REGRESION DE LA ATEROSCLEROSIS ¿MITO O REALIDAD?

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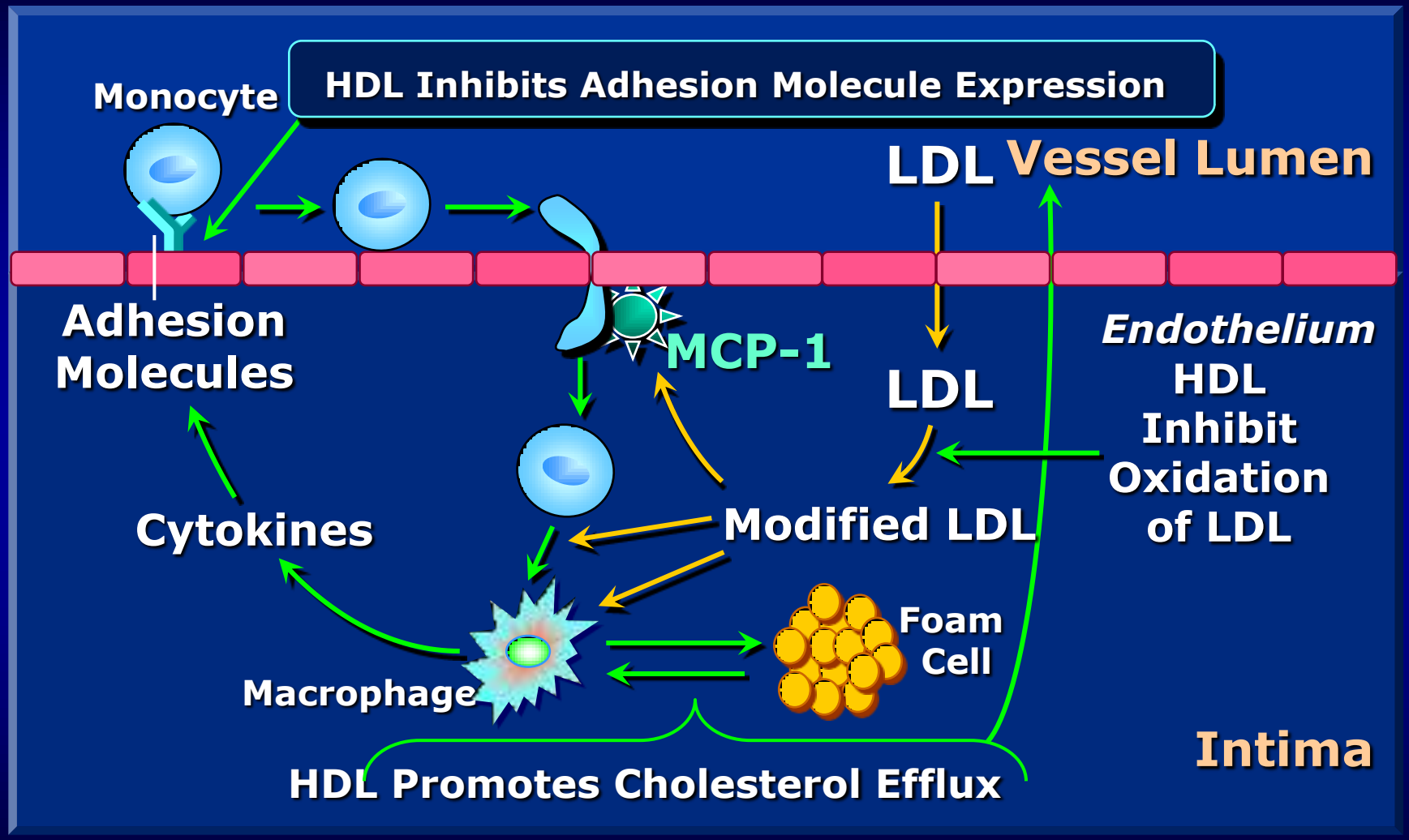
International Atherosclerosis Society
American Heart Association
American Stroke Association
Vascular Biology Working Group
American Society of Hypertension

REGRESION DE LA ATEROSCLEROSIS ¿MITO O REALIDAD?

DECLARACION DE INTERESES

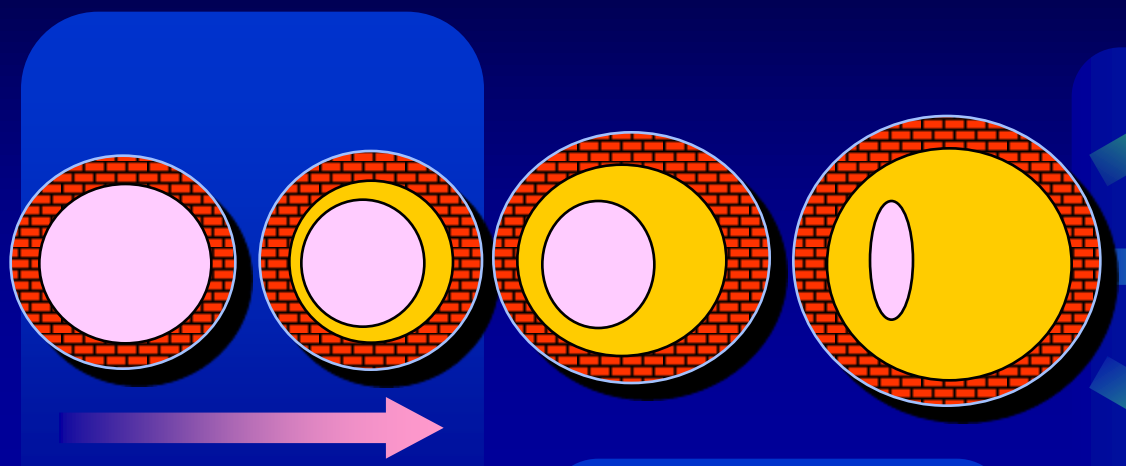
NINGUNA

INFLAMACION Y ATEROSCLEROSIS



Cockerill GW, *Arterioscler Thromb Vasc Biol.* 1995;15:1987-1994.

EVOLUCION DE LA ATEROSCLEROSIS



Lesion initiation

Ischemic Heart Disease

Cerebrovascular Disease

Peripheral Vascular Disease

No symptoms

± Symptoms

Symptoms

Time (y)

Cockerill GW, *Arterioscler Thromb Vasc Biol.* 1995;15:1987-1994.

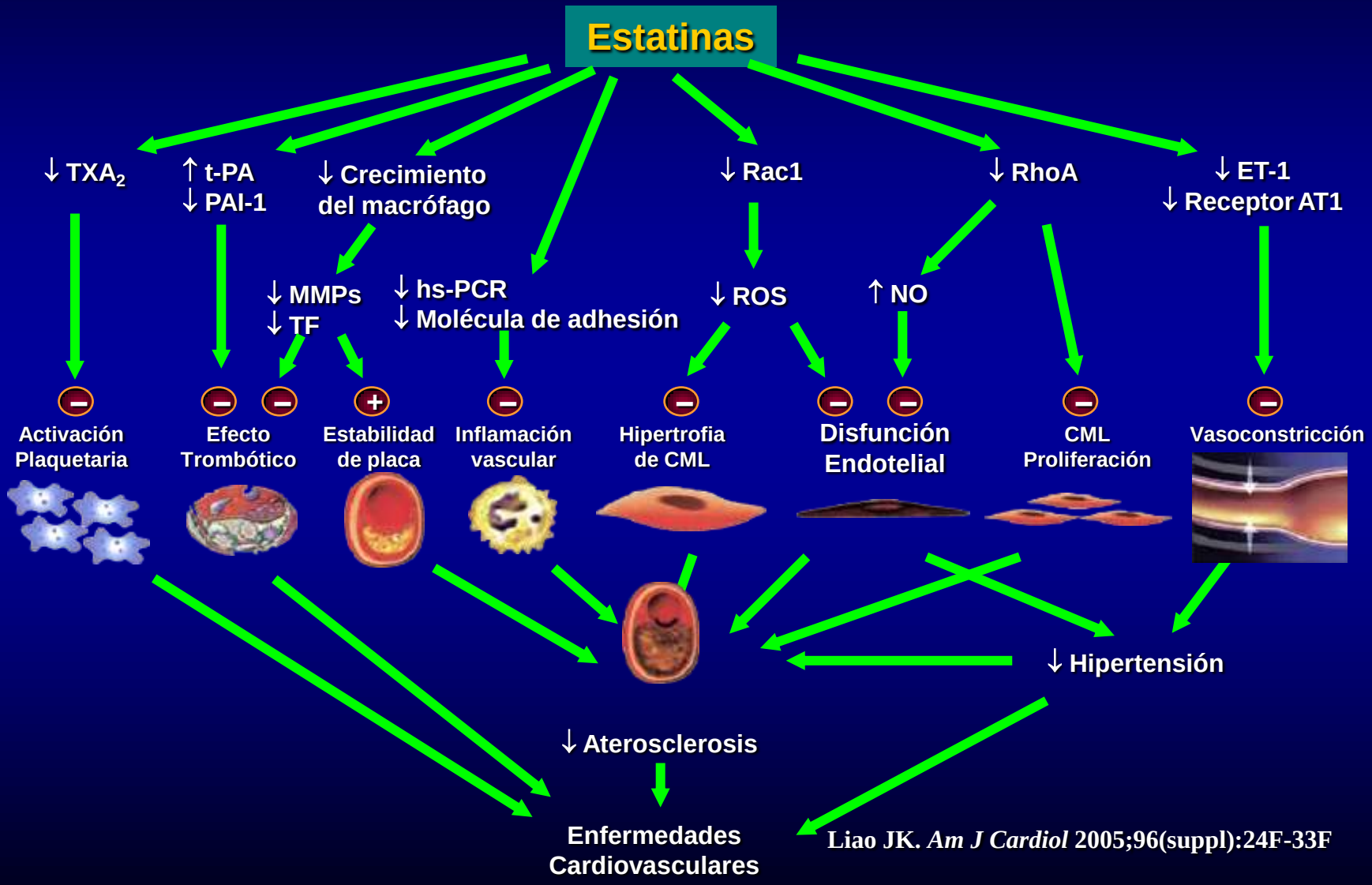
REGRESION DE LA ATEROSCLEROSIS ¿MITO O REALIDAD?

IMÁGENES EN ATEROSCLEROSIS

- *IVUS (ULTRASONOGRAFIA INTRAVASCULAR)*
- *CIMT (ENGROSAMIENTO IM CAROTIDEO)*
- *MRI (RESONANCIA MAGNETICA)*
- *PET/CT (F-FLUORODEOXYGLUCOSA)*

Arsenault BJ. *Curr Cardiol Rep* 2012;14:443-449.

ESTATINAS. EFECTOS PLEIOTROPICOS



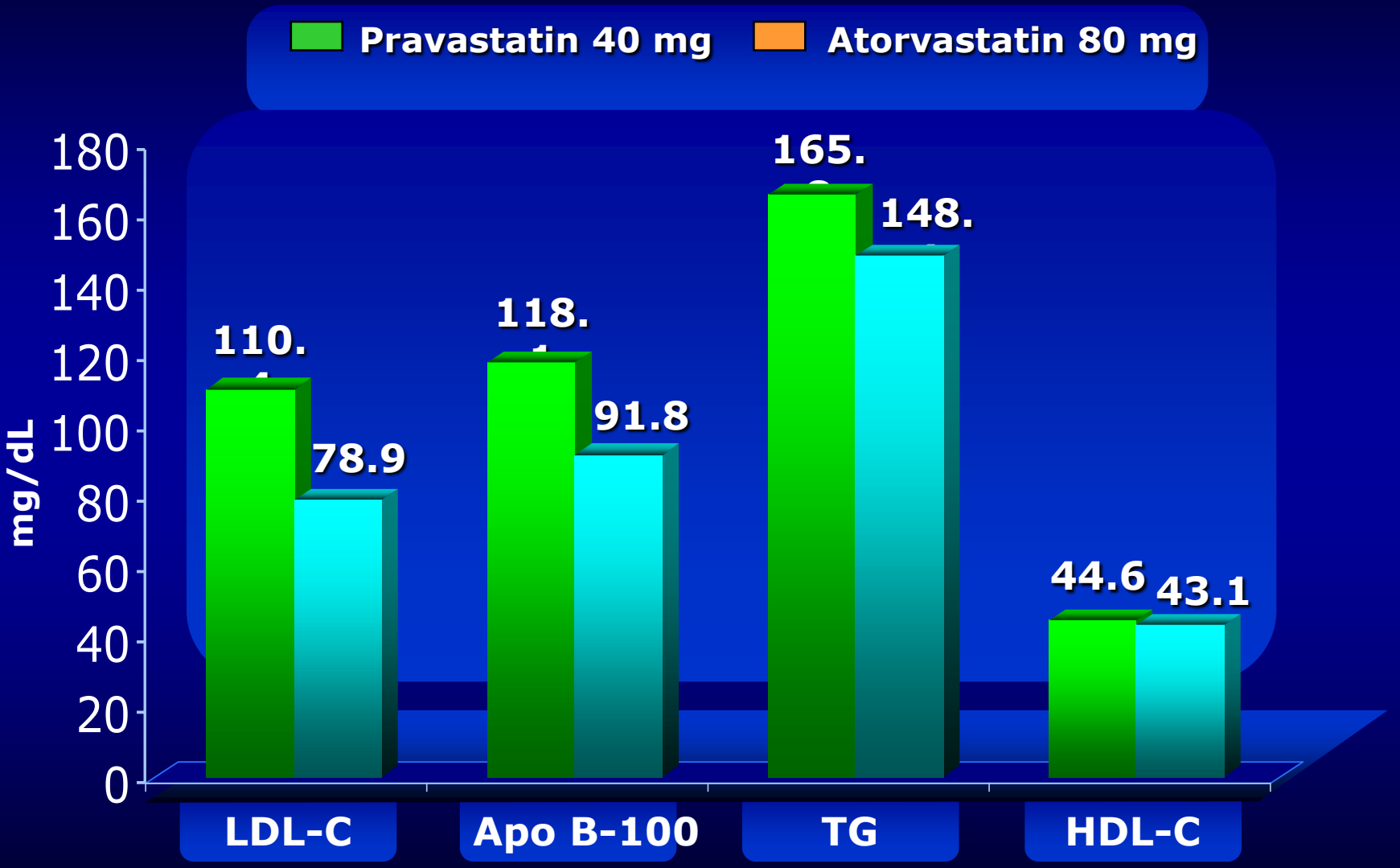
Liao JK. *Am J Cardiol* 2005;96(suppl):24F-33F

REVERSAL

- 654 patients with symptomatic CAD with angiographic stenosis >20% and LDL-C 125–210 mg/dL; 502 with evaluable follow-up
- Randomization to pravastatin 40 mg/d or atrovastatin 80 mg/d for 18 months
- IVUS performed at baseline and 18 months
- **Primary endpoint:** percent change in atheroma volume assessed with IVUS

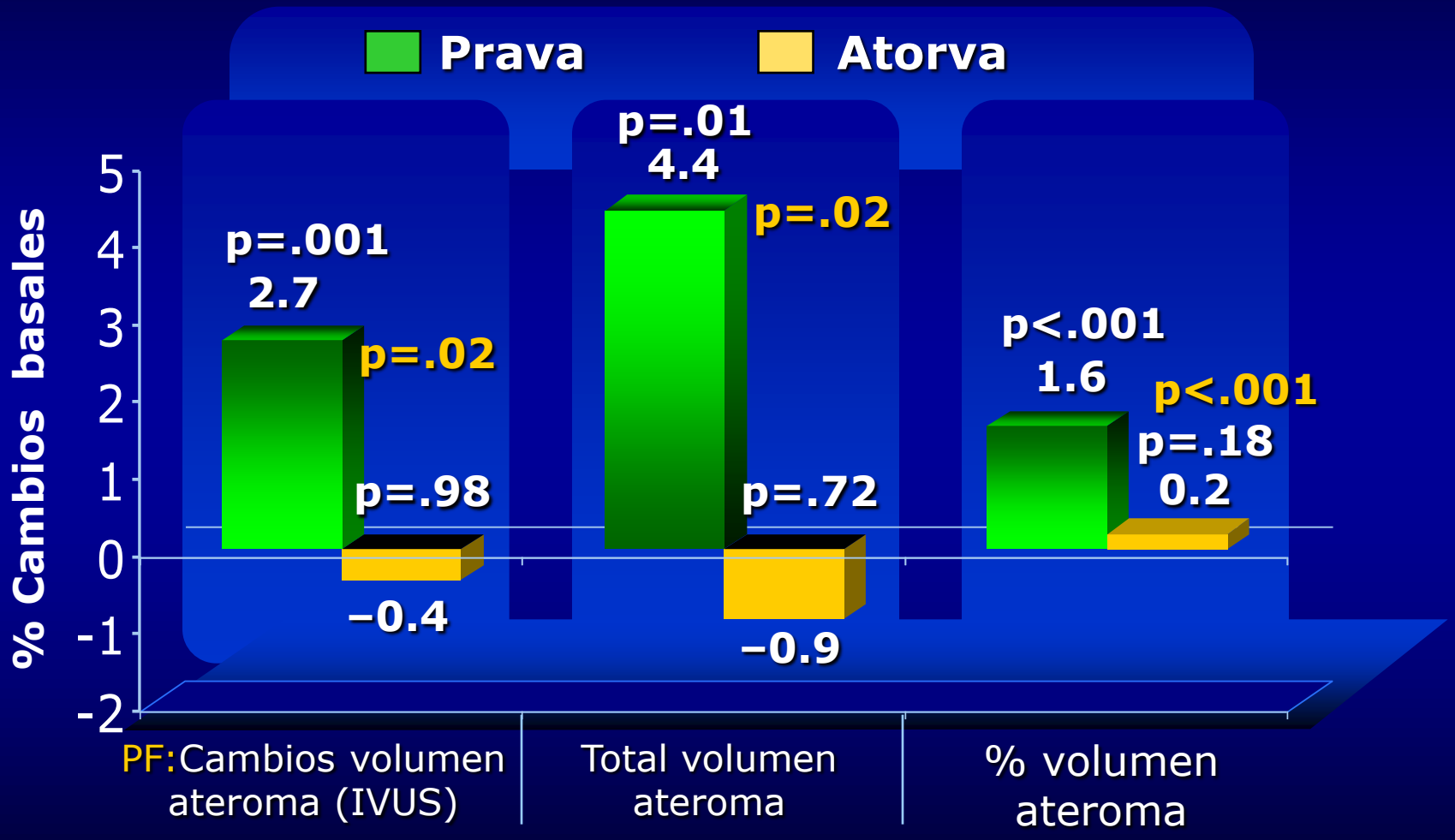
Nissen SE et al. *JAMA* 2004;291:1071-1080.

REVERSAL



Nissen SE et al. *JAMA* 2004;291:1071-1080.

REVERSAL



Nissen SE et al. *JAMA* 2004;291:1071-1080.

ASTEROID Trial

507 patients ≥ 18 years with angiographic evidence of CAD, excluding patients using lipid-lowering medication for more than 3 mos within the previous 12 mos, uncontrolled triglyceride levels, and poorly controlled diabetes.
Prospective. Multicenter. International. Open Label. Treatment for 24 mos. 292 patients with 613 matched stenoses at baseline and study end.

Rosuvastatin
40 mg/day n=292

24 month treatment

- Primary Endpoint: Rosuvastatin regression of coronary atherosclerosis by intravascular ultrasound (IVUS)
- Secondary Endpoint: Rosuvastatin regression of coronary atherosclerosis by quantitative coronary angiography (QCA).

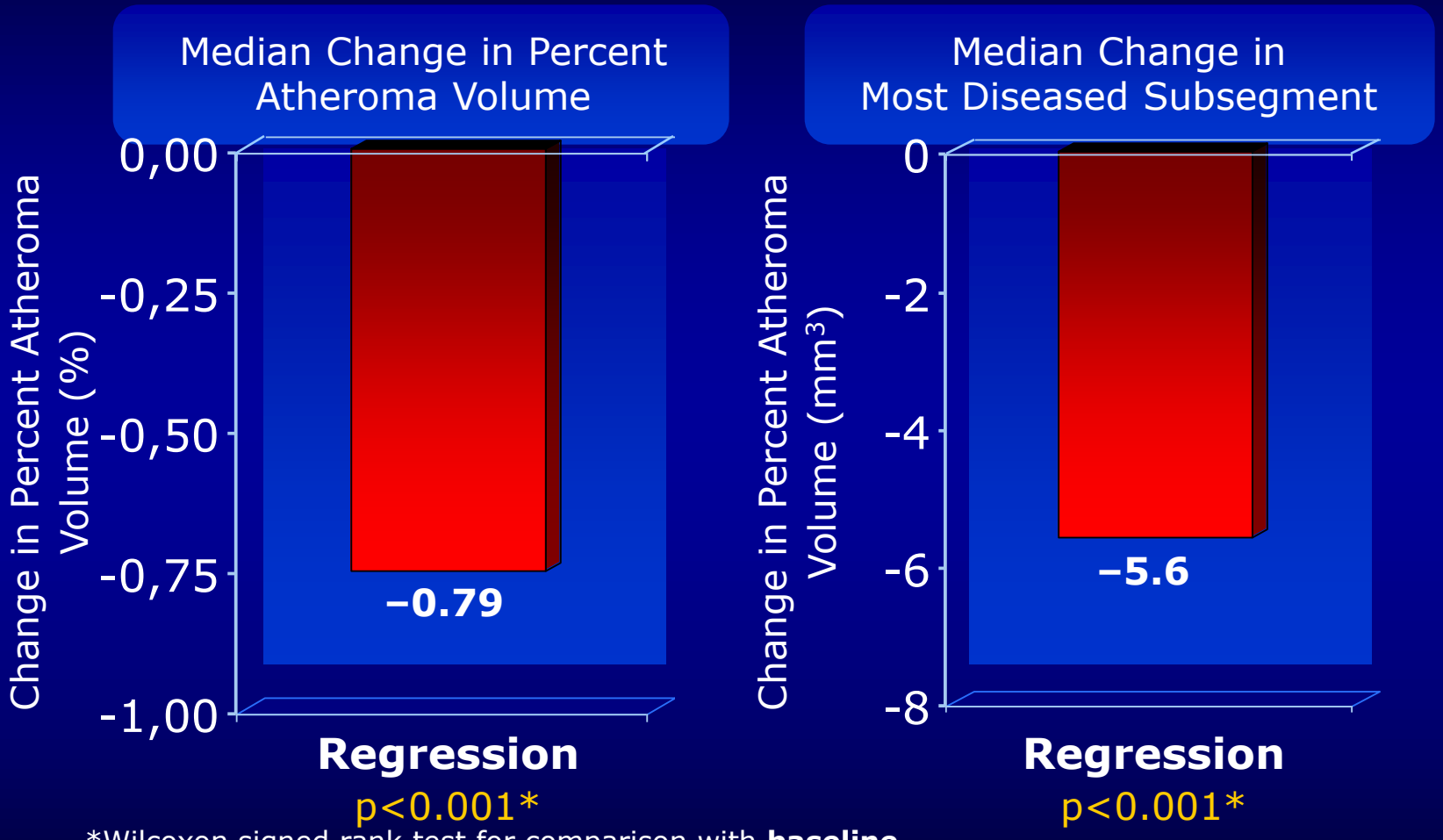
Nissen SE et al. *JAMA* 2006;295:1556-1565.

ASTEROID

	Mean Baseline	Mean during Treatment	Percent Change	p Value
CT (mg/dL)	204.0	133.8	–33.8	<0.001
LDL-C (mg/dL)	**130.4**	**60.8**	**–53.2**	<0.001
HDL-C (mg/dL)	43.1	49.0	**+14.7**	<0.001
TG (mg/dL)	152.2	121.2	–14.5	<0.001
LDL-C/HDL-C	**3.2**	1.3	**–58.5**	<0.001

Nissen SE et al. *JAMA* 2006;295:1556-1565.

ASTEROID

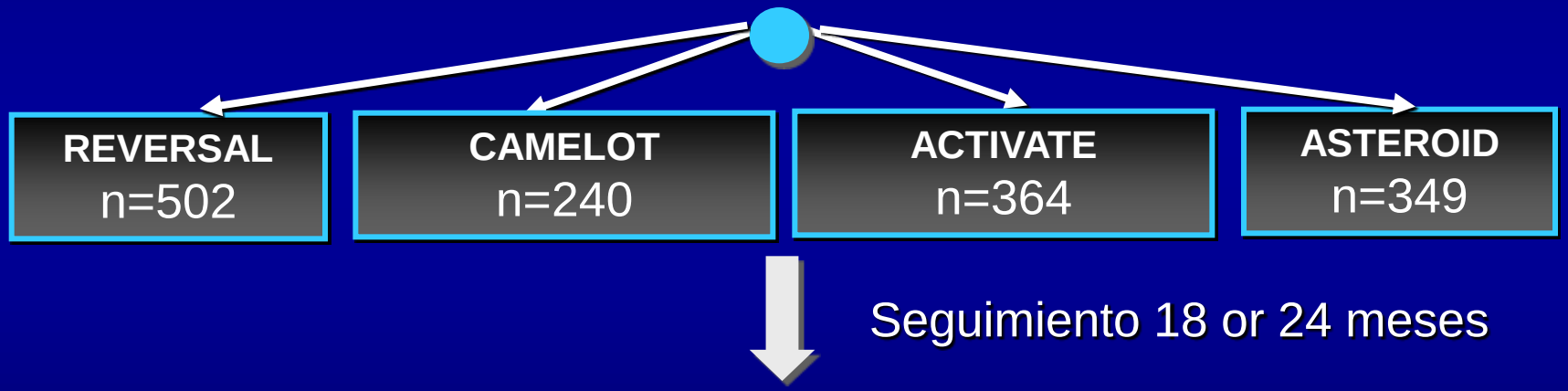


*Wilcoxon signed rank test for comparison with **baseline**

Nissen SE et al. *JAMA* 2006;295:1556-1565.

REGRESION DE LA ATEROSCLEROSIS ¿MITO O REALIDAD?

1455 pacientes de 4 estudios con EAC y recibiendo estatinas . Ultrasonografia intravascular seriada (IVUS)



- Puntos primarios: Cambios en los niveles de LDL-C and HDL-C y volumen del ateroma.

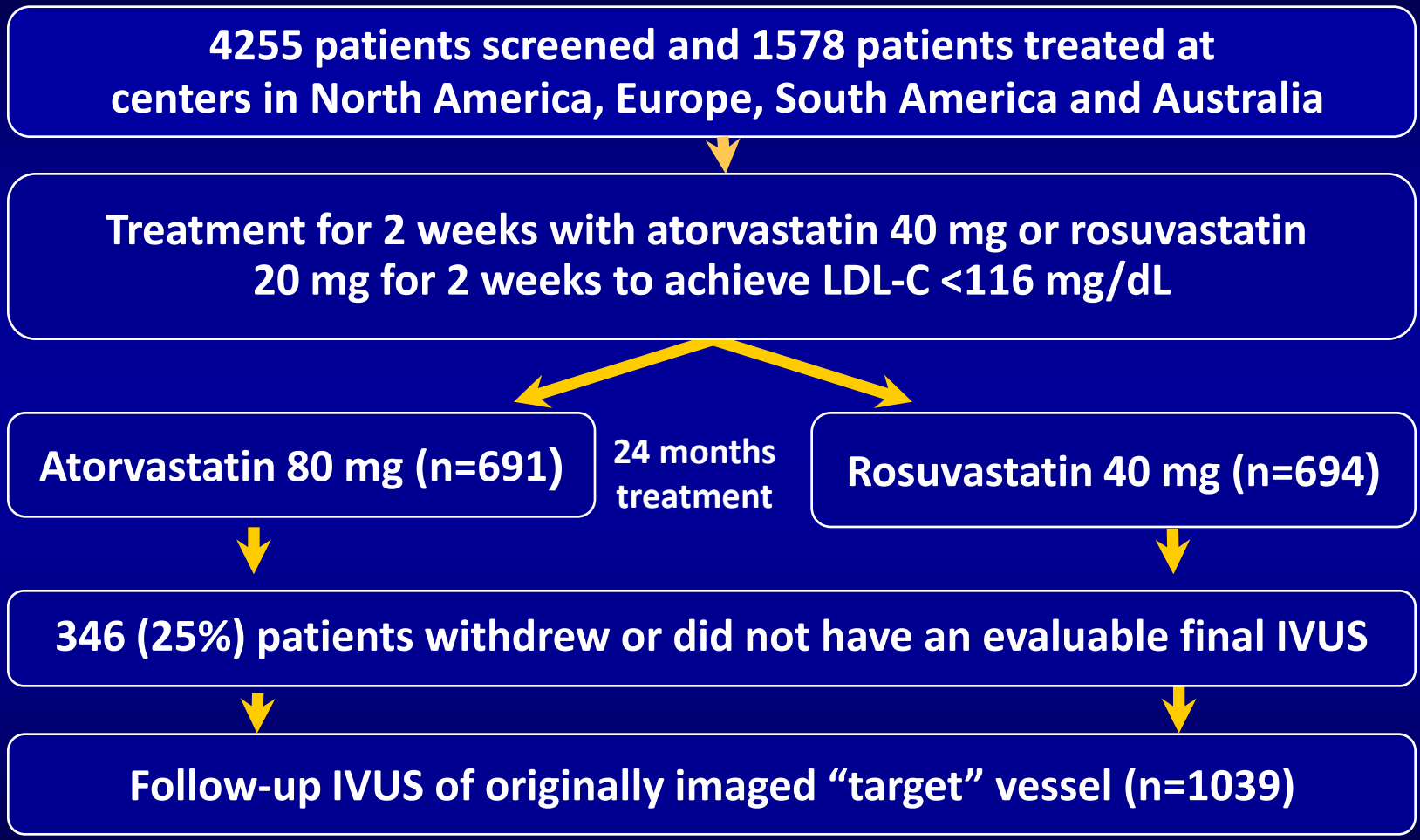
Nicholls SJ, et al. JAMA. 2007; 297(5): 499-508.

REGRESION DE LA ATEROSCLEROSIS ¿MITO O REALIDAD?

	Nivel,Media(SD) [Media]*			
	BASAL	TRATAMIENTO	Media (SD)	P
LDL-C HDL-C	124.0 (38.3)[126.0] 42.5 (11.0) [41.0]	87.5 (28.8) [85.6] 45.1 (11.4) [43.7]	-36.7 (41.1) 2.6 (6.7)	<0.001 <0.001
LDL/HDL	3.0 (1.1) [3.0]	2.1 (0.9) [1.9]	-1.0 (1.1)	<0.001
% volum. ateroma	39.7 (9.8) [40.0]	40.1 (9.7) [40.1]	0.5 (3.9)	0.001
Volumen ateroma Total,mm^3	186.8 (79.5) [176.2]	184.4 (78.2) [174.3]	-2.4 (23.6)	<0.001

Nicholls SJ, et al. JAMA. 2007; 297(5): 499-508.

SATURN



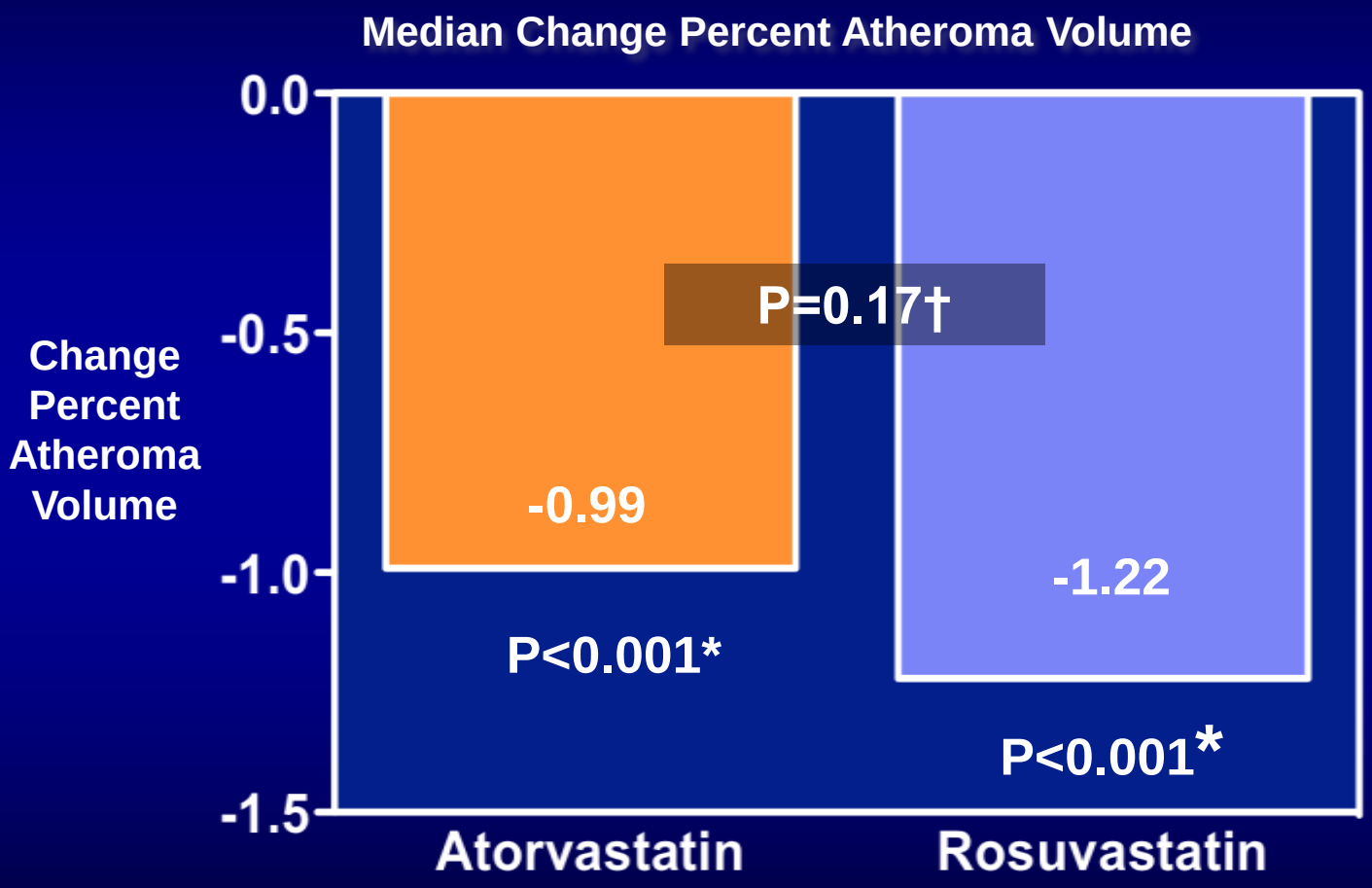
Nicholls SJ. *N Engl J Med* 2011;365:2078-87

SATURN

Parameter	ATORVA (n=519)	ROSU (n=520)	P Value
LDL cholesterol (mg/dL)	**70.2**	**62.6**	**<0.001**
HDL cholesterol (mg/dL)	**48.6**	**50.4**	**0.01**
Triglycerides (mg/dL)*	110	120	0.02
LDL:HDL cholesterol	1.5	1.3	<0.01
hsCRP (mg/L)*	1.0	1.1	0.05

Nicholls SJ. *N Engl J Med* 2011;365:2078-87

SATURN



† comparison between groups. * comparison from baseline

Nicholls SJ. *N Engl J Med* 2011;365:2078-87

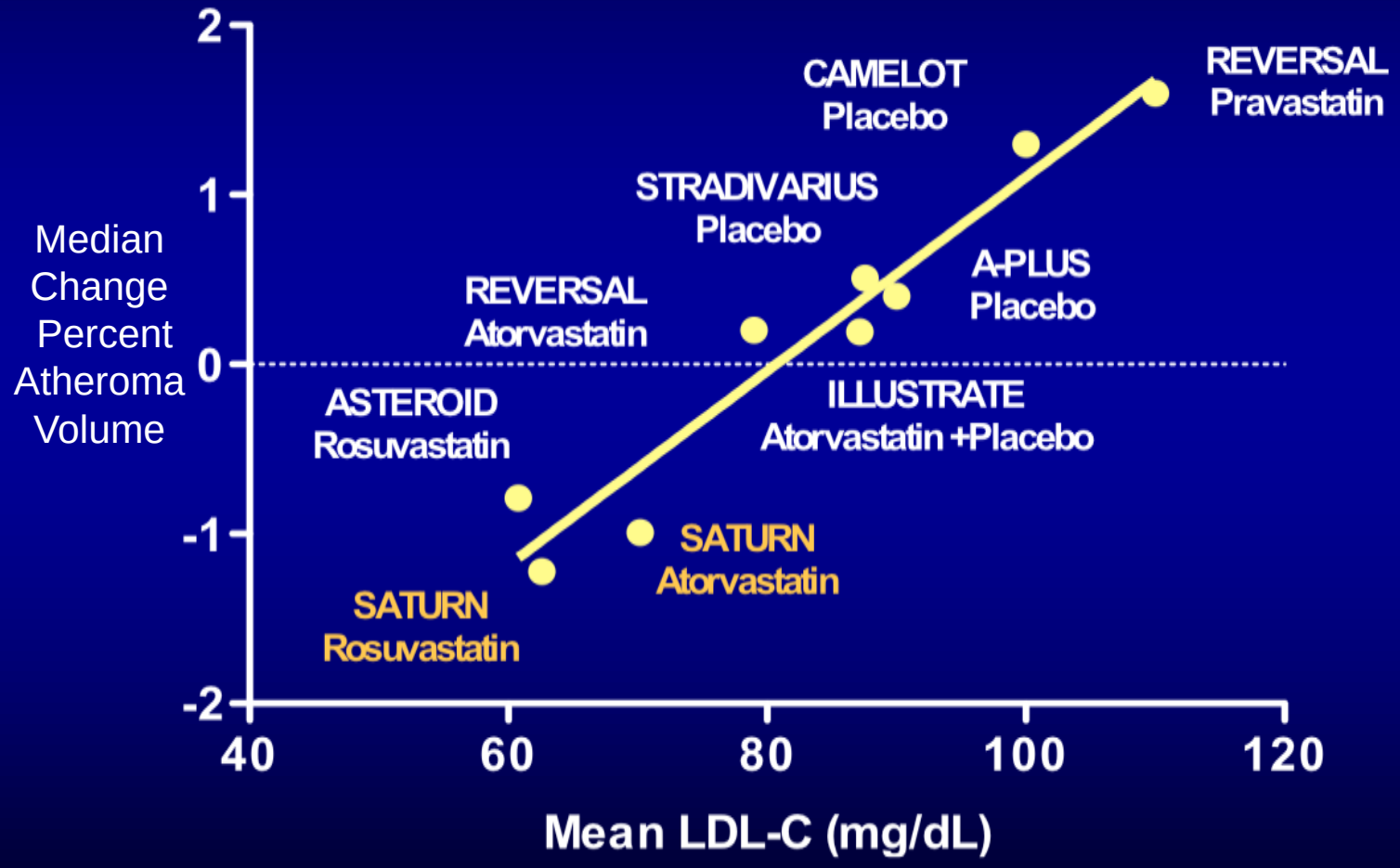
Adverse Events: Safety Population (n=1385)

Parameter	Atorvastatin (n=691)	Rosuvastatin (n=691)
Major cardiovascular event	7.1%	7.5%
ALT >3x ULN†	2.0%	0.7%
CK >5x ULN	0.7%	0.3%
Proteinuria*	1.7%	3.8%
Creatinine >ULN	3.0%	3.3%
Change HbA1c (%)	0.09	0.05

† P=0.04 and * P=0.02 for comparison between groups

Nicholls SJ. *N Engl J Med* 2011;365:2078-87

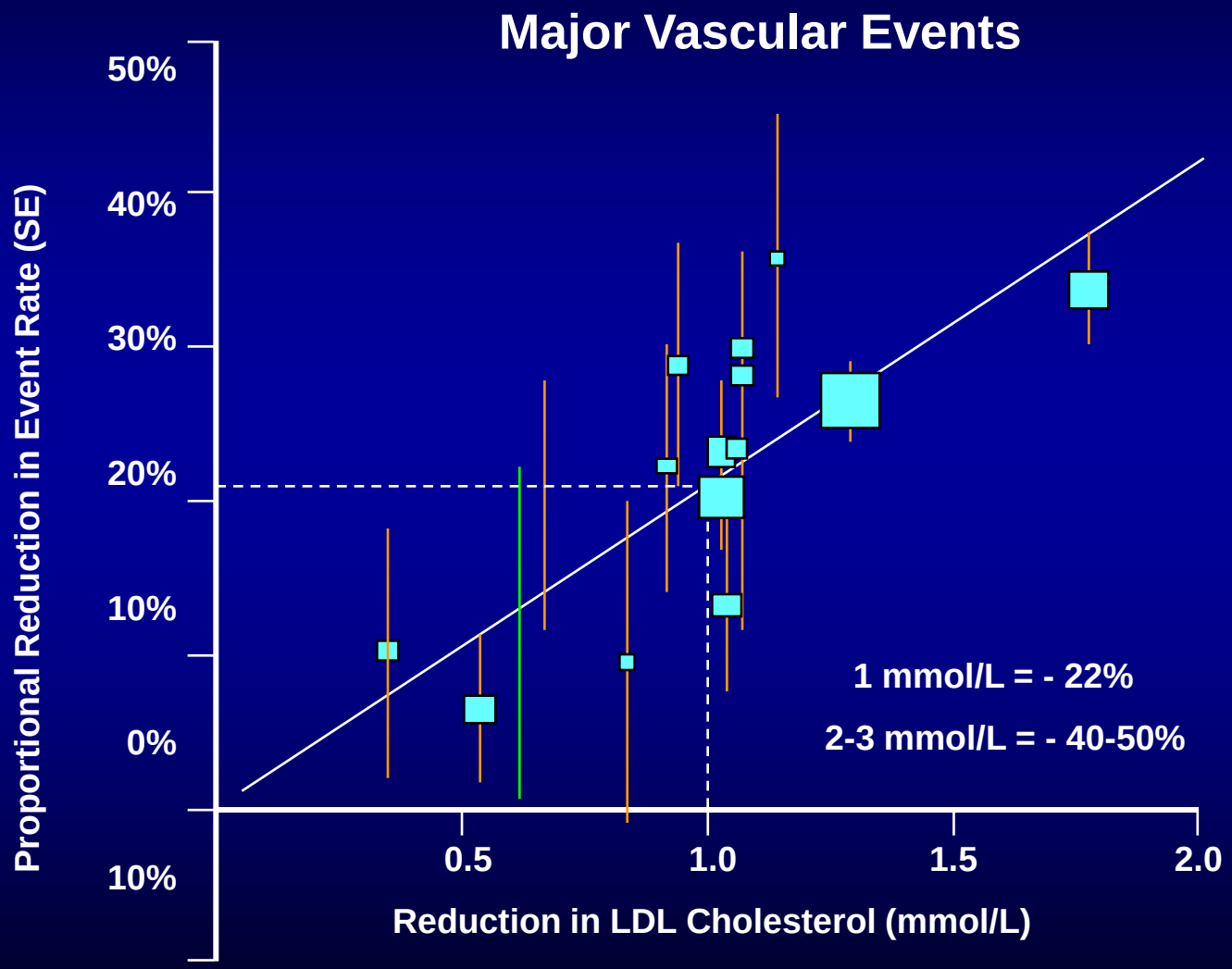
LDL-C and Disease Progression



Cholesterol Trialist Collaboration

Meta-Analysis of Dyslipidemia Trials

170000 participants in 26 randomised trials of statins



CTT Collaborators. *Lancet.* 2010; 376:1670-81

Cholesterol Trialist Collaboration

Meta-Analysis of Dyslipidemia Trials

170000 participants in 26 randomised trials of statins

- **ESTATINAS DISMINUYEN EL RIESGO DE ECV INDEPENDIENTE DEL NIVEL BASAL DE LDL-C Y CARACTERISTICAS DEL PACIENTE**

- **CADA - 39 mg/dl (1 mmol/L) de LDL-C**
  - **22% EVM (ECC,Stroke)**
  - **10% Mortalidad total (-ECV)**
  - **No cáncer**

- **ALTAS DOSIS DISMINUYE EL RIESGO DE ECV MEJOR QUE BAJAS DOSIS**

CTT Collaborators. *Lancet.* 2010; 376:1670-81

ESTATINAS, PREVENCION PRIMARIA

METAANALISIS DE 27 ESTUDIOS (n = 174149), RIESGO A 5 AÑOS DE EvCM

Baseline risk (risk of CV event over five years), %	Risk reduction (95% CI) per 1-mmol LDL reduction
<5	0.57 (0.36-0·89)
5-10	0.61 (0.50-0·74)
10-20	0.77 (0.69-0·85)
20-30	0.77 (0.71-0·83)
≥ 30	0.78 (0.72-0·84)
Overall	0.76 (0.73-0·79)

CTT Collaborators. *Lancet* 2012; DOI:10.1016/S0140-6736(12)60367-5 376:1670-81

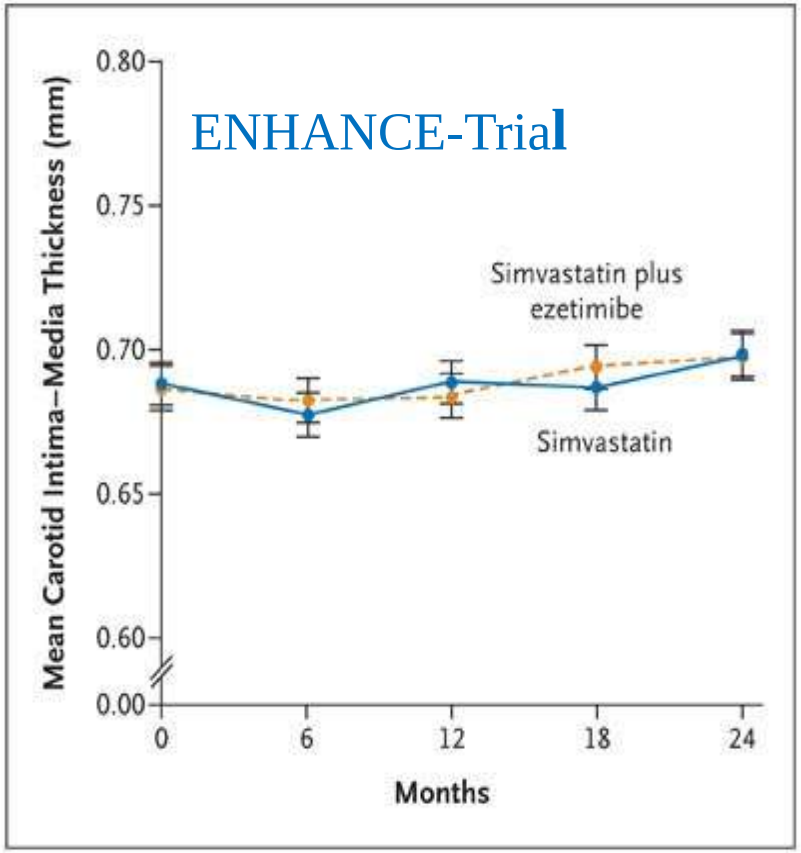
¡NUEVA ESTATINA! PCKS9

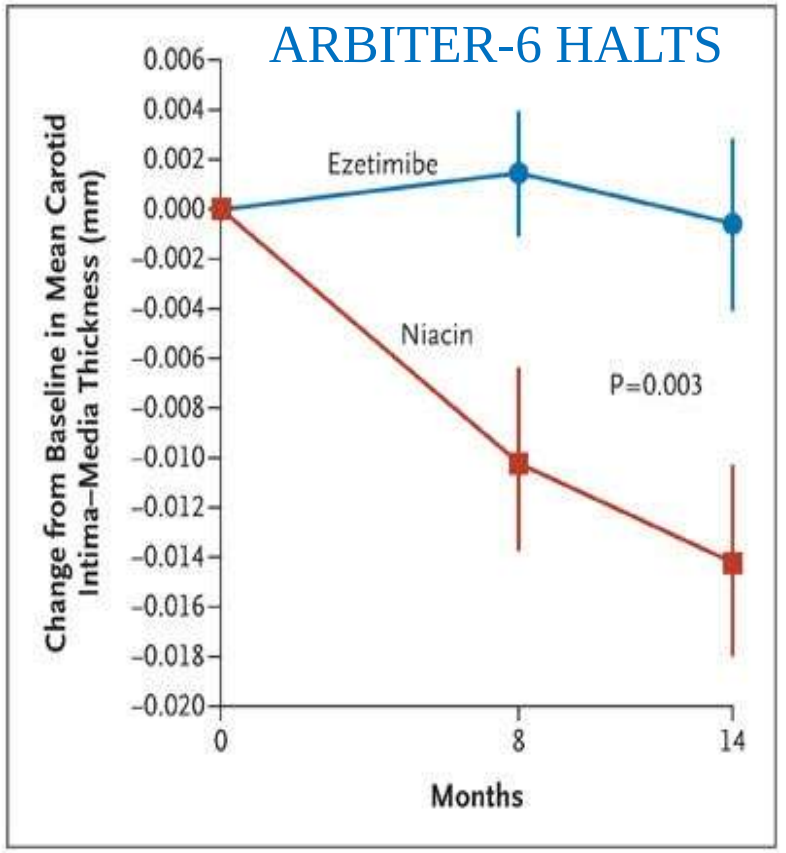
ANTICUERPO MONOCLONAL HUMANO ESPECIFICO PARA PROPROTEINA CONVERTASA SUBTILISIN/KEXIN 9

Intervención	LDL–C basal (mg/dL)	Cambios LDL-C (%)
Placebo	130.2	-5.1
REGN727 50 mg, cada 2 sem.	123.2	-39.6
REGN727 100 mg, cada 2 sem.	127.0	-64.2
REGN727 150 mg SC, cada 2 sem.	123.9	-72.4
REGN727 200 mg, cada 4 sem.	128.2	-43.2
REGN727 300 mg, cada 4 sem.	131.6	-47.7

Mckenney JM. *J Am Coll Cardiol* 2012; 59: 2344-2353

Intima-Media Thickness of the Carotid Artery during 24 and 14 Months of Therapy





Kastelein J et al. N Engl J Med 2008;358:1431-1443

Taylor A et al. N Engl J Med 2009;361:2113-2122

U.S. Department of Health and Human Services
NIH News
National Institutes of Health

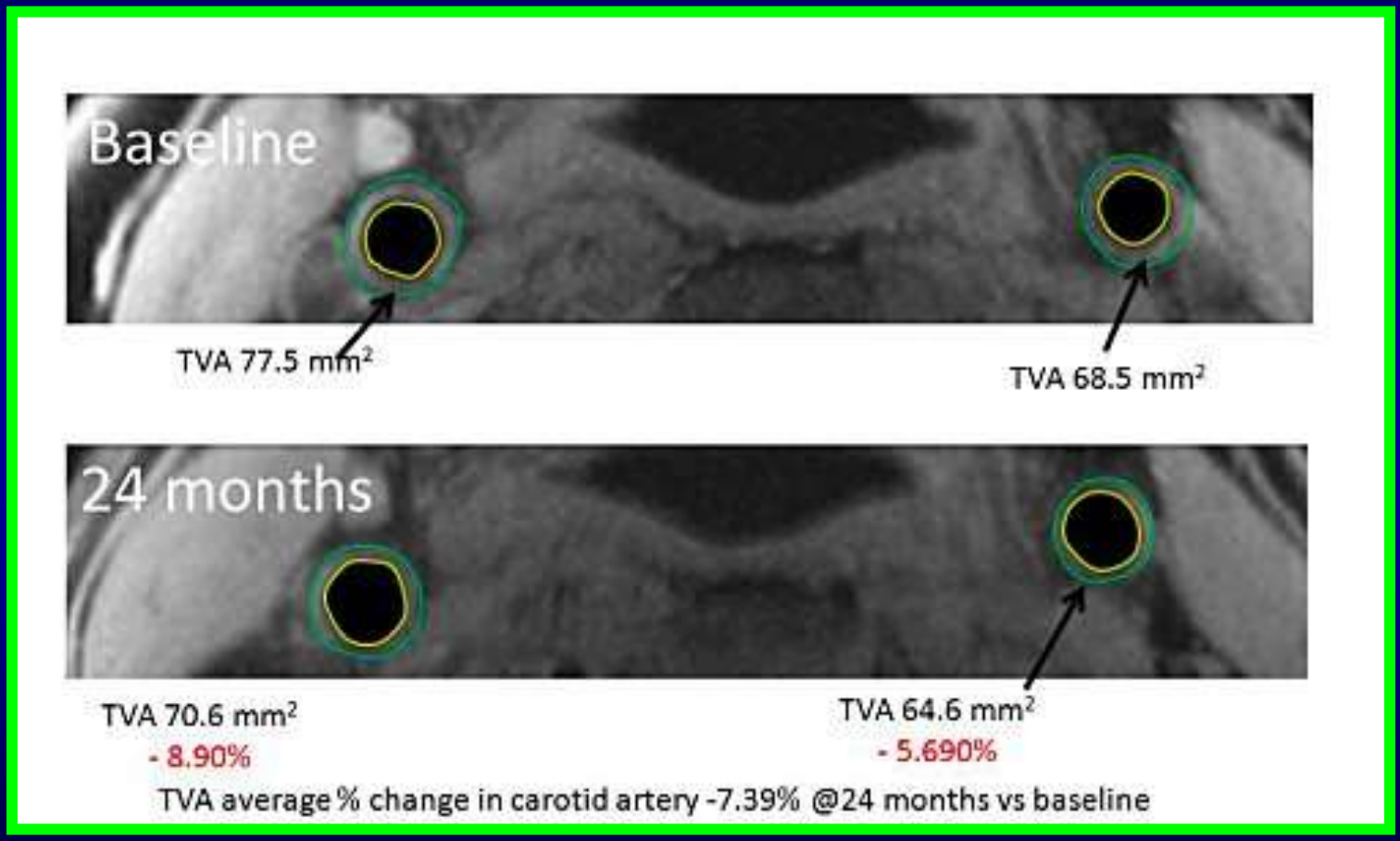
May 26,2011

ESTUDIO AIM-HIGH. NIACINA ER
DETENIDO A LOS 32 MESES

- 3414 PACIENTES CON HISTORIA DE ECV, BAJO HDL Y ALTOS TG CON LDL META 71 mg/dl (ESTATINA)
- NIACINA ER 2 G/DIA VS PLACEBO
- PUNTOS FINALES: IM FATAL Y NO FATAL,STROKE, SCA O REVASCULARIZACION
- RESULTADOS: PTOS.FINALES FRECUENCIA ANUAL NIACINA 5.8%(262),PLACEBO 5.6%(249).RR 1.05
- 20% DE AUMENTO DE HDL Y 25% REDUCCION TG
- STROKE: NIACINA 1.6%, PLACEBO 0.7%

INHIBIDORES DE LA CETP

DALCETRAPID. Dal-PLAQUE (HDL +31%, ApoA1 +10%)



The Lancet - 12 September 2011DOI: 10.1016/S0140-6736(11)61383-4

DALCETRAPID. Dal-OUTCOMES
DETENIDO ESTUDIO POR FALTA DE EFICACIA CLINICA

Basel, 7 May 2012

Roche provides update on Phase III study of dalcetrapib
Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that following the results of the second interim analysis of the dalcetrapib dal-OUTCOMES Phase III trial, the independent Data and Safety Monitoring Board (DSMB) has recommended stopping the trial due to a lack of clinically meaningful efficacy. The dal-OUTCOMES trial evaluated the efficacy and safety profile of dalcetrapib when added to existing standard of care in patients with stable coronary heart disease (CHD) following an acute coronary syndrome (ACS). No safety signals relating to the dal-OUTCOMES trial were reported from the DSMB

ANTIINFLAMATORIOS, sPLA2,LpPLA2

- **Varespladib, a secretory phospholipase A2 enzyme ($sPLA_2$) inhibitor(Anthera)**

March 9, 2012
Anthera detiene VISTA-16 Clinical Study debido a perdida de EFICACIA siguiendo las recomendaciones del independiente Data Safety Monitoring Board
VISTA-16 , 6500 patients con ACS,varespladib 500 mg /dia o placebo por 16 semanas + atorvastatin +cuidados estandares.

- **Lipoprotein-associated phospholipase A_2 ($Lp\text{-}PLA_2$) inhibitor darapladib (GlaxoSmithKline).**

STABILITY (Stabilizacion of Atherosclerotic Plaque by Initiation of Darapladib Therapy trial), estudio con 15000 pacientes para ser completado en Agosto del 2013
SOLID TIMI-52 (Stabilizacion of Plaque Using Darapladib-Thrombolysis in Myocardial Infarction 52 trial en Abril 2014

FUTURAS INVESTIGACIONES

- **ANTICUERPOS MONOCLONALES PARA P SELECTINAS(SELECT ACS, SELECT CABG)**
- **INHIBIDORES DE INTERLUKINA 1β (IL 1 β) ESTUDIO CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study)**
- **Antagonistas MicroRNA 33a, MicroRNA 33b**

Arsenault BJ. *Curr Cardiol Rep* 2012;14:443-449**.**

CIRT | CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

METOTREXATE (LDM) 15-20 mg/semana
7000 PACIENTES POST IM CON DIABETES MELLITUS o SINDROME METABOLICO (INICIO MARZO 2013)
PARA EFECTOS COLATERALES,ACIDO FOLICO 1.2 mg 6 dias/semana
PUNTOS FINALES PRIMARIOS: TIEMPO PARA EL 1ER EVENTO CV. (Compuesto de muerte CV, IM y stroke no fatal)

NHLBI 2012.

REGRESION DE LA ATEROSCLEROSIS ¿MITO O REALIDAD?

CONCLUSIONES

- LAS ESTATINAS PRODUCEN REGRESION DE LA ATEROSCLEROSIS Y LA DISMINUCION DE EVENTOS CARDIOVASCULARES ,ES INDEPENDIENTE DEL NIVEL BASAL "NORMAL" DE LDL
- LA EZETIMIBA NO DEMUESTRA REGRESION NI REDUCCION DE EVENTOS CARDIOVASCULARES
- TORCETRAPID, DALCETRAPID (INHIBIDORES CETP) Y LA NIACINA ,VARESPLADIB NO REDUCEN EVENTOS CV
- PCSK9,ANTIINFLAMATORIOS,MICRO RNAs