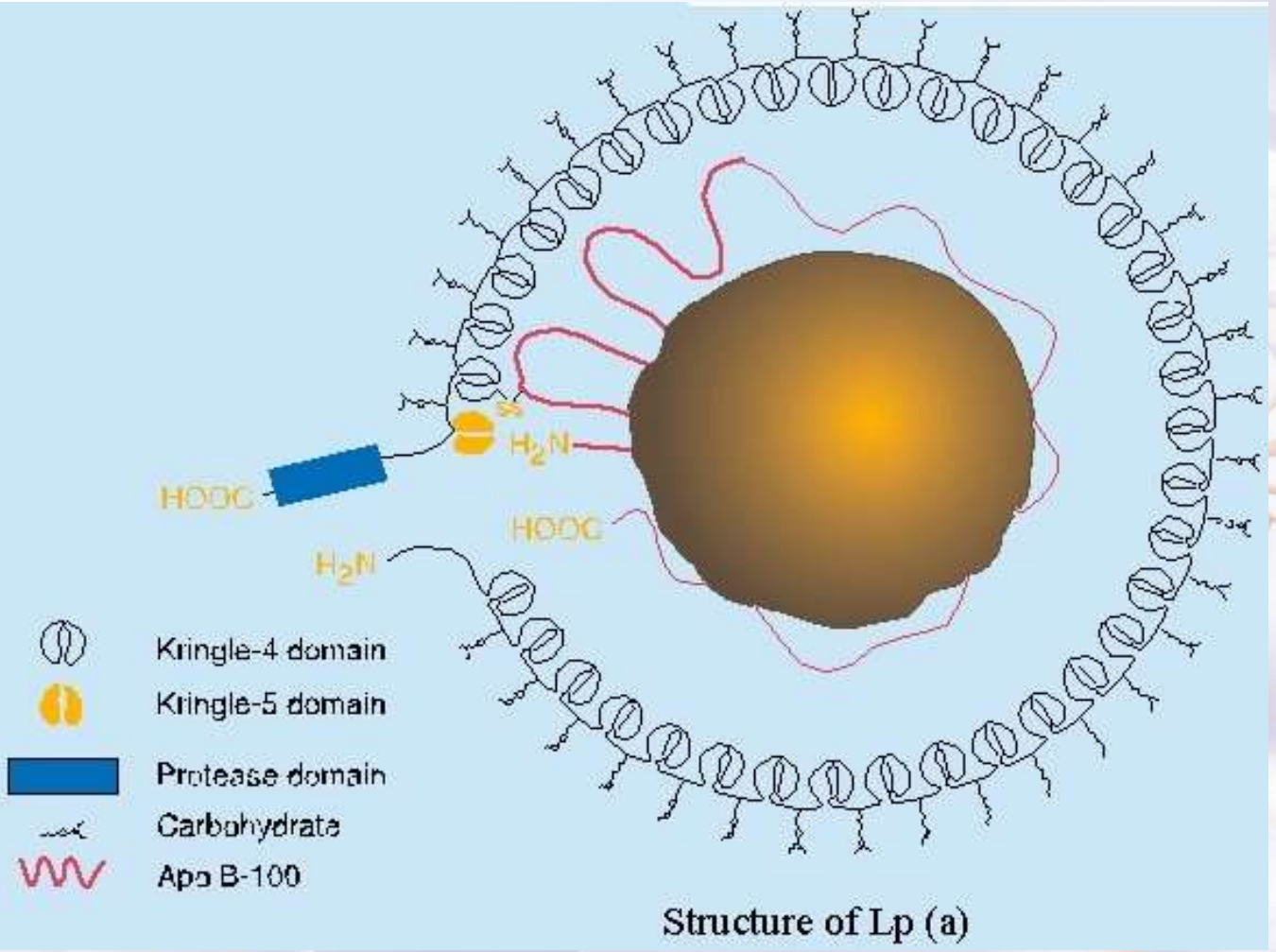
Lipoproteína (a) Lp(a)



Chromosome 6



Structure of Lp (a)

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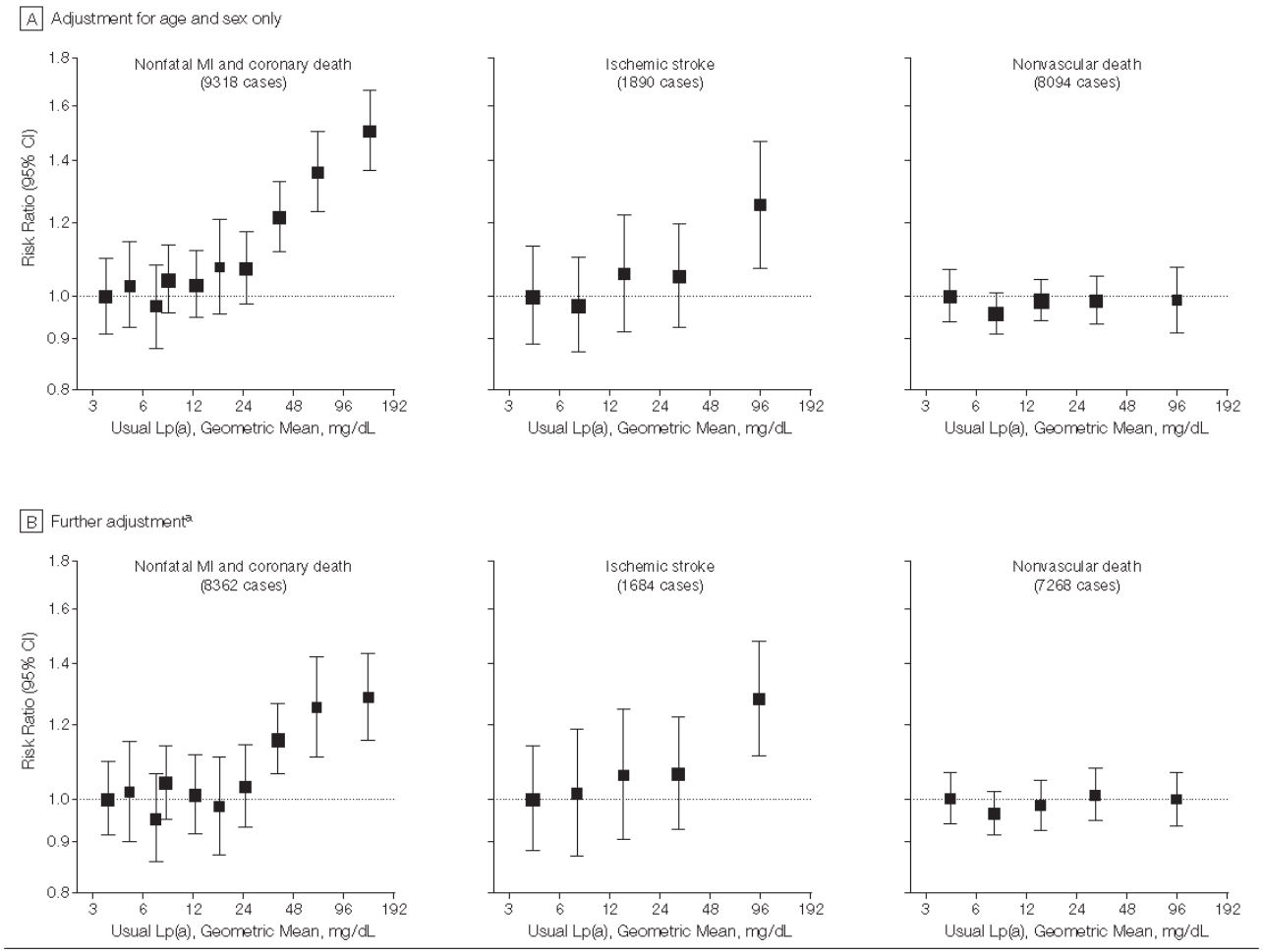
Lipoprotein(a) Concentration and the Risk of Coronary Heart Disease, Stroke, and Nonvascular Mortality

JAMA. 2009;302(4):412-423

Figure 2. Risk Ratios for Coronary Heart Disease, Ischemic Stroke, or Nonvascular Death by Quantile of Usual Lp(a) Level



Lp(a) indicates lipoprotein(a); MI, myocardial infarction. Sizes of data markers are proportional to the inverse of the variance of the risk ratios. Confidence intervals (CIs) were calculated using a floating absolute risk technique. Studies involving fewer than 10 cases of any outcome were excluded from the analysis of that outcome.

[a]Further adjustment for usual levels of systolic blood pressure, smoking status, history of diabetes, body mass index, and total cholesterol. The x- and y-axes are shown on a log scale. Lowest quantiles are referents.

Fármacos que descienden Lp(a)

- Niacina:
  - -20%
  - AIM-High, todavía no ha medido Lp(a)
  - Mecanismo ?
- Inhibidores de PCSK9
  - -25-35%
  - Responden mejor los sujetos con concentraciones bajas
  - Mecanismo ? Independiente de la reducción de cLDL, concentración basal de PCSK9
- Anacetrapib
  - -36%
  - Mecanismo:
    - Reducción de producción
    - Reducción conversión de IDL → LDL