New Advances in Coronary Imaging for Plaque Regression or Stability: IVUS, OCT, and Others

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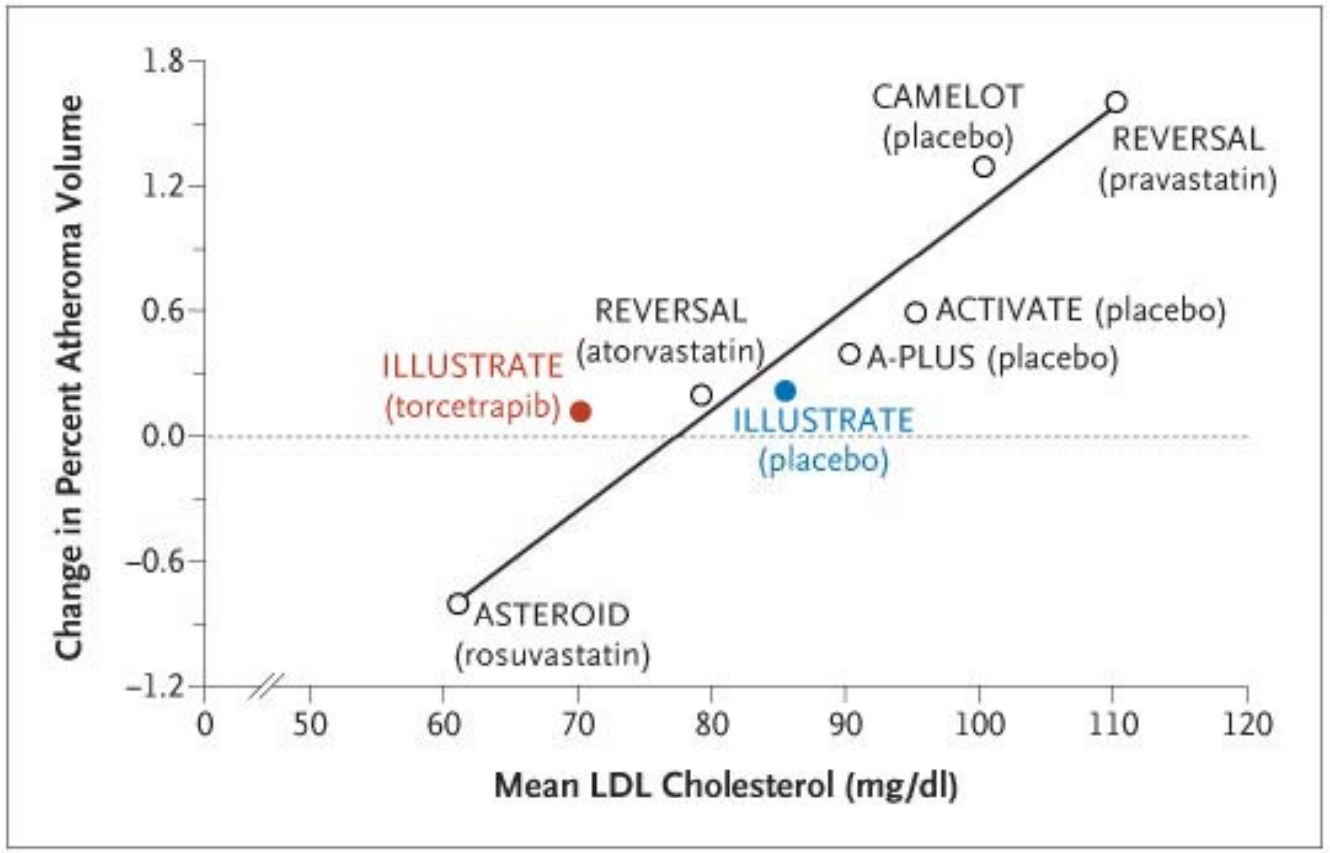
Limitations of Angiography in Trials of Progression and Regression

- Cardiovascular events correlate poorly with lumen size
- Surprisingly small angiographic differences are associated with a significant reduction in clinical events
- Underestimates the extent of atherosclerosis

Change in Plaque Burden Related to LDL Cholesterol in IVUS Progression-Regression Trials



Nissen et al N Eng J Med 2007;356:1304-16

SATURN

	80mg Atorvastatin	40mg Rosuvastatin	P-value
#	519	520	
Baseline LDL-C, mg/dl	119.9±28.9	120.0±27.3	0.94
Follow-up LDL-C, mg/dl	*70.2±1.0*	*62.6±1.0*	*<0.001*
Baseline HDL-C, mg/dl	44.7±10.7	45.3±11.8	0.41
Follow-up HDL-C, mg/dl	*48.6±0.5*	*50.4±0.5*	*0.01*
Baseline atheroma burden, %	36.2 (30.6, 41.4)	36.2 (31.4, 42.0)	0.33
24 month follow-up atheroma burden, %	34.9 (29.6, 40.3)	34.8 (29.5, 40.2)	0.6
Δ atheroma burden, %	*-0.99 (-1.19, -0.63)*	*-1.22 (-1.52, -0.90)*	*0.17**
Baseline atheroma vol, mm^3	136.6 (95.8, 182.9)	133.4 (95.9, 180.1)	0.99
Follow-up atheroma vol, mm^3	127.6 (91.0, 176.1)	124.9 (83.4, 167.7)	0.67
Δ atheroma vol, mm^3	-4.42 (-5.98, -3.26)	-6.39 (-7.52, -5.12)	0.01*

* Calculated using of analysis of covariance with rate of change as the independent variable, the rank of the corresponding baseline value as a covariate, & the treatment group as a factor

What is the link between IVUS-measures of progression and regression in an abitrarily selected coronary artery segment and clinical events?

Comparison of REVERSAL and PROVE-IT

Table 1. Key Findings in Two New Trials of Statin Drugs.*

Variable	REVERSAL	PROVE-IT
Clinical indication for therapy	Stable coronary disease	Acute coronary syndromes
Length of follow-up (mo)	18	24
LDL cholesterol†		
Base line (mg/dl)	150	106‡
Atorvastatin group (mg/dl)	79	62
Percent decrease	46	42
Pravastatin group (mg/dl)	110	95
Percent decrease	25	10
High-sensitivity CRP		
Base line (mg/liter)	3.0	12.3
Atorvastatin group (mg/liter)	1.8	1.3
Percent decrease	36	89
Pravastatin group (mg/liter)	2.9	2.1
Percent decrease	5	83

* REVERSAL denotes Reversing Atherosclerosis with Aggressive Lipid Lowering trial, PROVE-IT Pravastatin or Atorvastatin Evaluation and Infection Therapy trial, LDL low-density lipoprotein, and CRP C-reactive protein.
† To convert values for cholesterol to millimoles per liter, multiply by 0.02586.
‡ One fourth of the patients were taking a statin drug at the time of enrollment.

The inference was that because atorvastatin caused a similar reduction in LDL-C in REVERSAL and PROVE-IT, that the reduction in atheroma burden in REVERSAL was responsible for the reduction in events in PROVE-IT.

(Topol. N Engl J Med 2004;350:1562-1564)

ILLUSTRATE

	Atorvastatin	Atorvastatin+ Torcetrapib	p
#	446	464	
Δ % atheroma volume of total analysis segment			
Mean±SD	*0.019±2.83*	*0.12±2.99*	*0.72*
Mean±SE	*0.019±0.14*	*0.12±0.13*	*0.2*
Δ normalized atheroma volume or total analysis segment (mm^3)			
Mean±SD	*-6.3±22.2*	*-9.4±21.0*	*0.02*
Mean±SE	-6.3±1.0	-9.4±1.0	0.004
Δ atheroma volume of most-diseased 10mm (mm^3)			
Mean±SD	*-3.3±9.1*	*-4.1±8.6*	*0.12*
Mean±SE	-3.3±0.4	-4.1±0.4	<0.001

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Nissen, et al. N Engl J Med 2007;356:1304-16

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In the companion study ILLUMINATE, patients who received atorvastatin+torcetrapib had an increased risk of cardiovascular events (hazard ratio, 1.25; P=0.001) and death from any cause (hazard ratio, 1.58; P=0.006) despite (1) similar changes in HDL-c and LDL-c compared to patients receiving just atorvastatin and (2) no difference in primary IVUS endpoint in ILLUSTRATE

	ILLUSTRATE	ILLUMINATE
Baseline LDL-C, mg/dl	83.1±19.7	79.7±20.4
Follow-up LDL-C, mg/dl	70.1±25.4	
Δ LDL-C, %	-13.3±1.3	-24.9±28.5
Baseline HDL-C, mg/dl	46.0±12.8	48.6±12.0
Follow-up HDL-C, mg/dl	72.1±24.9	
Δ HDL-C, %	58.6±1.4	72.1±34.7
Baseline BP, mmHg	119.8/73.3	73.3-4.1±8.6
Follow-up BP, mmHg	126.4/76.0	
Δ BP, mmHg	6.5/2.8	5.4/2.0

Nissen, et al. N Engl J Med 2007;356:1304-16
Barter, et al. N Engl J Med 2007;357:2109-22

Association Between Baseline Atheroma Burden and Cardiovascular Events in 4137 Patients*

	Atheroma Burden (%)		
	No	Yes	P Value
Death, MI, coronary revasculatization (n=819)	38.0±9.0	41.3±9.2	<0.001
Death (n=38)	38.6±9.2	41.1±8.6	0.10
MI (n=75)	38.6±9.1	42.2±9.6	0.001
Coronary revascularization (n=776)	38.1±9.0	41.2±9.3	<0.001
Event	HR (95% CI)		P Value
Death, MI, coronary revascularization	1.32 (1.22-1.42)		<0.001
Death	0.73 (0.16-3.31)		0.69
MI	1.34 (1.00-1.80)		0.05
Coronary revascularization	1.31 (1.21-1.41)		<0.001

*ACTIVATE, CAMELOT, ILLUSTRATE, PERISCOPE, REVERSAL, STRADIVARIUS

Changes in Atheroma Burden, Controlling for Baseline Values, According to Incidence of Cardiovascular Events in 4137 Patients

	Δ Atheroma Burden (%)		
	No	Yes	P Value
Death, MI, coronary revascularization (n=819)	0.46±0.16	0.95±0.19	<0.001
Death (n=38)	0.56±0.17	-0.60±1.55	0.45
MI (n=75)	0.56±0.17	0.61±0.44	0.90
Coronary revascularization (n=776)	0.46±0.16	0.96±0.19	<0.001

*ACTIVATE, CAMELOT, ILLUSTRATE, PERISCOPE, REVERSAL, STRADIVARIUS

Nicholls et al. J Am Coll Cardiol 2010;55:2399-407

What about in ACS?

The ESTABLISH Study

Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event

	20mg Atorvastatin	Statin Naïve Controls	P-value
	24	24	
Length, mm	8.9±2.5	8.6±2.0	1.0
Baseline atheroma volume, mm^3	69.6±49.0	71.0±27.9	0.4
6-month follow-up atheroma volume, mm^3	61.4±44.9	63.7±40.1	0.9
Δ atheroma volume, mm^3	-8.3±9.0	4.2±8.6	<0.0001
% Δ atheroma volume	*-13.1±12.8%*	*8.7±14.9%*	*<0.0001*

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Okazaki et al. Circulation 2004;110:1061-8

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JAPAN-ACS

Clinically evident polyvascular disease and regression of coronary atherosclerosis after intensive statin therapy in patients with acute coronary syndrome: serial intravascular ultrasound from the Japanese assessment of pitavastatin and atorvastatin in acute coronary syndrome trial.

	4 mg Pitavastatin	20 mg Atorvastatin	P-value
	125	127	
Length, mm	6.1±2.8	7.3±3.1	0.0021
Baseline atheroma volume, mm^3	49.8±28.8	63.9±33.9	<0.001
8-12 month follow-up atheroma volume, mm^3	41.6±25.0	53.3±31.7	0.0013
Δ atheroma volume, mm^3	-8.2±8.9	-10.6±10.6	0.05
% Δ atheroma volume	-16.9±13.7%	-18.1±14.2%	0.5
Δ % atheroma volume	*-5.7±6.3%*	*-6.3±6.1%*	*0.5*

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Hiro et al. J Am Coll Cardiol 2009;54:293-302

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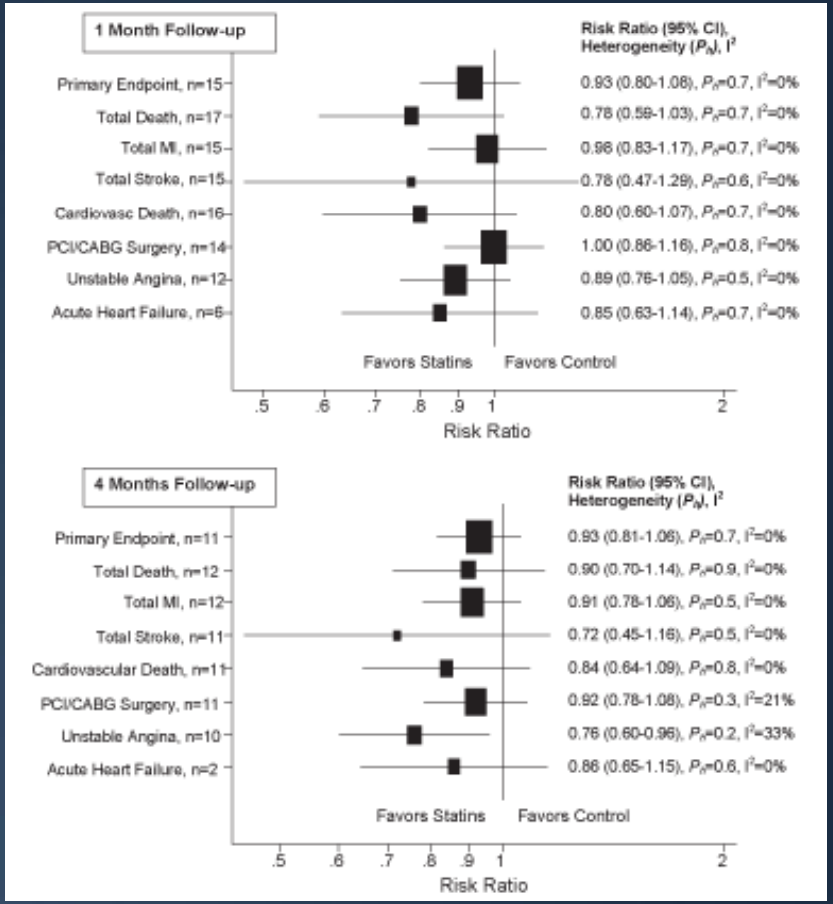
Updated evidence on early statin therapy for acute coronary syndromes: Meta-analysis of 18 randomized trials involving over 14,000 patients

Initiation of statin therapy within 14 days following ACS results in directionally favorable but non-significant reduction in death, myocardial infarction, or stroke up to 4months, and significant reduction in the occurrence of unstable angina at 4 months following ACS.



(Briel, et al. Int J Cardiol 2011, in press)

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Limitations of ~~Angiography~~ Grayscale IVUS in Trials of Progression and Regression

- Cardiovascular events correlate poorly with ~~lumen size~~ changes in plaque burden
- Surprisingly small ~~angiographic~~ grayscale IVUS differences are associated with a significant reduction in clinical events – although not in the same studies
- Underestimates the extent of ~~atherosclerosis~~ plaque vulnerability

IBIS-2

	160mg Darapladib + standard of care	Control
Analysis segment length, mm	49±16	49±16
Grayscale IVUS analysis		
Baseline atheroma volume, mm^3	***327±189***	***313±149***
Δ atheroma volume, mm^3	***−5.0±28.0 mm^3***	***−4.9±32.7 mm^3***
VH-IVUS analysis		
Baseline NC volume, mm^3	22.8±24.5 13.6 [7.3, 32.4]	21.5±21.9 14.8 [6.1, 28.2]
Baseline %NC volume	13.4±6.5% 12.5 [9.1, 17.5]	13.1±7.6% 12.6 [6.8, 16.8]

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Serruys et al. Circulation. 2008 ;118:1172-82

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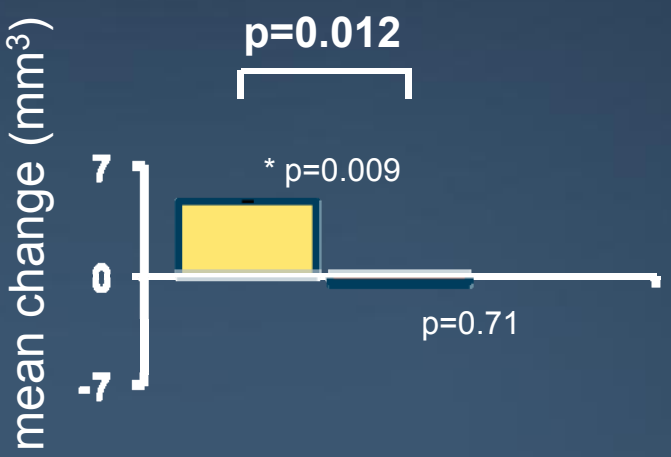
Plaque Composition by IVUS - VH

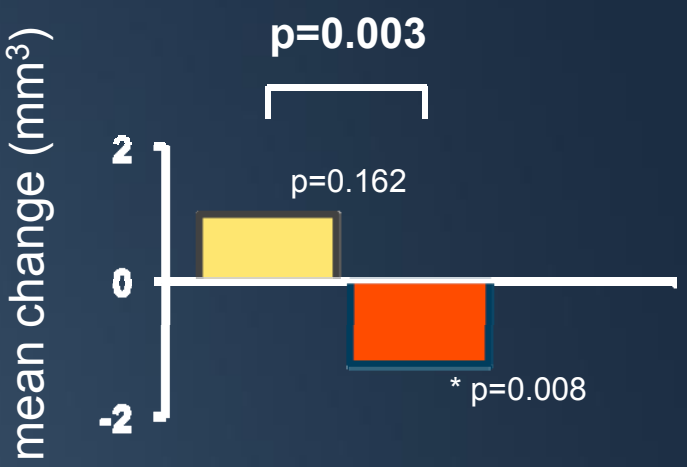
change from baseline in necrotic core volume

Entire region of interest

[mean 48 mm]



The worst 10 mm subsegment

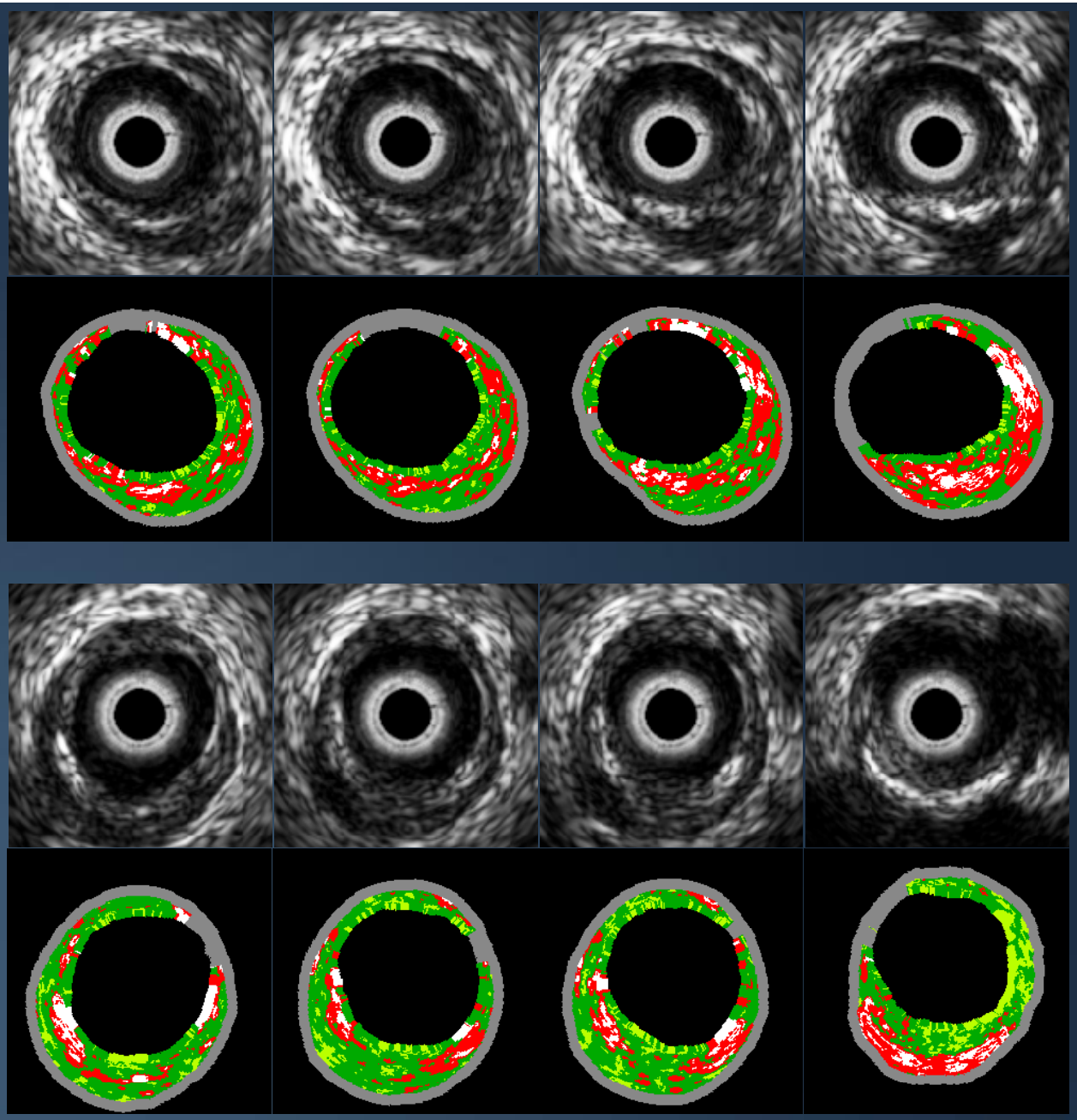


placebo (plus standard of care) n=110

darapladib 160 mg (plus standard of care) n=129

Serruys et al. Circulation. 2008 ;118:1172-82

Darapladib



Serruys et al. Circulation. 2008 ;118:1172-82

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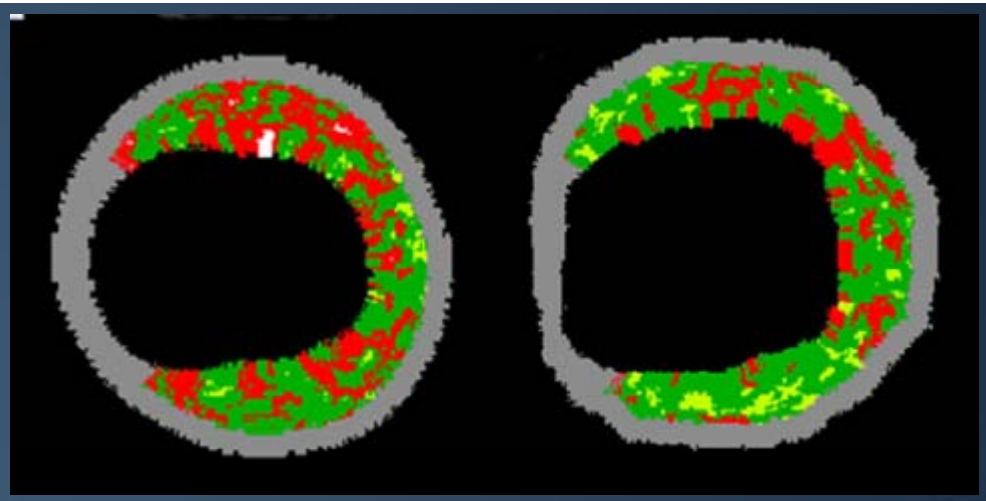
Randomized comparison of 20mg simvastatin (n=50) vs 10mg rosuvastatin (n=50) over a 10mm long segment centered on the MLA site with 1 year of follow-up

Primary endpoint: effect of statin treatment on VH-IVUS plaque composition			
	Baseline	Follow-up	P
Total atheroma volume	89.8±27.1mm^3	87.1±27.2mm^3	<0.0001
NC volume	*15.7±9.9mm^3*	*13.7±9.9mm^3*	*<0.0001*



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(Hong et al. J Am Coll Cardiol Intv, 2009;2:679-88)

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Secondary endpoint: simvastatin vs rosuvastatin

	Rosuvastatin	Simvastatin	P
Baseline LDL-C, mg/dl	119±30	116±28	0.6
Follow-up LDL-C, mg/dl	78±20	64±21	0.002
ΔLDL-C, mg/dl	-41±26	52±25	0.046
Baseline HDL-C, mg/dl	43±10	43±11	0.8
Follow-up hDL-C, mg/dl	48±12	52±14	0.13
ΔHDL-C, mg/dl	6±10	9±11	0.12
Baseline total atheroma volume	83.3±26.9mm^3	91.5±27.5mm^3	0.5
Baseline NC volume	15.8±11.3mm^3	15.5±8.4mm^3	0.9
Δplaque volume	-1.8±5.7mm^3	-3.6±7.2mm^3	0.16
Δnecrotic core volume	*-1.4±8.1mm^3*	*2.5±7.0mm^3*	*0.5*
Δ%necrotic core	*-3±13%*	*5±12%*	*0.3*

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(Hong et al. J Am Coll Cardiol Intv, 2009;2:679-88)

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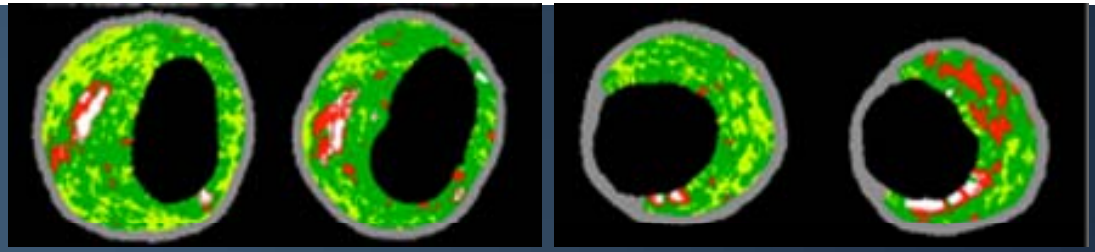
Non-randomized comparison of a >30mm long non-stented lesion (<50% angiographic diameter stenosis): fluvastatin (n=40) vs controls (n=40) with 1 year of follow-up

	Fluvastatin	Controls	P
Analysis segment length	52.9±23.3mm	52.0±23.6mm	0.9
Baseline total atheroma volume	440.2±220.3mm^3	432.9±233.5mm^3	0.9
Baseline NC volume	21.4±24.9mm^3	22.1±17.4mm^3	0.9
Δplaque volume	-36.4±42.6mm^3	11.2±7.6mm^3	<0.0001
Δfibrous tissue	16.8±15.0mm^3	4.4 ± 5.3mm^3	0.03
Δfibrofatty tissue	-48.4±47.2mm^3	23.6±16.7mm^3	<0.0001
Δdense calcium	0.4±3.4mm^3	6.5±14.5mm^3	0.01
Δnecrotic core	*-2.6±10.3mm^3*	*8.9±17.7mm^3*	*0.004*



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(Nasu et al. J Am Coll Cardiol Intv, 2009;2:689-96)

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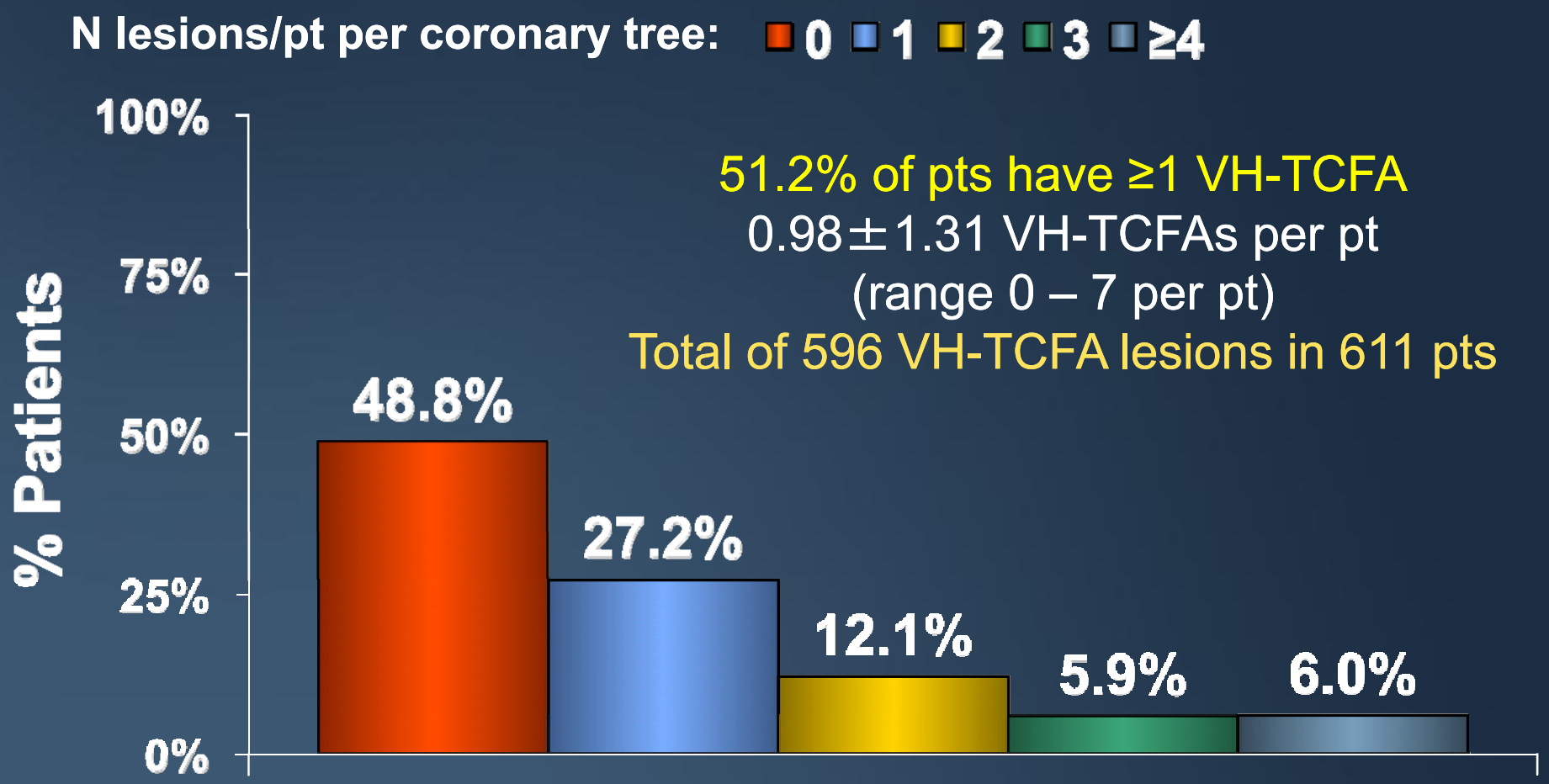
Per patient incidence of VH-TCFAs



51.2% of pts have ≥1 VH-TCFA

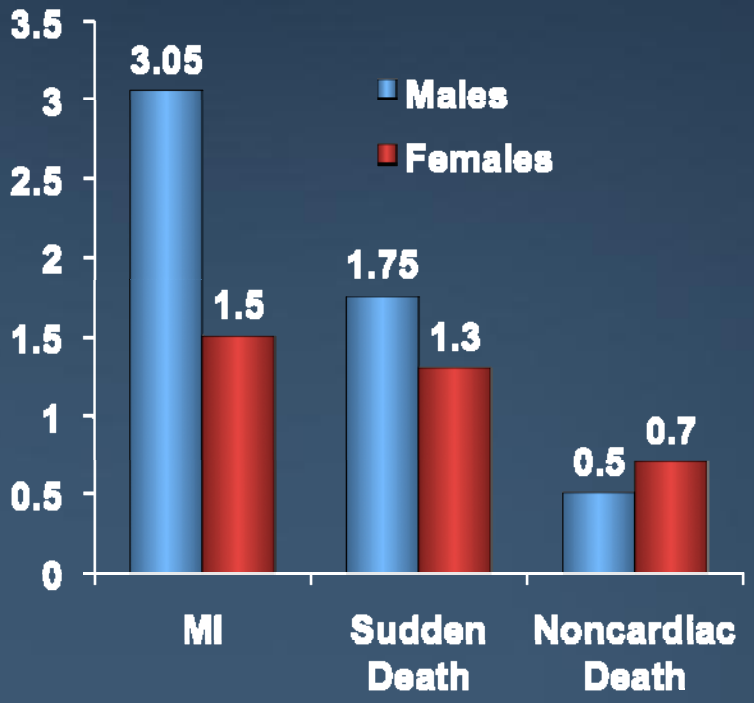
0.98±1.31 VH-TCFAs per pt

(range 0 – 7 per pt)

Total of 596 VH-TCFA lesions in 611 pts

Number of thin-cap fibroatheromas in patients dying with MI, sudden death, or noncardiac causes and studied at necropsy

Cross-sectional analysis

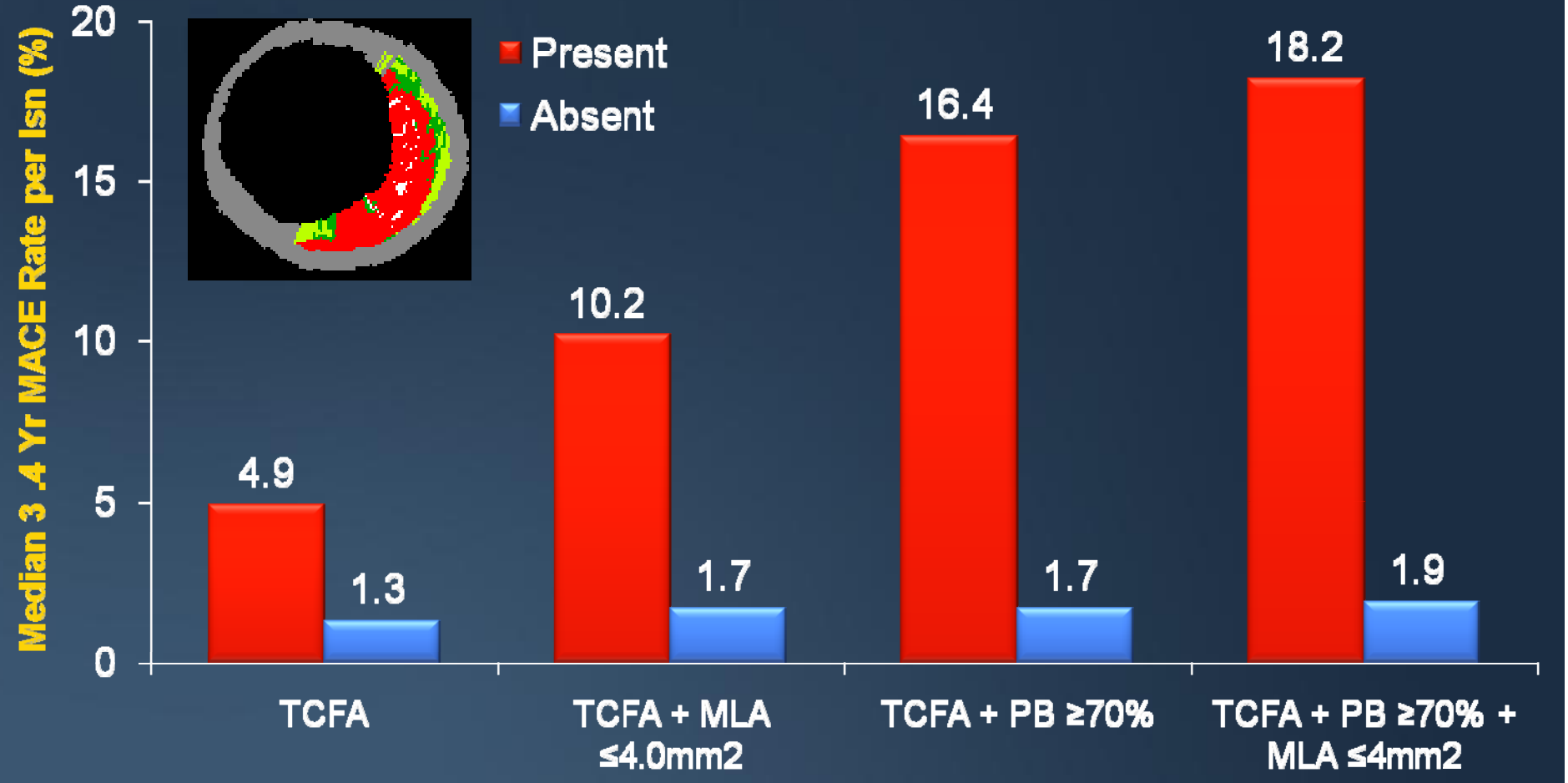


Longitudinal analysis

	All pts	Pts with ≥1 ruptured plaque	Pts with ≥1 TCFA or ruptured plaque	Pts with CV death
# of patients	50	14	20	33
# of ruptured plaques	19 (0.38/pt)		19 (0.95/pt)	15 (0.45/pt)
# fibroatheromas	193			
# TCFAs	23 (0.46/pt)	15 (1.21/pt)	23 (1.15/pt)	18 (0.55/pt)

Burke et al. J Am Coll Cardiol 2003;41:1874-86
Cheruvu et al. J Am Coll Cardiol 2007;50:940-9

VH-TCFA and Non Culprit Lesion Events



Lesion HR	3.90 [2.25, 6.76]	6.55 [3.43, 12.51]	10.83 [5.55, 21.10]	11.05 [4.39, 27.82]
P-value	<0.0001	<0.0001	<0.0001	<0.0001
Prevalence	4.67%	15.9%	10.1%	4.2%

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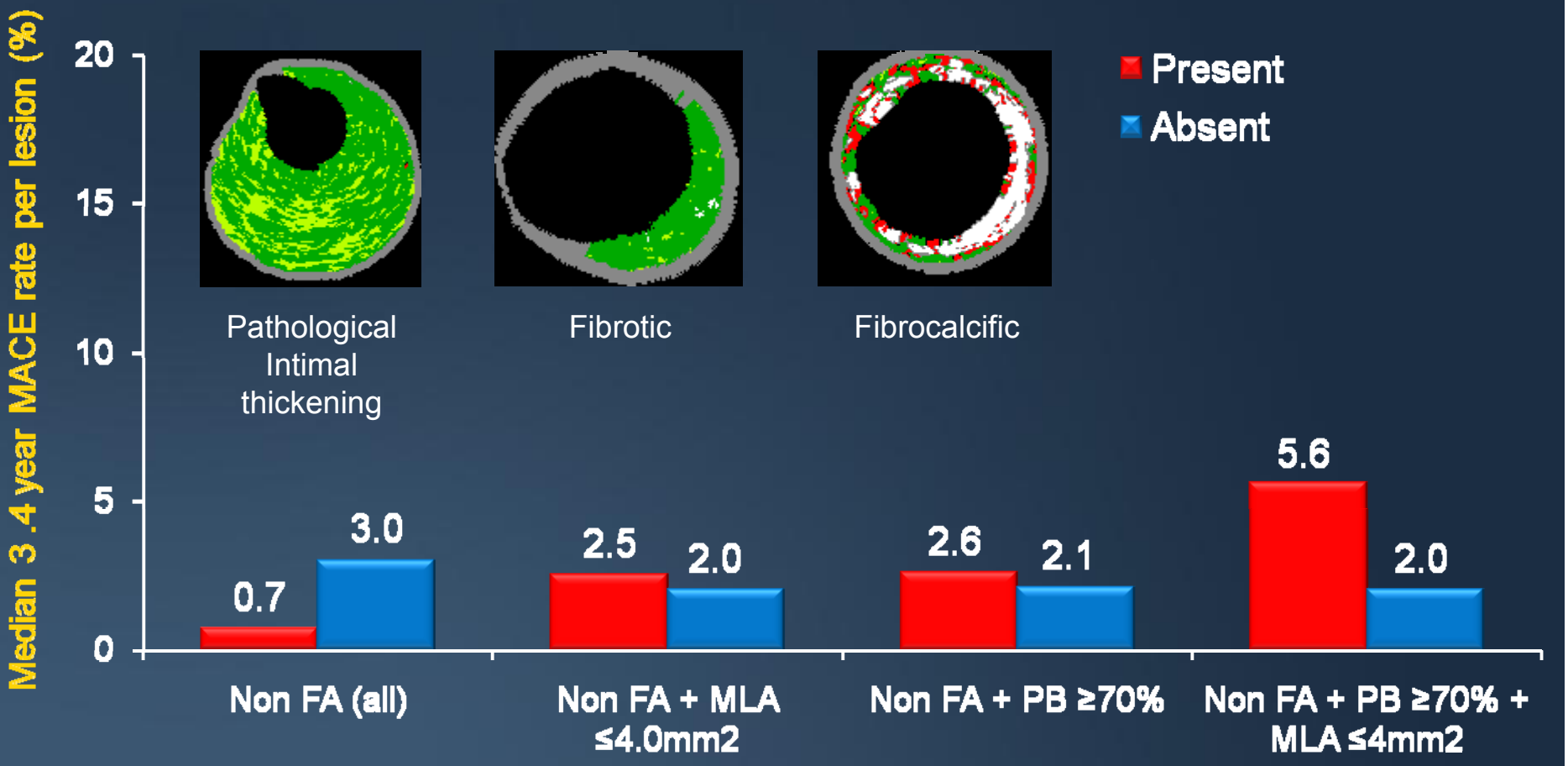
Non Fibroatheromas and Non Culprit Lesion Events

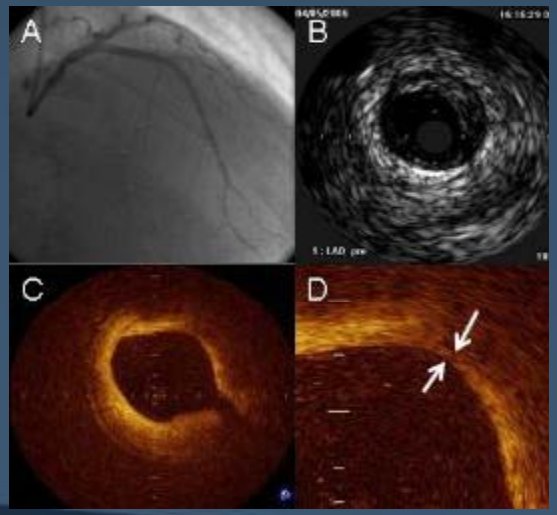


Lesion HR	0.22 [0.10, 0.49]	1.49 [0.44, 3.39]	1.25 [0.17, 9.01]	2.60 [0.36, 18.84]
P-value	0.0002	0.70	0.83	0.34
Prevalence	67.9%	19.7%	5.6%	2.7%

40 AMI patients with hyperlipidemia were divided into statin treatment (n=23) vs control (n=17). Serial OCT of a non-treated, lipid-rich lesion was performed at baseline and 9-month follow-up.

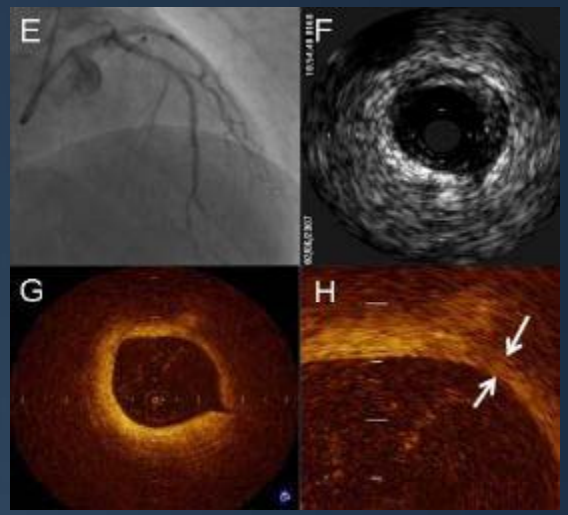
	Statin treatment			Control		
	Baseline	FU	*p*	Baseline	FU	*p*
Fibrous-cap thickness, μm	151±110	280±120	<0.001	153±116	179±124	<0.01
% Change in fibrous-cap thickness	188±64*			117±39		

Baseline



P<0.01 vs control

Follow-up



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Takarada et al. Atherosclerosis 2009;202:491-7

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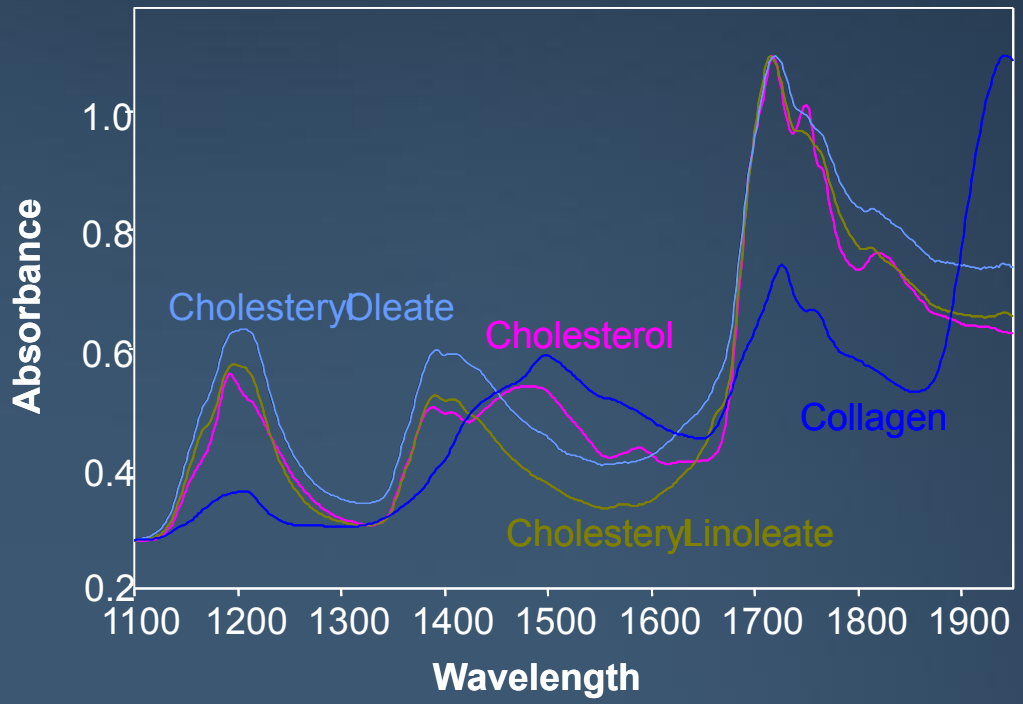
OCT findings and lesion progression

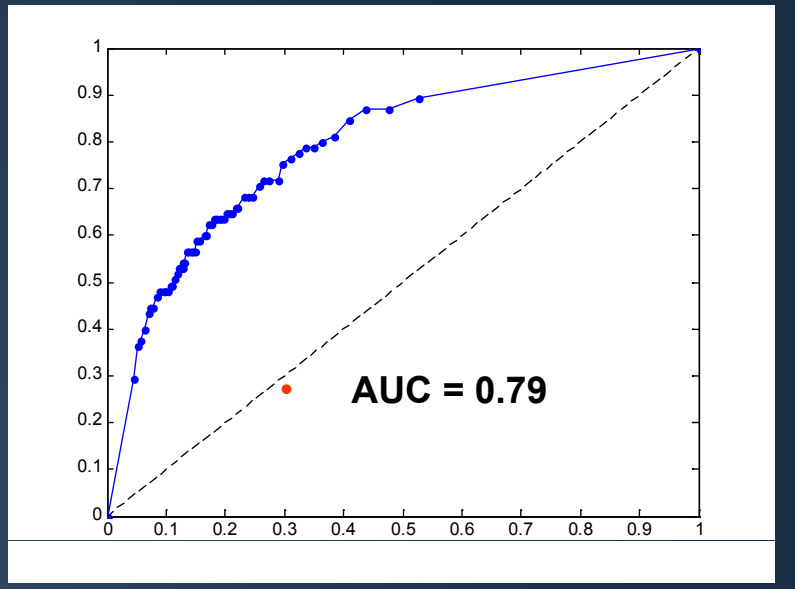
	Progression*	No Progression	P-value	OR	P-value
Plaque rupture	61.5%	8.9%	<0.01	10.2	<0.001
Microchannels	76.9%	14.3%	<0.01	20.0	<0.001
Lipid pools	100%	60.7%	0.02	2.16	0.2
TCFA	76.9%	14.3%	<0.01	20.0	<0.001
Macrophages	61.5%	14.3%	<0.01	9.0	0.001
Thrombus	30.8%	1.8%	<0.01	12.0	0.002

decrease in QCA MLD >0.4mm

Univariate analysis showed that OCT-TCFA and microchannels (both OR=20.0, p<0.01) correlated with progression

NIR Spectroscopy can identify the chemical composition of unknown substances and distinguish cholesterol from collagen. ROC Analysis of Validation of NIR Spectroscopy in 51 Autopsy Hearts (algorithm for detection of confluent [>0.2mm thick and >60°] and relatively superficial necrotic core [overlying mean fibrous cap thickness <0.45microns])





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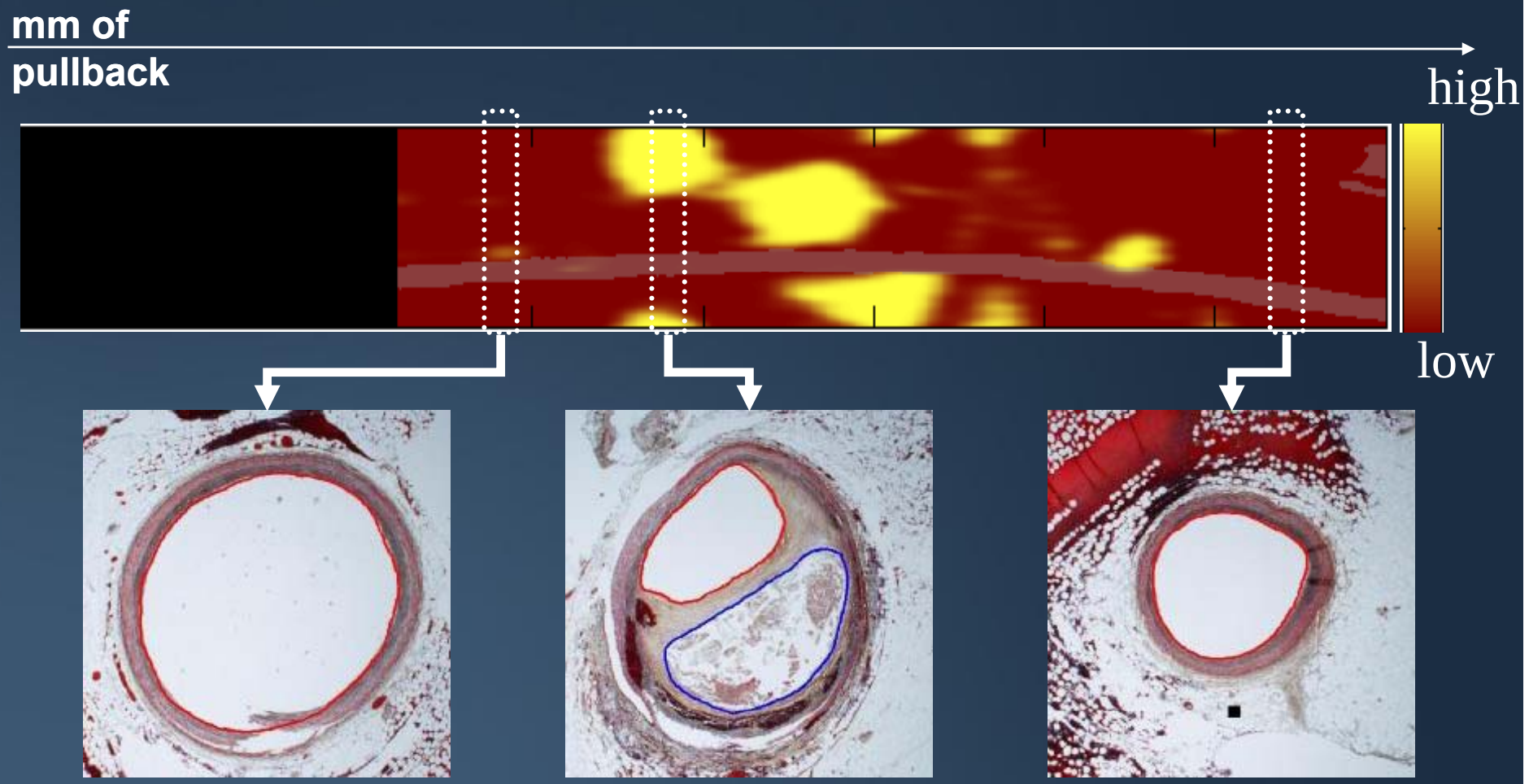
LipiScan vs Histology



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YELLOW

- 87 pts with multivessel disease who had undergone stenting of the target vessel and were scheduled for staged PCI of a second, obstructive lesion were randomized to rosuvastatin 40mg/day vs standard statin
- All lesions were characterized with IVUS, FFR, and NIRS at baseline and after 6 to 8 weeks

	40mg Rosuvastatin	Standard statin therapy	P
#	44	43	
Δtotal cholesterol, mg/dl	-20.0±4.8	5.2±5.4	0.001
ΔLDL-C, mg/dl	*-19.0±4.0*	*-0.2±4.7*	*0.003*
ΔHDL-C, mg/dl	*0.6±1.2*	*1.5±0.9*	*0.58*
Δ%atheroma volume	*0.24%*	*0.26%*	*1.0*
FFR >0.80	9.0%	4.6%	0.47

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(Kini et al. American College of Cardiology 2012)

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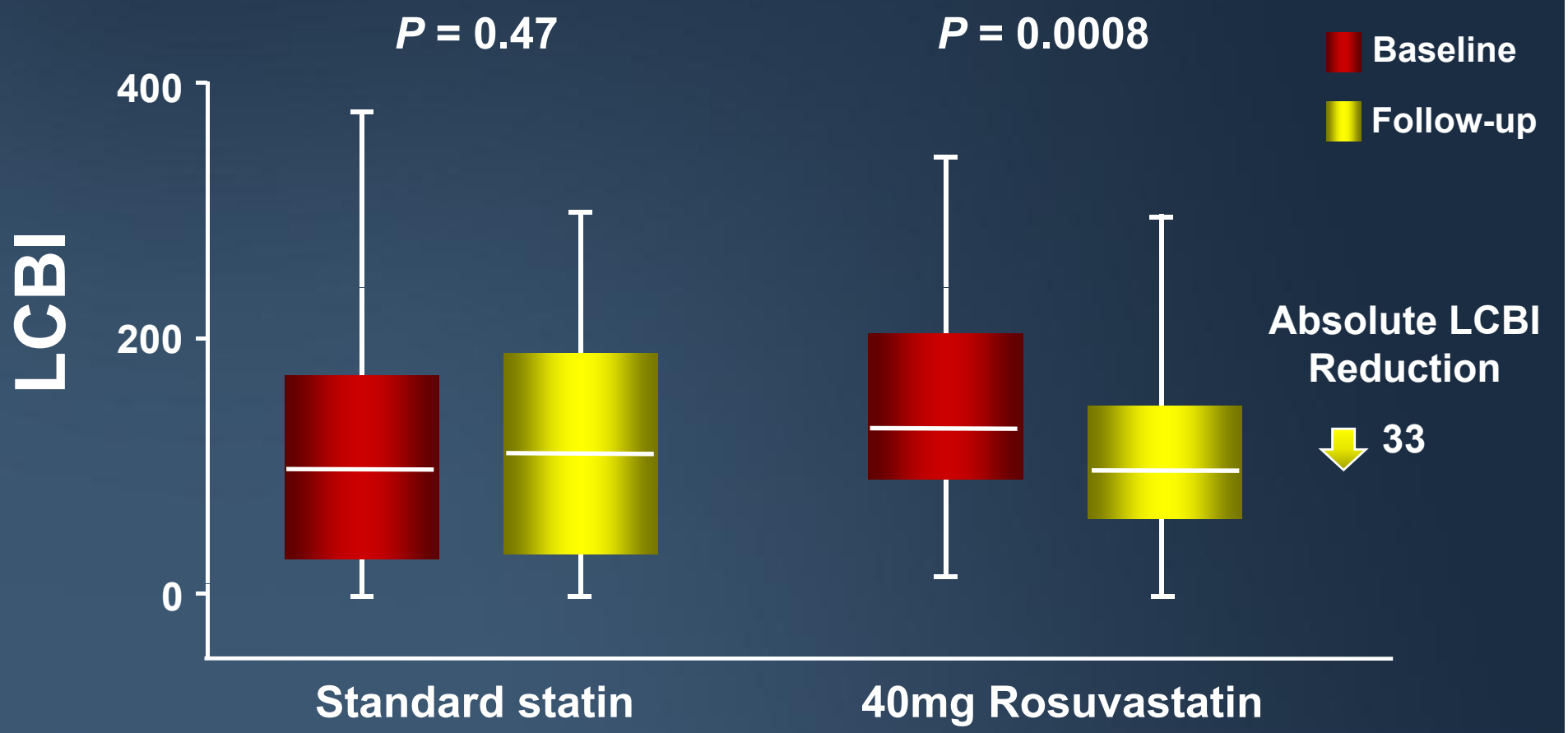
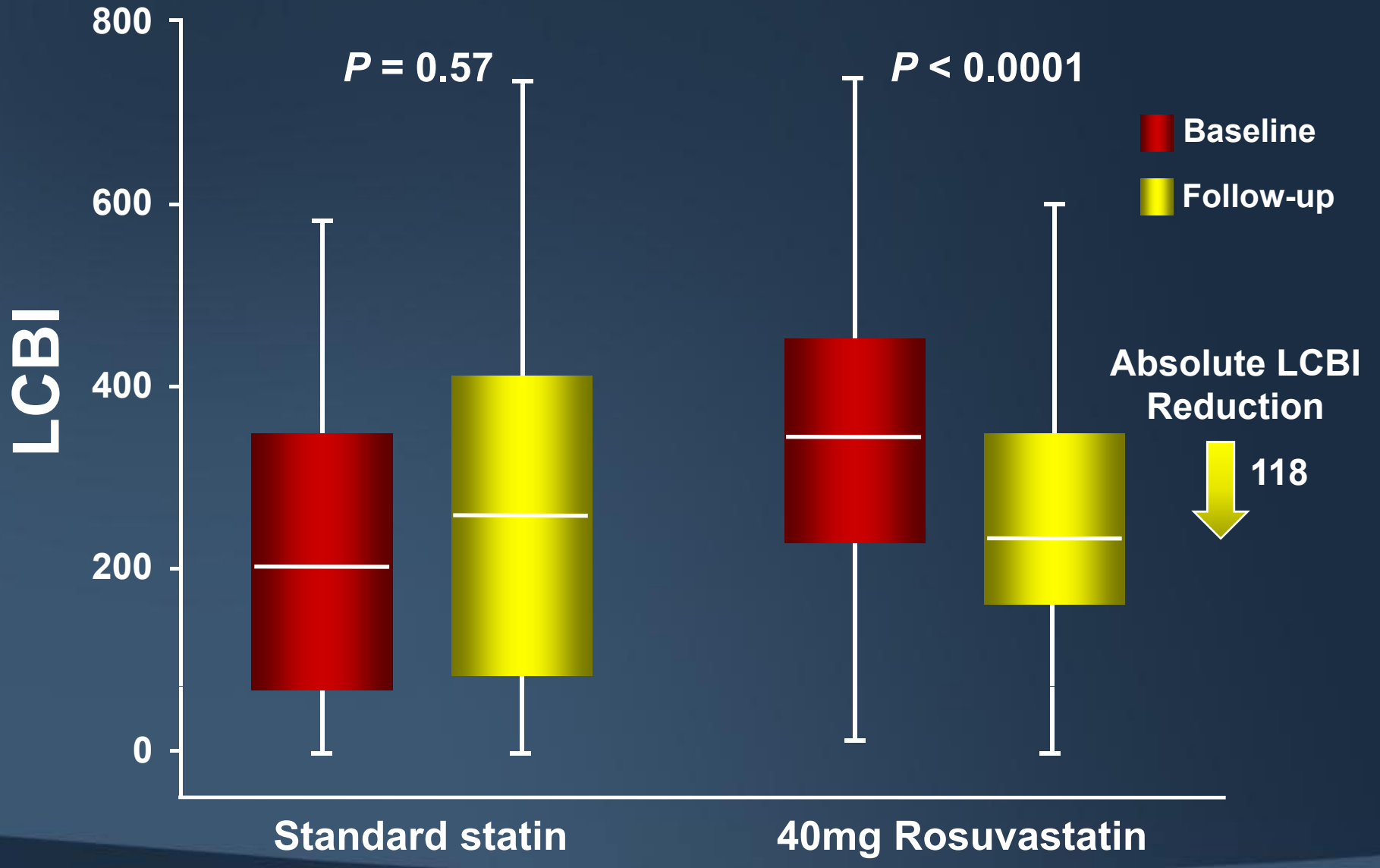
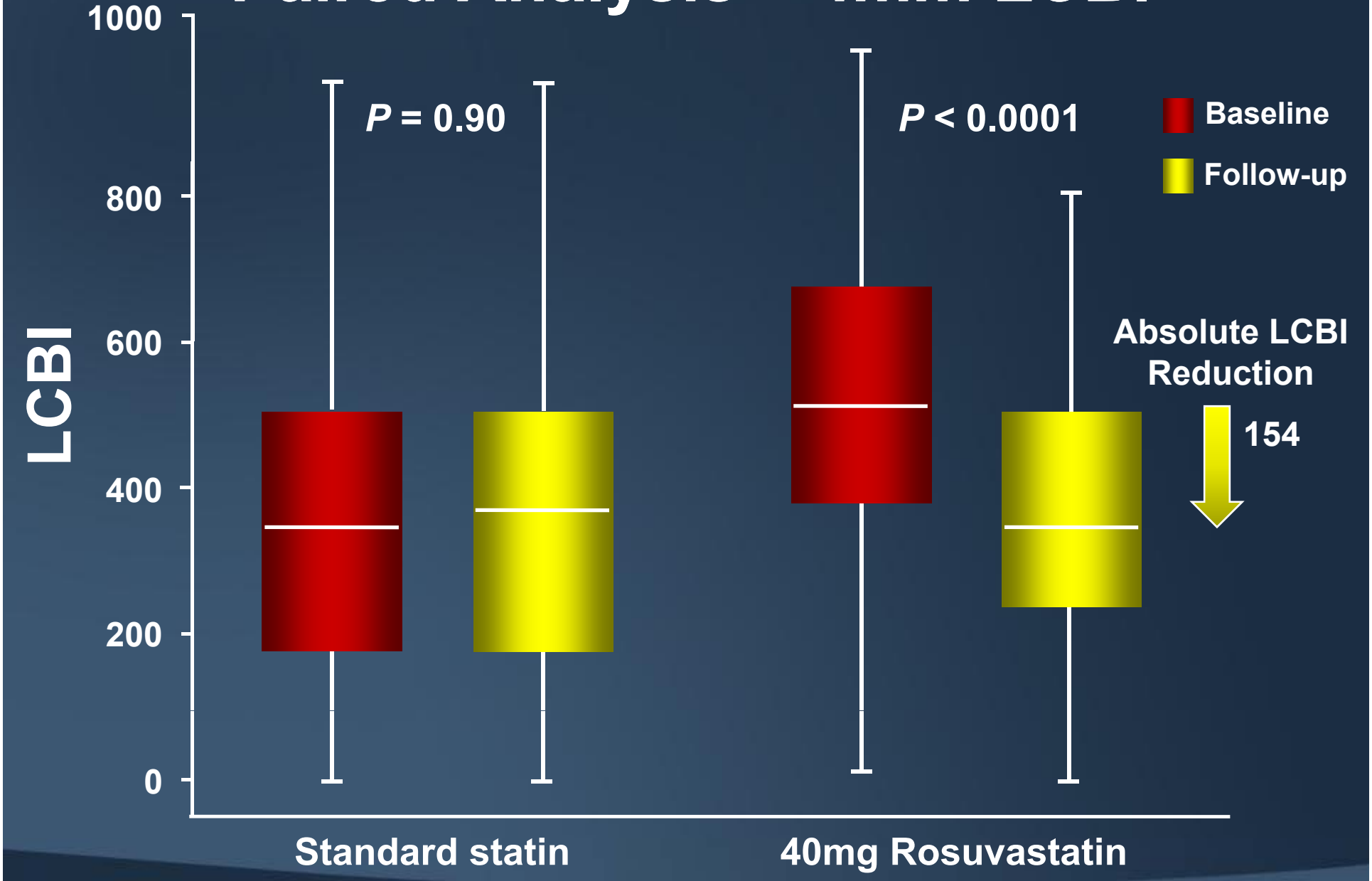
Paired Analysis – Lesion Lipid Core Burden Index (LCBI)



Paired Analysis – 10mm LCBI



Paired Analysis – 4mm LCBI



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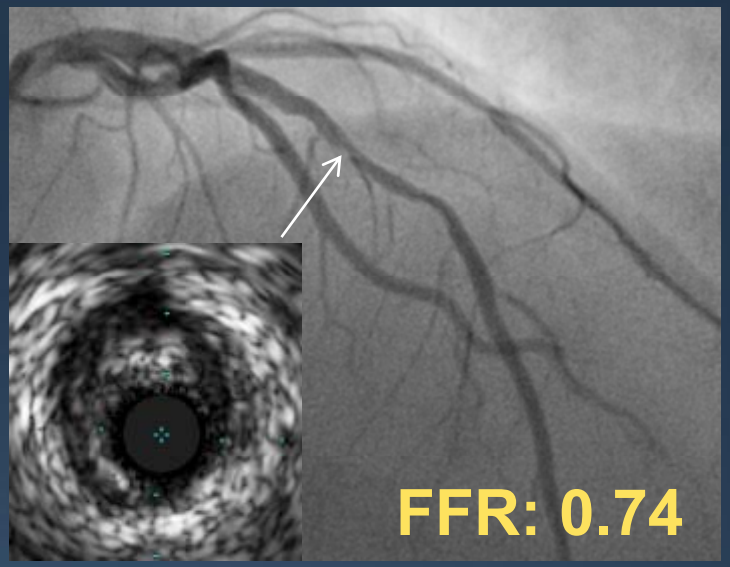
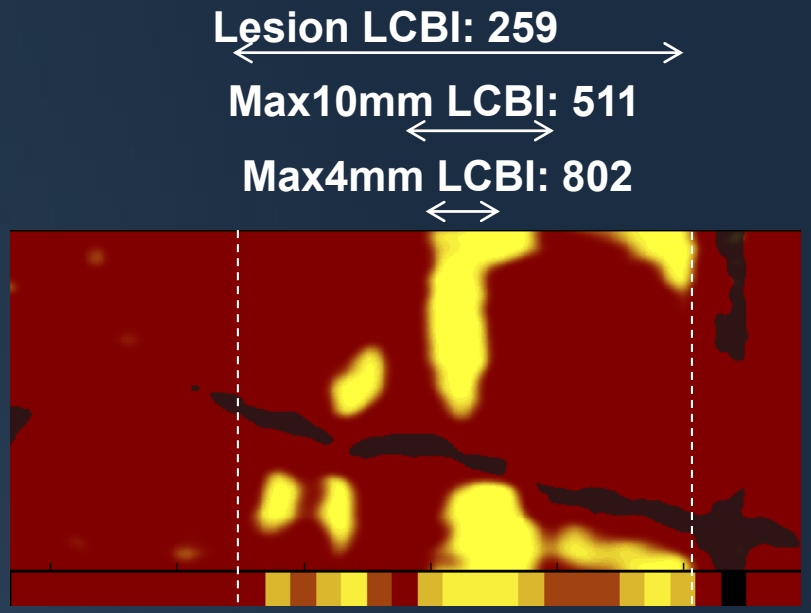
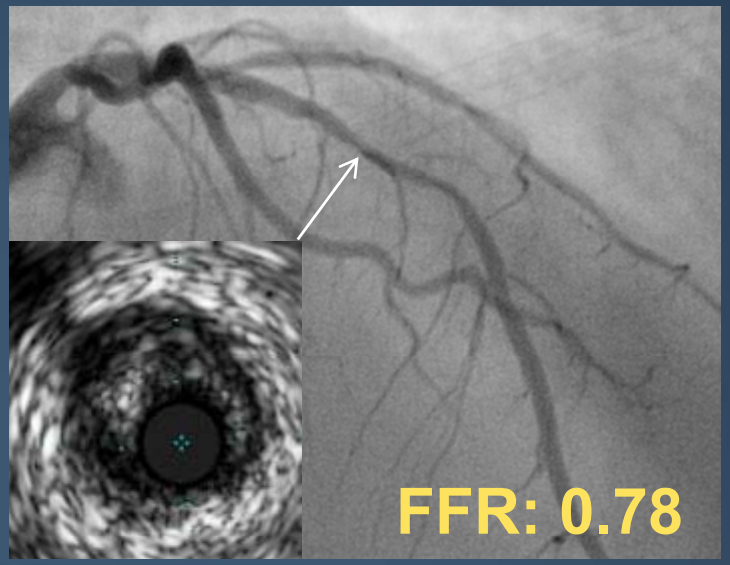
Baseline



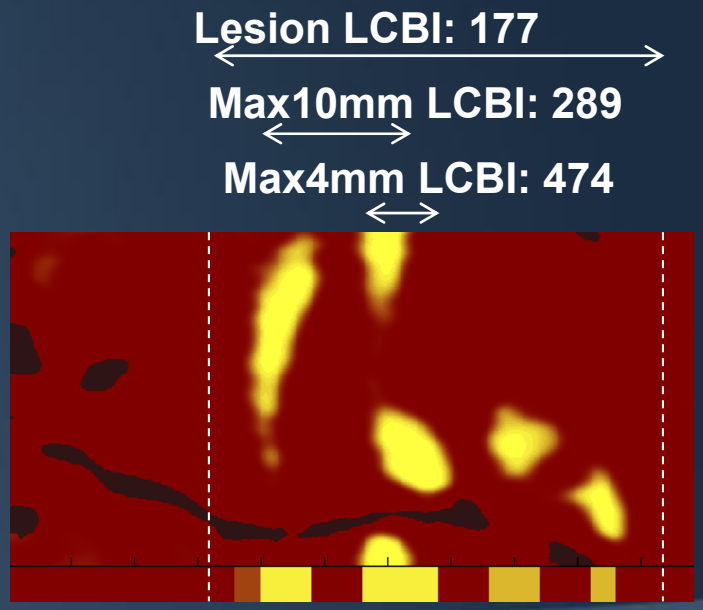
Plaque Area
5.6mm^2



Follow-up



Plaque Area
5.5mm^2



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In my opinion, we have "hit a wall" in terms of greyscale IVUS assessment of progression/regression. New invasive imaging modalities should focus on analysis of an arterial segment that contains a high-risk or vulnerable plaque and not just on an arbitrarily selected segment.