冠動脈疾患の重症化予防（急性冠症候群発症予防）への道：積極的脂質低下療法を中心に

神戸大学医学部附属病院　循環器内科

大竹　寛雅

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COI Disclosure

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The Japanese Multidisciplinary Academy of the Prevention

Use Form 1-A when you have conflicts of interest to disclose concerning a presentation. Give the name of commercial entity involved.

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②Stock ownership/profit: None
③Patent fees: None
④Remuneration for lecture: Astellas AMGEN biopharma, Sanofi, HeartFlow Inc.
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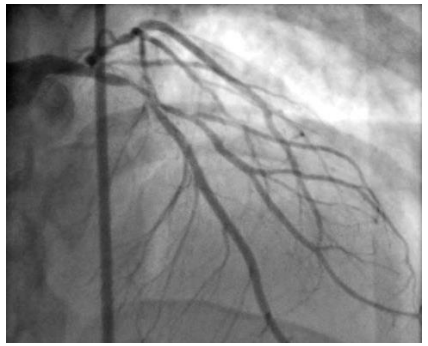
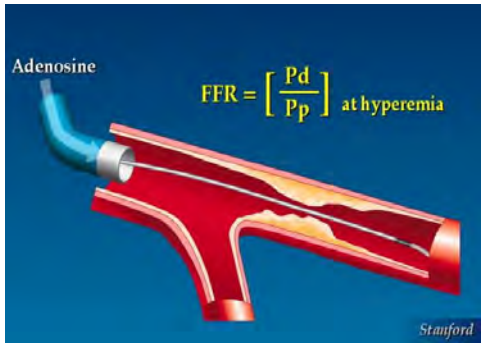
⑦Scholarship fund: Astellas, Sanofi
⑧Affiliation with Endowed Department: None
⑨Other remuneration such as gifts: None

本日の内容

- FFR-CTによる心血管イベント予測(Emerald研究)
- 脂質低下療法が冠動脈プラークに与える影響：冠動脈イメージングを用いた検討
- PCSK9阻害薬投与後血管内イメージングで連続的に観察できた１例

冠動脈疾患における解剖学的診断と機能的診断法

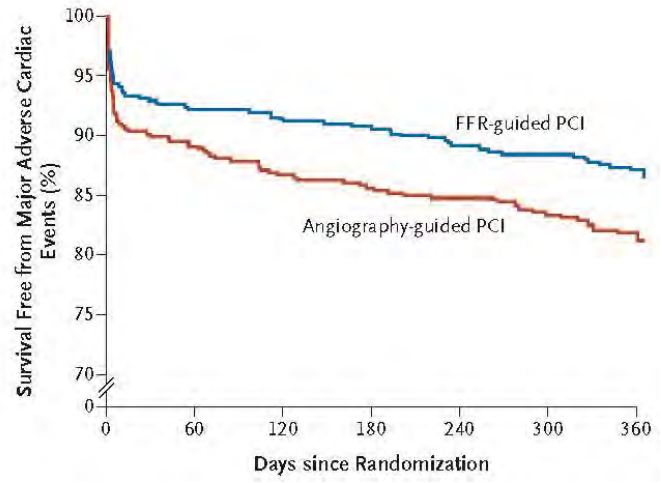
	解剖学的診断 閉塞部位の確認	機能的診断 PCI施行判断の虚血診断
侵襲的		

FFRの果たす役割：
FFR is the Gold Standard to Identify Vessel-Specific Ischemia

FAME

The NEW ENGLAND JOURNAL of MEDICINE

Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention

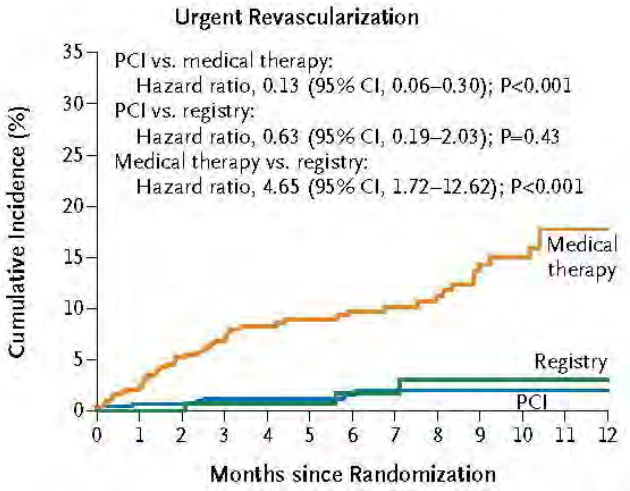


- 虚血の有無を考慮したPCIは形態的評価に基づくPCIより予後を改善する

FAME II

The NEW ENGLAND JOURNAL of MEDICINE

Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease



- いったん虚血が証明されればPCIは薬物療法より予後を改善する

Tonino et al., NEJM 2009, 360:213

De Bruyne et al., NEJM 2012, 367:991

冠動脈疾患における解剖学的診断と機能的診断法

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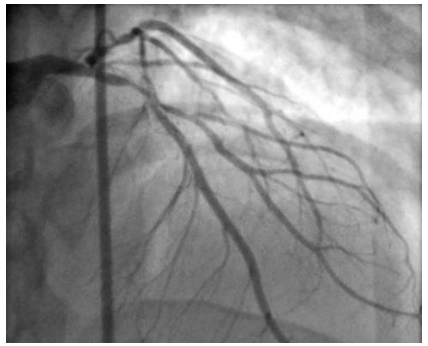
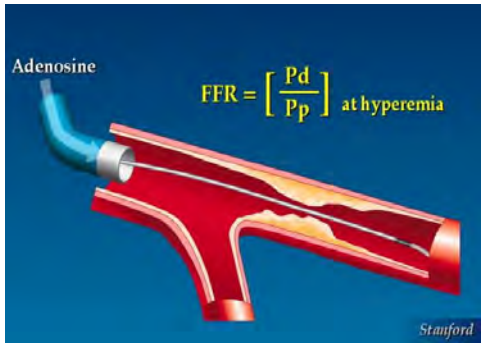
侵襲的		

- どちらも重要で、一方が他方を補うことは難しい

冠動脈疾患における解剖学的診断と機能的診断法

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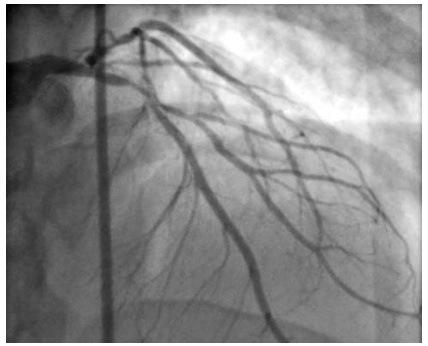
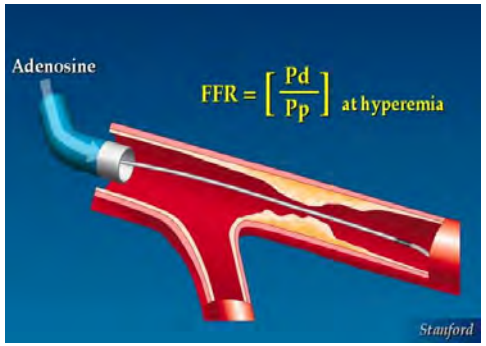
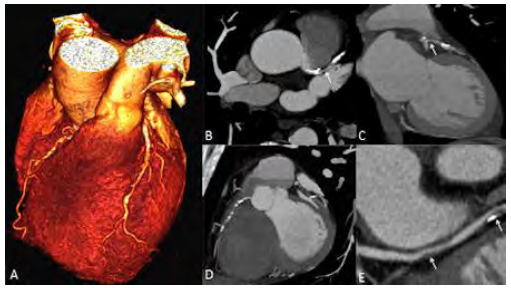
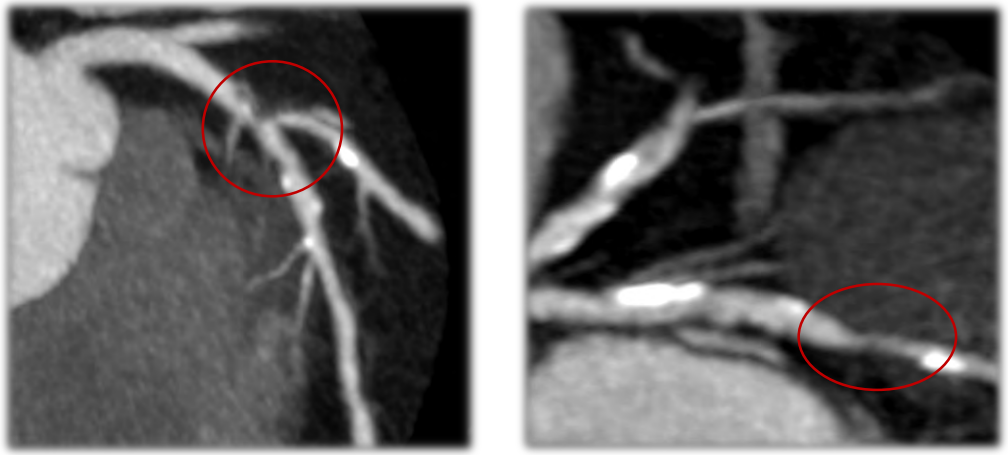
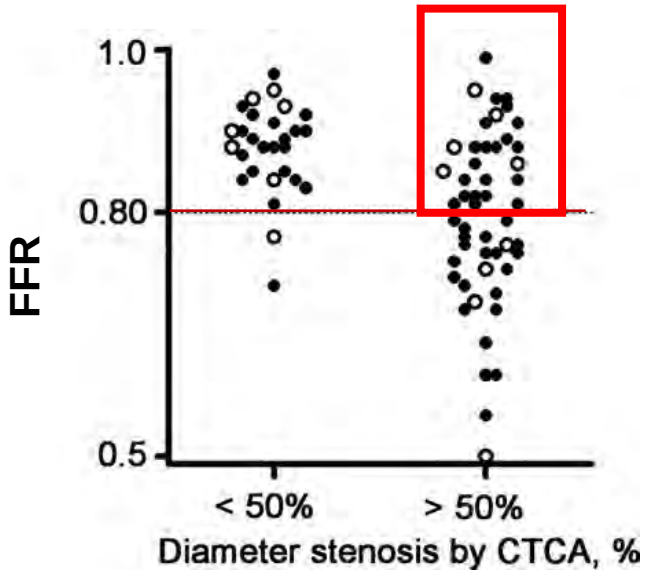
侵襲的		
非侵襲的		

冠動脈CTAによる形態的評価による虚血診断は困難

- Coronary CTA has a high sensitivity and high negative predictive value for diagnosis of obstructive CAD
- However, coronary CTA cannot define the hemodynamic significance of coronary lesions



Both of these patients have >50% diameter stenosis, but only one of these patients has FFR<=0.80



Meijboom et al, JACC 2008

冠動脈疾患における解剖学的診断と機能的診断法

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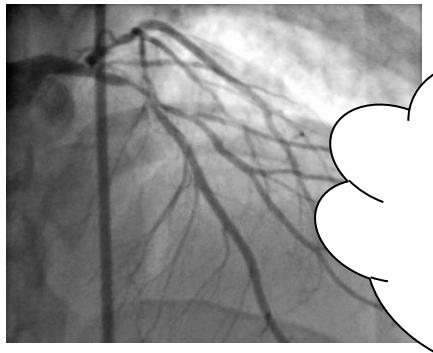
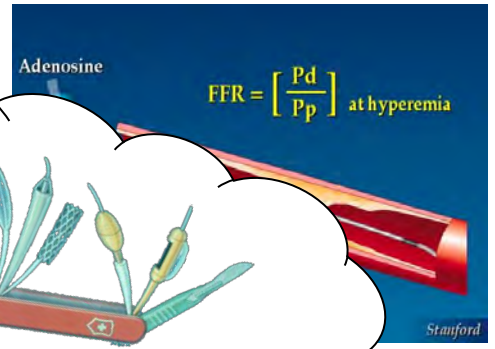
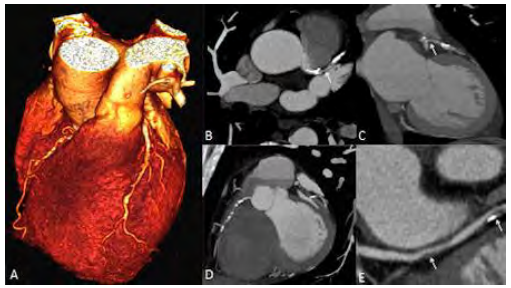
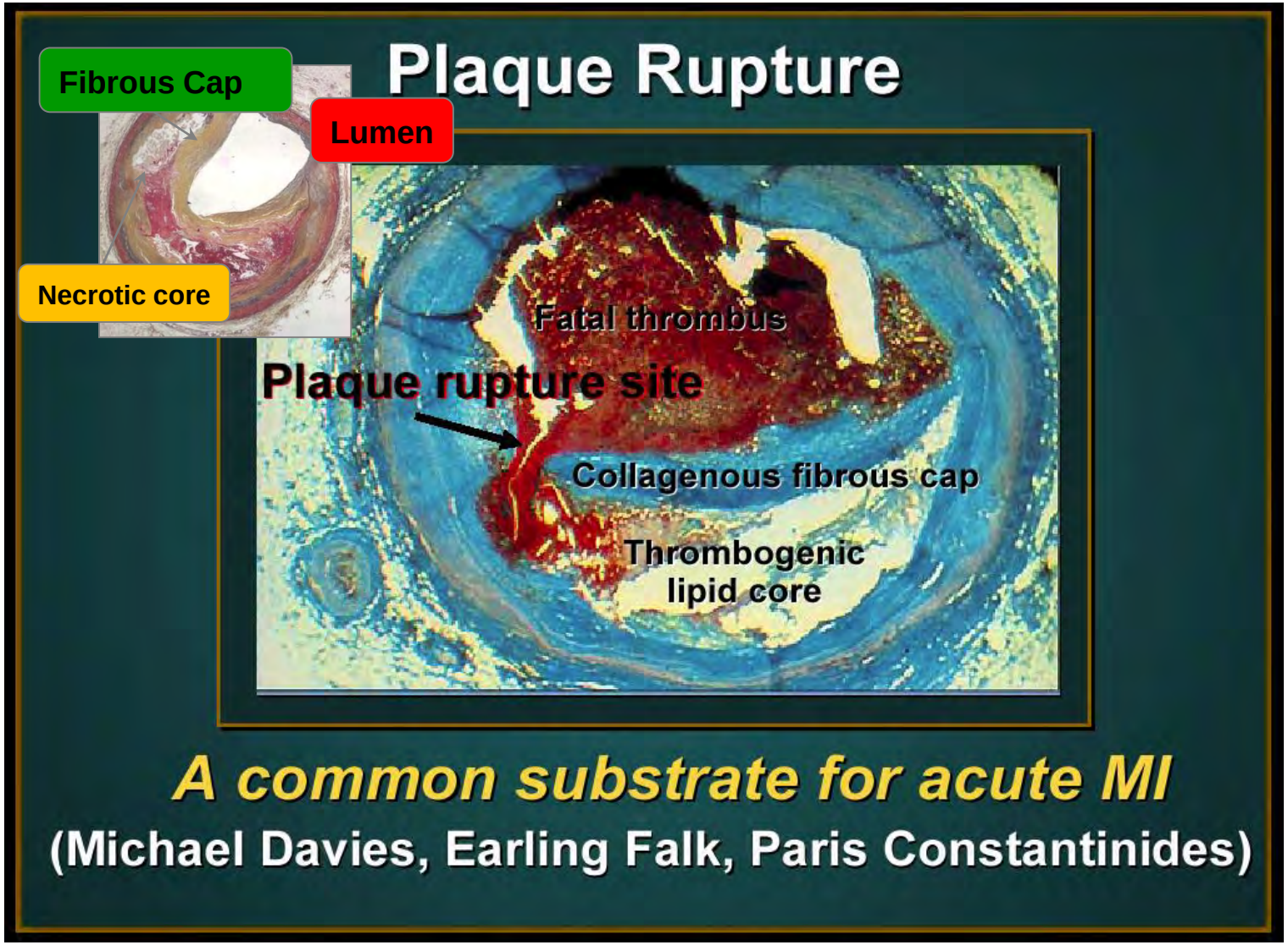
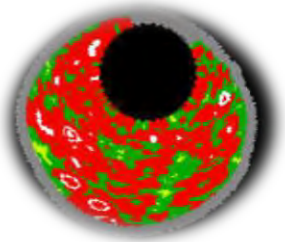
侵襲的		
非侵襲的		• 負荷心エコー • SPECT • MRI

ACSの病態生理: プラークの破綻

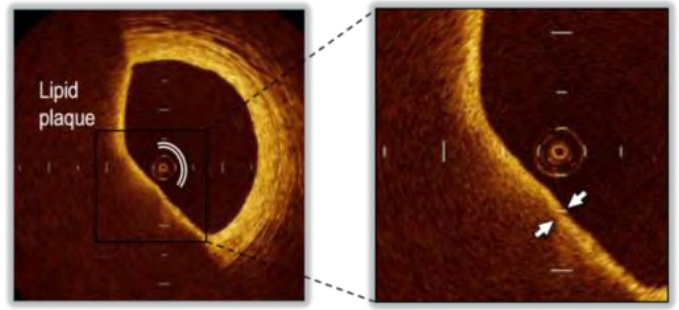


不安定プラークの画像的特徴

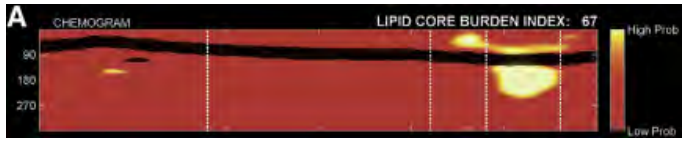
- VH-IVUS: %NC>10%, >30degree of NC
  abutted to the lumen in > 3 consecutive frames



- OCT: Cap thickness<65um, large lipid core



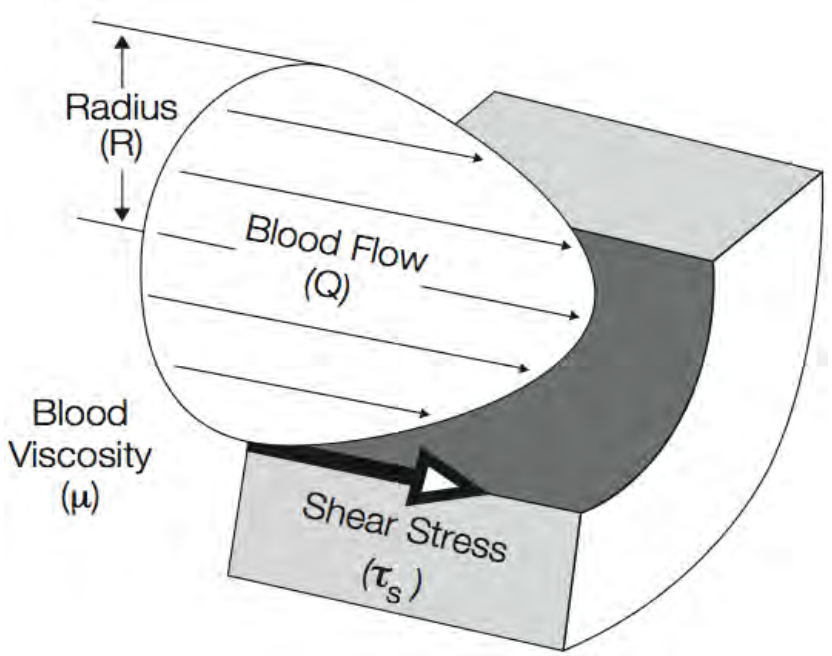
- NIRS IVUS: fibroatheroma with
  lipid core>60° >200 um thick
  with a fibrous cap having a mean thickness <450 um



- CTCA: Low attenuation plaque, spotty calc, positive remodeling

What is the shear stress?

Poiseuille's Law: shear stress $Ts = \frac{4\mu Q}{\pi R^3}$



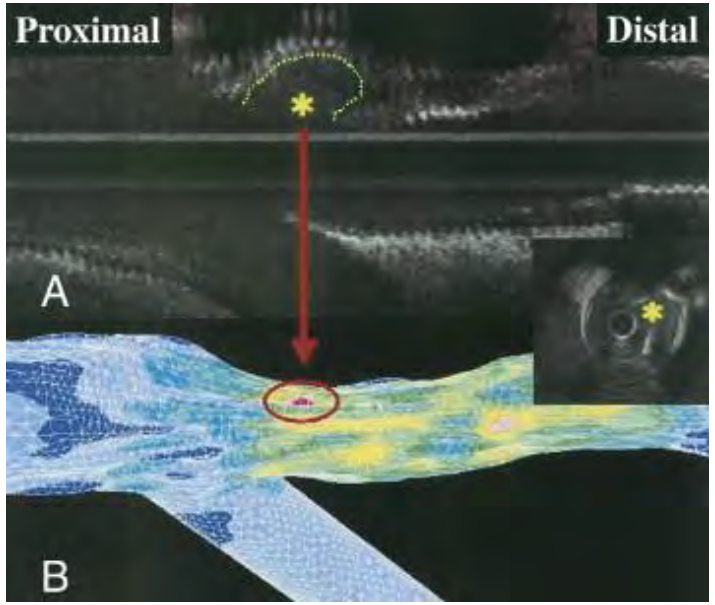
Shear stressは、

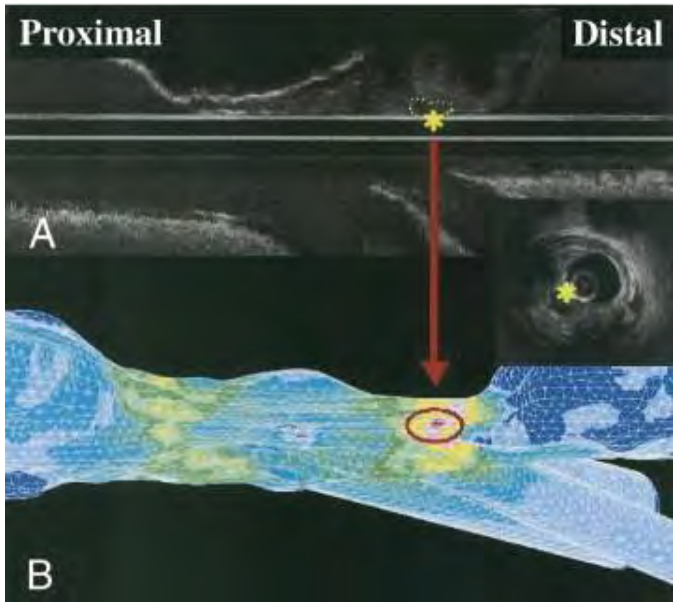
Flow velocityに比例

血管径（その部分から血管壁までの距離）に反比例

Malek et al, JAMA, 1999

Shear stress の果たす役割：プラークの破綻



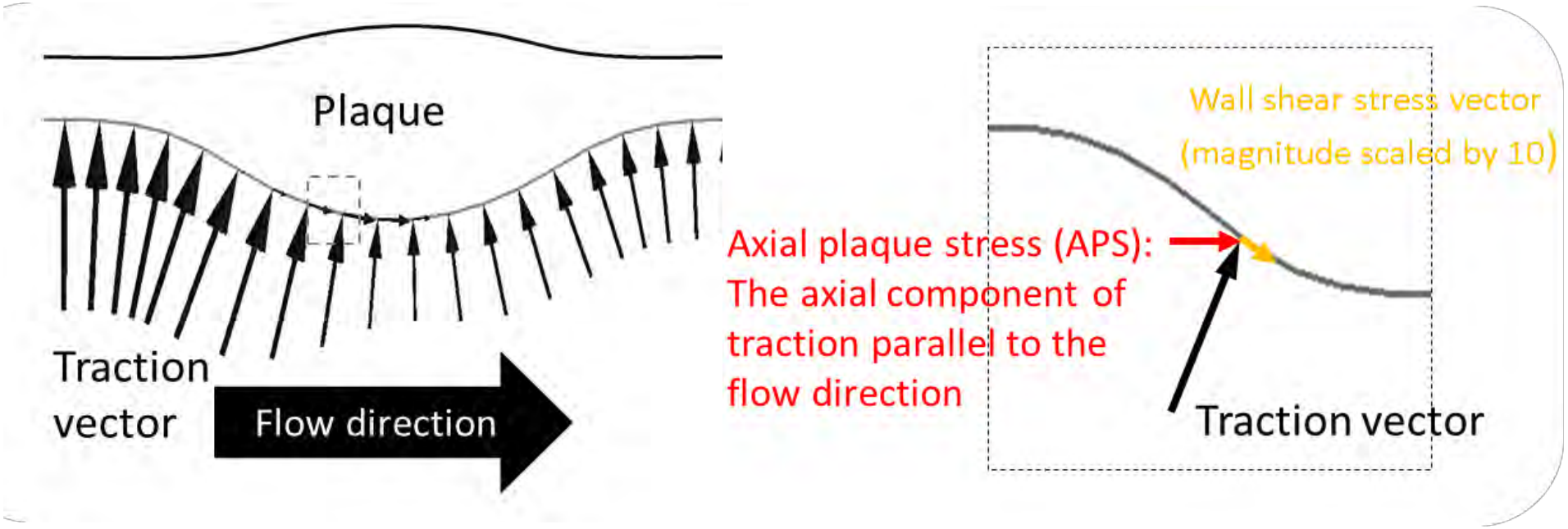


- Plaque ruptureをきたした部分のWSSは周囲に比べ有意に高値であった
- 従来より、Plaque ruptureはPositive remodelingをきたした血管の狭窄部位よりProximal siteにおこりやすいことが指摘されてきた
- この部分は、WSSの急峻な増加が認められる部分であり、High shear+急峻なWSSの増加がRuptureのリスクとなることが示唆された

Fukumoto et al, JACC, 2008

A new concept: axial plaque stress (APS)

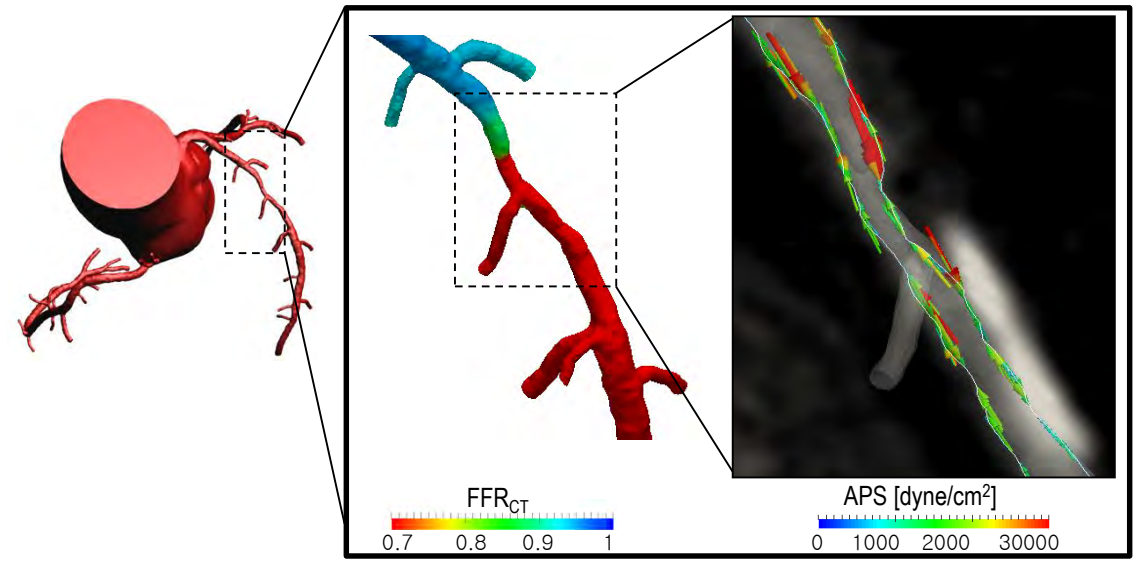
The axial component of traction parrallel to the flow direction

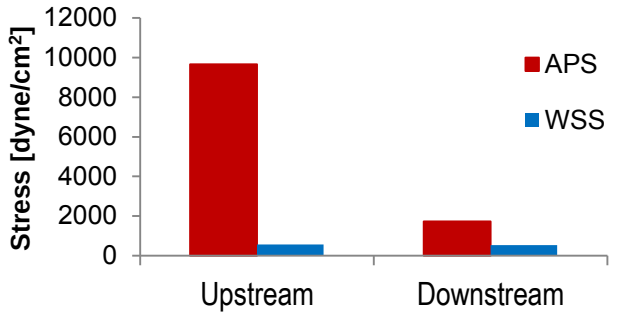


- Potential contribution of APS on plaque rupture has been demonstrated in a recent human study using computational fluid dynamics (CFD) simulation.

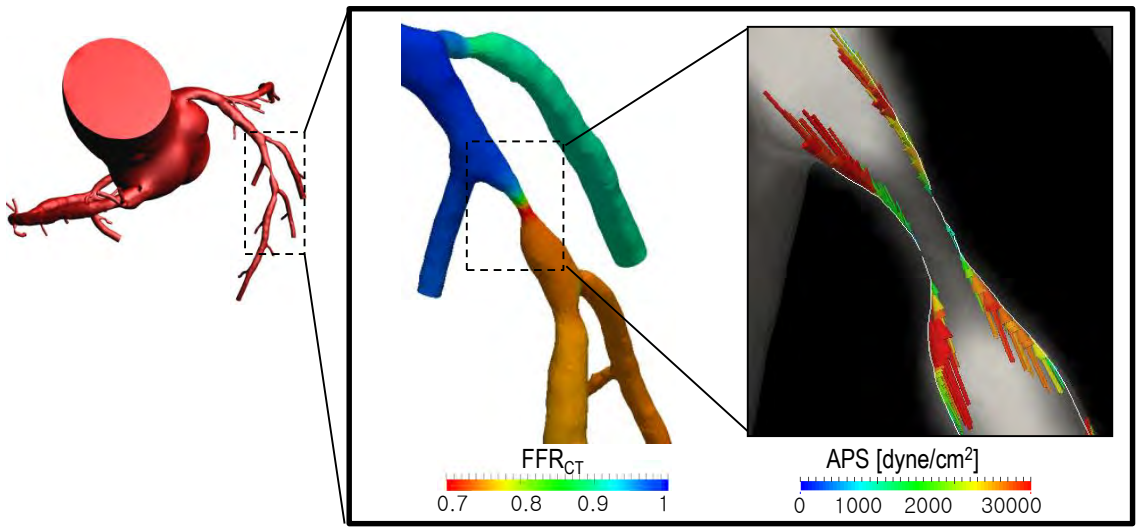
(G. Choi, H Otake et al. J Am Coll Cardiol Img 2015;8(10):1156-1166)

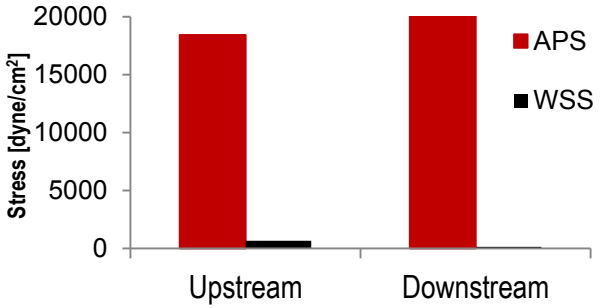
病変形態によってはretrogradeのAPSの方が大きくなる





	Upstream	Downstream
|Radius Gradient|	0.14	0.049
|APS| (dyne/cm^2)	9660	1740



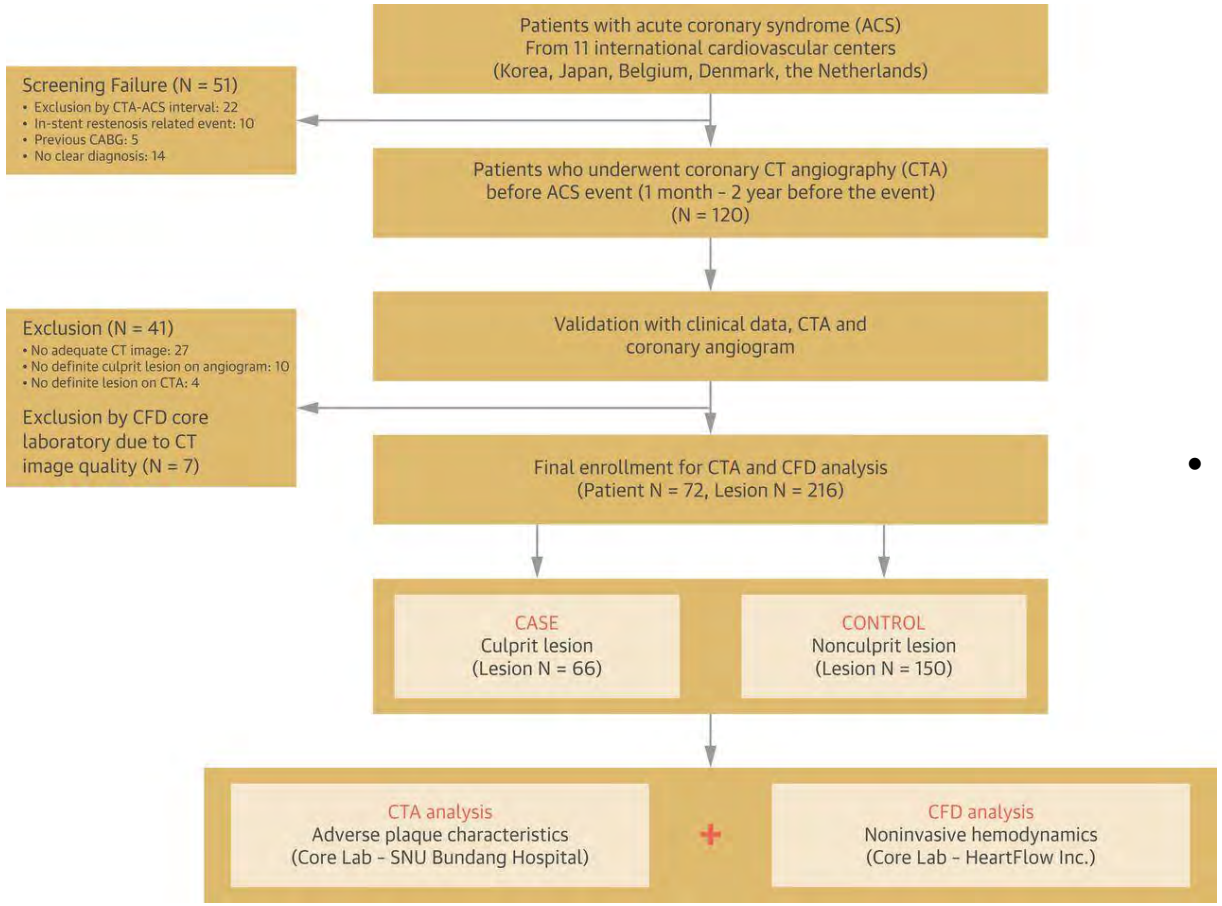


	Upstream	Downstream
|Radius Gradient|	0.14	0.22
|APS| (dyne/cm^2)	18428	21383

(G. Choi, H Otake et al. J Am Coll Cardiol Img 2015;8(10):1156-1166)

Emerald study design

- ACSを起こし、それ以前2年以内にcCTAを施行された患者216人を登録
- 責任病変と非責任病変における病変形態、性状（cCTA）、血行力学的因子の違いを比較検討



- 後ろ向き研究ではあるが、同一患者からcaseとcontrolをとってきており患者背景は完全にマッチしている

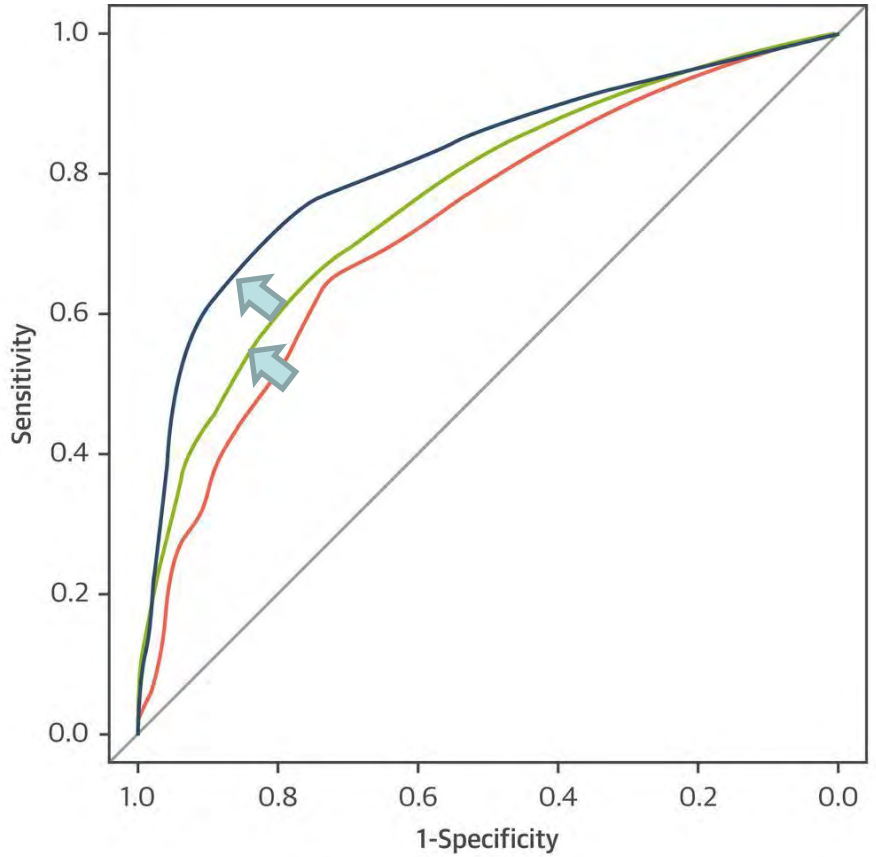
(Joo Myung Lee, Otake et a. et al. JACC Imaging 2019; 12(6):1032-1043)

Lesion characteristics

	Nonculprit Lesion (N = 150)	Culprit Lesion (N = 66)	p Value
Vessel location			0.001
LAD	48 (32.0)	39 (59.1)	
LCX	39 (26.0)	9 (13.6)	
RCA	63 (42.0)	18 (27.3)	
Lesion location			0.193
Proximal	62 (41.3)	36 (54.5)	
Mid	61 (40.7)	20 (30.3)	
Distal	27 (18.0)	10 (15.2)	
Anatomical severity			
Lesion length, mm	16.9 ± 7.0	19.2 ± 8.1	0.038
MLA, mm^2	3.02 ± 1.58	2.11 ± 1.43	<0.001
Diameter stenosis, %	43.1 ± 15.0	55.5 ± 15.4	<0.001
Distance from ostium, mm	47.8 ± 20.4	45.5 ± 27.2	0.489
Adverse plaque characteristics			
Low-plaque density	43 (28.7)	41 (62.1)	<0.001
Positive remodeling	16 (10.7)	23 (34.8)	<0.001
Napkin-ring sign	13 (8.7)	22 (33.3)	<0.001
Spotty calcification	31 (20.7)	28 (42.4)	0.001
Any adverse plaque characteristics*	63 (42.0)	53 (80.3)	<0.001
Hemodynamic parameters			
FFR_{CT}	0.79 ± 0.14	0.72 ± 0.17	0.006
ΔFFR_{CT}	0.06 ± 0.07	0.17 ± 0.17	<0.001
Wall shear stress, dyn/cm^2	145.5 ± 87.6	221.8 ± 113.2	<0.001
Axial plaque stress, dyn/cm^2	1,734.7 ± 1,896.8	2,585.9 ± 2,401.3	0.006

(Joo Myung Lee, Otake et a. et al. JACC Imaging 2019; 12(6):1032-1043)

Predictive model of ACS culprit plaque



Prediction Model	C-index	Difference with previous model	P value	NRI	P value	IDI	P value
Model 1	0.709						
Model 2	0.747	0.038	0.006	0.355	0.001	0.671	<0.001
Model 3	0.789	0.025	0.014	0.287	0.047	0.368	<0.001

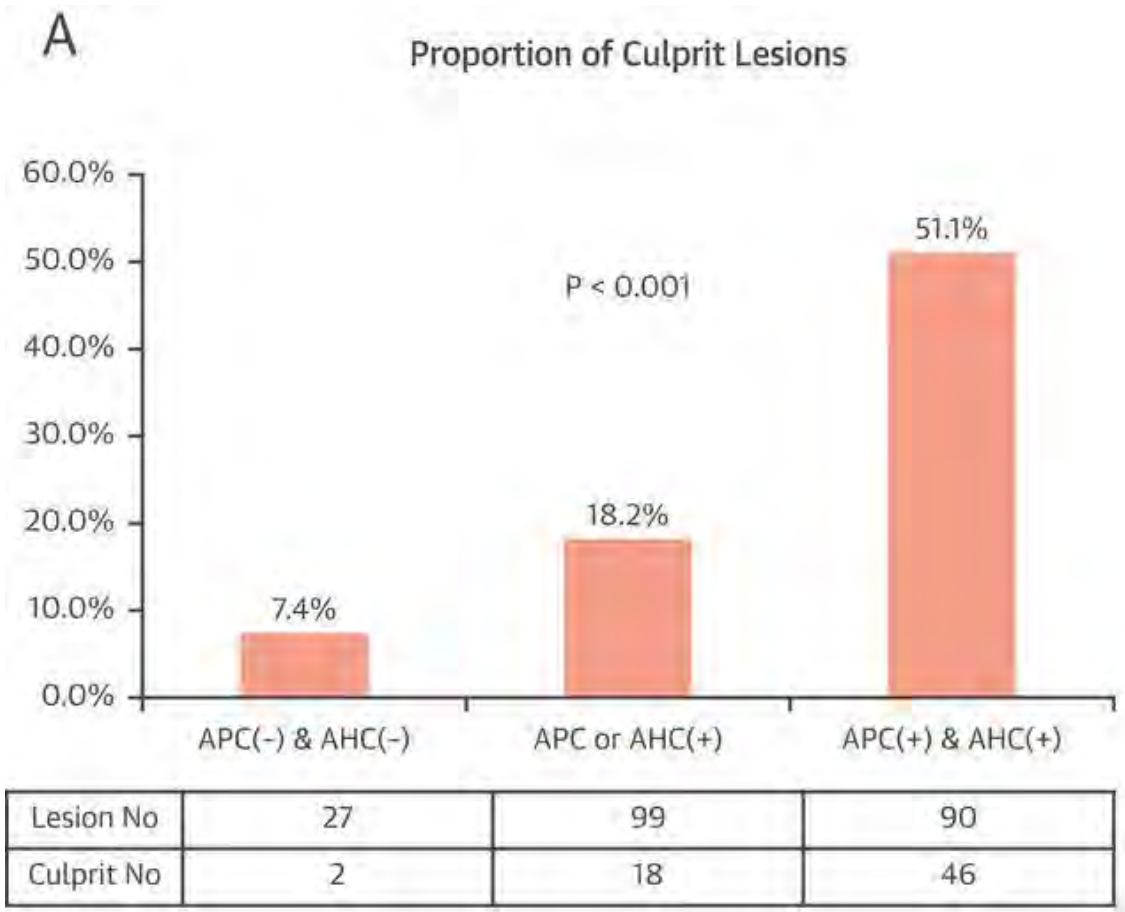
Model 1: Anatomical info
%DS and lesion length

Model 2: Anatomical +
Adverse plaque characteristics
(PR, SC, and LAP)

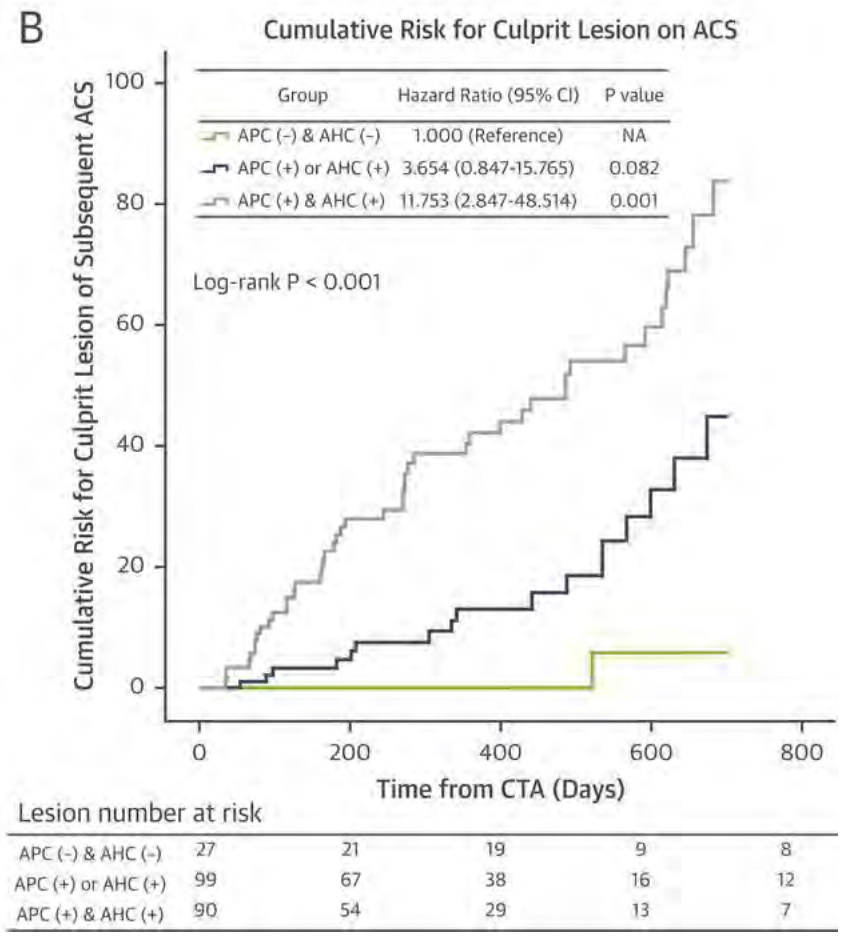
Model 3: Anatomical +
Adverse plaque characteristics+
Adverse hemodynamic chara
(WSS, APC)

(Joo Myung Lee, Otake et a. et al. JACC Imaging 2019; 12(6):1032-1043)

Impact of hemodynamic analysis



Lesion No	27	99	90
Culprit No	2	18	46



(Joo Myung Lee, Otake et a. et al. JACC Imaging 2019; 12(6):1032-1043)

本日の内容

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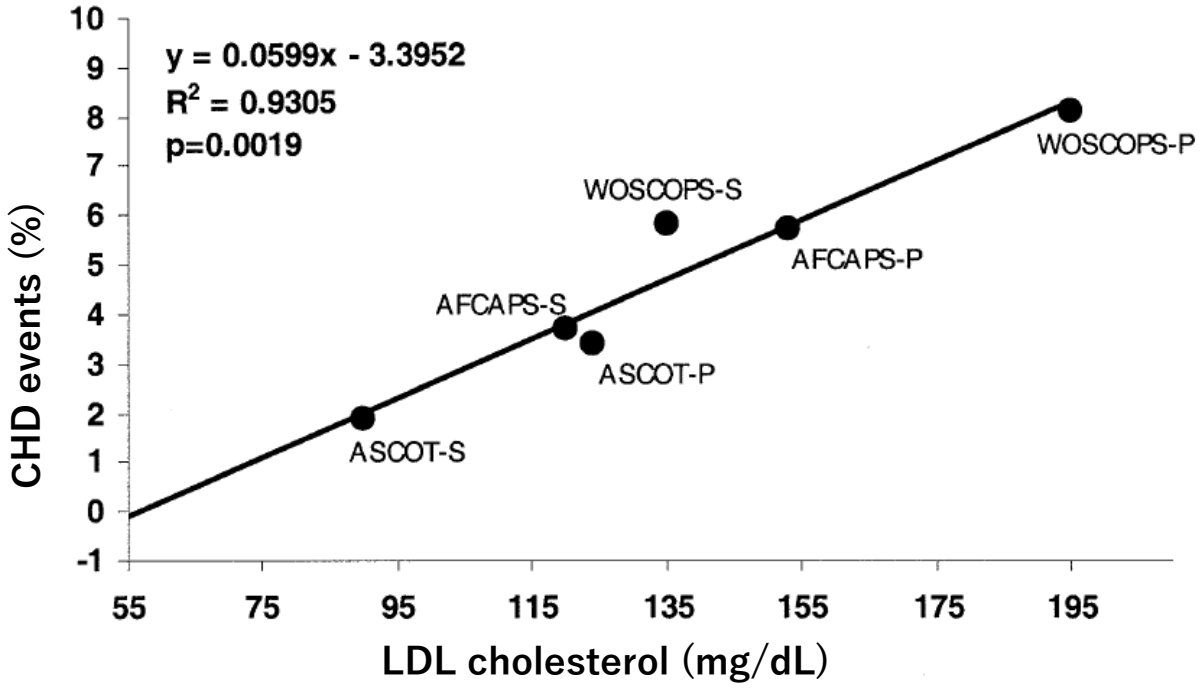
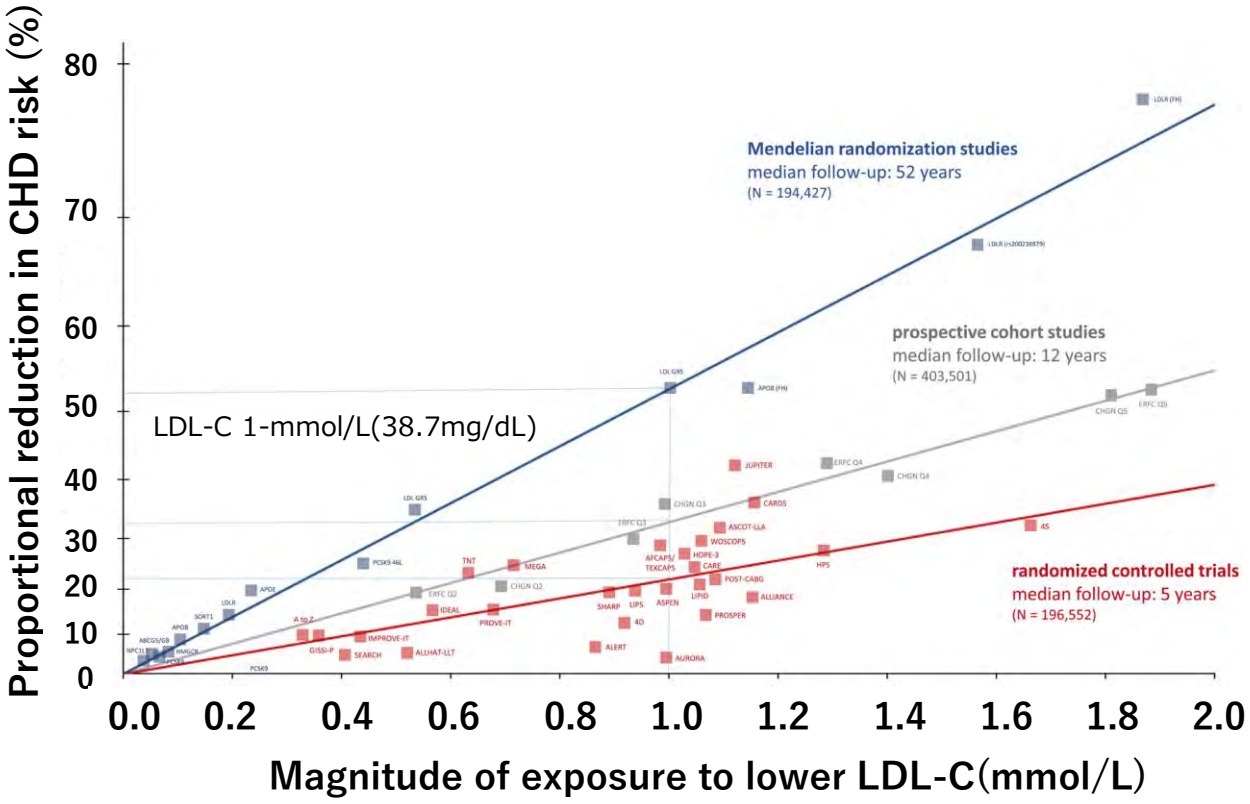
- 脂質低下療法が冠動脈プラークに与える影響：冠動脈イメージングを用いた検討

- PCSK9阻害薬投与後血管内イメージングで連続的に観察できた１例

LDL-Cは有用な脂質管理指標である（2017EAS Consensus Statementより）



(JACC Vol. 43, No. 11, 2004)



(European Heart Journal 2017: 0, 1–14)

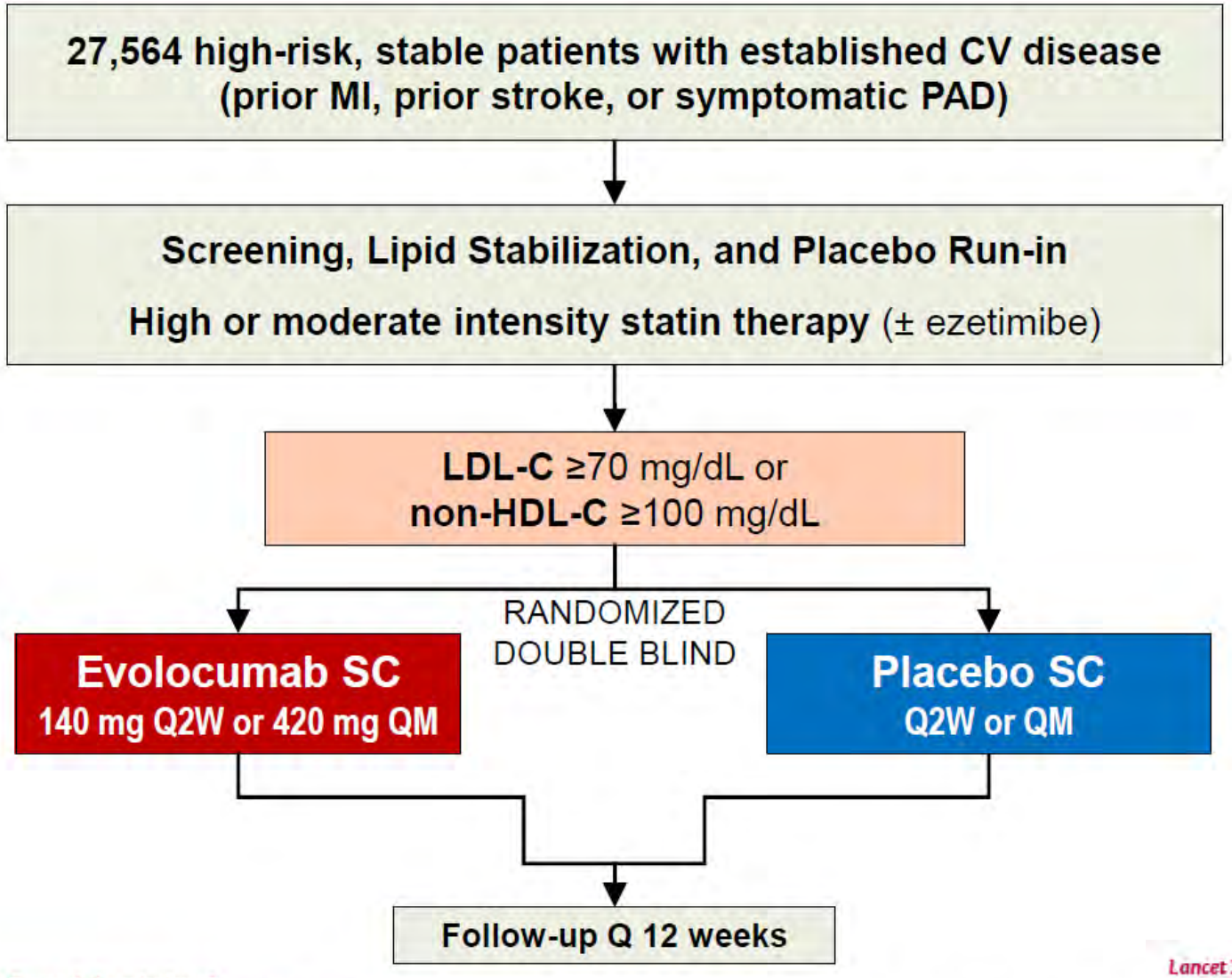
A surrogate is most useful when…

- Consistently predicts events in the future

- The response of the surrogate to an intervention predicts the response to the intervention in an endpoints trial.

(Weintraub WS et al. The perils of surrogate endpoints European Heart Journal (2015) 36, 2212–2218)

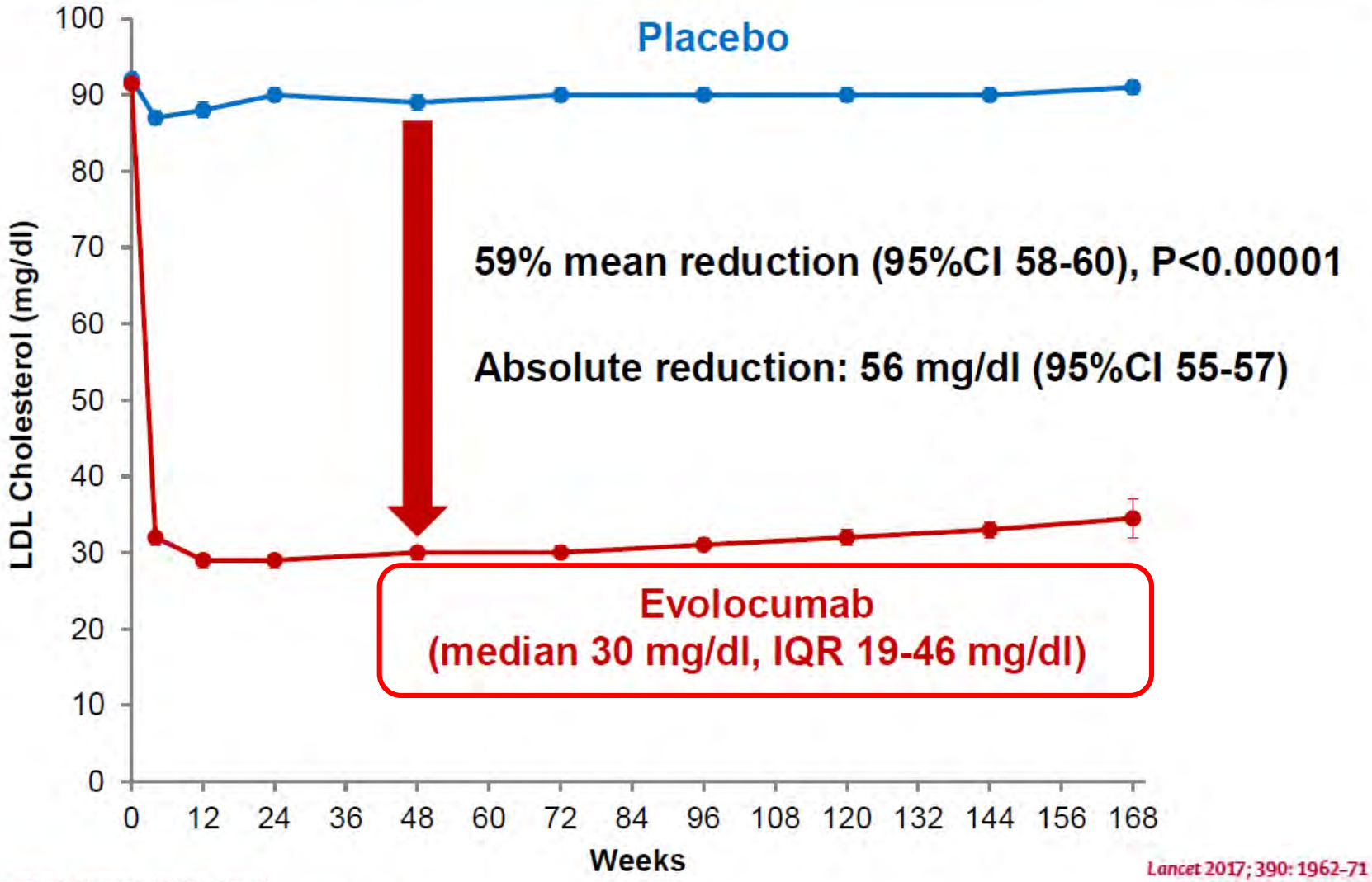
Trial Design



Lancet 2017; 390: 1962–71

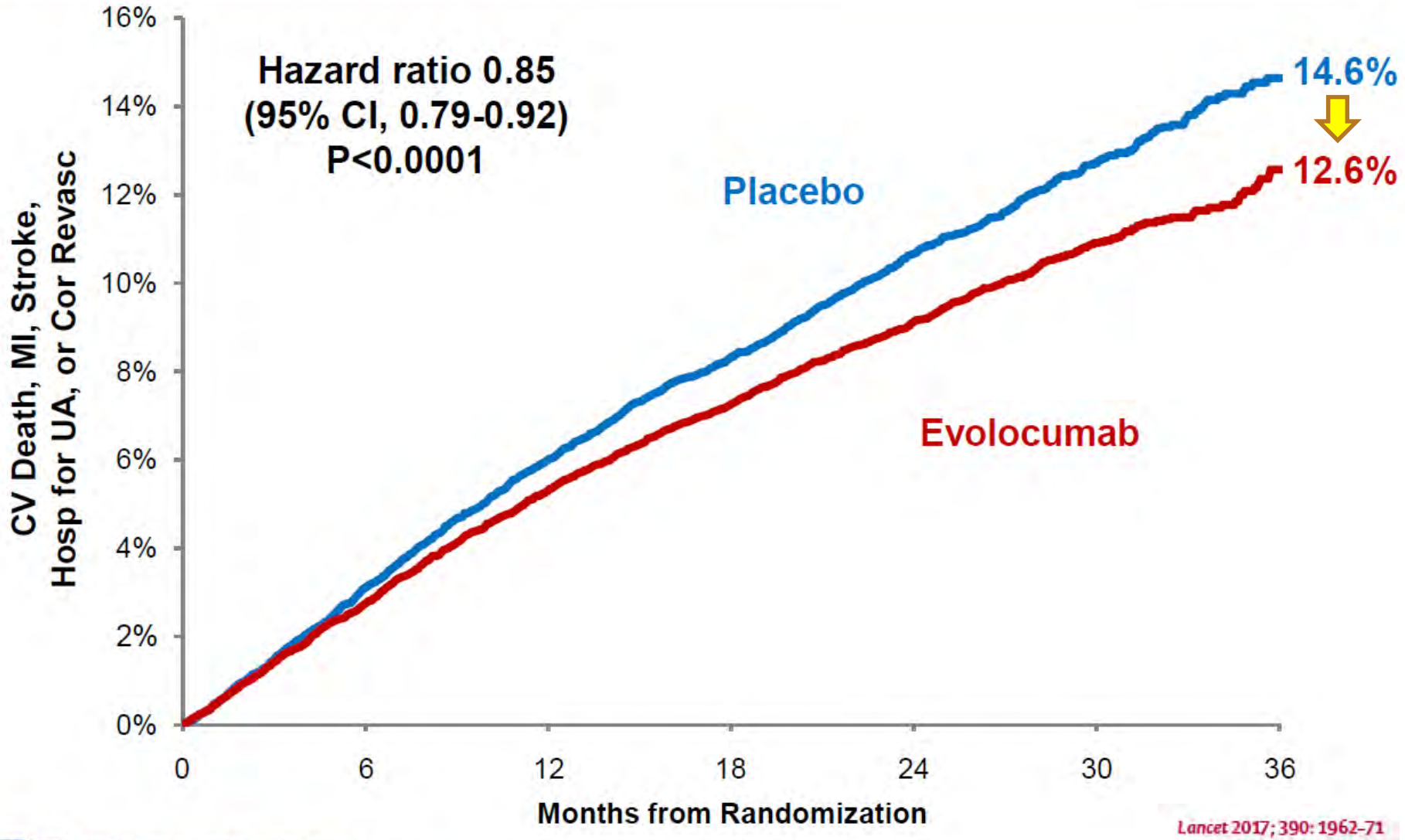
Sabatine MS et al. *Am Heart J* 2016;173:94-101

LDL Cholesterol



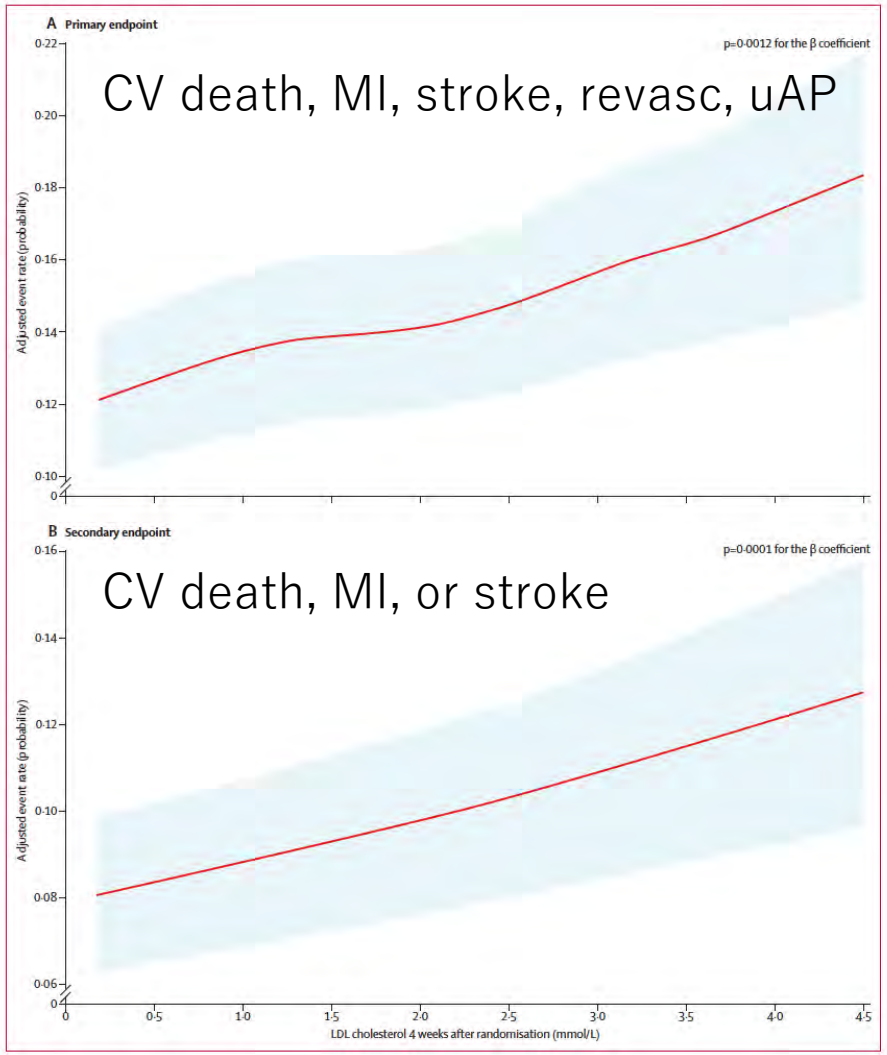
Lancet 2017; 390: 1962–71

Primary Endpoint



Lancet 2017; 390: 1962–71

The lower is the better …



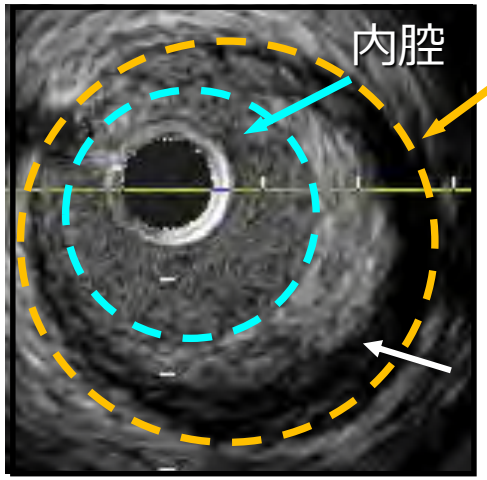
Adjusted event rate

LDL-C 4ws after randomization

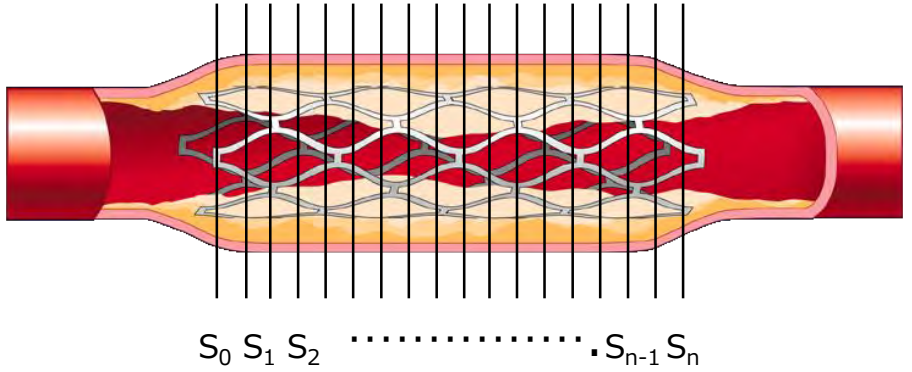
Lancet 2017; 390: 1962–71

IVUSを用いたプラークの定量評価

Cross-sectional → Volumetric



Area: 血管, 内腔



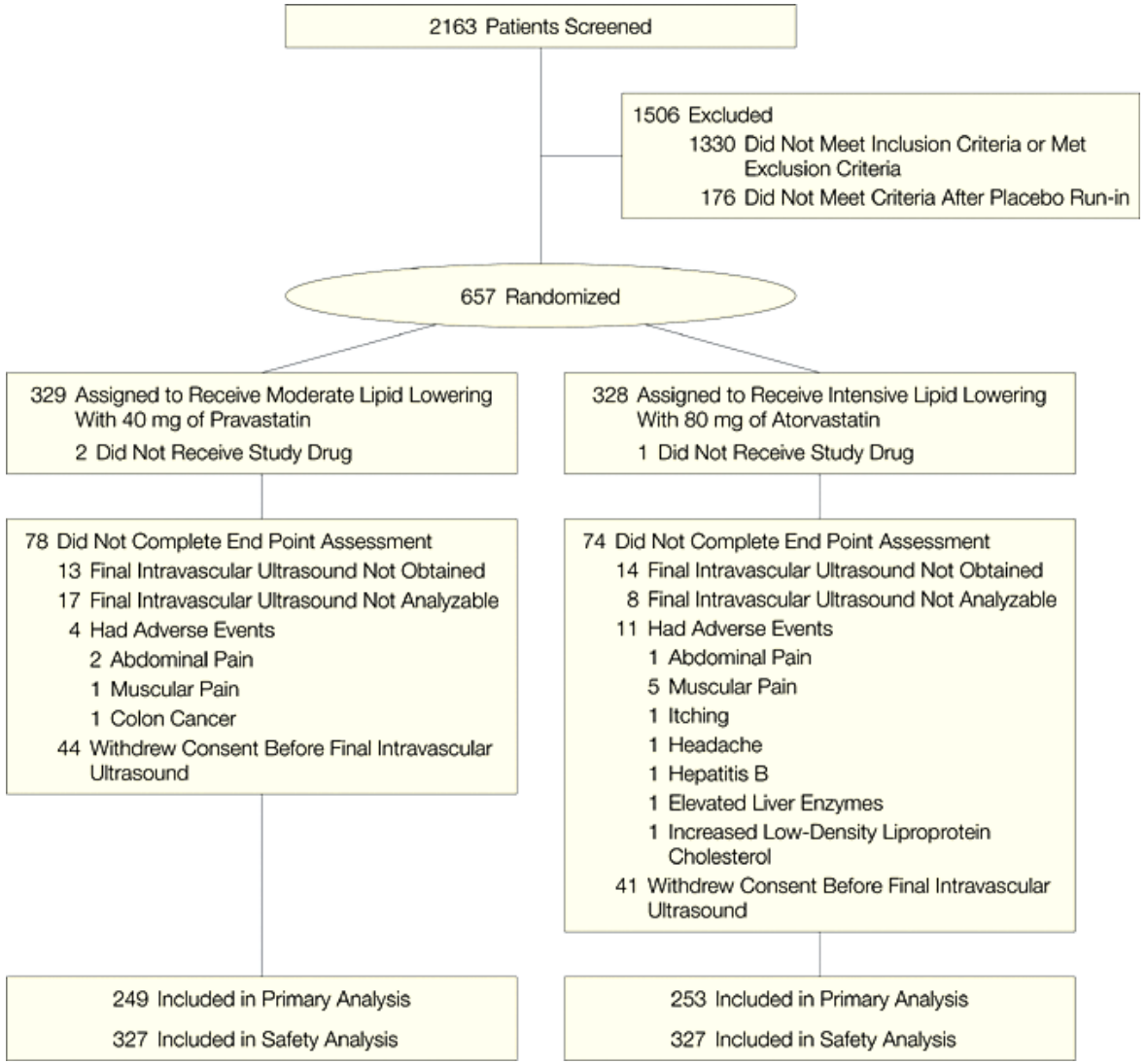
Frame interpolation by Simpson's Rule

Volume: 血管、内腔

$$\text{Total atheroma volume}_{\text{normalized}} = \frac{\sum(\text{EEM}_{\text{area}} - \text{Lumen}_{\text{area}})}{\text{number of images in pullback}} \times \text{median number of images in cohort}$$

$$\text{Percent atheroma volume} = \frac{\sum(\text{EEM}_{\text{area}} - \text{Lumen}_{\text{area}})}{\sum \text{EEM}_{\text{area}}} \times 100$$

Reversal Trial: study design



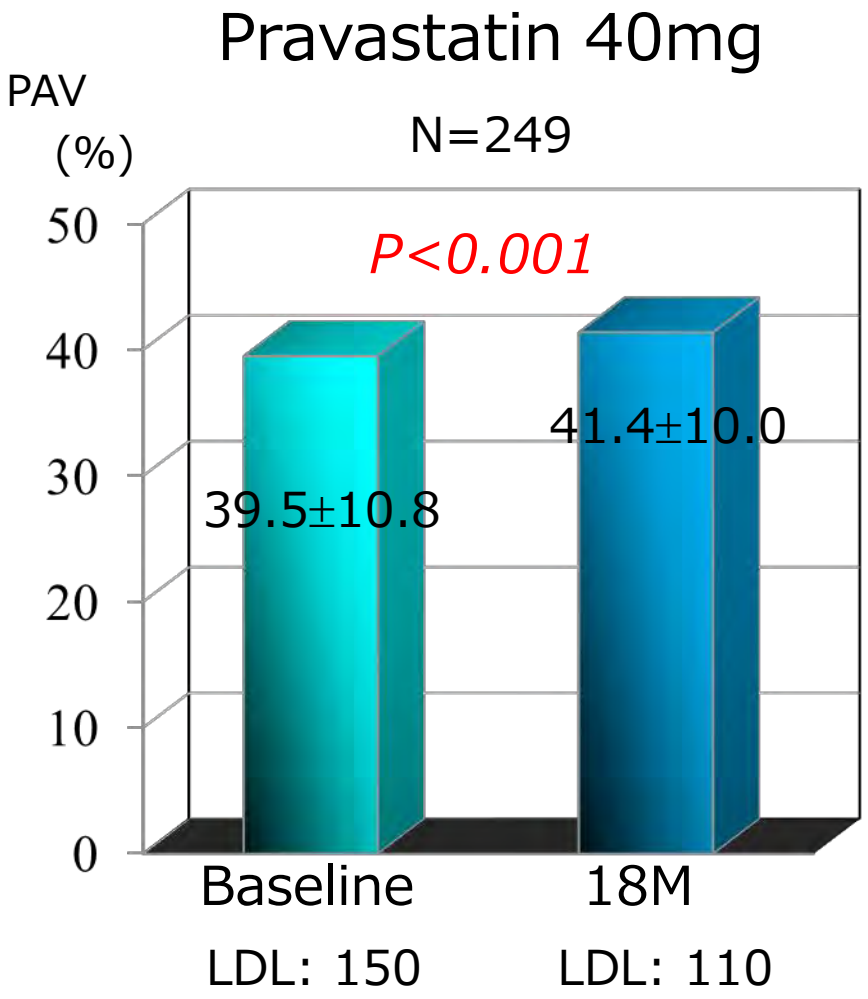
IVUS

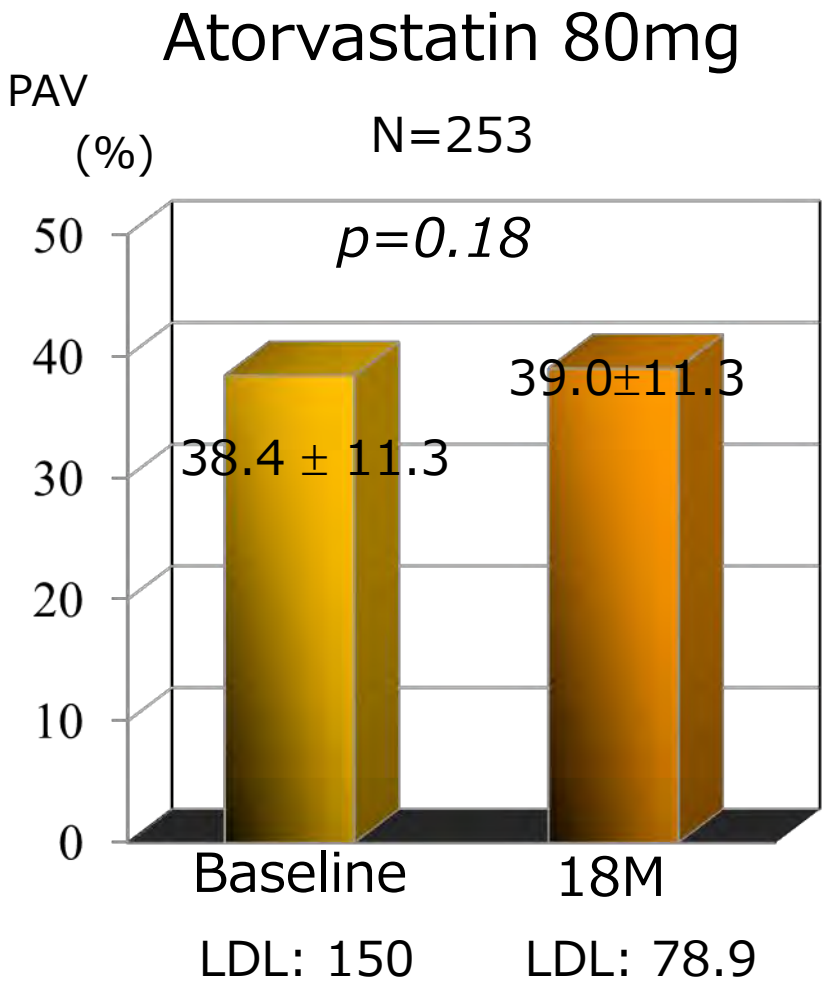
18M

IVUS

(Nissen et al. JAMA 2004;291:1071-1080)

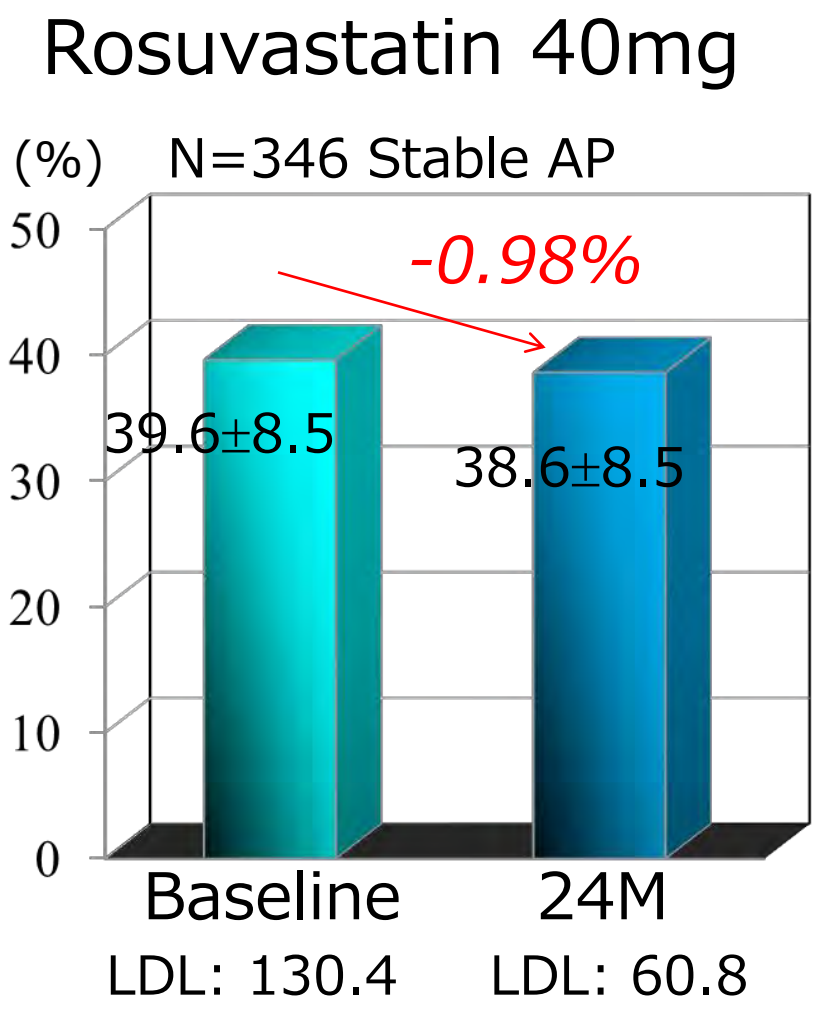
Reversal Trial: results 高強度のスタチンはプラークの進展を止めた！





(Nissen et al. JAMA 2004;291:1071-1080)

Asteroid Trial: results 高強度のスタチンがプラークを退縮させた！



(Nissen et al. JAMA 2006;295:1556-1565)

IVUSを使ったプラーク退縮のランダム化研究: n=56

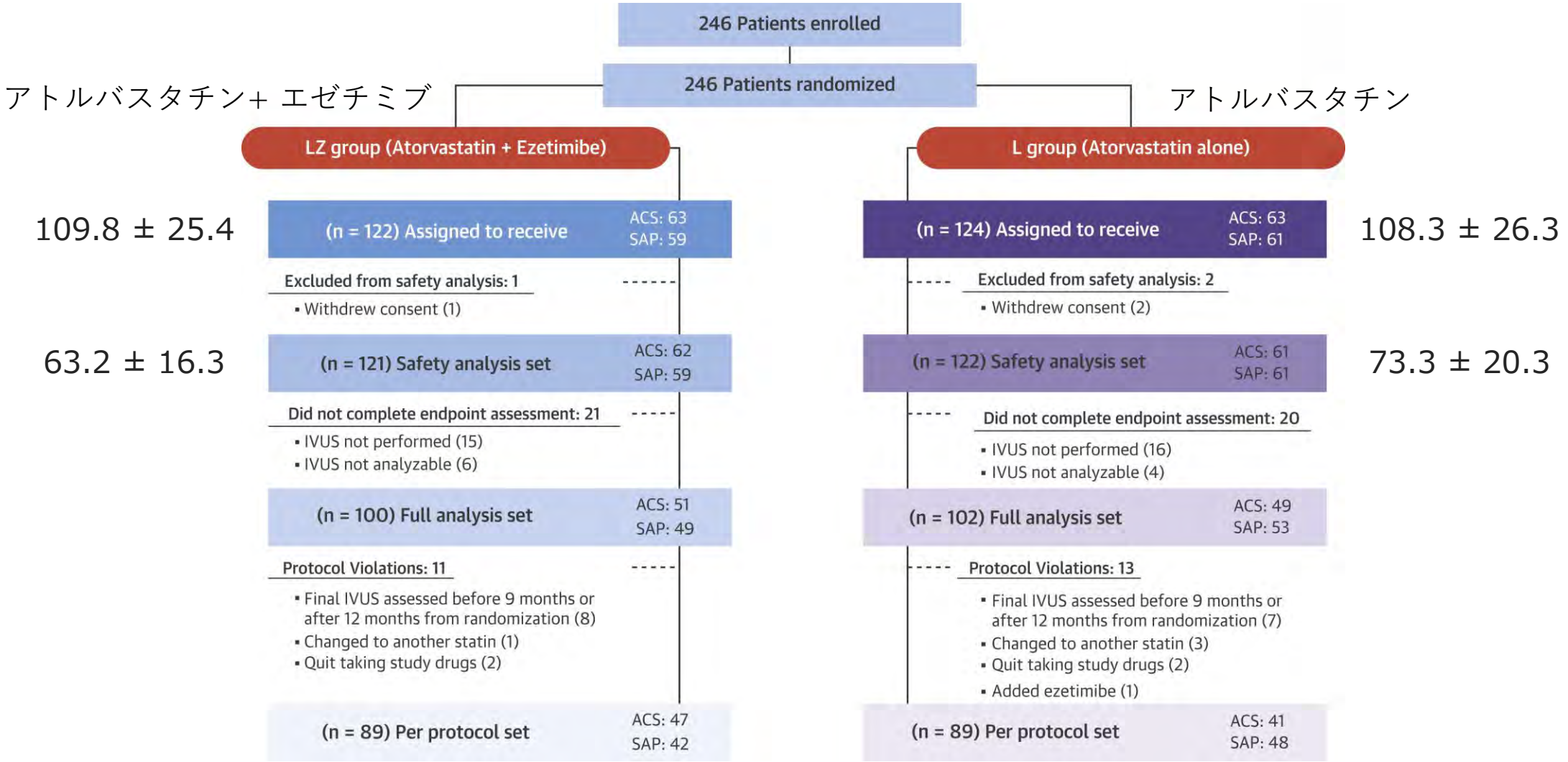
Table 1
Included study characteristics

Study	Year	Randomized Number	Duration (years)	Age (years)	Men (%)	Patients	Used Drug
GAIN[7]	2001	131	1	60	85	PCI, LDL-C >160/130 mg/dl	Atorvastatin
CART-1[8]	2003	305	0.5	59	81	PCI	Probucol/AGI-1067
Nissen et al[9]	2003	57	5/52	57	62	ACS, CAG	Apo A-I Milano
REVERSAL[10]	2004	654	1.5	56	72	CAG, LDL-C 125–210 mg/dl	Pravastatin/atorvastatin
ESTABLISH[11]	2004	70	0.5	61	86	ACS, PCI, LDL-C >150 mg/dl	Atorvastatin
NORMALISE[12,*]	2004	431	2	58	74	CAG, diastolic BP <100 mm Hg	Amlodipine/enalapril
A-PLUS[13]	2004	639	2	58	81	CAG, LDL-C <125 mg/dl	Avasimibe
Petronio et al[14]	2005	71	1	62	75	PCI, LDL-C <130 mg/dl	Simvastatin
Kawasaki et al[15]	2005	57	0.5	66	75	SAP, PCI, TC >220 mg/dl	Pravastatin/atorvastatin
Yokoyama et al[16]	2005	50	0.5	63	90	SAP, PCI, TC 170–230 mg/dl	Atorvastatin
Tani et al[17]	2005	82	0.5	63	76	SAP, PCI	Pravastatin
ACTIVATE[18]	2006	534	1.5	59	69	CAG	Pactimibe
ILLUSTRATE[19]	2007	1,188	2	57	71	CAG	Torcetrapib
ERASE[20]	2007	183	7/52	58	83	ACS, CAG	Reconstituted HDL
PERSPECTIVE[21,*]	2007	244	3	57	81	SAP, CAG	Perindopril
REACH[22]	2007	69	1	67	72	CAG, LDL-C 100–140 mg/dl	Atorvastatin
CART-2[23]	2008	1,240[†]	1	61	80	PCI	AGI-1067
STRADIVARIUS[24]	2008	839	1.5	58	65	CAG, MS, or current smoker	Rimonabant
PERISCOPE[25]	2008	543	1.5	60	67	CAG, HbA_{1c} 6%–10%	Pioglitazone
IBIS-2[26]	2008	330	1	58	82	CAG	Darapladib
Ogasawara et al[27]	2009	54	0.5	68	65	SAP, PCI, DM	Pioglitazone
ENCORE II[28]	2009	272[‡]	2	58	82	CAG	Nifedipine
Hong et al[29]	2009	100[‡]	1	59	77	CAG?	Simvastatin/rosuvastatin
JAPAN-ACS[30]	2009	307	1	62	82	ACS, PCI, TC >220 mg/dl or LDL-C >140 mg/dl	Atorvastatin/pitavastatin
Toi et al[31]	2009	160[‡]	3/52	62	76	ACS, PCI	Atorvastatin/pitavastatin
PIGEON[32]	2010	26	0.5	65	80	SAP, PCI, DM or IGT	Pioglitazone

* IVUS substudy.

(Kaneda et al. Am J Cardiol 2010;106:1735–1746)

PRECISE-IVUS Trial: study design



(Tsujita et al. J Am Coll Cardiol 2015;66:495–507)

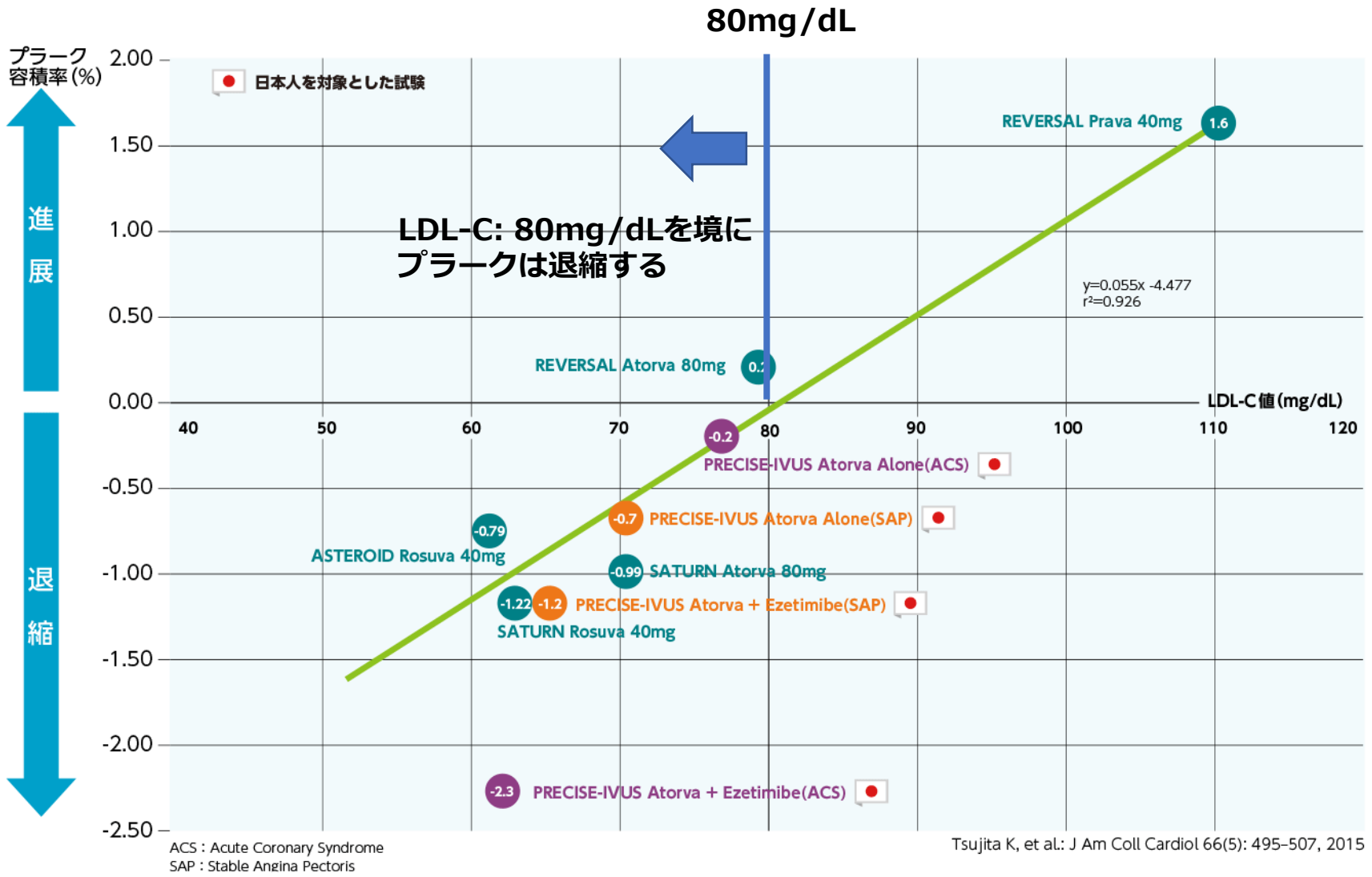
PRECISE-IVUS Trial: results

	Absolute Change				
	LZ Group (n = 100)	p Value Compared With Baseline	L Group (n = 102)	p Value Compared With Baseline	p Value Between Groups
Plaque volume, mm^3	-3.9 (-10.6 to 0.0)	<0.001	-1.0 (-6.8 to 5.7)	0.4	0.001
Percent atheroma volume, %	-1.4 (-3.4 to -0.1)	<0.001	-0.3 (-1.9 to 0.9)	0.03	0.001
ACS cohort	-2.3 (-3.7 to -0.5)	<0.001	-0.2 (-1.3 to 0.5)	0.2	<0.001
SAP cohort	-1.2 (-2.2 to -0.1)	0.001	-0.7 (-2.3 to 1.1)	0.08	0.2
TAV_{norm}, mm^3	-5.3 (-12.4 to 0.1)	<0.001	-1.2 (-5.7 to 3.3)	0.1	<0.001
Vessel volume, mm^3	-4.1 (-12.6 to 3.1)	0.001	-0.6 (-11.8 to 10.6)	0.9	0.04
Lumen volume, mm^3	-0.3 (-4.9 to 4.0)	0.4	0.8 (-5.6 to 6.9)	0.5	0.4

➡ 必ずしもスタチンでなくてもplaqueのregressionは起こる

(Tsujita et al. J Am Coll Cardiol 2015;66:495–507)

LDL-C lowering and plaque regression

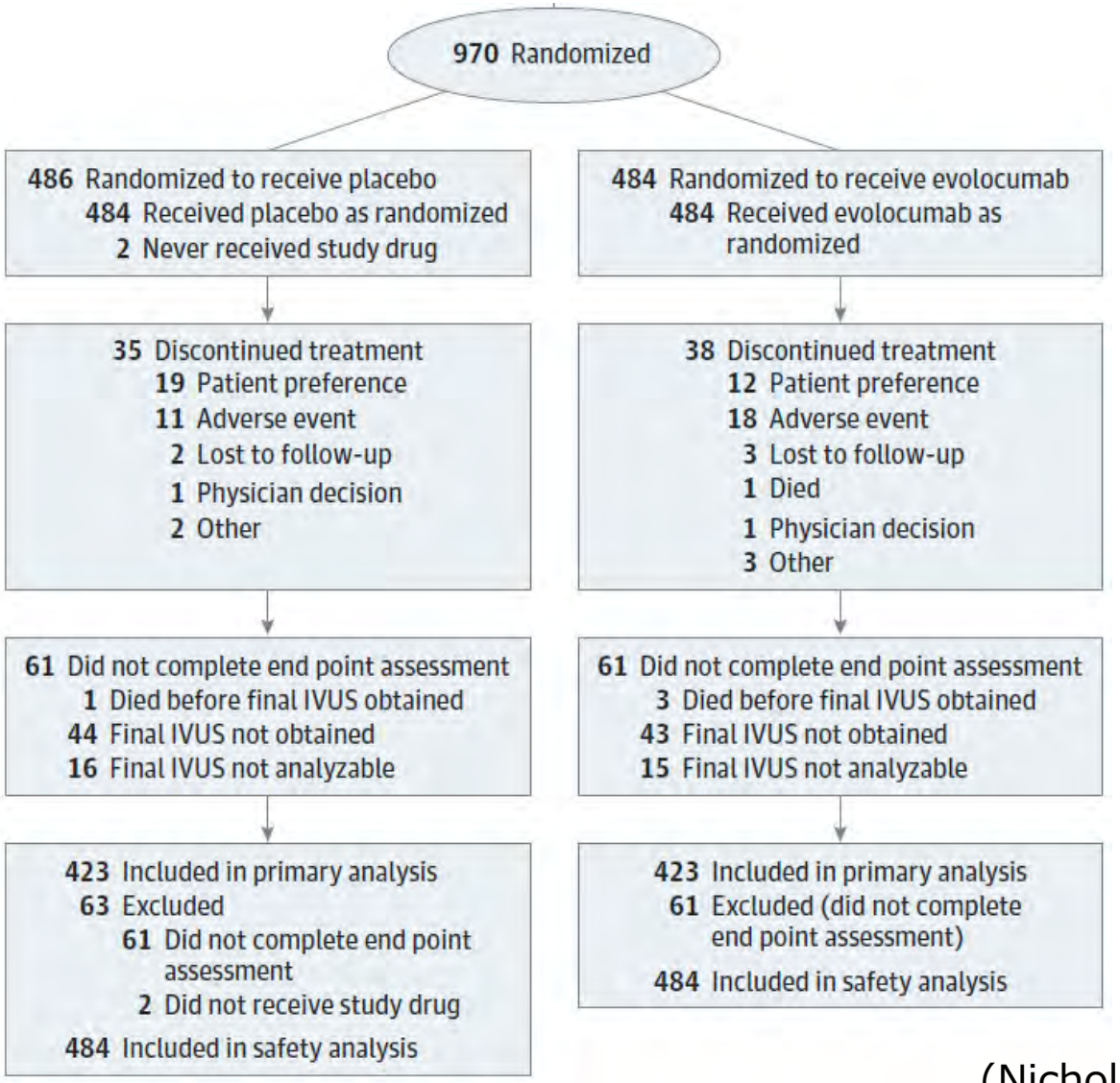


ACS : Acute Coronary Syndrome
SAP : Stable Angina Pectoris

Tsujita K, et al.: J Am Coll Cardiol 66(5): 495–507, 2015

SAJP.ALI.16.09.2180

The GLAGOV Randomized Clinical Trial: design

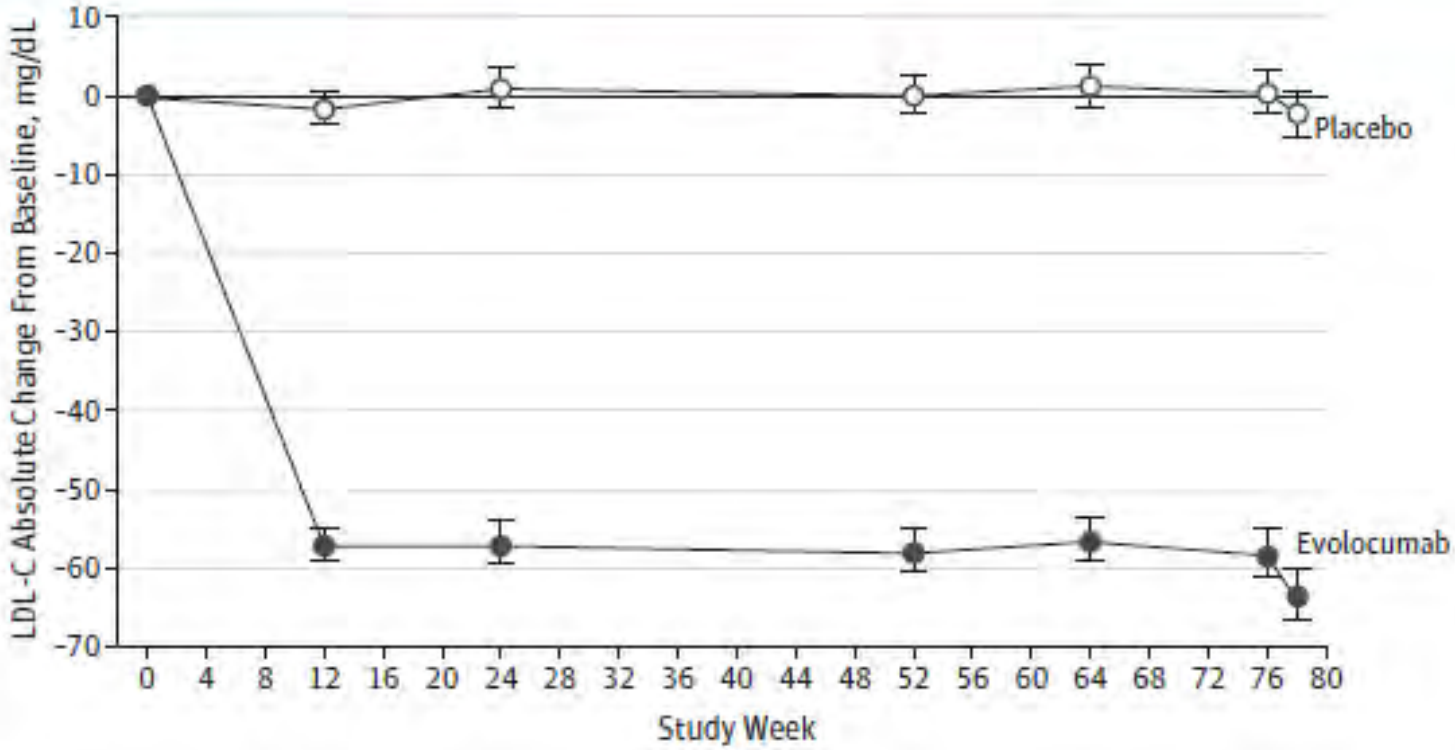


Participants with angiographic coronary disease were randomized to receive monthly evolocumab (420mg) (n = 484) or placebo (n = 484) via subcutaneous injection for 76 weeks, in addition to statins.

(Nicholls et al. JAMA. 2016;316(22):2373-2384)

The GLAGOV Randomized Clinical Trial: results

Figure 2. Mean Absolute Change in LDL-C Level



No. of patients																				
Placebo	484						446					441					447		441	425	418
Evolocumab	484						456					452					444		449	426	434

(Nicholls et al. JAMA. 2016;316(22):2373-2384)

The GLAGOV Randomized Clinical Trial: results

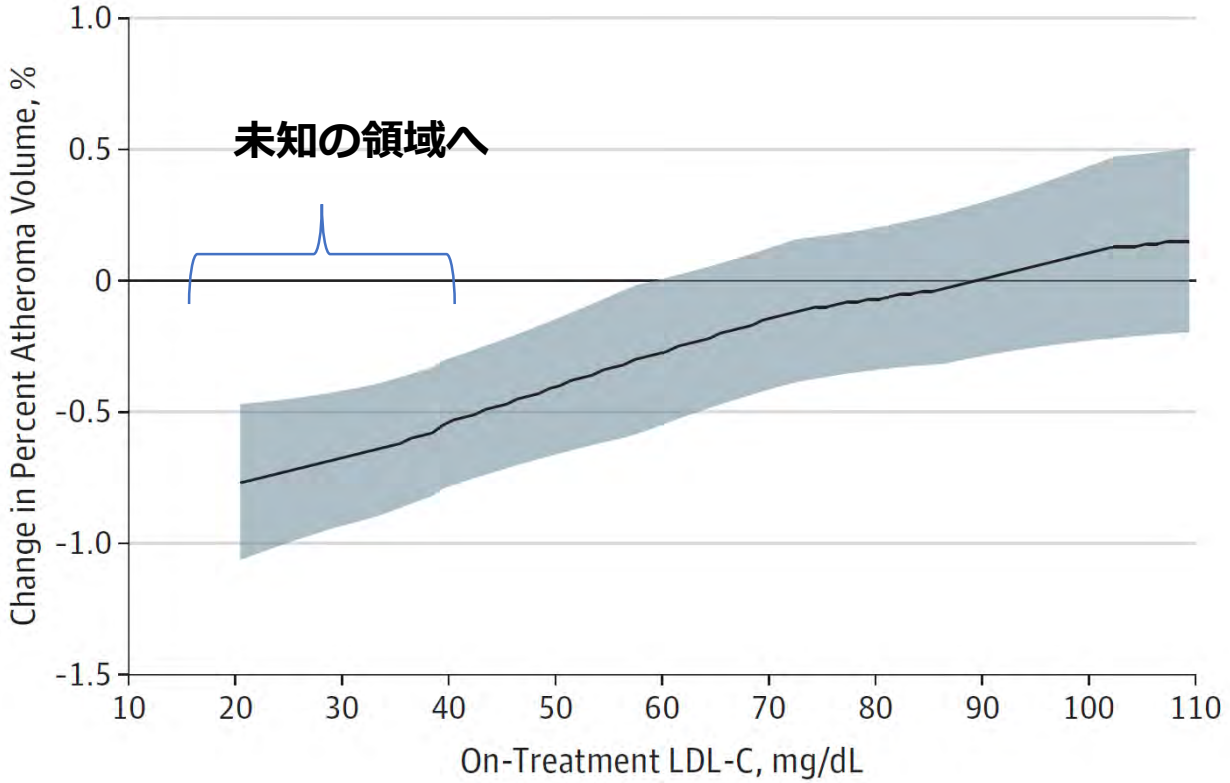
1.5 Year

Parameter	Placebo (n = 423)	Evolocumab (n = 423)	Between Group Differences, Least Squares Means (95% CI)	*P* Value
Change From Baseline				*P* Value for Between Groups[a]
Percent atheroma volume				
Least squares mean (95% CI)	0.05 (−0.32 to 0.42)	−0.95 (−1.33 to −0.58)	−1.0 (−1.8 to −0.64)	<.001
P value for change from baseline	.78	<.001		
Total atheroma volume, mm^3				
Least squares mean (95% CI)	−0.91 (−3.29 to 1.47)	−5.80 (−8.19 to −3.41)	−4.9 (−7.3 to −2.5)	<.001
P value for change from baseline	.45	<.001		

(Nicholls et al. JAMA. 2016;316(22):2373-2384)

The GLAGOV Randomized Clinical Trial: results

Figure 4. Post Hoc Analysis Examining the Relationship Between Achieved LDL-C Level and Change in Percent Atheroma Volume



(Nicholls et al. JAMA. 2016;316(22):2373-2384)

The GLAGOV Randomized Clinical Trial: results

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- このような微細な変化が本当に臨床イベントと関連するのか？
- なぜこのような微細な変化が臨床イベントと関連するのか？

(Nicholls et al. JAMA. 2016;316(22):2373-2384)

どういった人がplaque regressionしやすいのか?
Lessons from SATURN trial

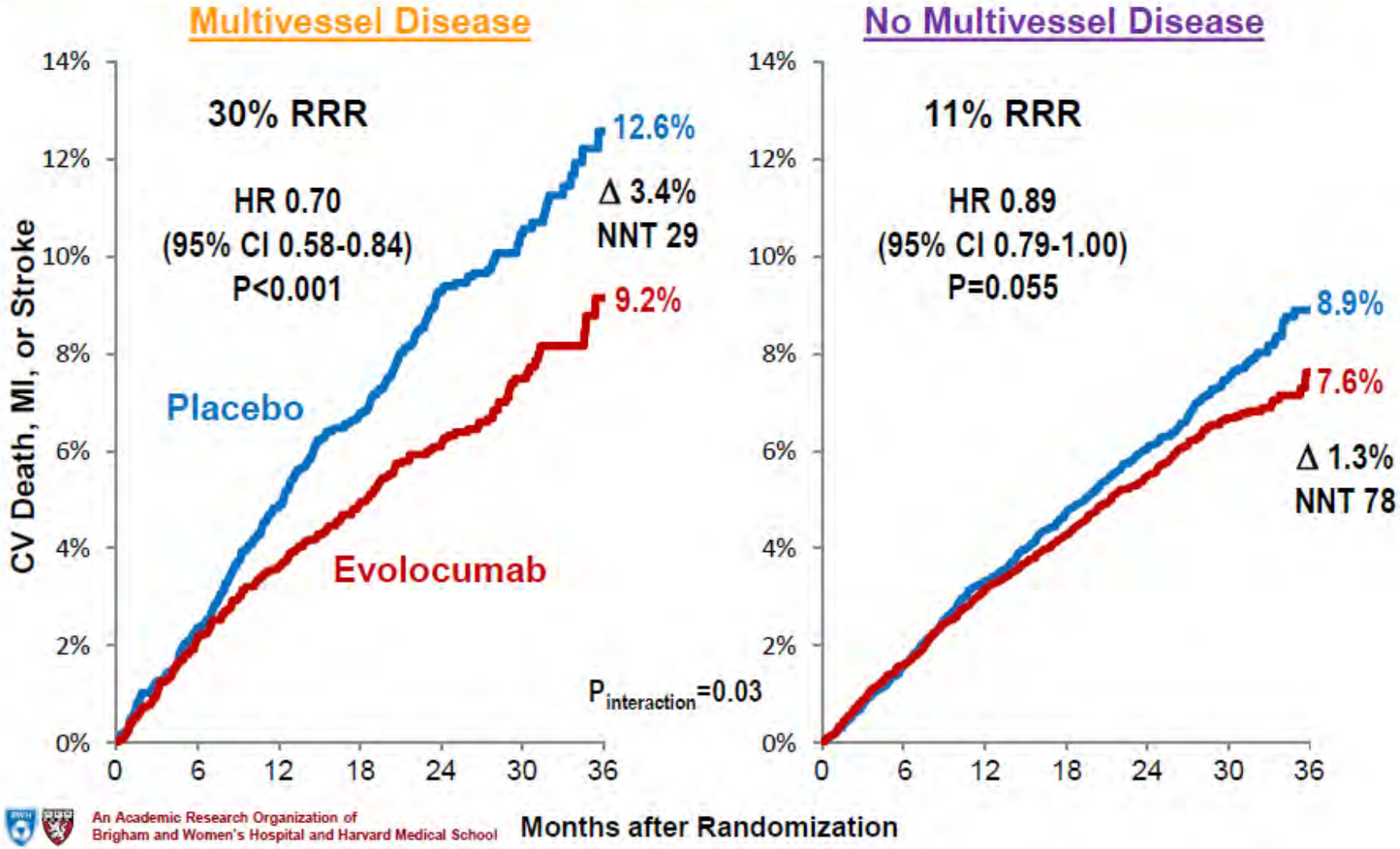
1039 patients with CAD BL and 104 weeks: IVUS
Atorvastatin: 80 mg daily, or rosuvastatin: 40 mg daily

Multivariable Linear Regression Model for Changes in Coronary Atheroma Volume

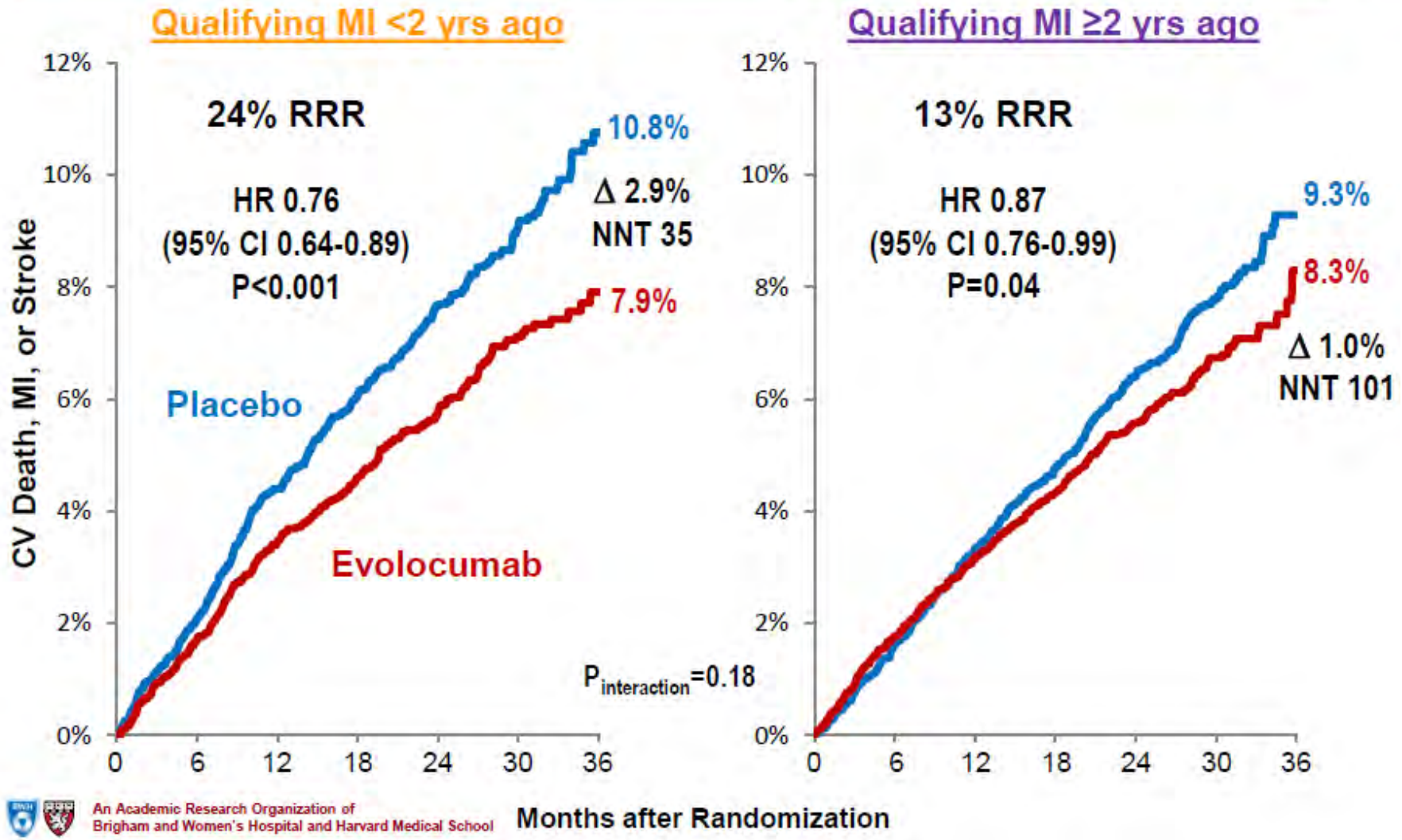
Covariate	Estimated β-Coefficient (95% CI)	*P* Value
PAV		
Baseline PAV	−0.57 (−0.75, −0.38)	<0.001
ACS (vs no ACS)	−0.51 (−0.88, −0.14)	0.007
Average follow-up LDL-C	0.49 (0.41, 0.92)	<0.001
TAV		
Baseline TAV	−4.07 (−4.96, −3.18)	<0.001
ACS (vs no ACS)	−2.65 (−4.44, −0.87)	0.004
Rosuvastatin (vs atorvastatin)	−2.57 (−4.35, −0.80)	0.005
Average follow-up LDL-C	0.94 (0.09, 1.80)	0.030
History of PCI	3.23 (1.16, 5.30)	0.002
BMI	0.96 (0.10, 1.82)	0.03

(Nicholls et al. N Engl J Med 2011;365:2078-87.)

Benefit of EvoMab Based on Multivessel Disease



Benefit of EvoMab Based on Time from Qualifying MI



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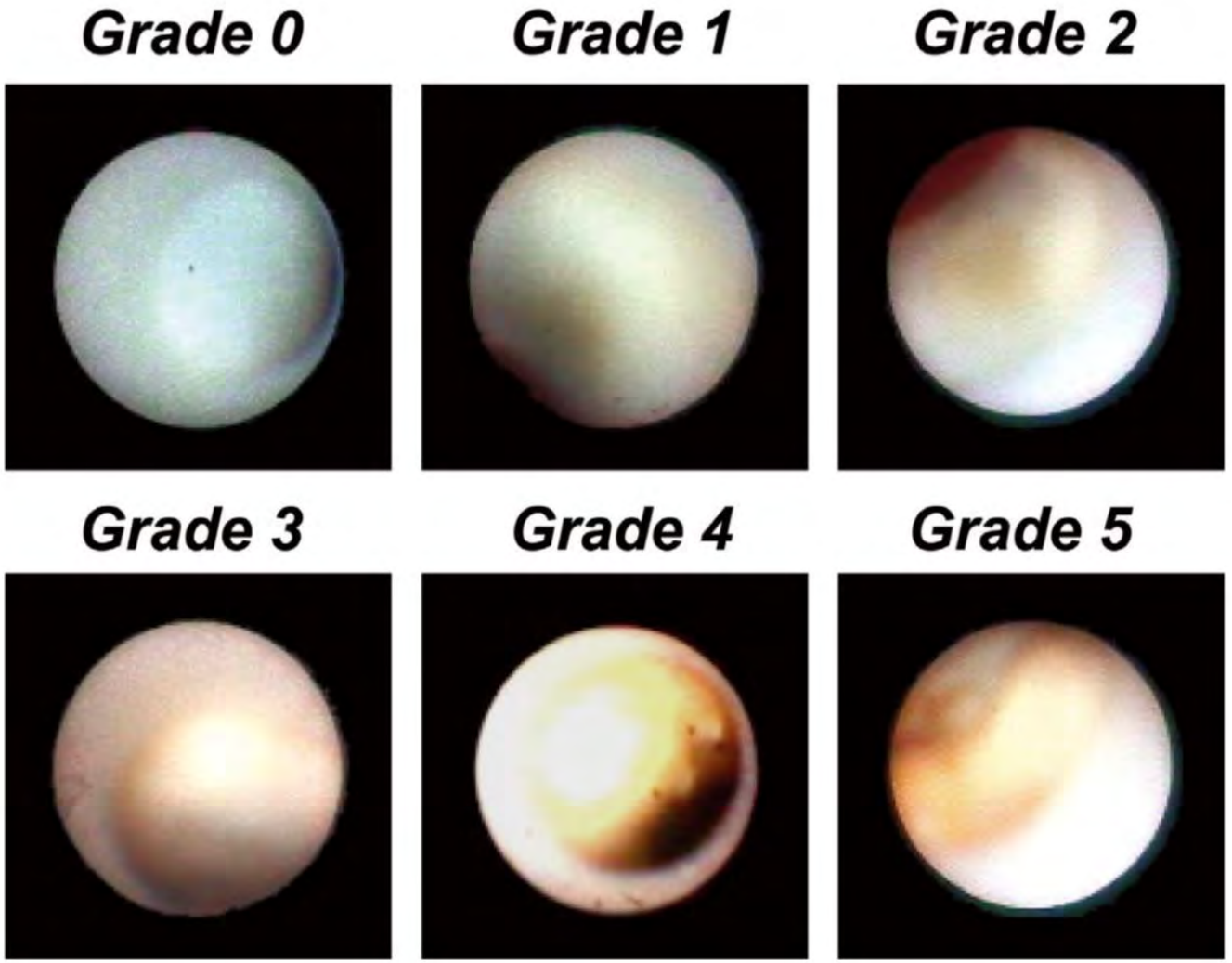
(Nicholls et al. JAMA. 2016;316(22):2373-2384)

TWINS STUDY

Atorvastatin (10—20mg/day)
28週と 80週後血管内視鏡 & IVUS

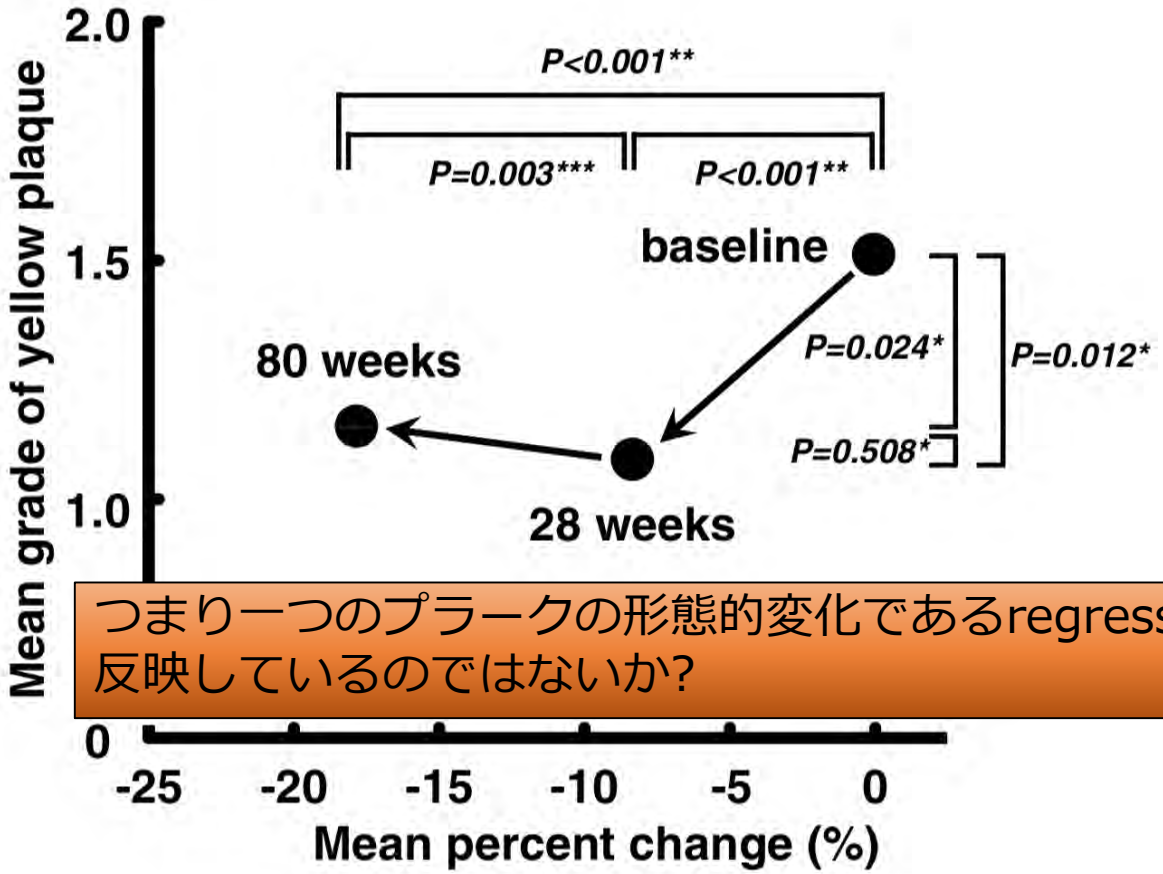


(Hirayama et al. *Circ J 2009; 73: 718 – 725*)

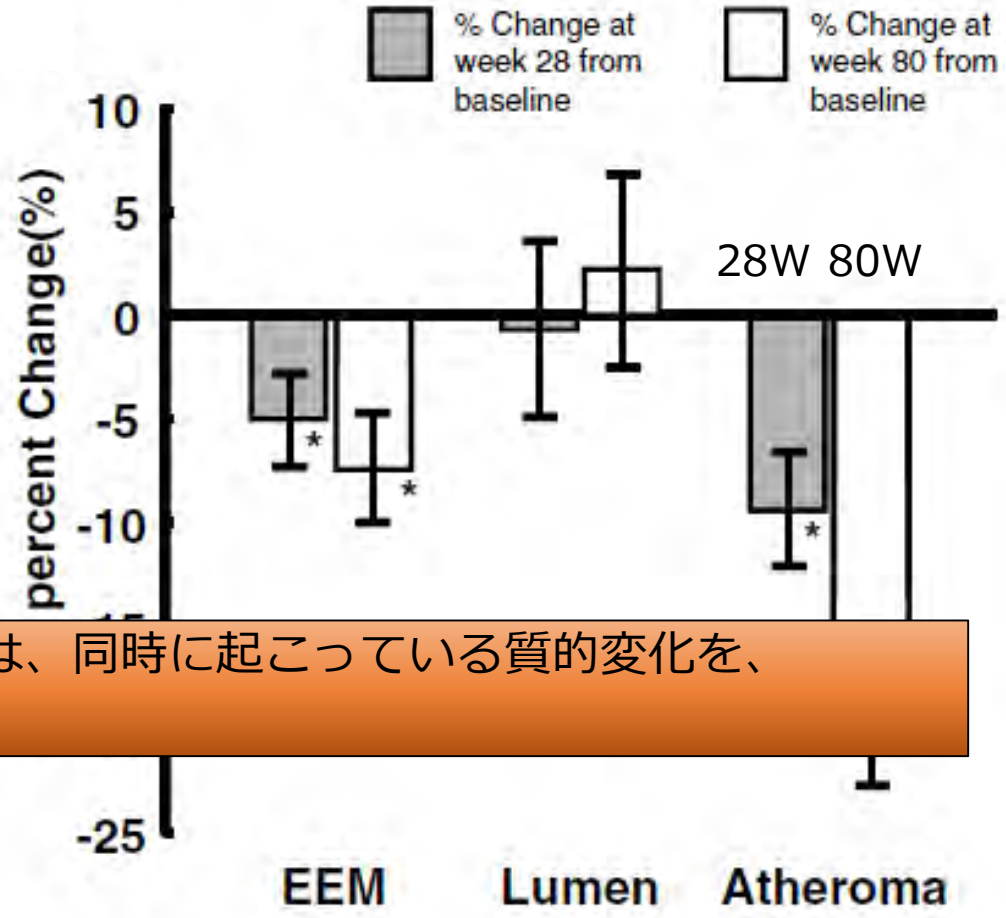
TWINS STUDY

Atorvastatin (10—20mg/day)
28週と 80週後血管内視鏡 & IVUS

血管内視鏡：プラークの質



IVUS:プラーク量



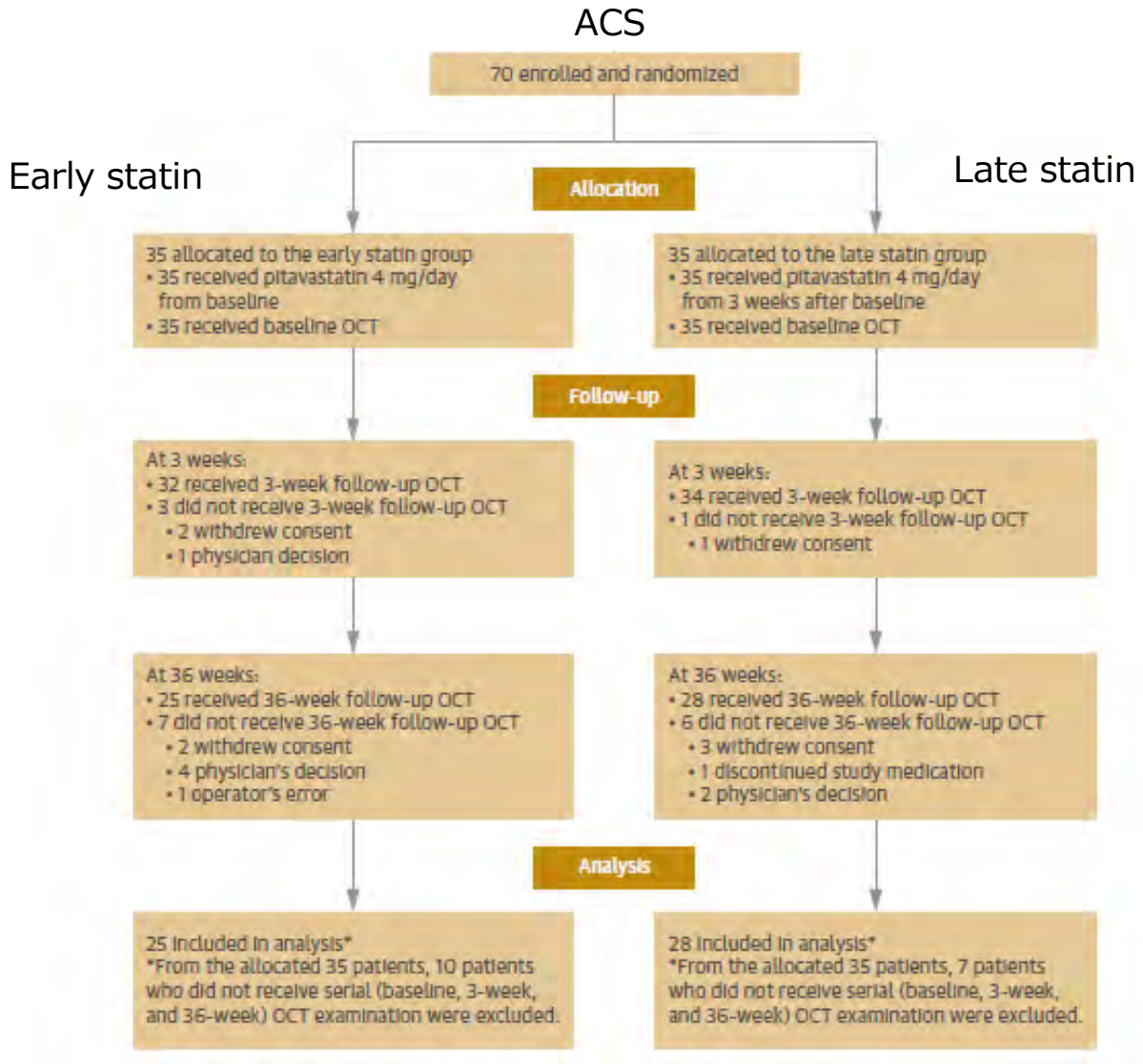
つまり一つのプラークの形態的変化であるregressionは、同時に起こっている質的変化を、反映しているのではないか?

(Hirayama et al. *Circ J 2009; 73: 718 – 725*)

ESCORT study

Pitavastatin 4 mg/days

early vs. late administration



(Kubo et al. J Am Coll Cardiol imaging 2017;64:2207–17)

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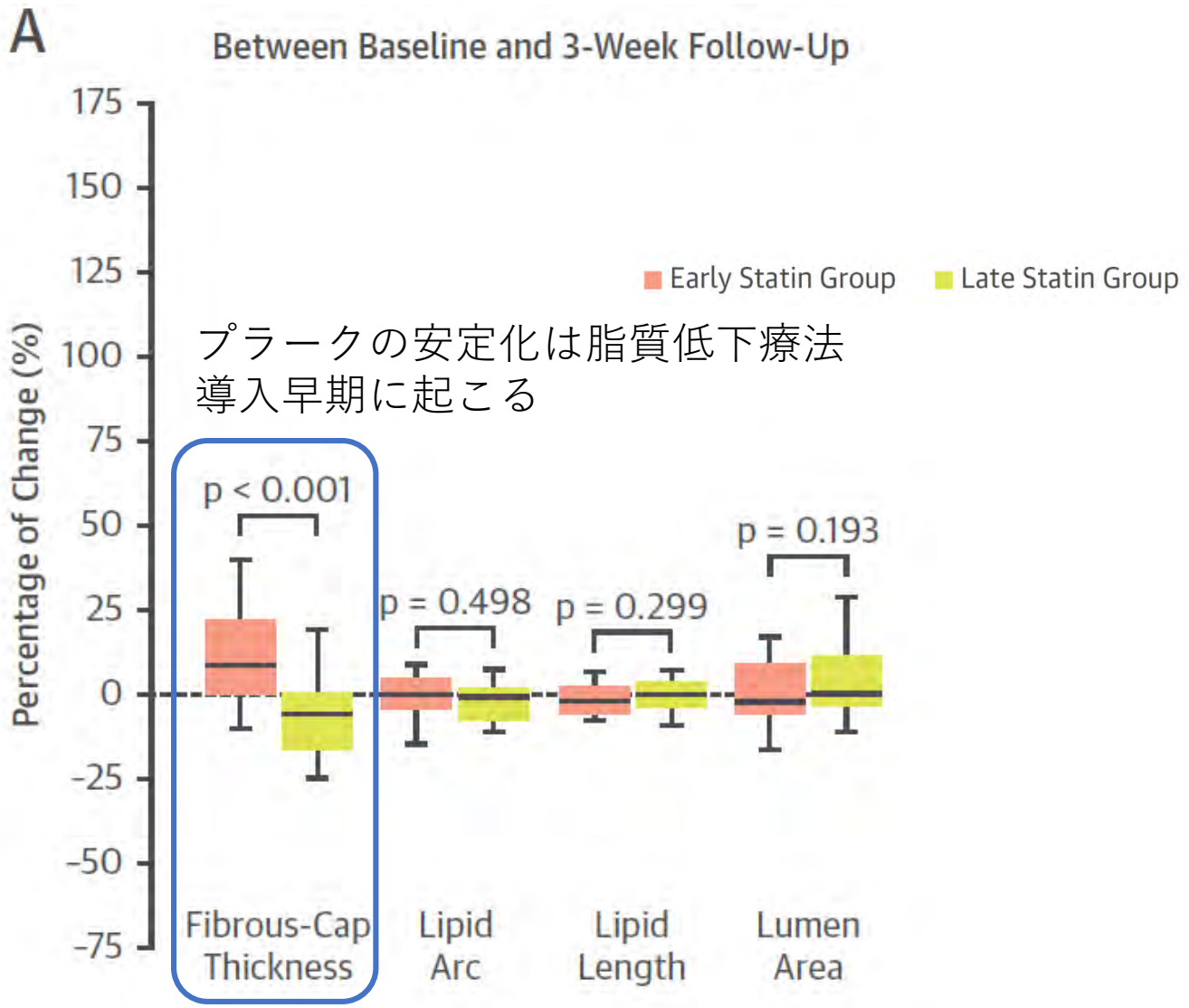
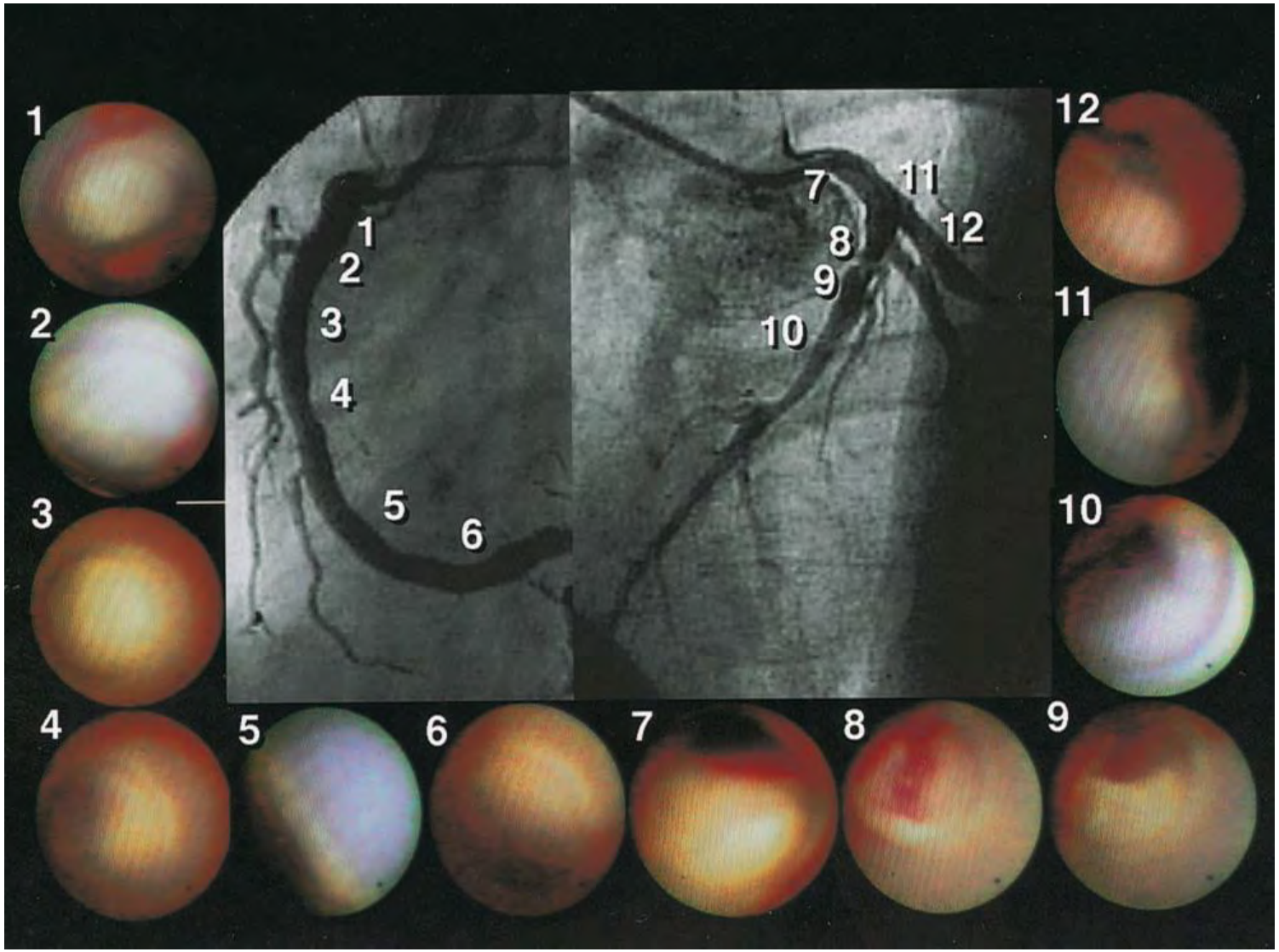


(Kubo et al. J Am Coll Cardiol imaging 2017;64:2207–17)

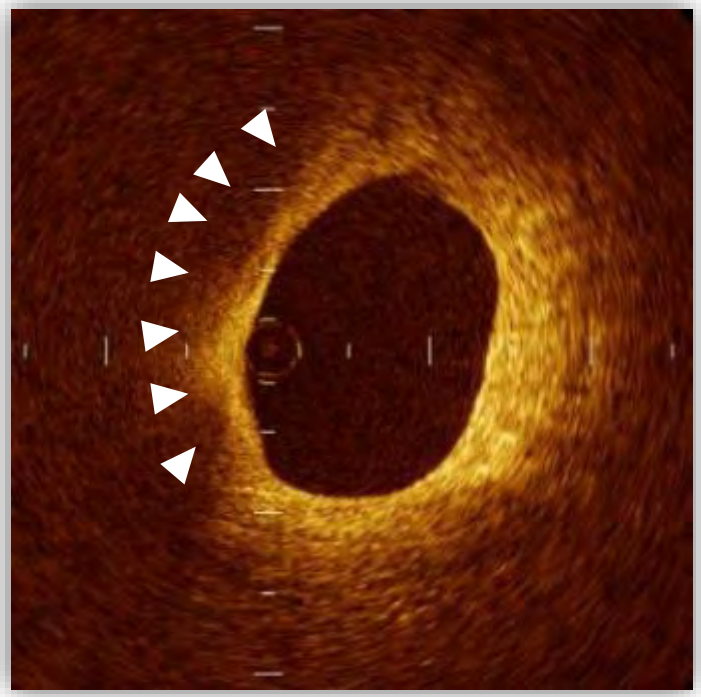
ACS患者は複数のplaque rupture, unstable plaqueを持っている



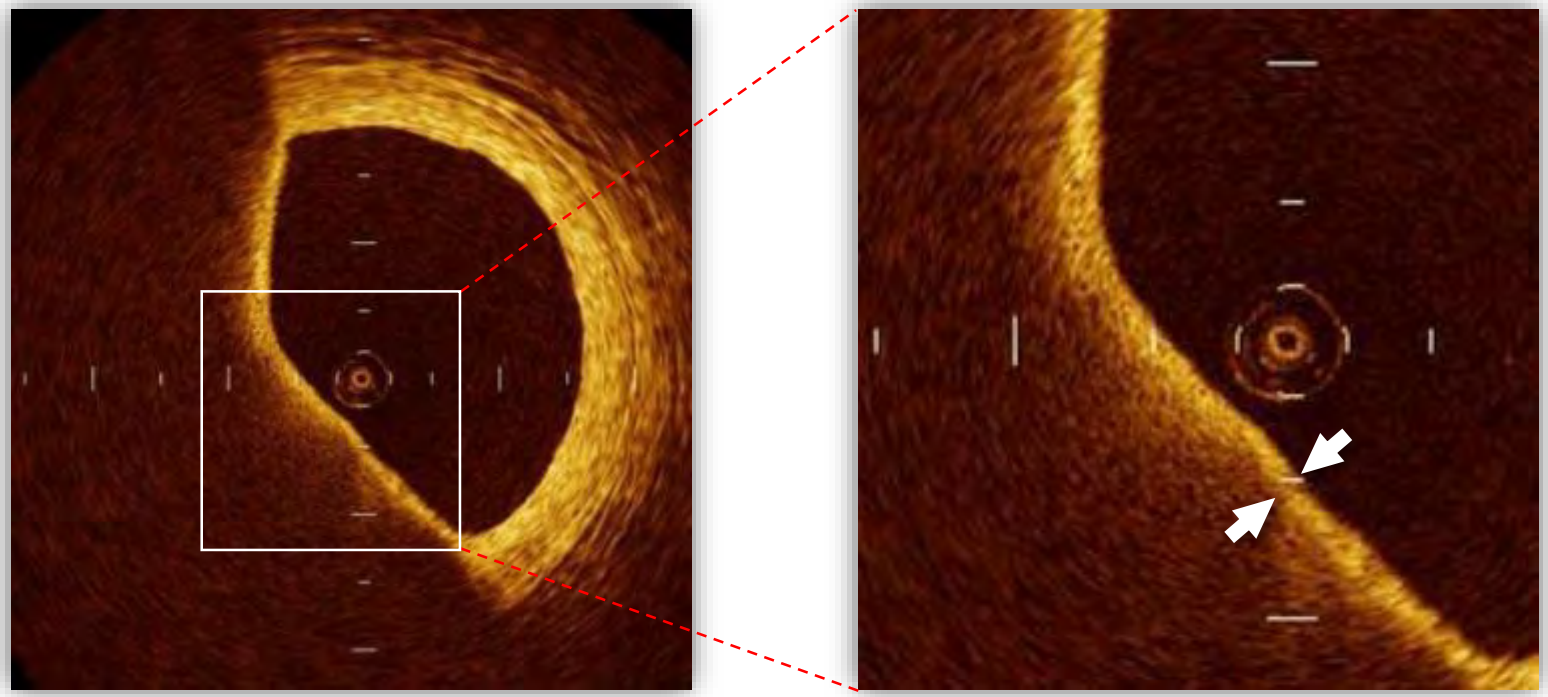
Asakura et al. J Am Coll Cardiol 2001;37:1284–8

ハイリスクプラーク: LRP & TCFA

OCT: Lipid rich plaque

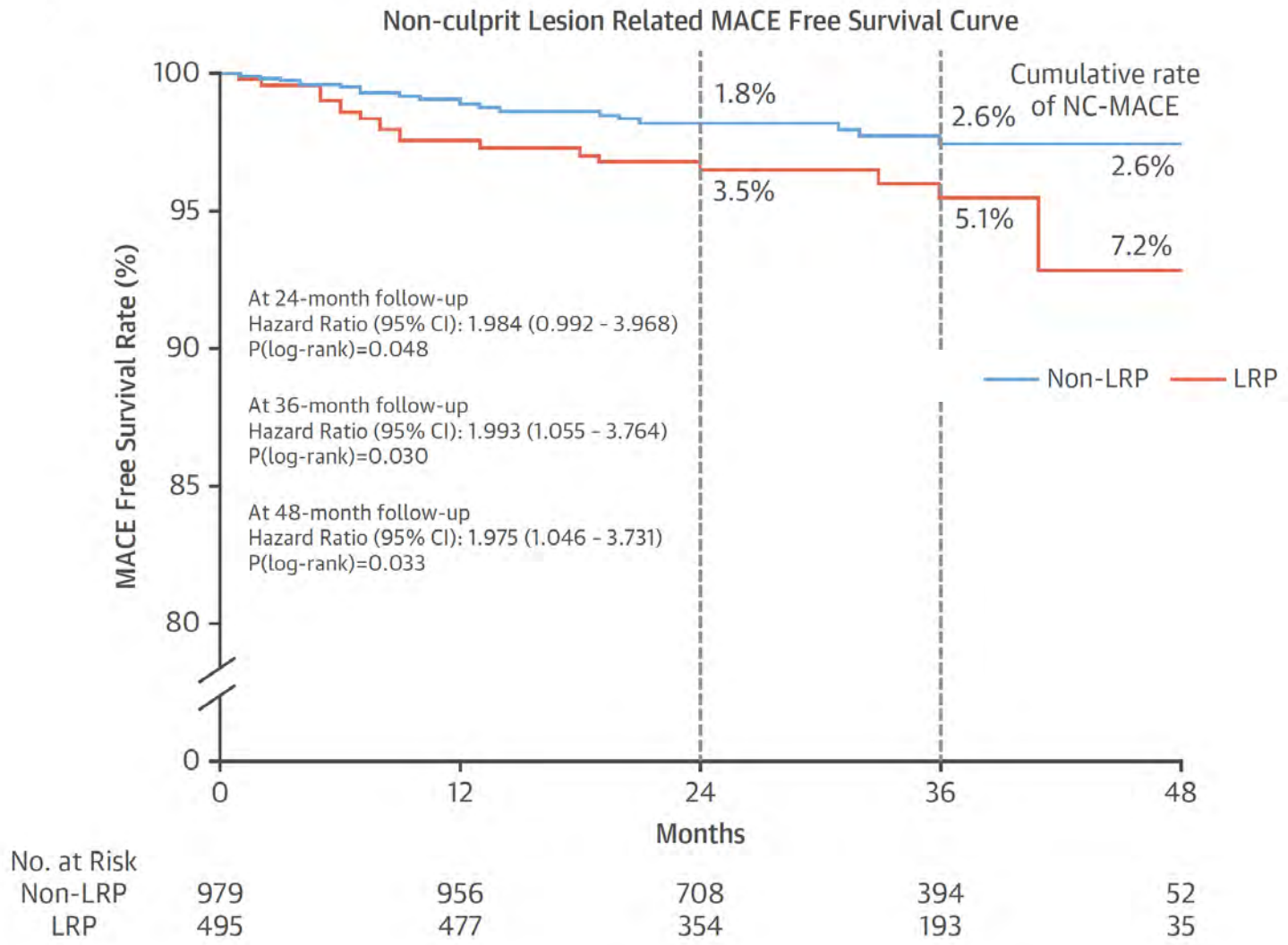


Thin-cap fibroathroma (TCFA)



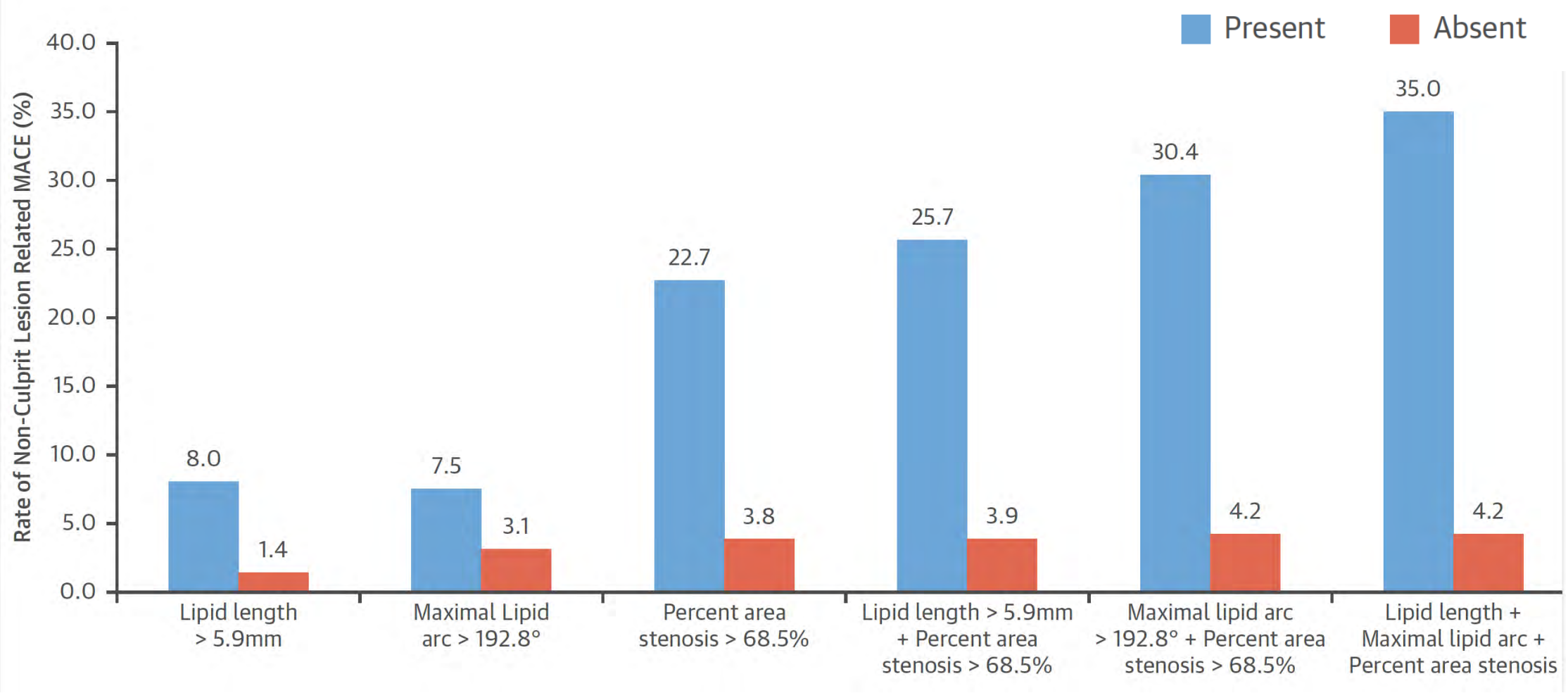
血管内OCTイメージング用語集より抜粋

ハイリスクプラーク: LRP & TCFA



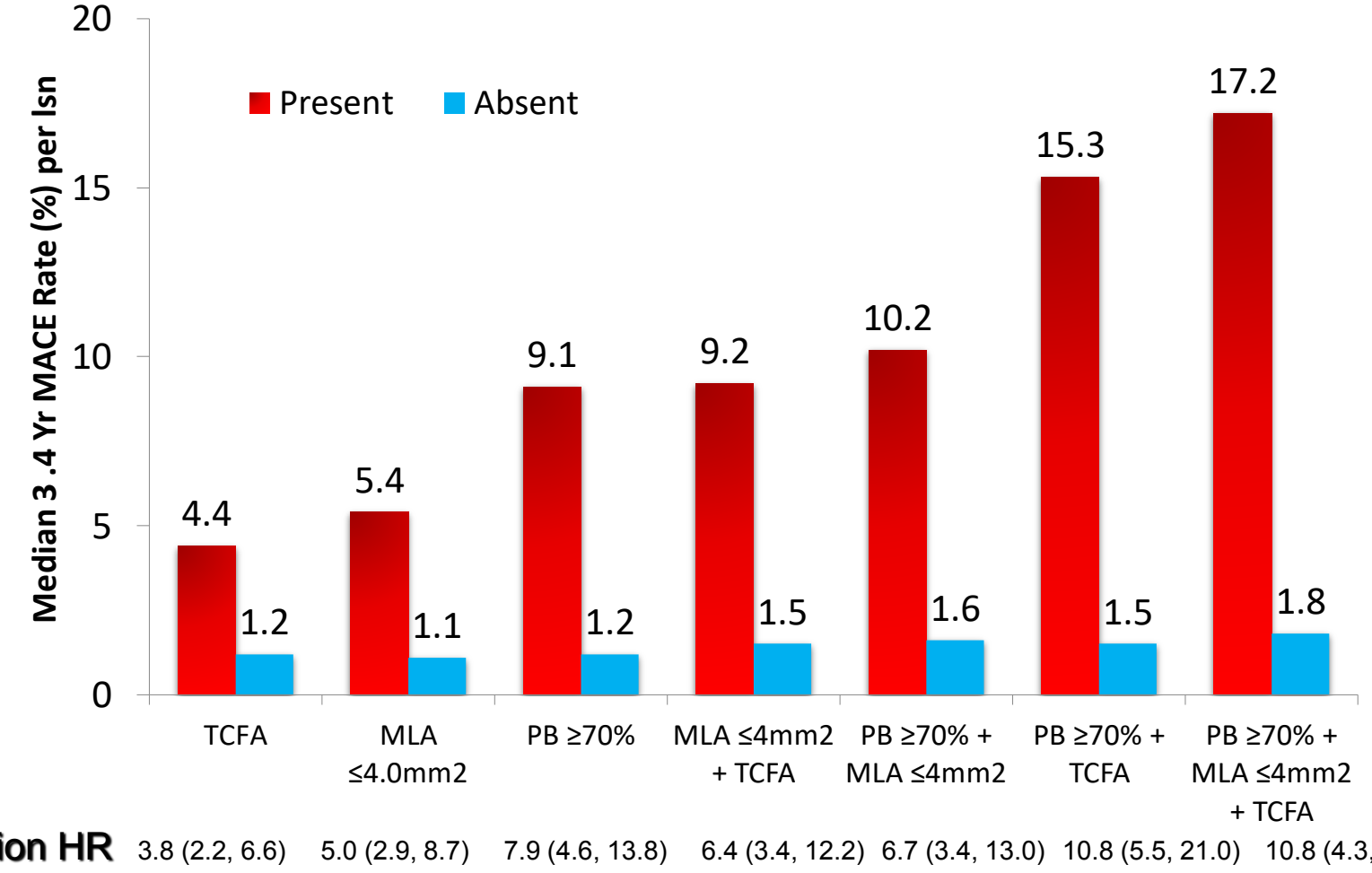
(Xing L et al. J Am Coll Cardiol. 2017;69(20):2502-2513)

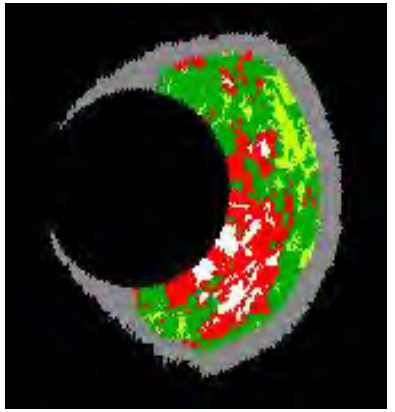
ハイリスクプラーク: LRP & TCFA



(Xing L et al. J Am Coll Cardiol. 2017;69(20):2502-2513)

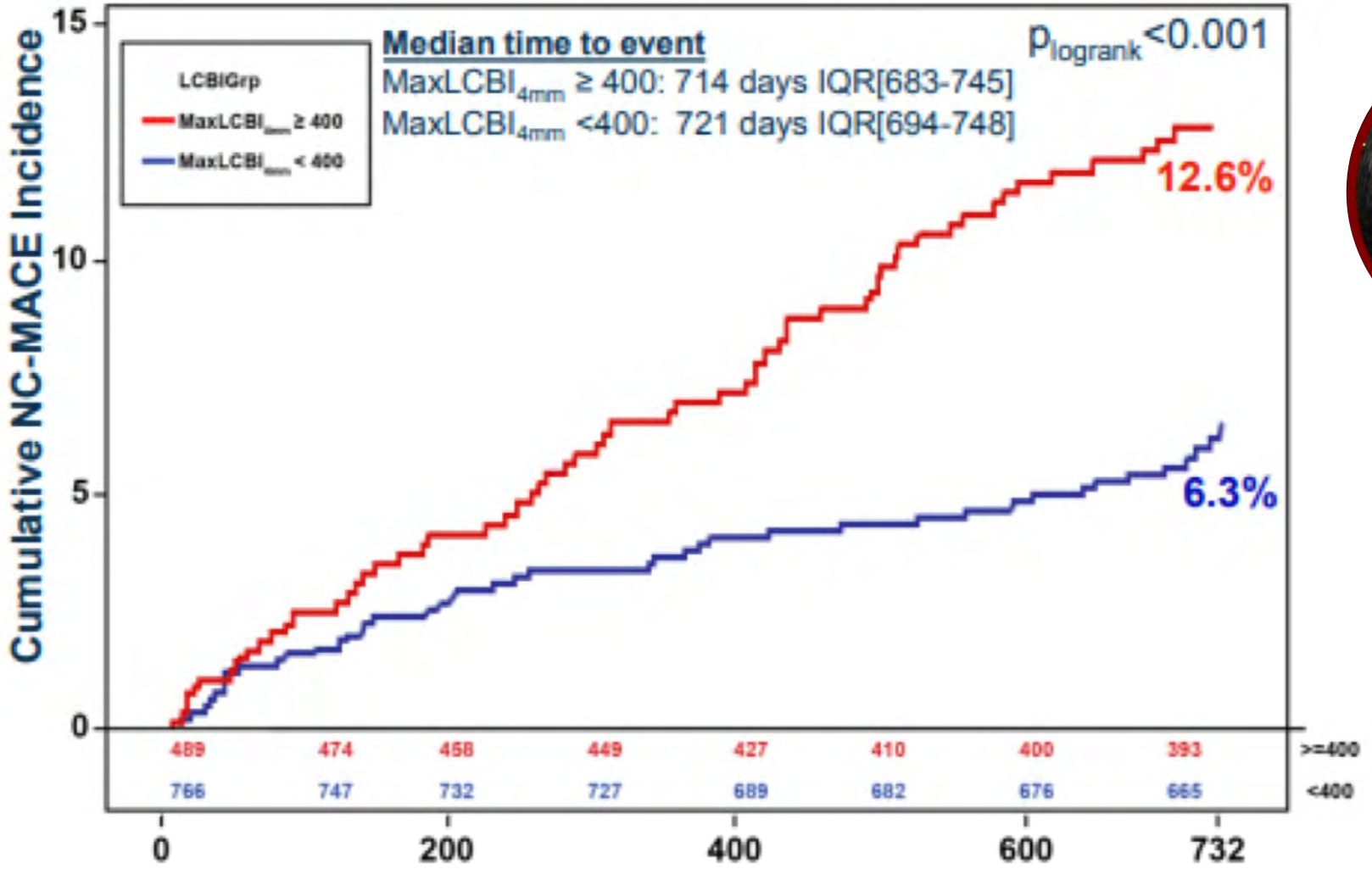
ハイリスクプラーク: PB>70%, MLA<4.0mm^2, TCFA

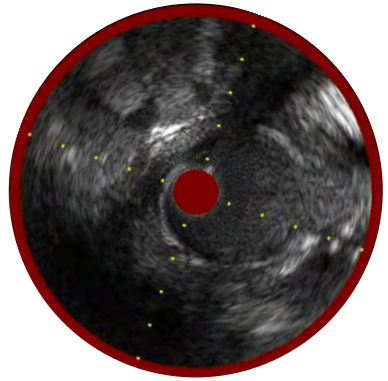




(Stone GW, et al: NEJM. 2011 ;364(3):226-35)

ハイリスクプラーク by NIRS IVUS: maxLCBI>400





Ron Waksman TCT 2018

急性冠症候群発症予防への道 積極的脂質低下療法を中心に: まとめ

- 脂質に対する介入はプラークの退縮や安定化を経て将来の臨床イベントの減少に寄与する可能性がある
- 多枝疾患患者、プラーク量の多い患者、ACSの患者は将来イベントを起こすハイリスクな一群である一方でメリットを得やすい一群でもある
- 冠動脈CTや血管内イメージングを用いることでハイリスクな一群を抽出し、治療効果を見ながら患者管理に反映させていくことが重要である