Effect of Rosuvastatin Therapy on Coronary Artery Stenosis Assessed by Quantitative Coronary Angiography in ASTEROID

CM Ballantyne,[1] JS Raichlen,[2] SJ Nicholls,[3] R Erbel,[4]
J-C Tardif,[5] SJ Brener,[3] VA Cain,[2] SE Nissen,[3]
For the ASTEROID Investigators

1 Baylor College of Medicine and
Methodist DeBakey Heart & Vascular Center, Houston, Texas

2 AstraZeneca, Wilmington, Delaware

3 Cleveland Clinic Foundation, Cleveland, Ohio

4 University Clinic Essen, Essen, Germany

5 Montreal Heart Institute, Montreal, Quebec, Canada

Presenter Disclosure Information

<Christie M. Ballantyne, MD>

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Consulting Fees	*Abbott, AstraZeneca, Atherogenics, Merck/Schering-Plough, Novartis, Pfizer, Sanofi-Synthelabo, Schering-Plough, Takeda, GlaxoSmithKline*	*Modest Level*
Speakers Bureau	*AstraZeneca, Merck*	*Significant Level*
Speakers Bureau	*Pfizer, Reliant, Schering-Plough*	*Modest Level*

Background

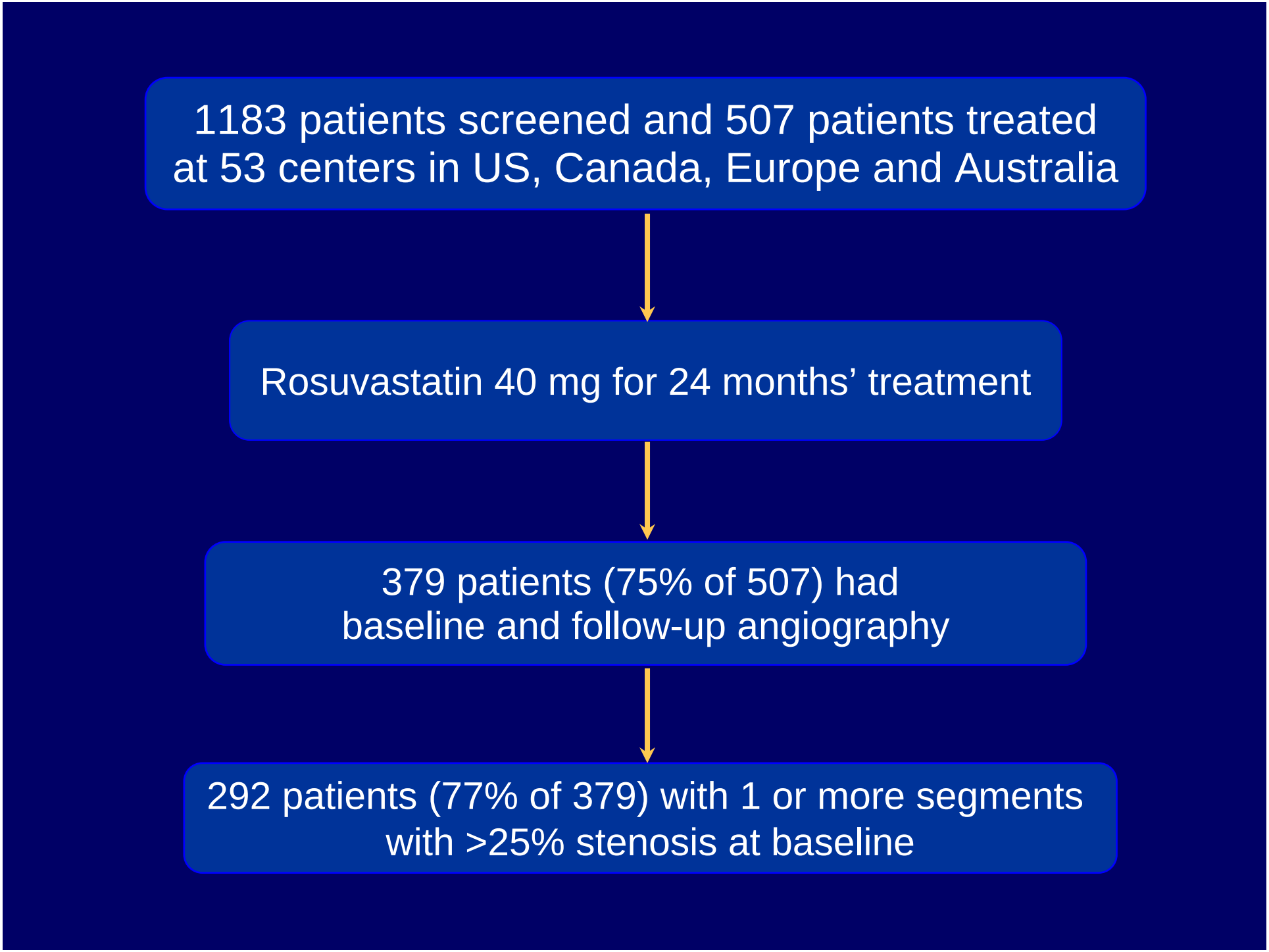
- Atherosclerosis is usually viewed as a chronic progressive disease characterized by continuous accumulation of atheroma within the arterial wall
- Until the ASTEROID trial, prior angiographic and IVUS trials had shown reduced progression of coronary atherosclerosis with statin therapy, but not regression
- In the primary ASTEROID analysis, rosuvastatin 40 mg/day for 24 months produced significant regression of all IVUS measures of atheroma volume within the wall of a major coronary artery ($p<0.001$)

ASTEROID QCA of Coronary Stenoses

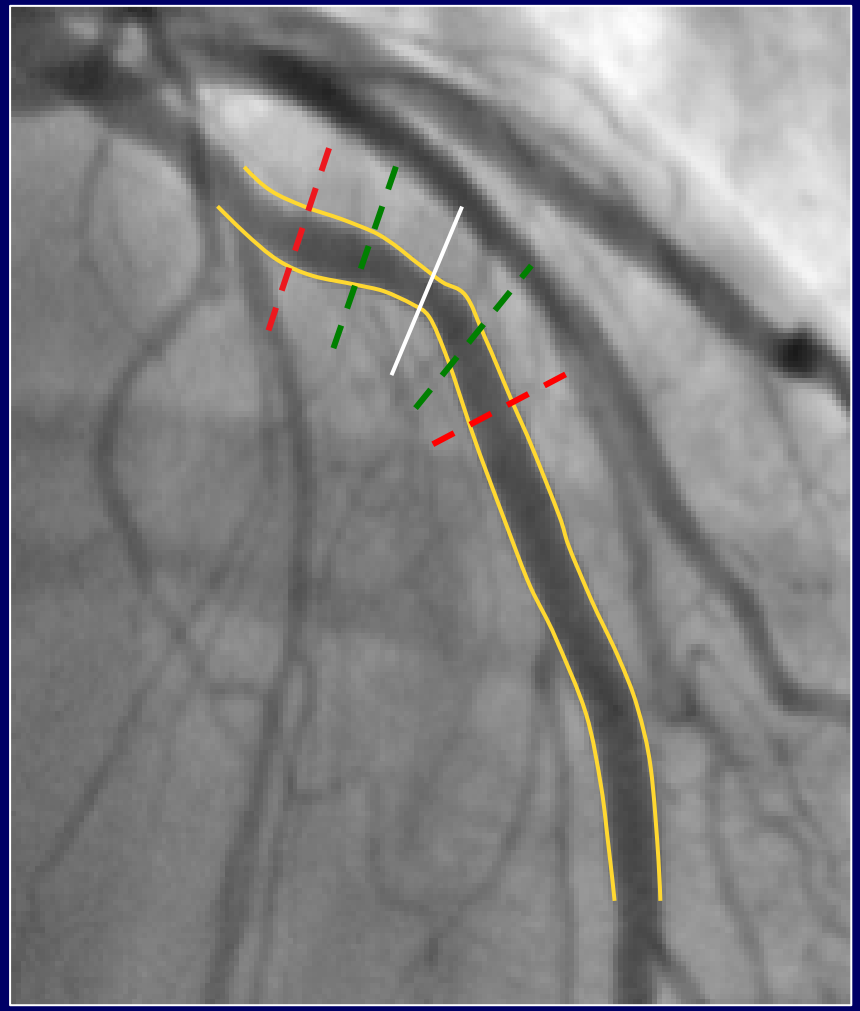
- **Objective:**
  - To evaluate effect of 24 months of treatment with rosuvastatin 40 mg on coronary artery stenoses as measured by quantitative coronary angiography (QCA)
- **Protocol pre-specified analysis:**
  - Does treatment with 40 mg rosuvastatin reduce the percent diameter stenosis in segments with >25% stenosis at baseline?
- **Supportive post-hoc analysis:**
  - Does treatment with 40 mg rosuvastatin increase the minimum lumen diameter (MLD) of segments with >25% stenosis at baseline?

Study Population and Measurements

- Statin naïve: No use of lipid-lowering agents for >3 months within the previous 12 months
- Angiographic CAD: >20% stenosis in any coronary artery
- The “target vessel” for IVUS was a major coronary artery with no more than 50% stenosis throughout at least 40 mm
- Target segments for QCA: all stenoses >25% at baseline
- IVUS and QCA examinations read by the Cleveland Clinic Core Laboratories

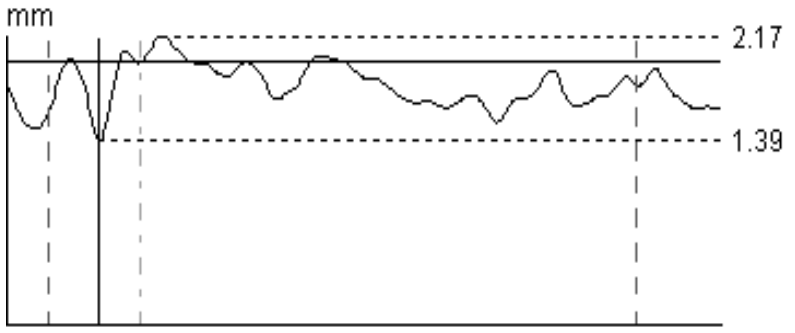

1183 patients screened and 507 patients treated at 53 centers in US, Canada, Europe and Australia
Rosuvastatin 40 mg for 24 months' treatment
379 patients (75% of 507) had baseline and follow-up angiography
292 patients (77% of 379) with 1 or more segments with >25% stenosis at baseline

QCA of the mid LAD

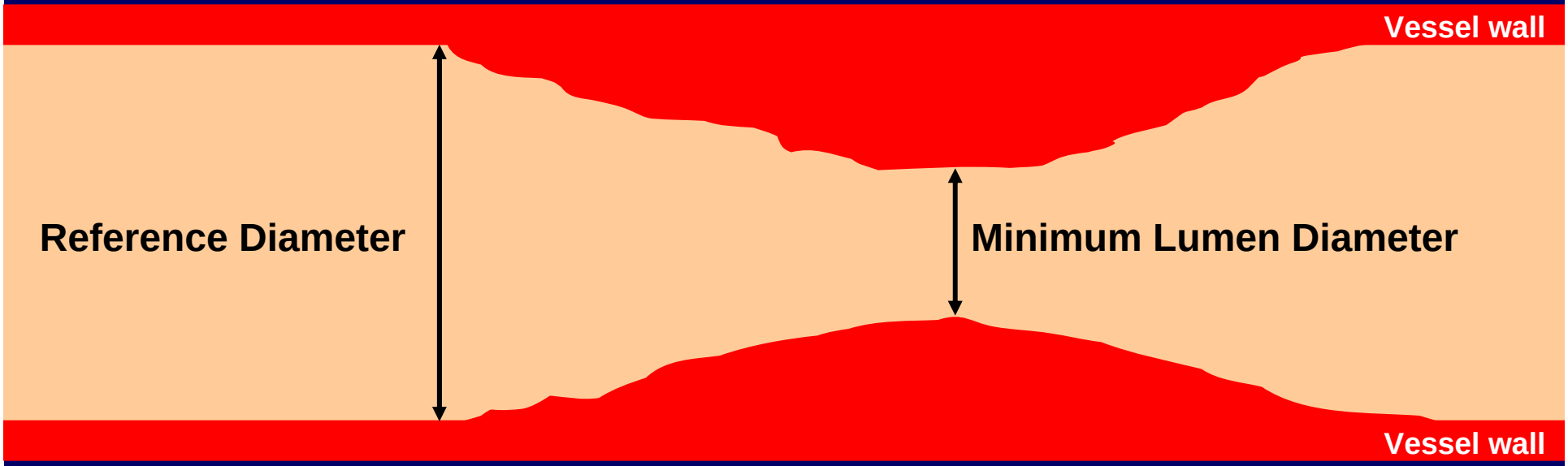


MLD	:	**1.39**	mm
% diameter stenosis	:	**30**	%
Reference diameter	:	**1.99**	mm
Position reference diameter	:	13.38	mm
Length stenotic segment	:	**53.01**	mm
Position of proximal border	:	4.53	mm
Position of distal border	:	57.72	mm
Minimum area absolute	:	0.33	mm2
MLA densitometry	:	1.97	mm2
MLA circular	:	1.52	mm2
% area stenosis densitometry	:	**37**	%
% area stenosis circular	:	**51**	%
Reference area	:	3.10	mm2

Diameter



QCA Measurements



Outcome variable: change in percent diameter stenosis for all stenoses > 25% at baseline

$$\text{Percent diameter stenosis} = \frac{\text{Reference Diameter} - \text{Minimum Lumen Diameter}}{\text{Reference Diameter}} \times 100$$

ASTEROID Population at Baseline (n=507)

	Patients Included (n=292)	Patients Not Included (n=215)
Age in years (mean)	58.9	58.0
Male	73.3%	67.9%
Weight (kg)	85.1	86.5
Median Body Mass Index	28.3	28.7
History of Hypertension	98.0%	91.6%
History of Diabetes Mellitus	13.0%	12.1%
Concomitant Medications		
Aspirin	83.6%	83.7%
ACE inhibitors	54.8%	45.6%
Angiotensin receptor antagonists	19.2%	13.5%
Organic nitrates	84.9%	87.0%
Beta blockers	86.0%	74.0%

Baseline and On-Treatment Lipids

N= 292	Mean Baseline	During treatment*	Percent Change†
Total Cholesterol (mg/dL)	204.7	133.9	–33.9
LDL-C (mg/dL)	131.5	61.1	–53.3
HDL-C (mg/dL)	42.8	48.3	+13.8
Non-HDL-C (mg/dL)	161.9	85.6	–47.0
LDL-C/HDL-C ratio	3.24	1.33	–58.2
Triglycerides (mg/dL)	151.8	123.5	–12.3

* Time-weighted average

† From least square means; all p<0.001

Change in Percent Diameter Stenosis

N= 292	Mean (SD)	Median (Range)	Mean Change (SD)	Median Change (Q1, Q3)*	p†
Baseline	37.3% (8.4)	35.7% (26.0–73.0)			
End of Study	36.0% (10.1)	34.5% (8.0–74.0)	–1.30% (8.00)	–0.50% (–4.00, 2.00)	<0.001

* Q1 = 25th percentile; Q3 = 75th percentile

† Wilcoxon Signed Rank test

Change in Minimum Lumen Diameter

N= 281	Mean (SD)	Median (Range)	Mean Change (SD)	Median Change (Q1, Q3)*	p†
Baseline, mm	1.65 (0.36)	1.62 (0.56–2.65)			
End of Study, mm	1.68 (0.38)	1.67 (0.76–2.77)	+0.03 (0.20)	+0.02 (–0.04, 0.11)	< 0.001

* Q1 = 25th percentile; Q3 = 75th percentile

† Wilcoxon Signed Rank test

Progression / Regression in Percent Diameter Stenosis

Nominal Changes	N (Total=292)	
Stenosis reduced (regression*)	156	53.4%
No change	17	5.8%
Stenosis increased (progression*)	119	40.8%
Clinically Relevant Changes		
Stenosis reduced by ≥10% (regression*)	22	7.5%
Stenosis changed by <10%	261	89.4%
Stenosis increased by ≥ 10% (progression*)	9	3.1%

* Proportion of regressors greater than progressors, both p <0.03

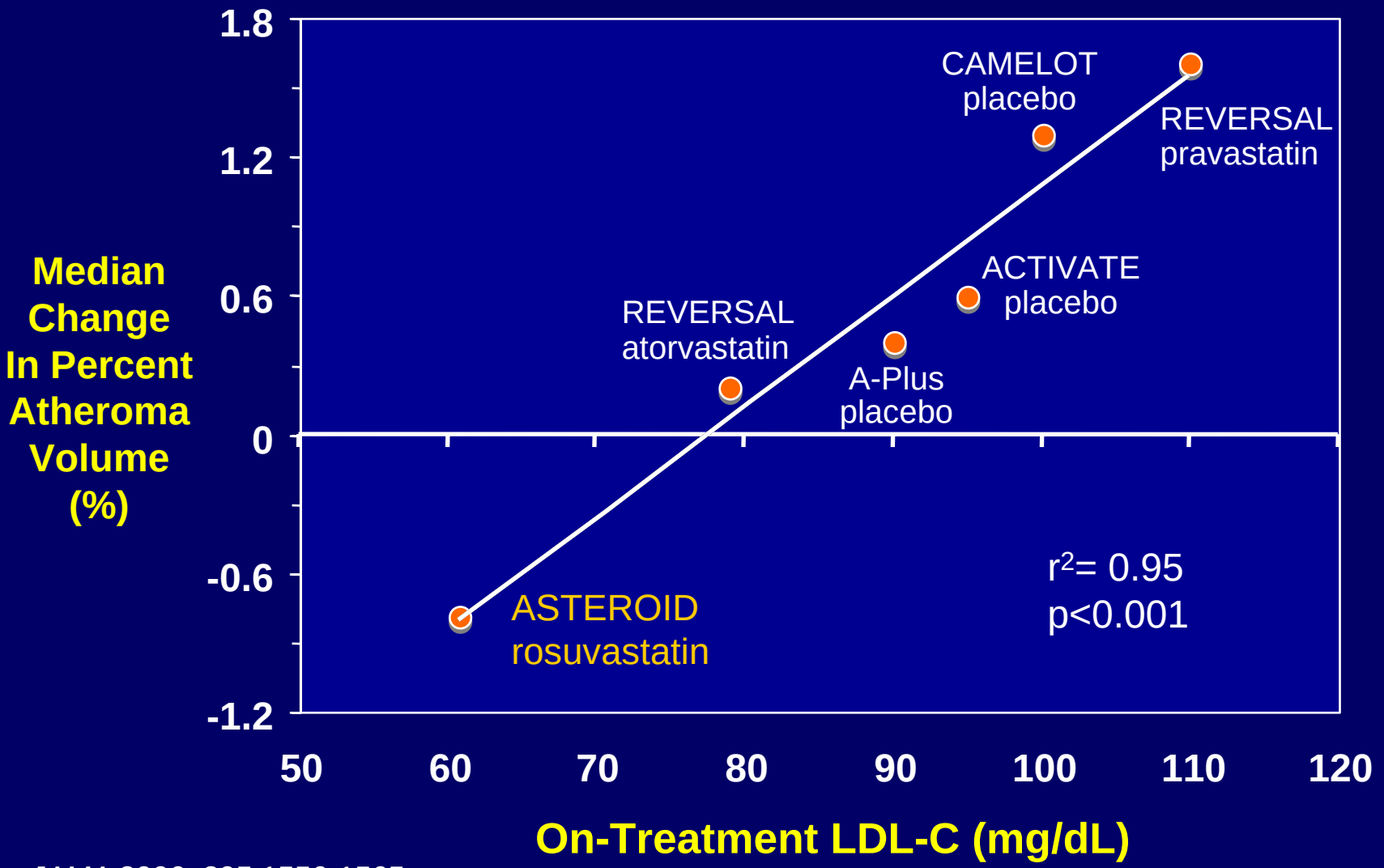
Progression / Regression in Minimum Lumen Diameter (MLD)

Nominal Changes	N (Total=281)	
MLD larger (regression*)	155	55.2%
No change	12	4.3%
MLD smaller (progression*)	114	40.6%
Clinically Relevant Changes†		
MLD larger by ≥0.2 mm (regression*)	34	12.1%
Change < 0.2 mm	230	81.9%
MLD smaller by ≥0.2 mm (progression*)	17	6.0%

* Proportion of regressors greater than progressors, both p <0.02

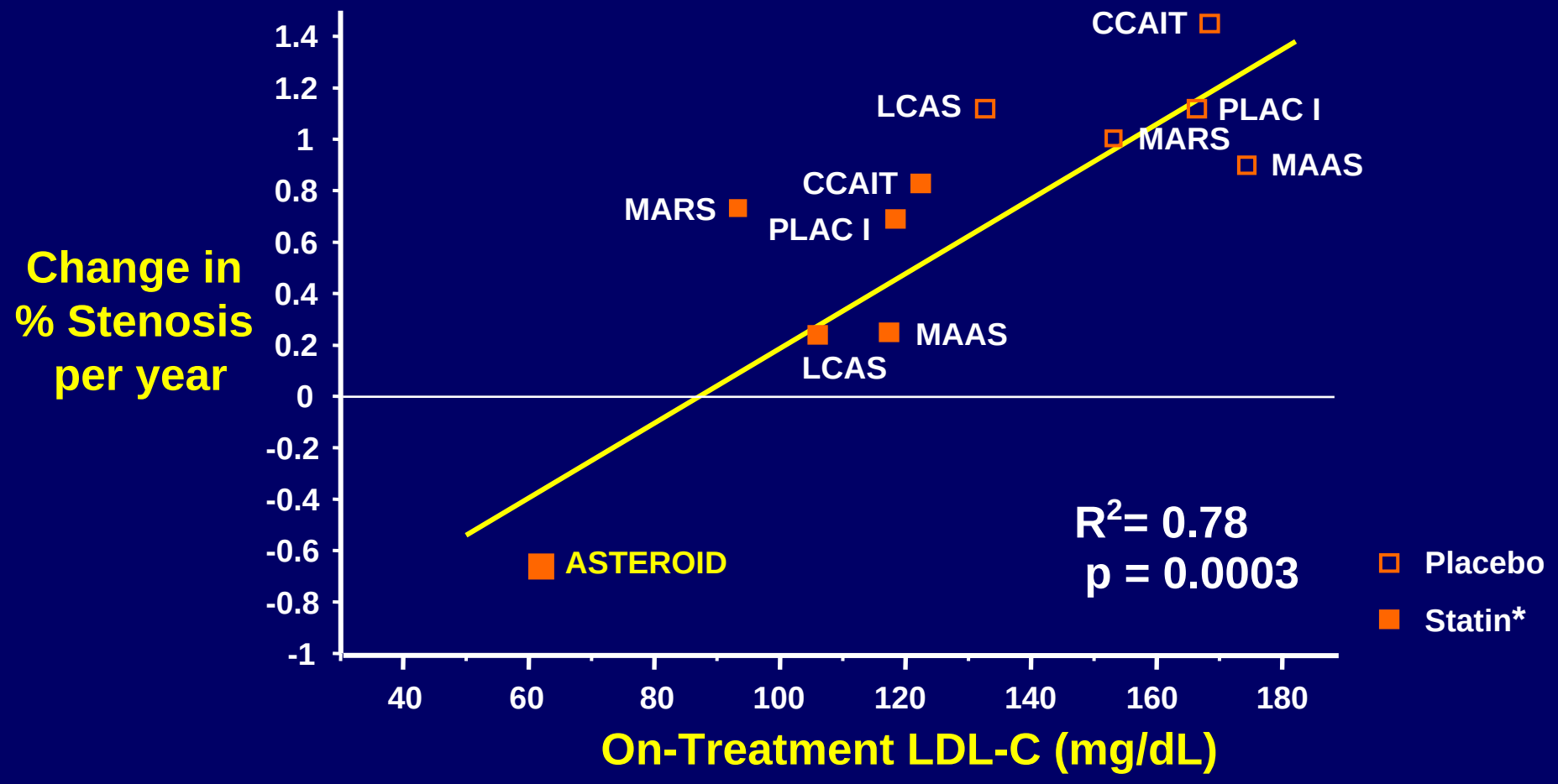
† Pre-specified category

Change in Progression of IVUS Percent Atheroma Volume versus LDL-C in IVUS Trials

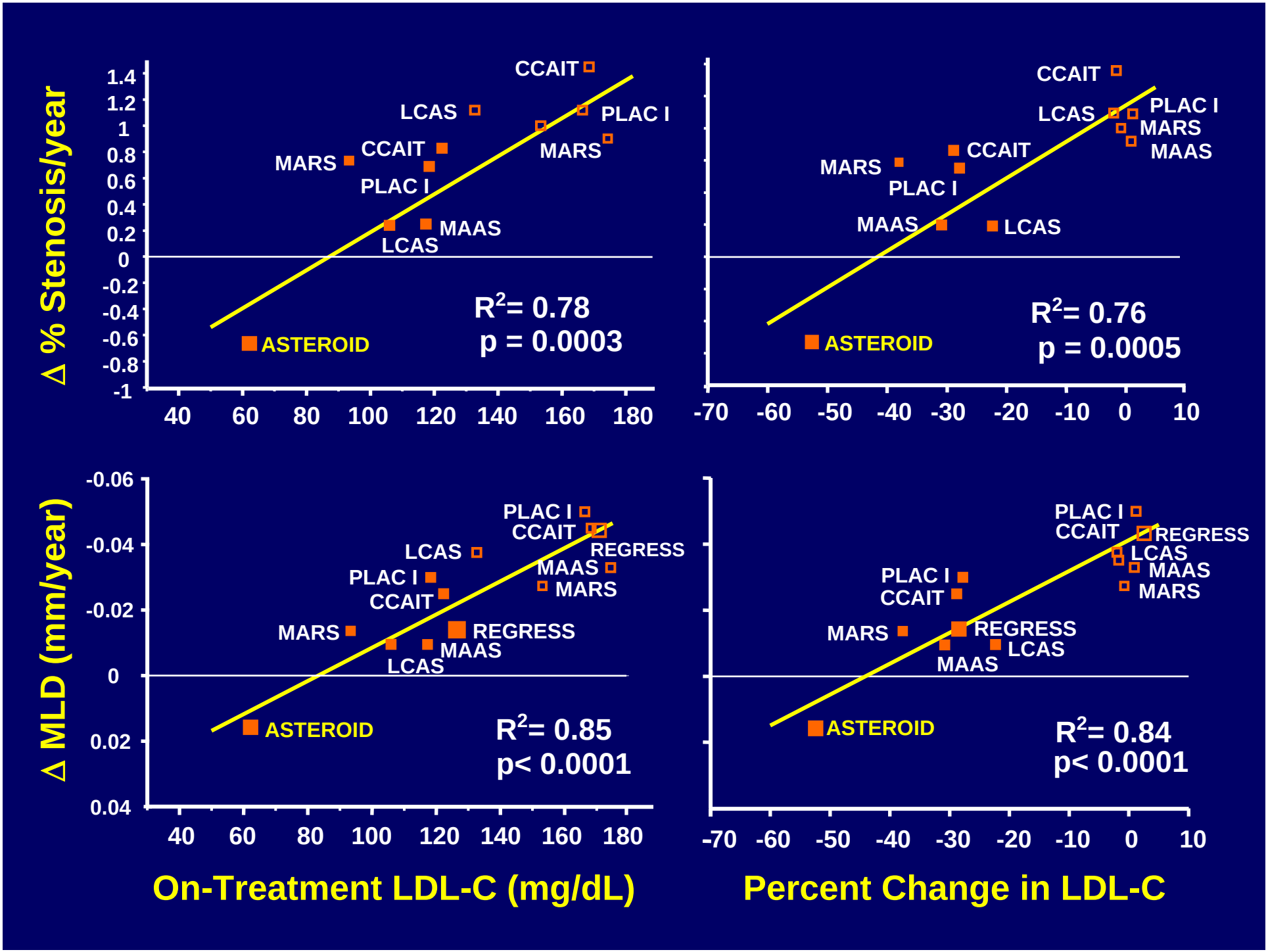


JAMA 2006; 295:1556-1565
Cleve Clin J Med 2006;73:937-944

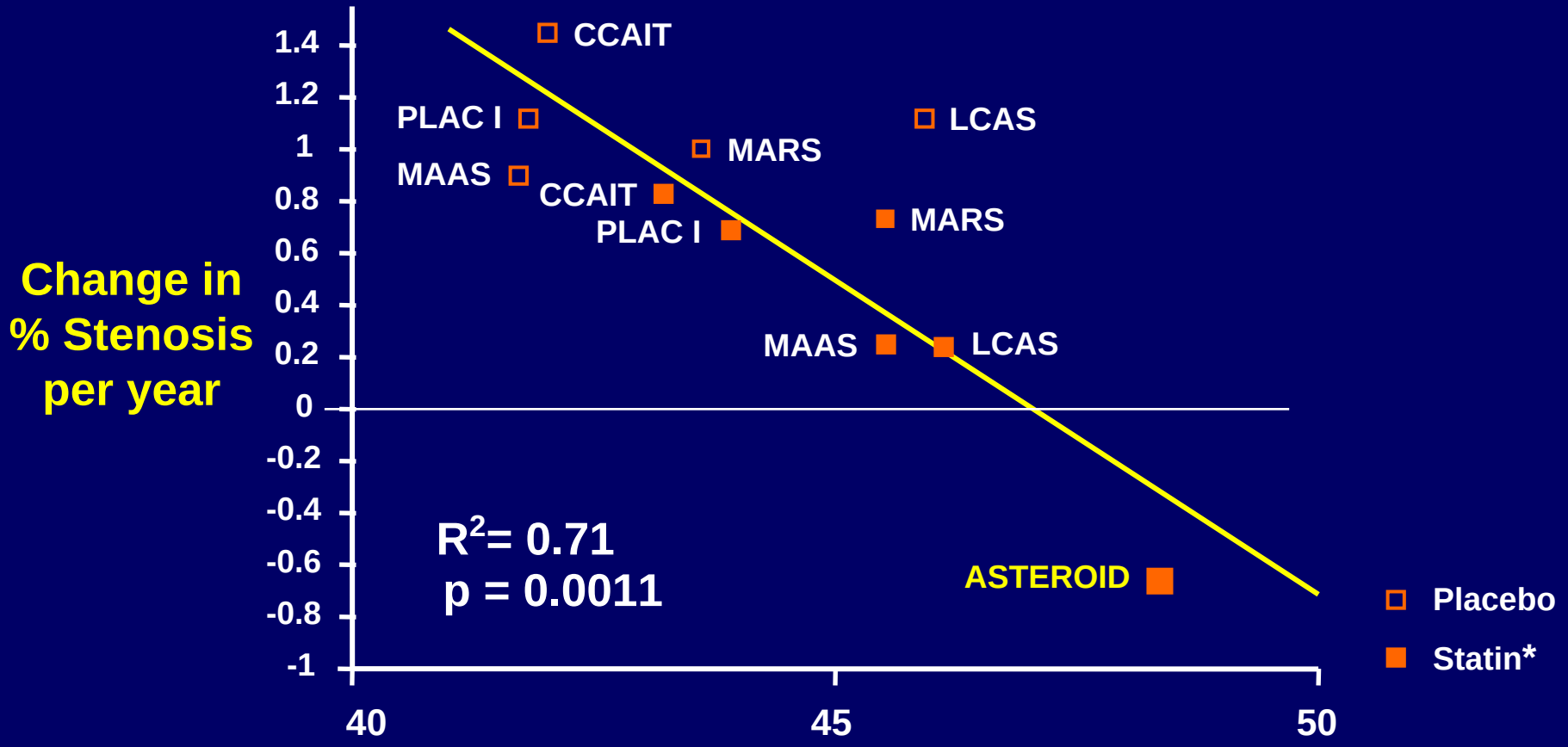
Change in Percent Diameter Stenosis vs On-Treatment LDL-C in QCA Trials



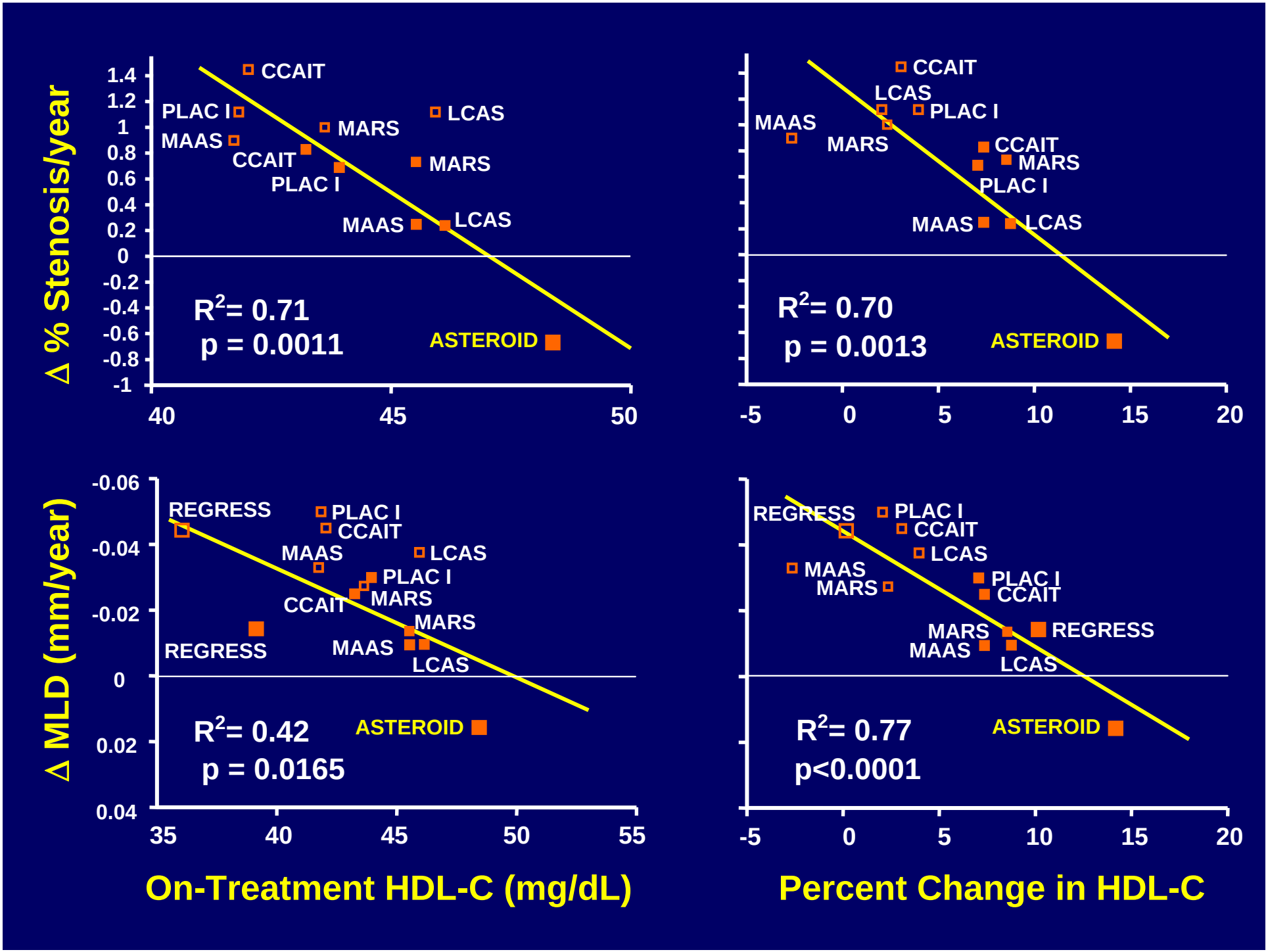
* ASTEROID rosuvastatin
CCAIT lovastatin
LCAS fluvastatin
MAAS simvastatin
MARS lovastatin
PLAC I pravastatin


Δ % Stenosis/year
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
40
60
80
100
120
140
160
180
CCAIT
LCAS
PLAC I
MARS
CCAIT
MARS
PLAC I
MAAS
LCAS
ASTEROID
R2= 0.78
p = 0.0003
CCAIT
LCAS
PLAC I
MARS
MAAS
MARS
CCAIT
PLAC I
MAAS
LCAS
ASTEROID
R2= 0.76
p = 0.0005
-70
-60
-50
-40
-30
-20
-10
0
10
Δ MLD (mm/year)
-0.06
-0.04
-0.02
0
0.02
0.04
PLAC I
CCAIT
REGRESS
LCAS
MAAS
PLAC I
MARS
CCAIT
MARS
REGRESS
MAAS
LCAS
ASTEROID
R2= 0.85
p< 0.0001
PLAC I
CCAIT
REGRESS
LCAS
MAAS
MARS
PLAC I
CCAIT
MARS
REGRESS
LCAS
MAAS
ASTEROID
R2= 0.84
p< 0.0001
On-Treatment LDL-C (mg/dL)
Percent Change in LDL-C

Change in Percent Diameter Stenosis vs On-Treatment HDL-C in QCA Trials



* ASTEROID rosuvastatin
CCAIT lovastatin
LCAS fluvastatin
MAAS simvastatin
MARS lovastatin
PLAC I pravastatin


Δ % Stenosis/year
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
40
45
50
CCAIT
PLAC I
MAAS
MARS
LCAS
CCAIT
PLAC I
MARS
MAAS
LCAS
ASTEROID
R2= 0.71
p = 0.0011
CCAIT
LCAS
PLAC I
MAAS
MARS
CCAIT
MARS
PLAC I
MAAS
LCAS
ASTEROID
R2= 0.70
p = 0.0013
-5
0
5
10
15
20
Δ MLD (mm/year)
-0.06
-0.04
-0.02
0
0.02
0.04
35
40
45
50
55
REGRESS
PLAC I
CCAIT
MAAS
LCAS
PLAC I
CCAIT
MARS
MARS
REGRESS
MAAS
LCAS
ASTEROID
R2= 0.42
p = 0.0165
On-Treatment HDL-C (mg/dL)
REGRESS
PLAC I
CCAIT
LCAS
MAAS
MARS
PLAC I
CCAIT
MARS
REGRESS
MAAS
LCAS
ASTEROID
R2= 0.77
p<0.0001
-5
0
5
10
15
20
Percent Change in HDL-C

Limitations

- Because administering low-intensity statin therapy to CAD patients was deemed ethically unacceptable, we did not include a placebo or low-dose control group.
- We compensated for the absence of controls by randomly re-sequencing examinations to eliminate observer bias in the QCA measurements.
- The degree to which regression by QCA will translate into changes in plaque composition or to reduced morbidity and mortality is unknown.
- Clinical outcome trials always provide more convincing evidence of benefit than intermediate endpoint studies.

Conclusions

- Treatment with rosuvastatin 40 mg in statin-naïve patients with CAD reduced LDL-C to 61.1 mg/dL and raised HDL-C by 13.8%.
- This produced significant regression by decreasing percent diameter stenosis and improving MLD as measured by QCA in CAD patients (both $p<0.001$).
- This complements the results of the previous IVUS findings to indicate that two imaging modalities focusing on different coronary segments demonstrated concordant regression and stabilization of atherosclerosis with intensive statin therapy.

Conclusions II

- Both imaging and outcome studies suggest that intensive statin treatment to lower LDL-C seems warranted in high-risk CAD patients.
- The relative importance of LDL-C reduction and HDL-C elevation with statin therapy in producing these results on atherosclerosis in both IVUS and QCA trials will require further investigation.
- Future clinical trials should address whether treating LDL-C or HDL-C to goal, or achieving maximal percent decrease in LDL-C or increase in HDL-C represents the optimal strategy.

Circulation Publication Available On-line

Effect of Rosuvastatin Therapy on Coronary Artery Stenoses Assessed by Quantitative Coronary Angiography in a Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden

Christie M. Ballantyne, MD; Joel S. Raichlen, MD; Stephen J. Nicholls, MBBS, PhD; Raimund Erbel, MD; Jean-Claude Tardif, MD; Sorin J. Brener, MD; Valerie A. Cain, MS; Steven E. Nissen, MD; for the ASTEROID Investigators

Background—Previous studies using quantitative coronary angiography have demonstrated that statin therapy slows the progression of coronary stenoses in proportion to average low-density lipoprotein cholesterol levels during therapy. However, no statin monotherapy has halted progression or caused regression of angiographic disease. A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) assessed whether rosuvastatin could regress coronary atherosclerosis by intravascular ultrasound and quantitative coronary angiography. Intravascular ultrasound showed atheroma volume regression in a single coronary artery with <50% angiographic luminal narrowing.

Methods and Results—ASTEROID treated 507 coronary disease patients with rosuvastatin 40 mg/d for 24 months. Blinded quantitative coronary angiography analyses of percent diameter stenosis and minimum lumen diameter were performed for up to 10 segments of coronary arteries and major branches with >25% diameter stenosis at baseline. For each patient, the mean of all matched lesions at baseline and study end was calculated. There were 292 patients with 613 matched stenoses. Rosuvastatin reduced low-density lipoprotein cholesterol by 53.3% to 61.1±20.3 mg/dL and increased high-density lipoprotein cholesterol by 13.8% to 48.3±12.4 mg/dL. Mean±SD percent diameter stenosis decreased from 37.3±8.4% (median, 35.7%; range, 26% to 73%) to 36.0±10.1% (median, 34.5%; range, 8% to 74%; $P<0.001$). Minimum lumen diameter increased from 1.65±0.36 mm (median, 1.62 mm; range, 0.56 to 2.65 mm) to 1.68±0.38 mm (median, 1.67 mm; range, 0.76 to 2.77 mm; $P<0.001$).

Conclusions—Rosuvastatin treatment for 24 months to average low-density lipoprotein cholesterol levels well below 70 mg/dL, accompanied by significant increases in high-density lipoprotein cholesterol, produced regression by decreasing percent diameter stenosis and improving minimum lumen diameter as measured by quantitative coronary angiography in coronary disease patients. (***Circulation*. 2008;117:000-000.**)