Recurrent Event After ACS: Why It Happen & How to Stop IT?

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- **Grant/Research Support** : **Abbott Vascular Japan**
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  St. Jude Medical Japan
  Terumo Inc.

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  Goodman Inc.
  St. Jude Medical Japan
  Terumo Inc.

Recurrent Event After ACS

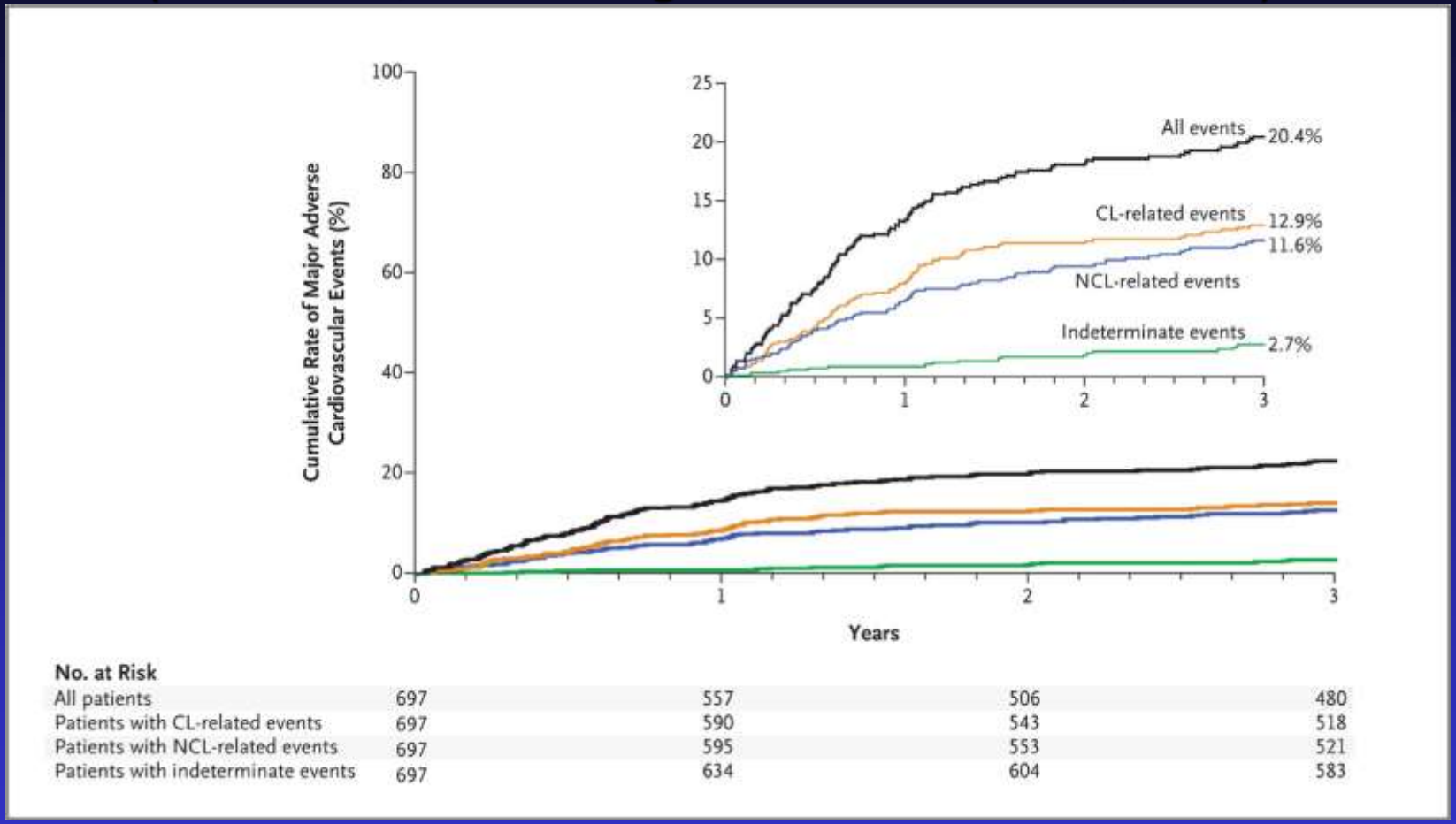
(Shah NS, et al. J Am Heart Assoc. 2015;4:e001709, doi:10.1161/JAHA.114.001709)

Cardiovascular diseases, including heart disease and stroke, are leading causes of morbidity and mortality in the United States.[1] Recurrent myocardial infarction (MI) events represent one fourth of the ≈915 000 coronary events that occur in the United States each year,[2] and ≈7% of nondiabetic US adults self-reported a history of MI from 1999 to 2001.[3] In individuals who have experienced an MI,

(Go AS, et al. Circulation. 2014;129:e28-e292)

PROSPECT trial

(Stone GW, et al. N Engl J Med 364:226-235, 2011)



No. at Risk

All patients	697	557	506	480
Patients with CL-related events	697	590	543	518
Patients with NCL-related events	697	595	553	521
Patients with indeterminate events	697	634	604	583

Study population; 697 ACS (Median follow-up; 3.4 years)

IVUS; 3160 non-culprit lesions of 673 ACS

Composite cardiac events; 104 out of 3160 non-culprit lesions

74 out of 673 pts

PROSPECT trial

(Stone GW, et al. N Engl J Med 364:226-235, 2011)

Table 2. Kaplan–Meier Estimates for Cumulative Rates of Major Adverse Cardiovascular Events at 3 Years.*

Event	Events Related to Culprit Lesions	Events Related to Nonculprit Lesions	Indeterminate Events	All Events
	percent (number of patients)			
Composite cardiac events†	12.9 (83)‡	11.6 (74)	2.7 (17)	20.4 (132)
Death from cardiac causes, cardiac arrest, or myocardial infarction	2.2 (14)	1.0 (6)	1.9 (12)	4.9 (31)
Death from cardiac causes	0.2 (1)	0	1.8 (11)	1.9 (12)
Cardiac arrest	0.3 (2)	0	0.2 (1)	0.5 (3)
Myocardial infarction	2.0 (13)	1.0 (6)§	0.3 (2)	3.3 (21)
Rehospitalization for unstable or progressive angina	11.5 (74)	10.8 (69)	0.8 (5)	17.5 (113)
Other events				
Revascularization	10.9 (70)	10.5 (67)	0	17.1 (110)
Stent thrombosis¶	2.0 (13)	0	1.3 (8)	3.3 (21)

Study population; 697 ACS (Median follow-up; 3.4 years)

IVUS; 3160 non-culprit lesions of 673 ACS

Composite cardiac events; 104 out of 3160 non-culprit lesions

74 out of 673 pts

Extensive Development of Vulnerable Plaques as a Pan-Coronary Process in Patients With Myocardial Infarction: An Angioscopic Study

Masanori Asakura, MD,* Yasunori Ueda, MD, PHD,† Osamu Yamaguchi, MD,* Takayoshi Adachi, MD,‡ Atsushi Hirayama, MD, PHD,† Masatsugu Hori, MD, PHD, FACC,* Kazuhisa Kodama, MD, PHD, FACC†

Suita and Osaka, Japan

OBJECTIVES To test our hypothesis that the development of vulnerable plaques is not limited to the culprit lesions, but is a pan-coronary process, we directly observed all three major coronary arteries by angioscopy and evaluated the prevalence of yellow plaques in patients with myocardial infarction (MI).

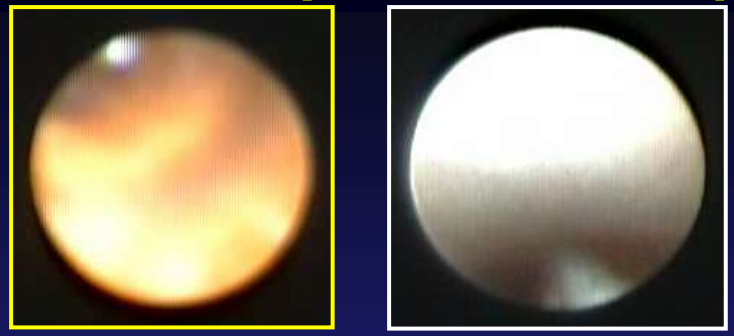
BACKGROUND Although pathologic studies have suggested that the disruption of atheromatous plaque plays a major role in the development of acute MI, the prevalence of yellow plaques in the whole coronary arteries of patients with MI has not been clarified.

METHODS Thirty-two patients undergoing follow-up catheterization one month after the onset of MI were prospectively and consecutively enrolled in this study. The prevalence of yellow plaques and thrombus in the major coronary arteries was successfully evaluated in 20 patients (58 coronary arteries, 21 culprit lesions) by coronary angioscopy. The diameter stenosis (DS) of the culprit lesions and the maximal diameter stenosis (maxDS) of nonculprit segments were angiographically measured for each coronary artery.

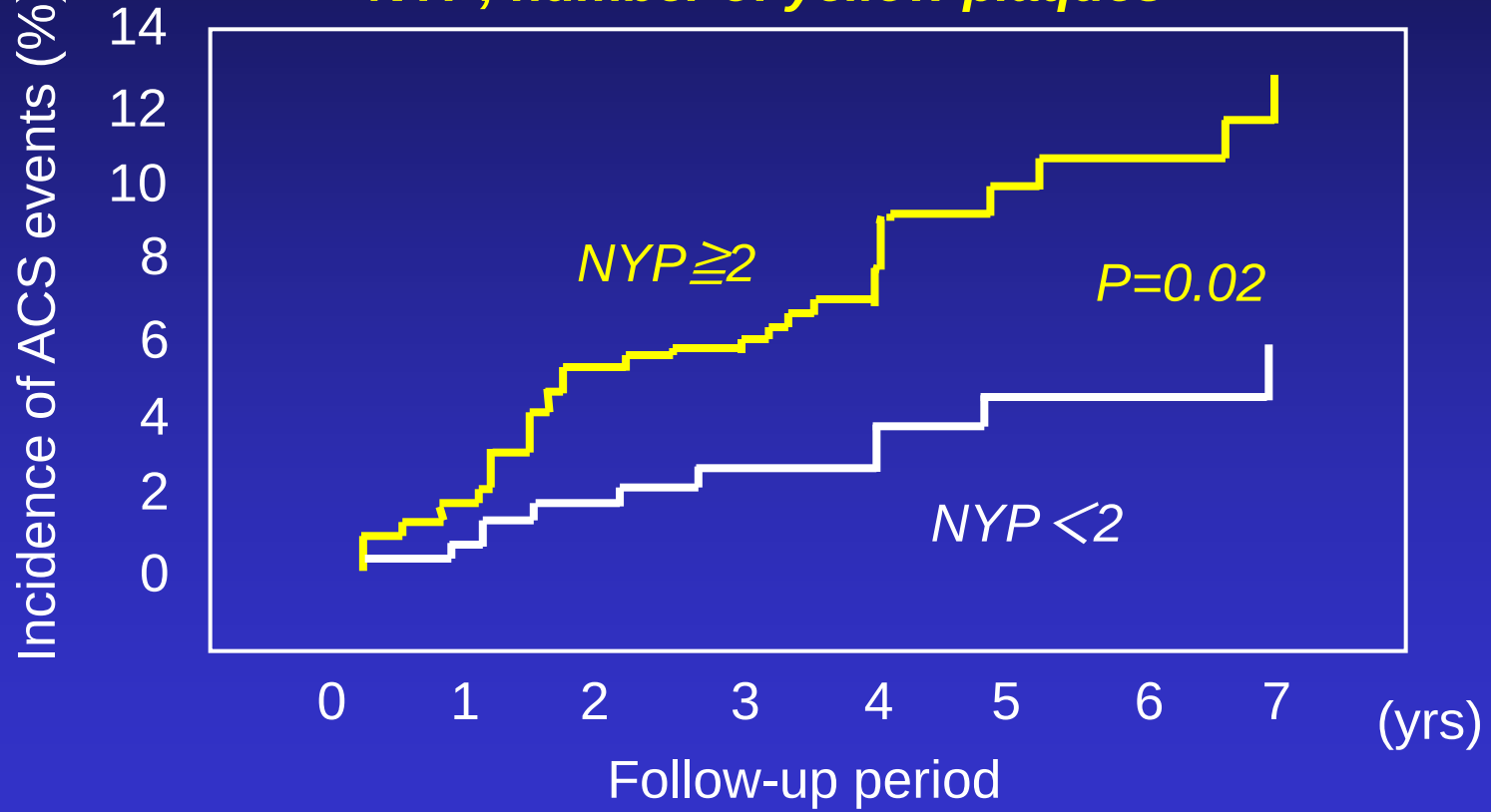
RESULTS The DS of the culprit lesions and maxDS were 27 ± 17% and 19 ± 13%, respectively. Yellow plaques and thrombus were detected in 19 (90%) and 17 (81%) of 21 culprit lesions, respectively. Yellow plaques were equally prevalent in the infarct-related and non–infarct-related coronary arteries (3.7 ± 1.6 vs. 3.4 ± 1.8 plaques/artery). However, thrombus was only detected in the nonculprit segments of one (2%) coronary artery.

CONCLUSIONS In patients with MI, all three major coronary arteries are widely diseased and have multiple yellow though nondisrupted plaques. Acute MI may represent the pan-coronary process of vulnerable plaque development. (J Am Coll Cardiol 2001;37:1284–8)

Incidence of ACS events in pts with multiple yellow plaques



NYP; number of yellow plaques



Ohtani T, et al. J Am Coll Cardiol. 47(11):2194-2200, 2006

Number of yellow plaques detected in a coronary artery is associated with future risk of ACS: detection of vulnerable patients by angioscopy.

Demonstration of Multi-vessel Instability by Invasive Imaging

Angioscopy

- Asakura M, et al. : J Am Coll Cardiol 2001;37:1284-1288
- Ohtani T, et al. : J Am Coll Cardiol 2006;47:2194-2200

Gray Scale IVUS

- Rioufol, et al. : Circulation 2002;106:804-808
- Hong MK, et al. : Circulation 2004;110:928-933

VH-IVUS

- Hong MK, et al. : Am J Cardiol 2008;101:568-572

OCT

- Kubo, et al. : Am J Cardiol 2010;105:318-322
- Fukunaga M, et al. : EuroInterv 2012;8:955-961

How to prevent recurrent event after ACS ?

= How to stabilize multi-vessel instability (vulnerable plaque) ?

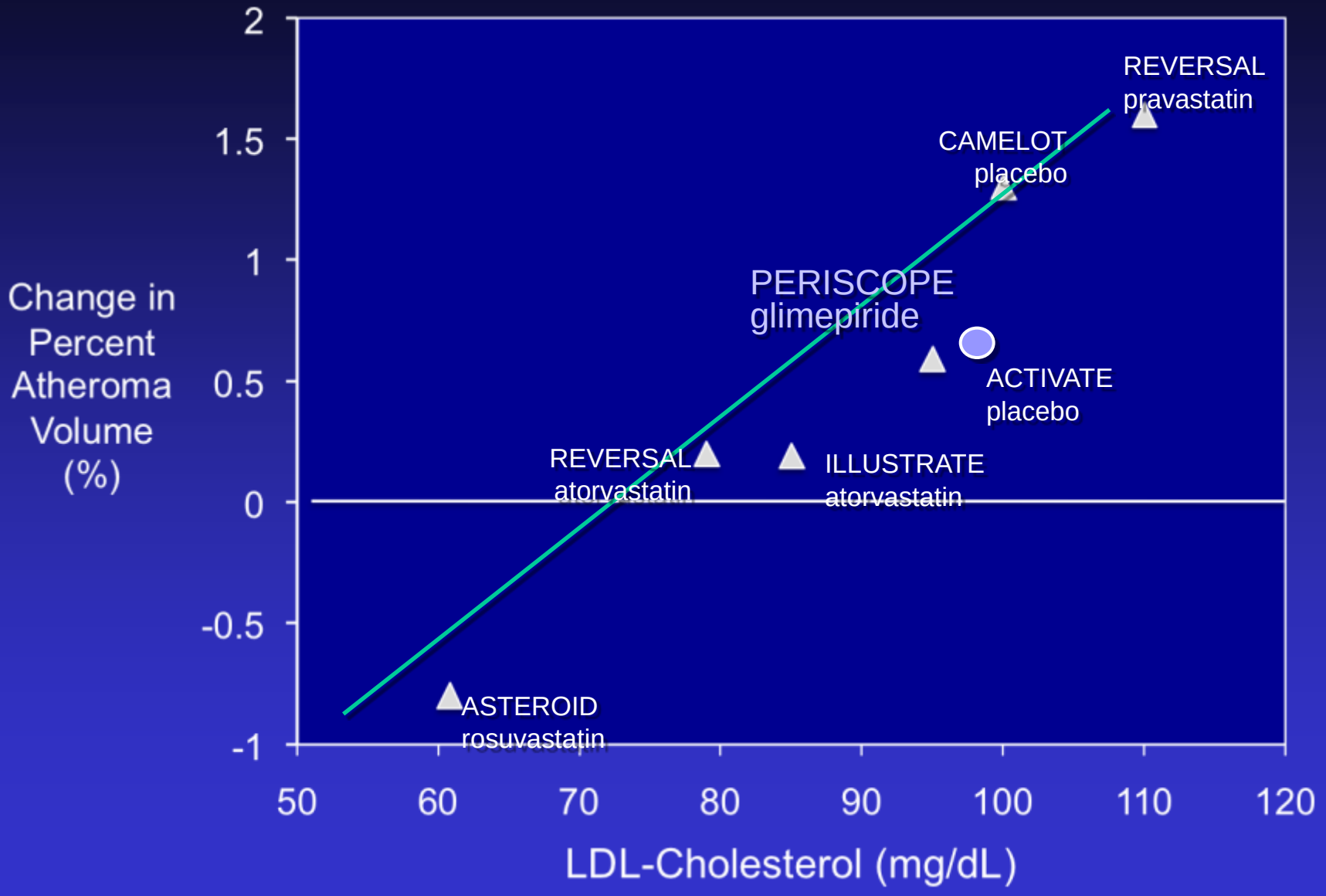
Systemic approach to vulnerable plaque

- High dose statin
- PCSK-9
- Ezetimibe
- EPA
- Other vascular protective agents (aspirin, β-blocker, ACE-I, ARB, etc.)

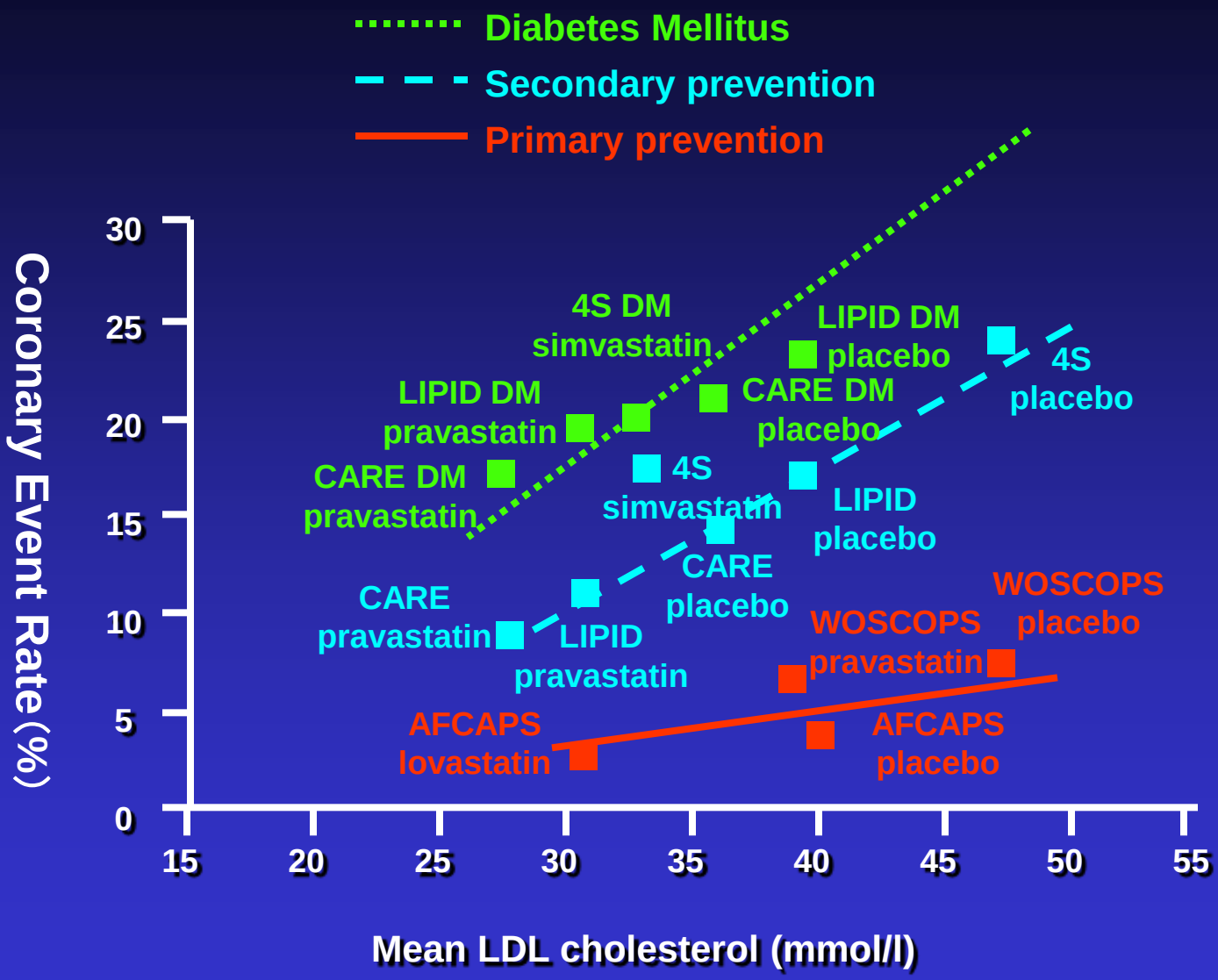
Local approach (Plaque sealing) to vulnerable plaque

- Bio-absorbable scaffold (BVS)
- DEB
- Others

Relation between %change of plaque volume & LDL-C

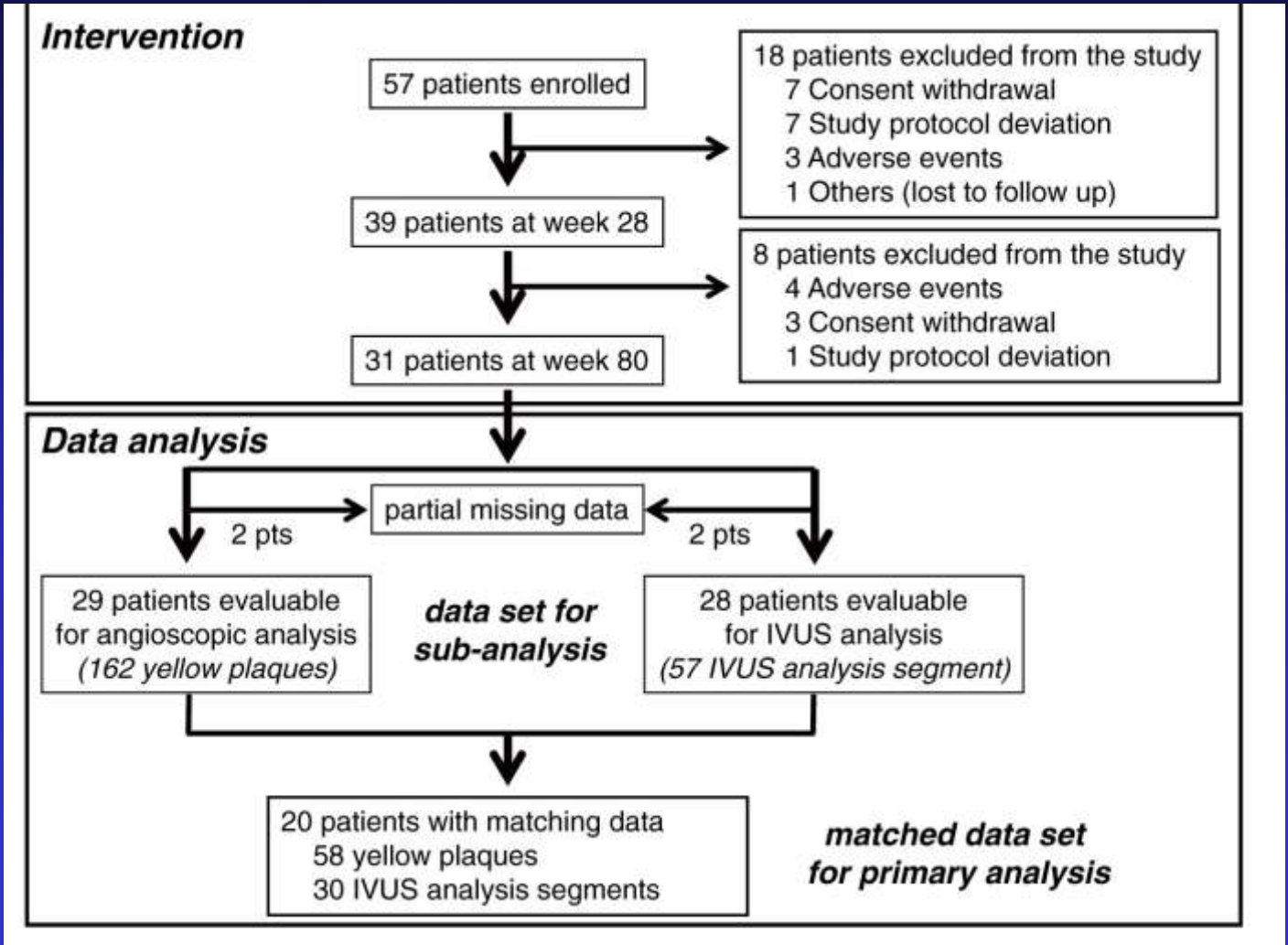


LDL-C level & Coronary Event Rate

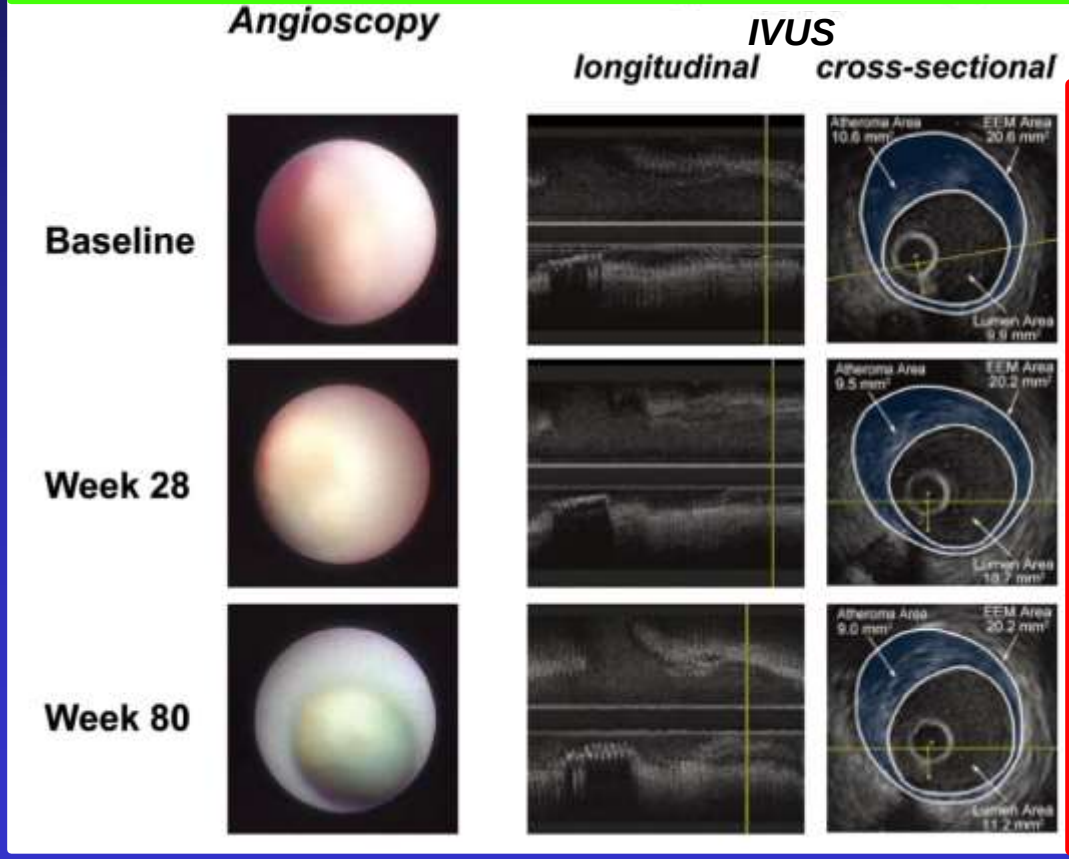


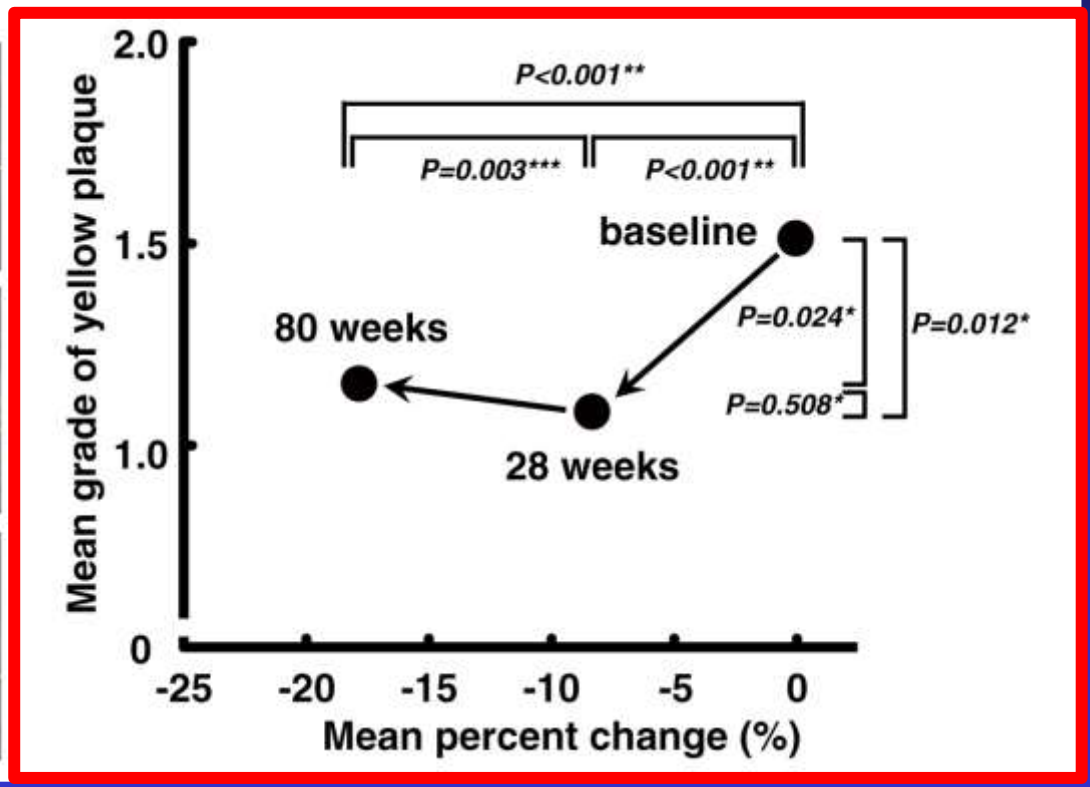
Qualitative & Quantitative Changes in Coronary Plaque Associated with Atrovastatin Therapy: Evaluation with simultaneous angioscopy & intaravascular ultrasound (TWINS) study

Hirayama A, et al. Circ J 73:718-725, 2009



Qualitative & Quantitative Changes in Plaque by Atrovastatin





Hirayama A, et al. Circ J 73:718-725, 2009

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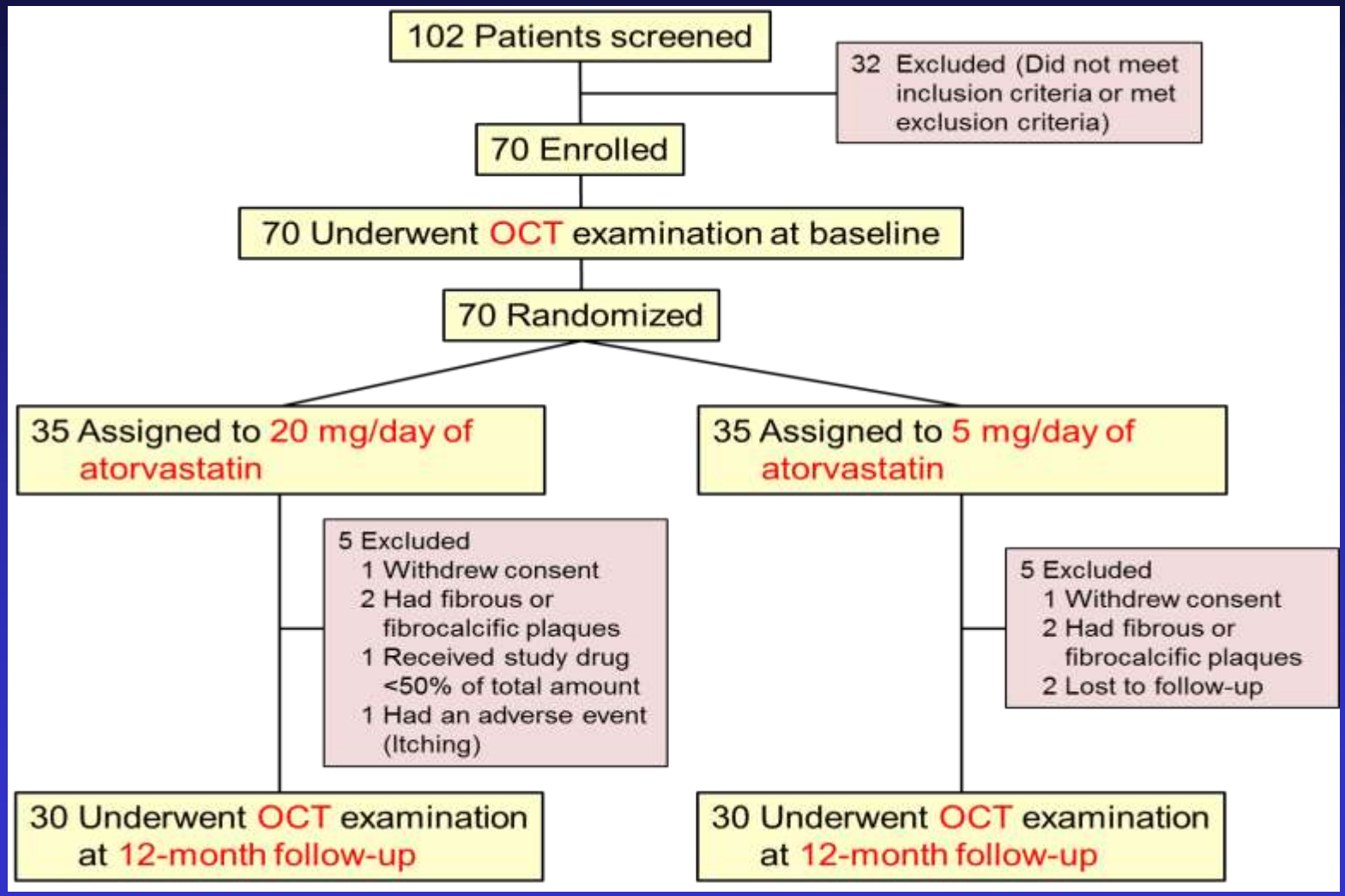
Effect of Atorvastatin Therapy on the Fibrous Cap Thickness in Coronary Atherosclerotic Plaque as Assessed by OCT (EASY-FIT)

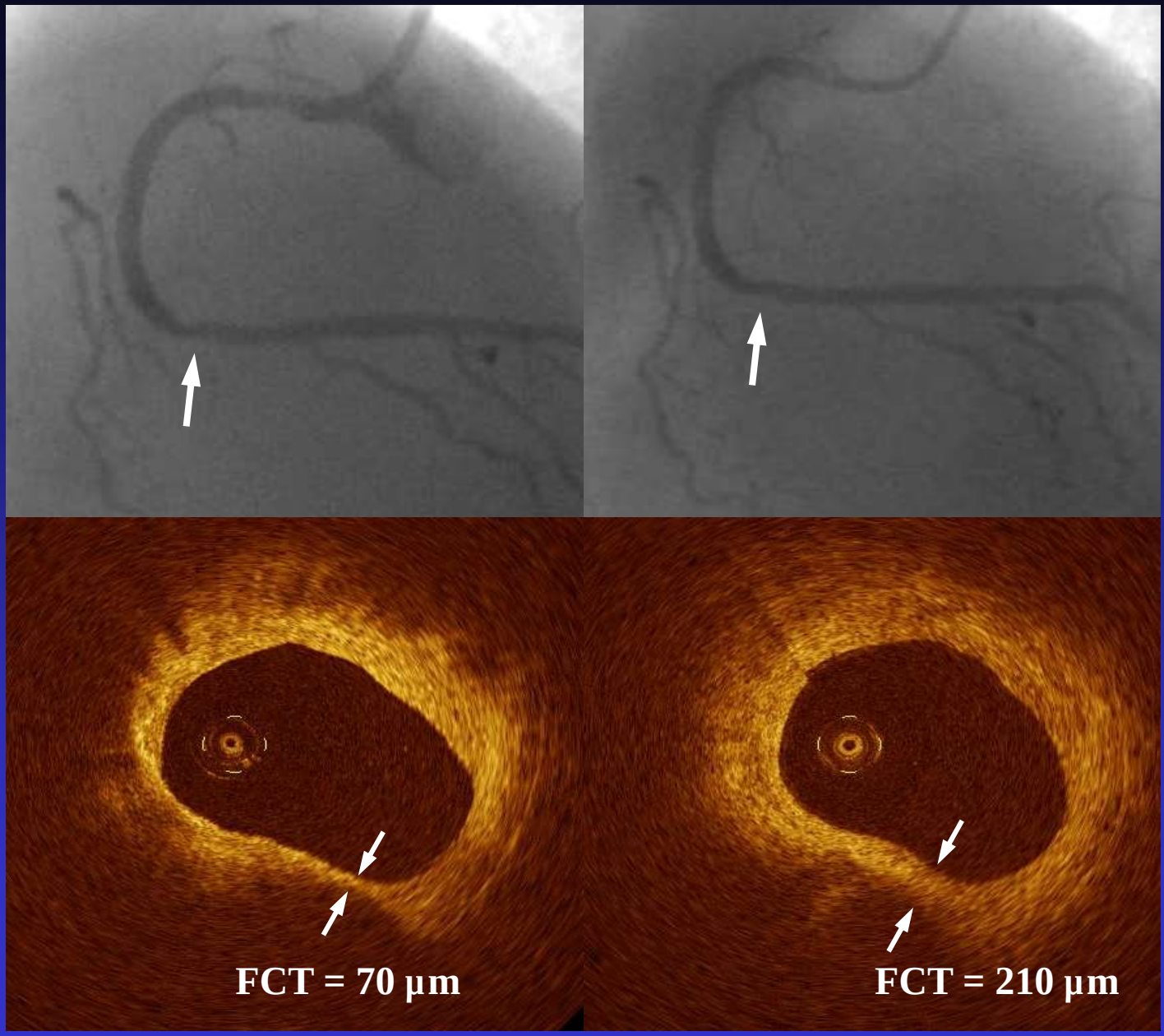
Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217



National Clinical Trial Identifier Number: 00700037

Wakayama Medical University

An example demonstrating change of FC thickness during 12 months



Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217

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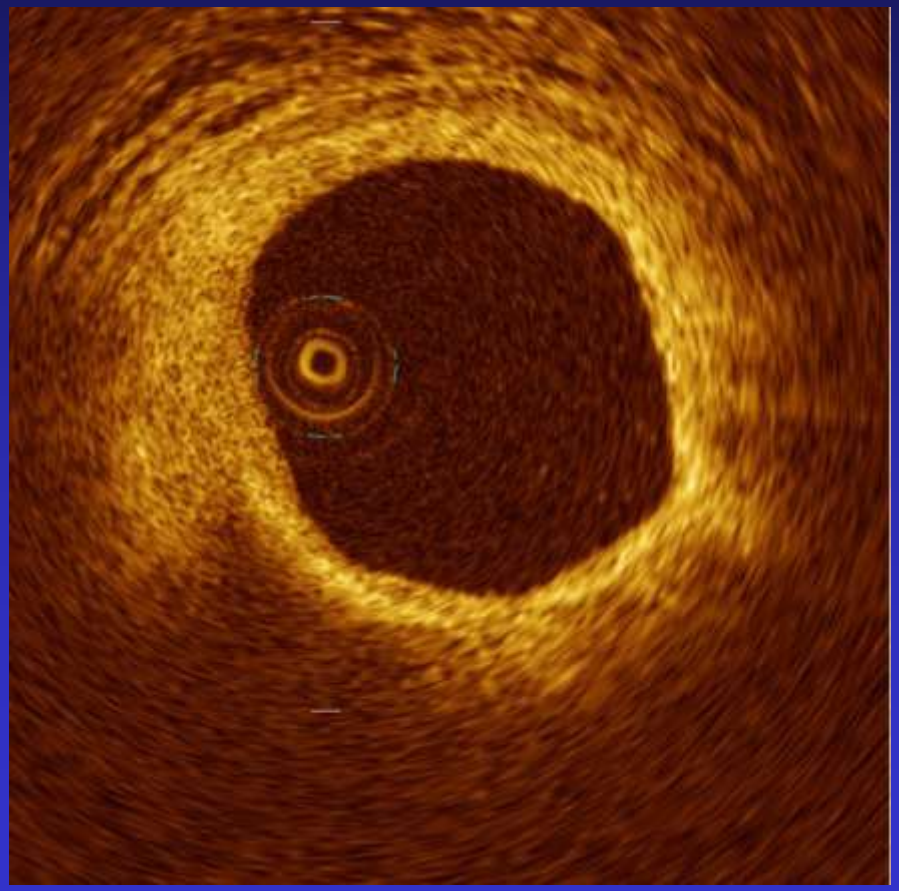
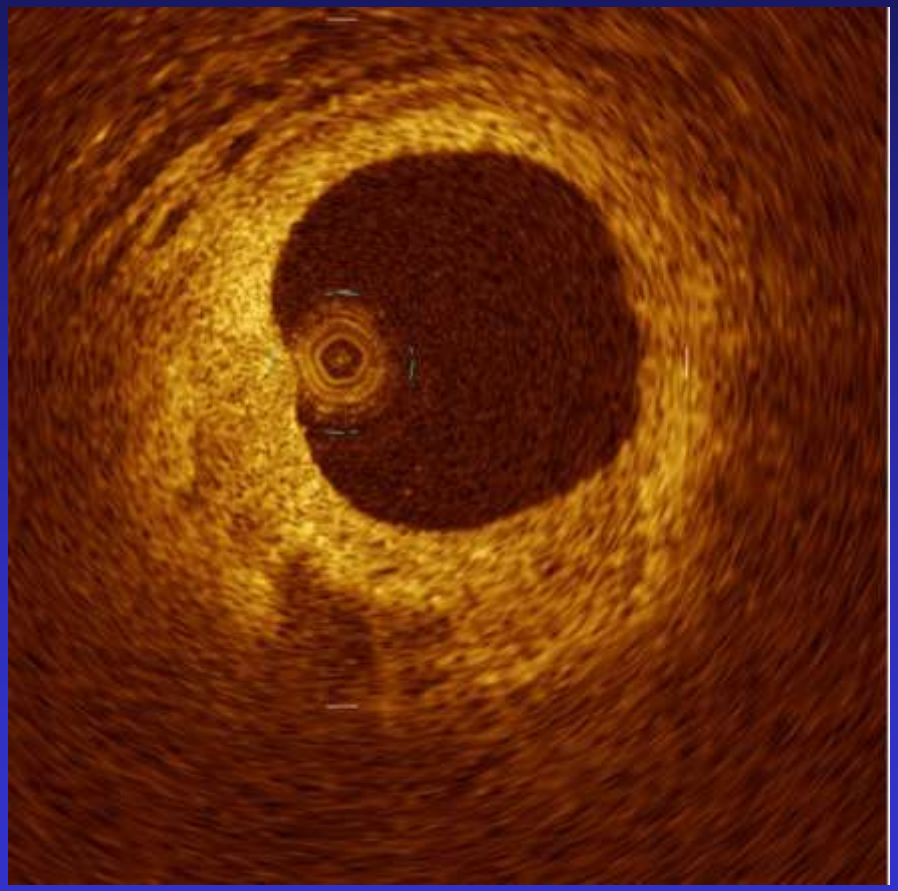
Decrease of macrophage density during 20mg/day of Atorvastatin

Baseline

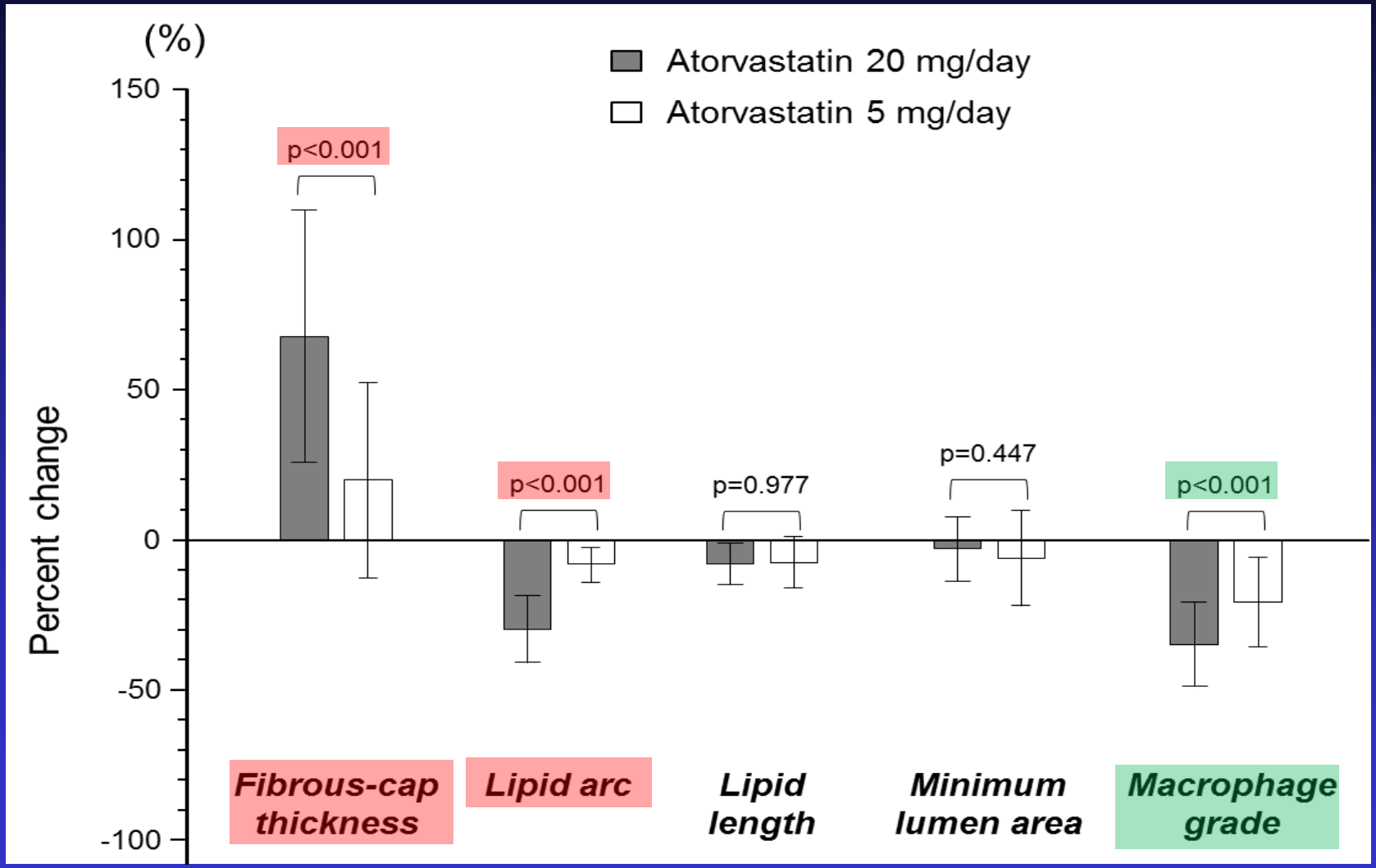


12-month follow-up



Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217

Percent change in OCT measurements between baseline and 12-month follow-up



Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217

Effect of EPA & statin on TCFA

Stabilizing effect of combined eicosapentaenoic acid and statin therapy on coronary thin-cap fibroatheroma

Ryo Nishio, Toshiro Shinke*, Hiromasa Otake, Masayuki Nakagawa, Ryoji Nagoshi, Takumi Inoue, Amane Kozuki, Hirotoshi Hariki, Tsuyoshi Osue, Yu Taniguchi, Masamichi Iwasaki, Noritoshi Hiranuma, Akihide Konishi, Hiroto Kinutani, Junya Shite, Ken-ichi Hirata

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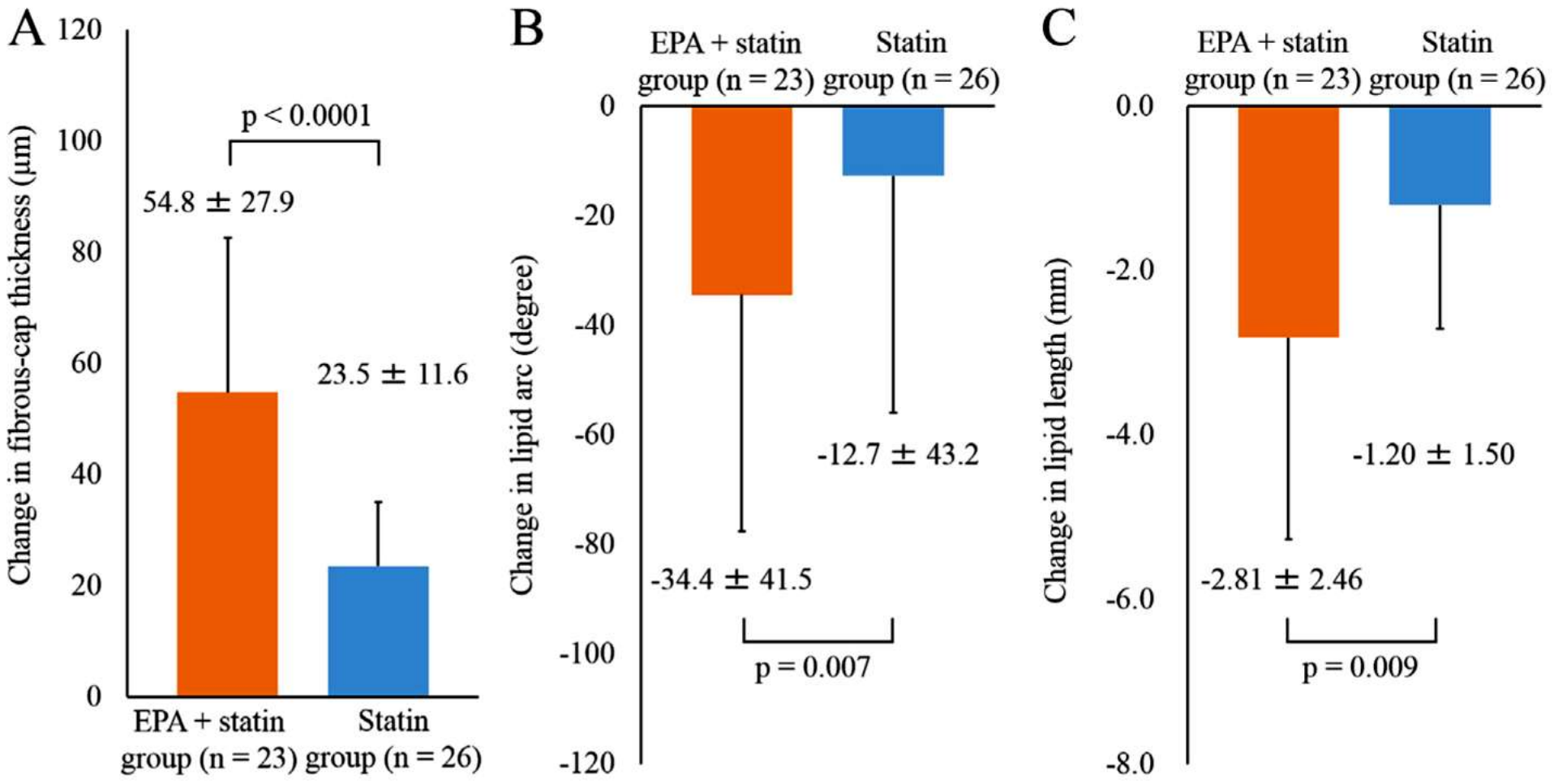
ABSTRACT

Background: The addition of highly purified eicosapentaenoic acid (EPA) to statin therapy prevents cardiovascular events. However, the impact of this treatment on vulnerable plaques remains unclear. The aim of this study was to assess the impact of adding EPA to a standard statin therapy on vulnerable plaques by serial optical coherence tomography (OCT).
Methods: Forty-nine non-culprit thin-cap fibroatheroma (TCFA) lesions in 30 patients with untreated dyslipidemia were included. Patients were randomly assigned to EPA (1800 mg/day) + statin (23 TCFA, 15 patients) or statin only (26 TCFA, 15 patients) treatment. The statin (rosuvastatin) dose was adjusted to achieve a target low-density lipoprotein (LDL) level of <70 mg/dL. Post-percutaneous intervention and 9-month follow-up OCT were performed to evaluate morphological changes of TCFAs. The EPA/arachidonic acid (EPA/AA) ratio and pentraxin-3 (PTX3) levels were also evaluated.
Results: Despite similar follow-up LDL levels, the EPA + statin group had higher EPA/AA ratios and lower PTX3 levels than the statin group. OCT analysis showed that the EPA + statin group had a greater increase in fibrous-cap thickness, with a greater decrease in lipid arc and lipid length. Macrophage accumulation was less frequently detected in the EPA + statin group than in the statin group at follow-up. When the patients were categorized according to their follow-up PTX3 tertiles, fibrous-cap thickness showed significant increase, and the incidence of macrophages accumulation decreased with lower PTX3 levels.
Conclusion: The concomitant use of EPA and rosuvastatin may stabilize vulnerable plaques better than the statin alone, possibly by suppressing arterial inflammation.

Nishio R, et al. Atherosclerosis 2014;234:114 - 119

Effect of EPA & statin on TCFA

Change in Cap Thickness **Change in Lipid Arc** **Change in Lipid Length**



Nishio R, et al. Atherosclerosis 2014;234:114 - 119

Trends in Myocardial Infarction Secondary Prevention: The National Health and Nutrition Examination Surveys (NHANES), 1999–2012

Nilay S. Shah, MD, MPH; Mark D. Huffman, MD, MPH; Hongyan Ning, MD, MS; Donald M. Lloyd-Jones, MD, ScM

Background—Nationally representative data evaluating recent trends and future projections of vascular risk factor treatment and control rates in secondary prevention of ischemic heart disease are sparse.

Methods and Results—We evaluated sex- and race-stratified cholesterol, blood pressure, and hemoglobin A1c levels and risk factor treatment and control rates in 1580 individuals who self-reported a history of myocardial infarction from The National Health and Nutrition Examination Surveys (NHANES) 1999 to 2012. We used weighted linear regression to estimate time trends and created forward linear projections to 2020. Participants were 30% to 41% women, 73% to 85% white, and had a mean age of 63 to 66 years. Cholesterol treatment rates increased and reached above 80% in men and women by 2011–2012, with significant increases in control rates (as then defined) in men to 85% in 2011–2012, with projections to reach 100% by 2020. Cholesterol treatment rates significantly increased in non-Hispanic whites and Hispanics. Statin use increased significantly to 73% of myocardial infarction survivors by 2011–2012, and aspirin use increased significantly but only to 28% by 2011–2012. There were no changes in blood pressure treatment or control rates by sex, and hypertension treatment increased only in non-Hispanic blacks. Projected hypertension control rates remained suboptimal.

Conclusions—While temporal trends suggest improvements in cholesterol treatment, unchanged treatment and control of blood pressure and persistently low aspirin use represent missed opportunities. Urgent action is needed to improve secondary prevention rates projected by 2020 to reduce recurrent events in this high-risk group. (***J Am Heart Assoc.*** **2015;4:e001709 doi: 10.1161/JAHA.114.001709**)

How to treat recurrent event after ACS ?

= How to stabilize multi-vessel instability (vulnerable plaque) ?

Systemic approach to vulnerable plaque

- High dose statin
- PCSK-9
- Ezetimibe
- EPA
- Other vascular protective agents (aspirin, β-blocker, ACE-I, ARB, etc.)

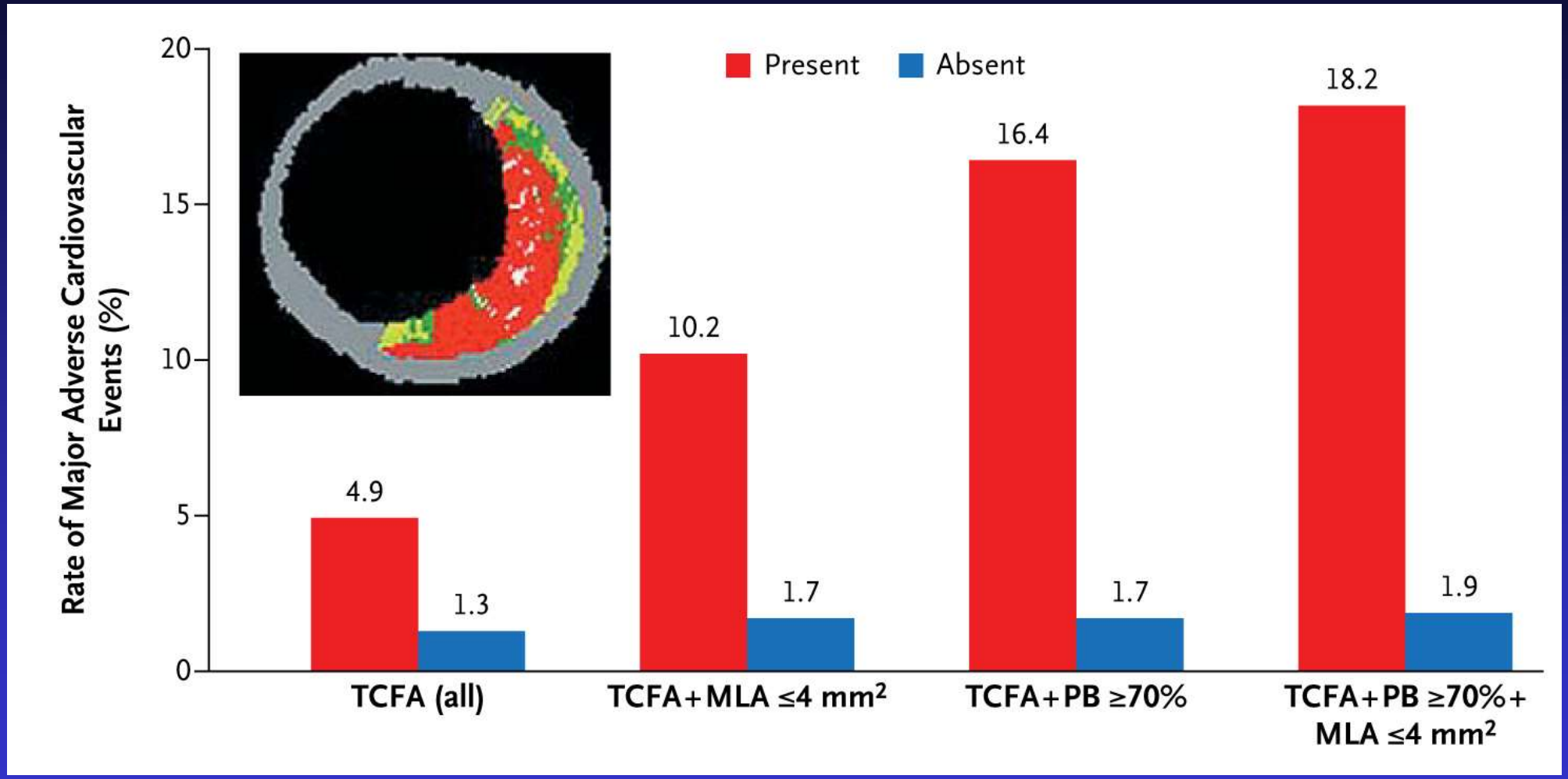
Local approach (Plaque sealing) to vulnerable plaque

- Bio-absorbable scaffold (BVS)
- DEB
- Others

To promote local approach, it is very important to predict the future events of each vulnerable plaque by various imaging modalities and/or biological markers.

PROSPECT trial

(Stone GW, et al. N Engl J Med 364:226-235, 2011)

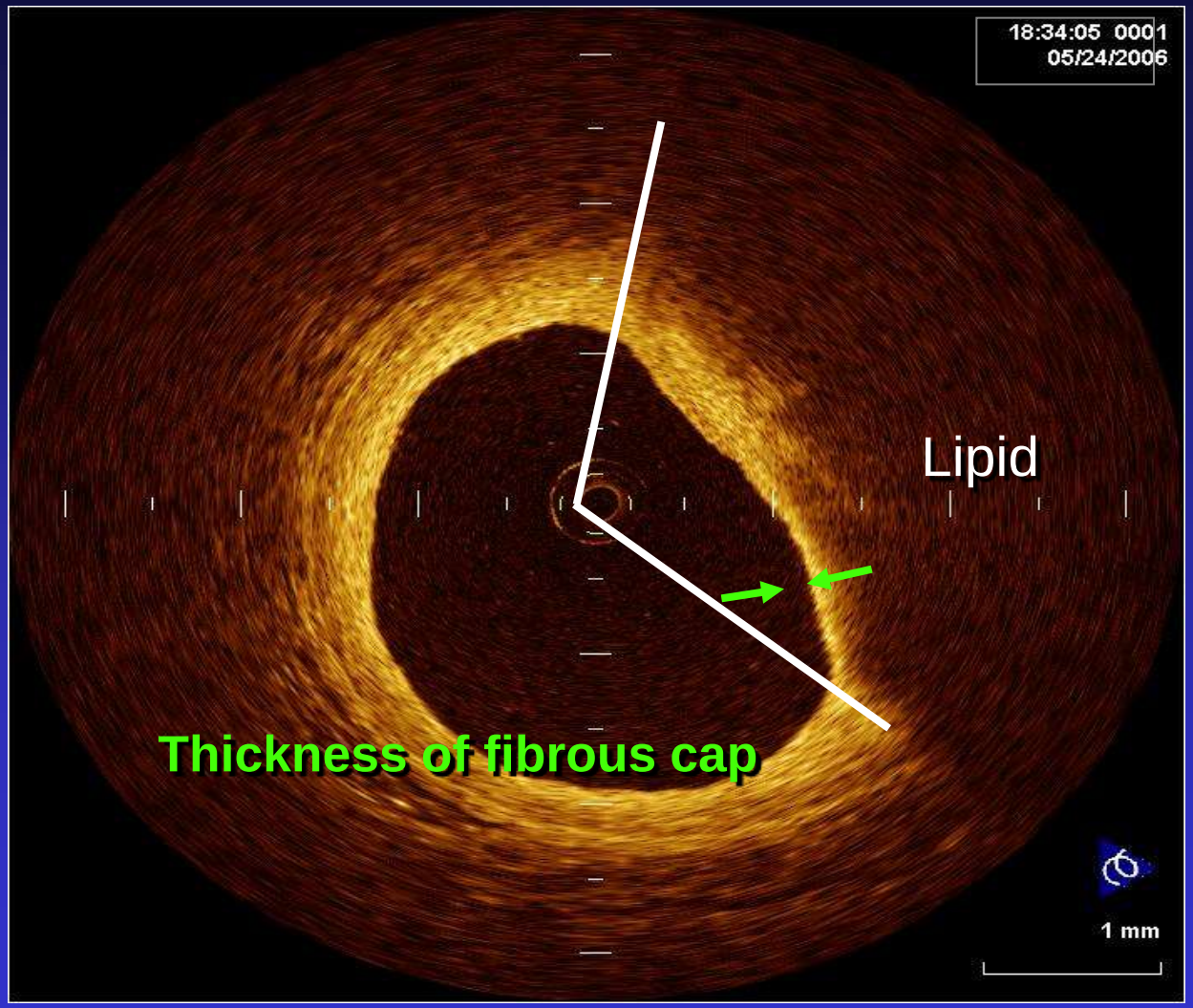


IVUS tissue characterization in addition to gray-scale IVUS information such as MLA & PB may improve prediction of future events.

Thin-capped Fibroatheroma (TCFA)

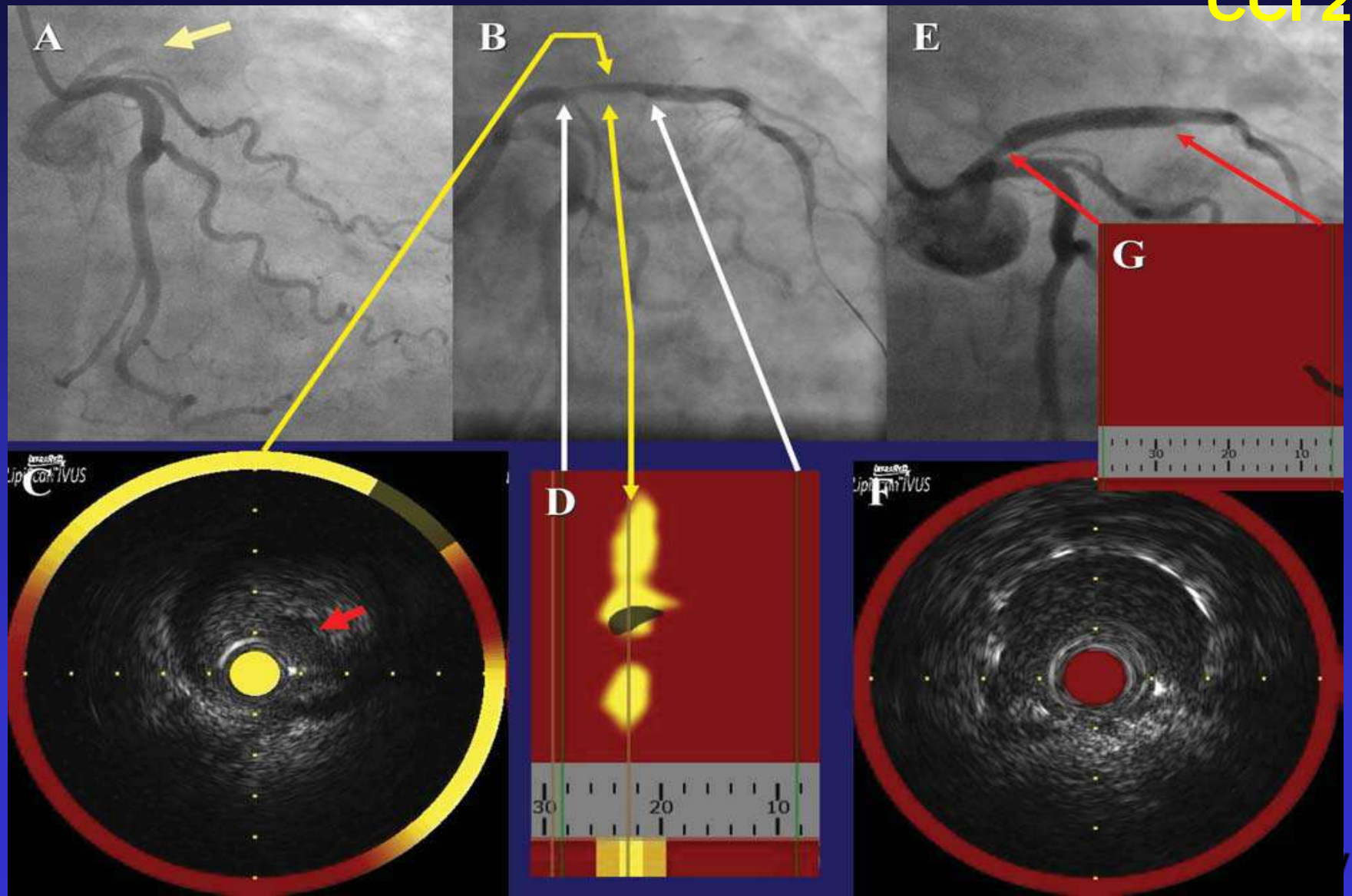
The TCFA was defined as a plaque with lipid content in more than 2 quadrants and the thinnest part of a fibrous cap measuring less than 65 μm by histology.

The cap thickness is measured from the surface of the lumen to the portion just starting the attenuation

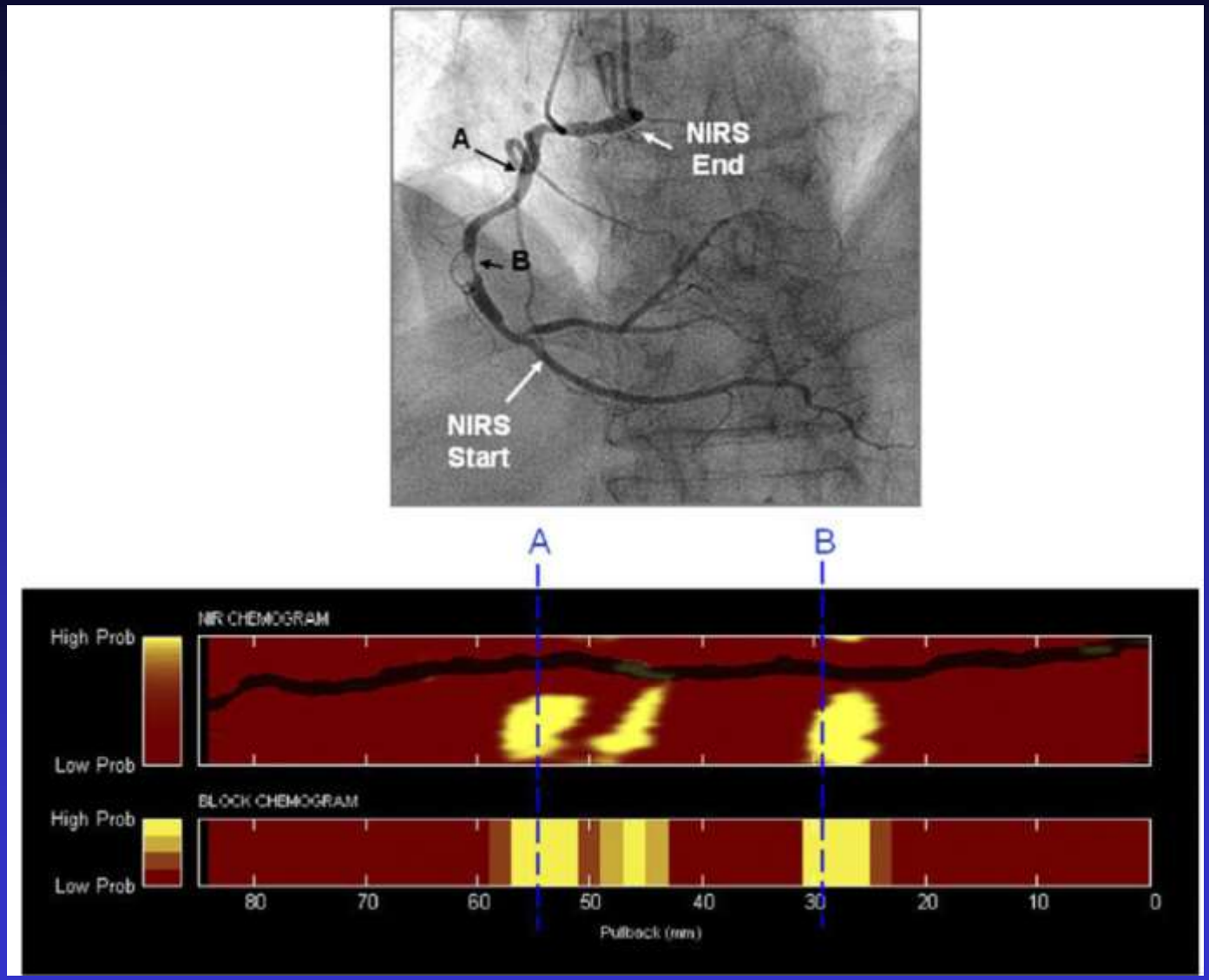


NIR IVUS findings pre and post stenting for STEMI

Madder et al, CCI 2012

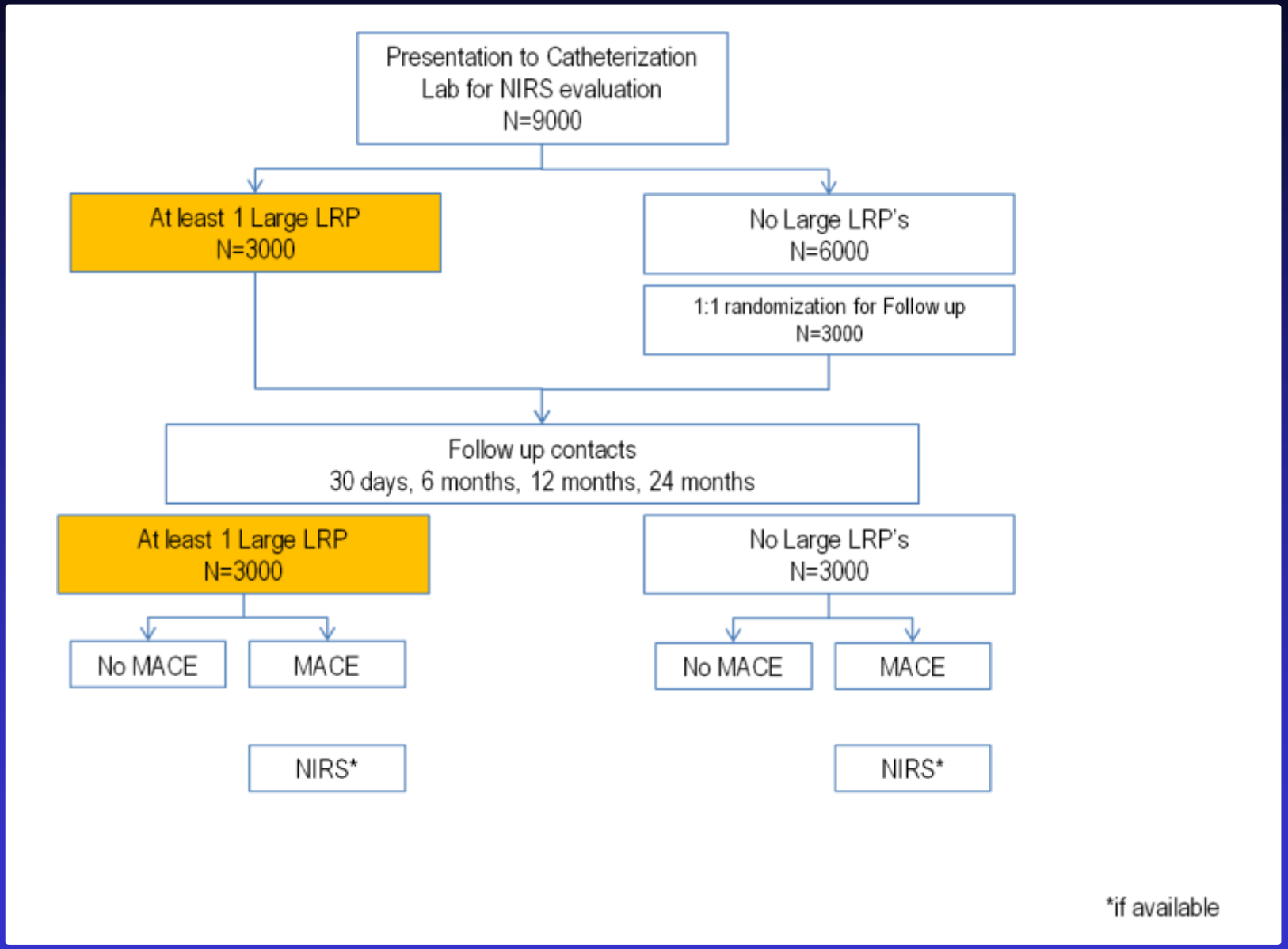


Near-infrared Spectroscopy (SPECTACL Study)



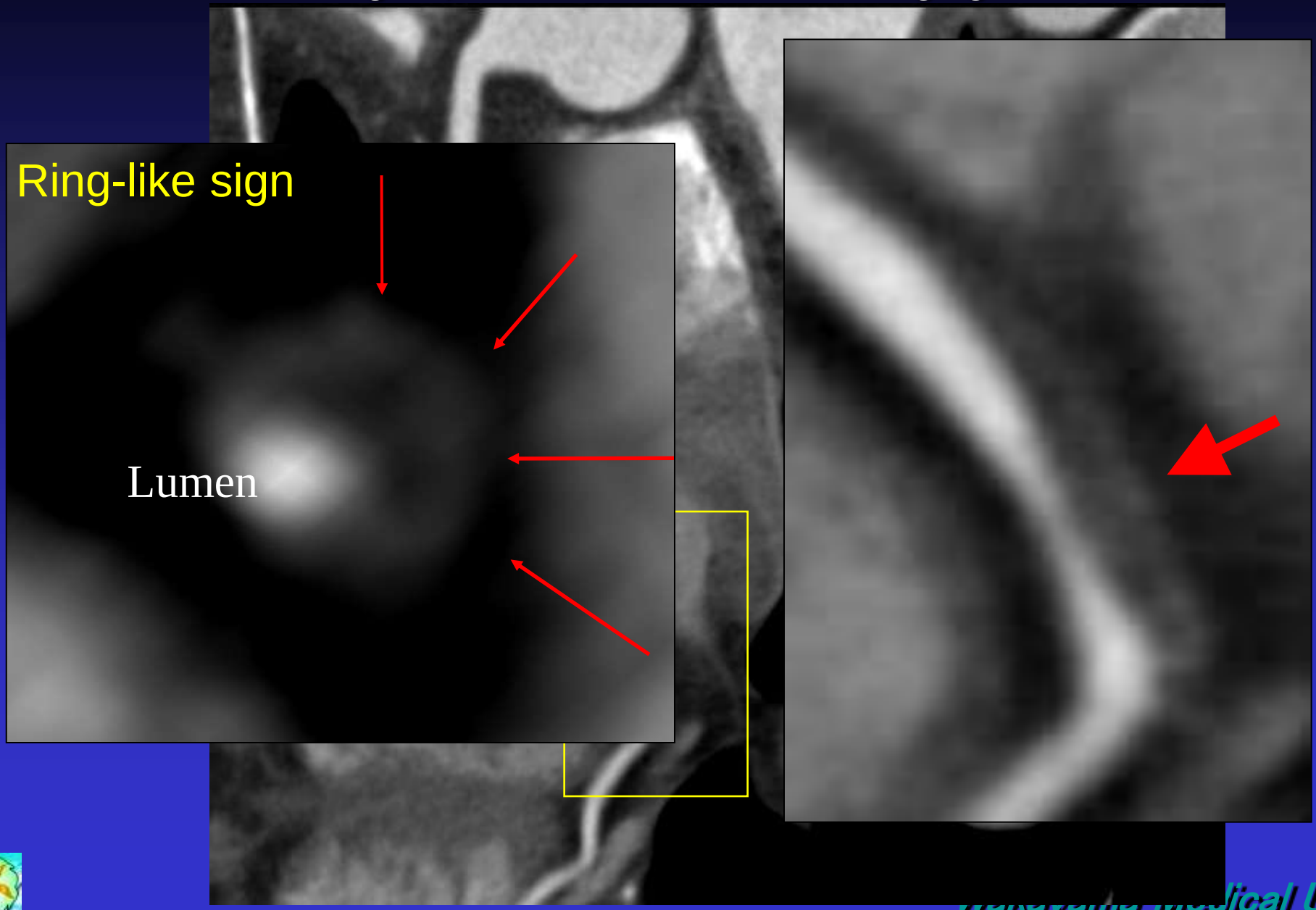
(Waxman S, et al. J Am Coll Cardiol Img 2009;2:858-868)

Lipid-rich Plaque Predictive Study



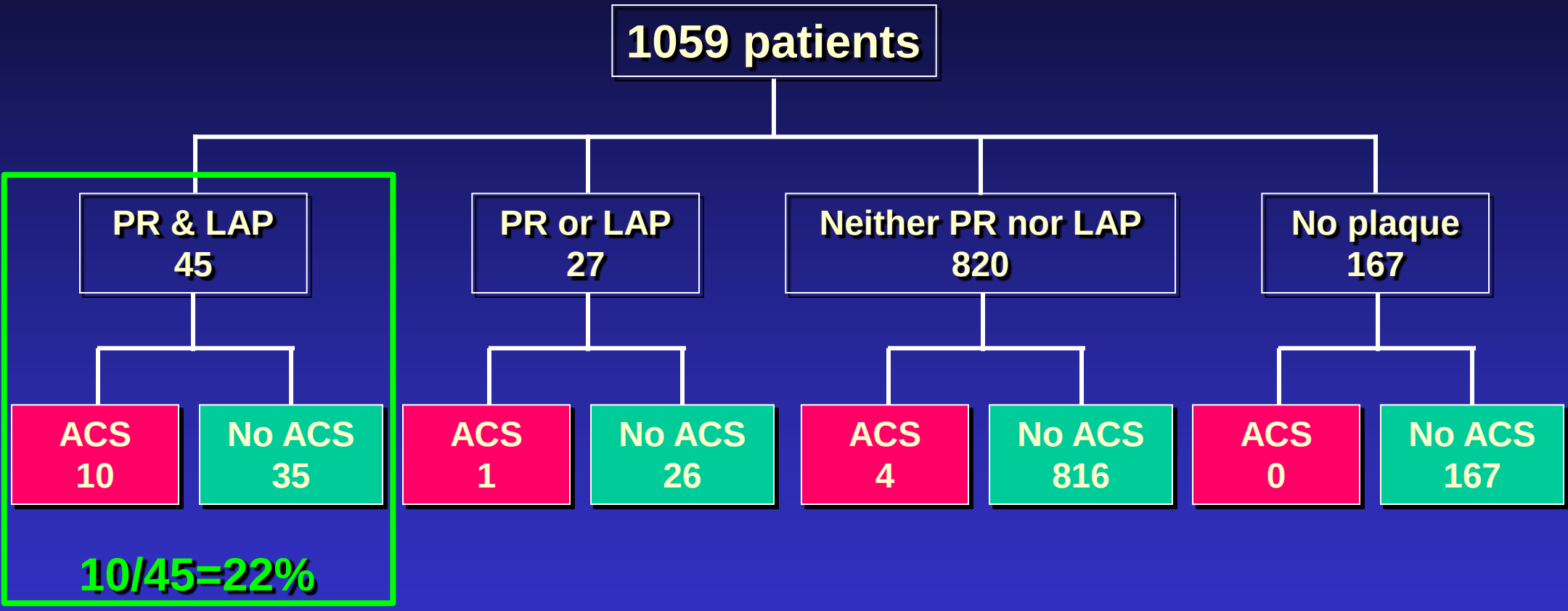
Ring-like Sign and TCFA

Kashiwagi M, et al. JACC Cardiovasc Imaging 2: 1412-1419, 2009



Patient population & event

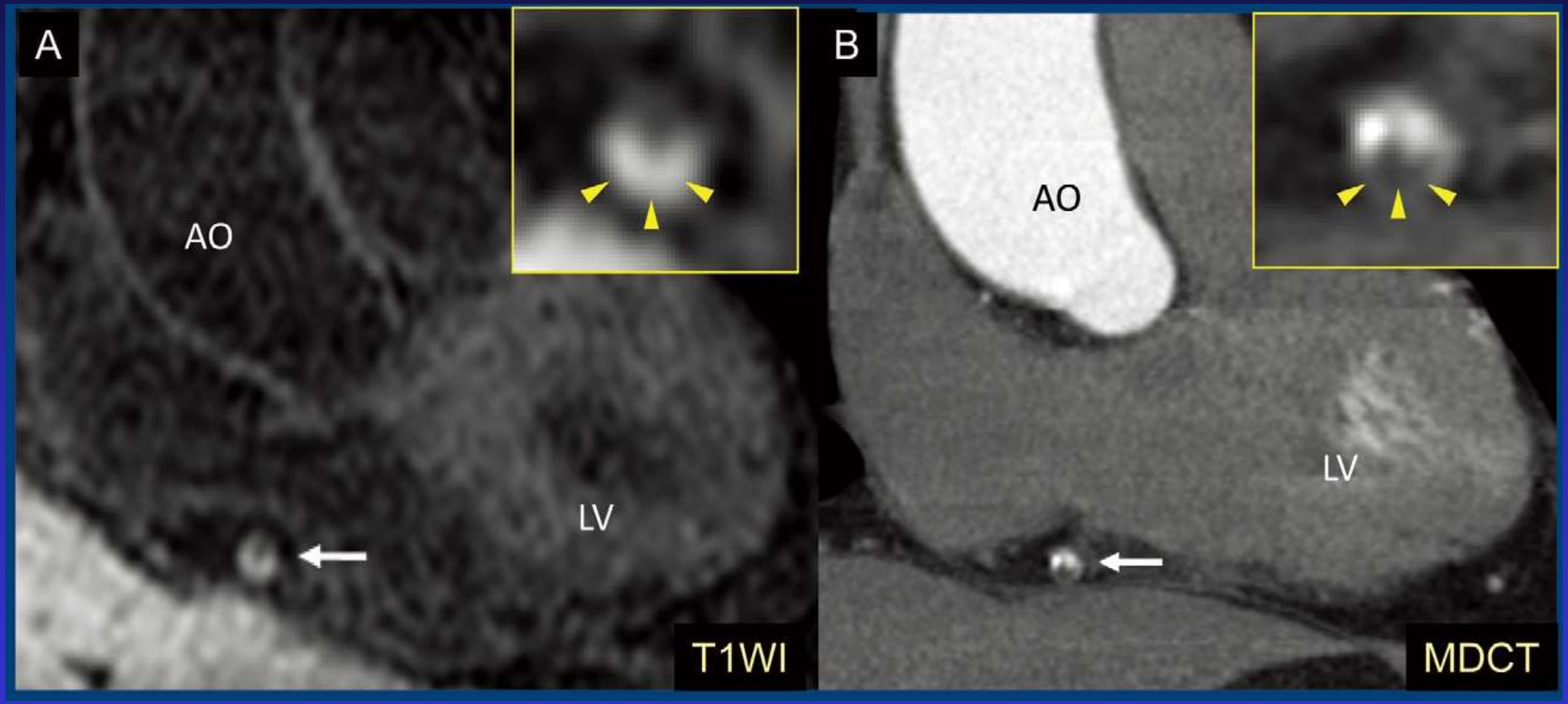
Motoyama S, et al. J Am Coll Cardiol 54: 49-57, 2009



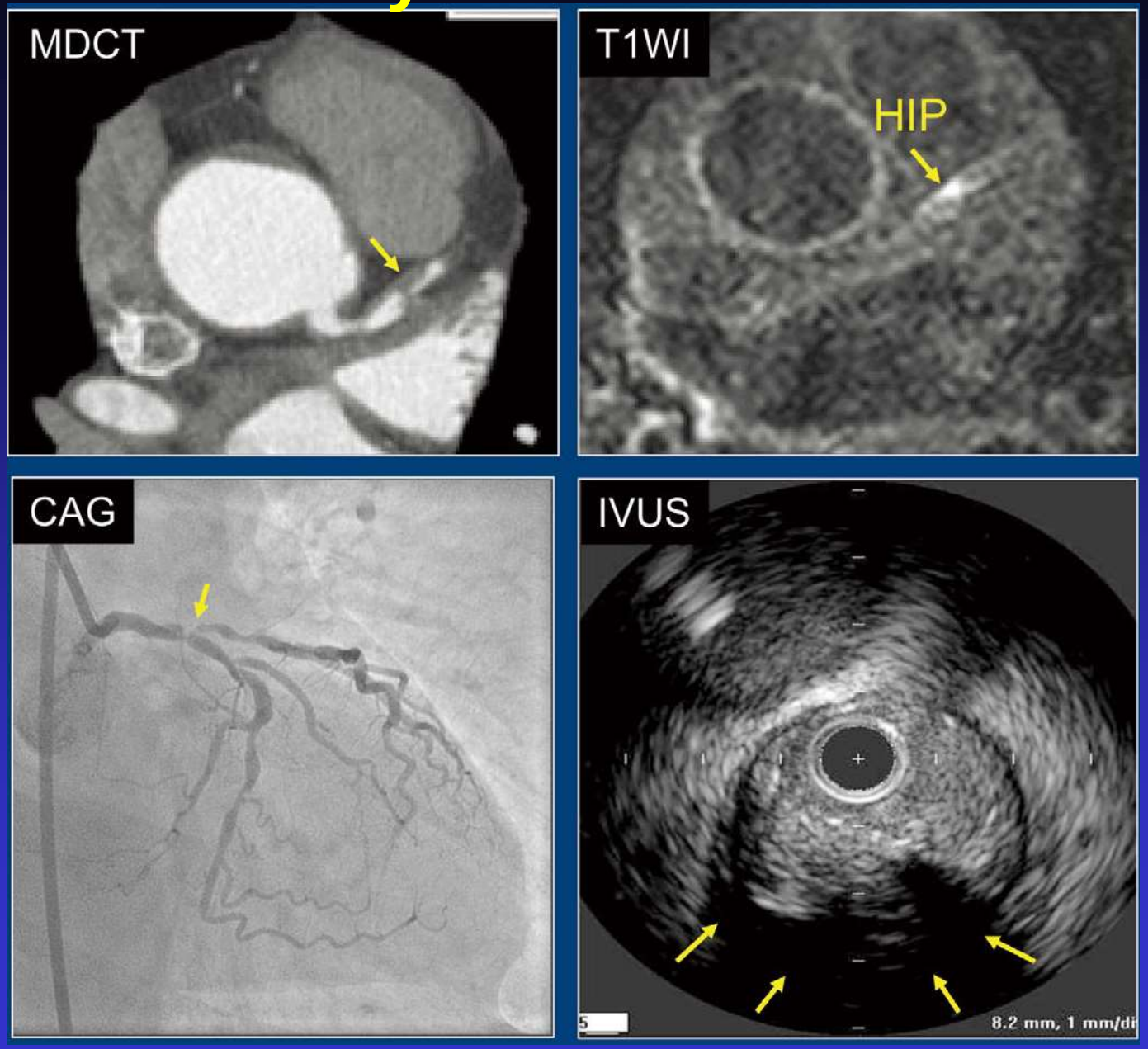
PR: positive remodeling
LAP: low-attenuation plaque

HIP by T1-enhanced MRI

(Noguchi T, et al. Circ J 2013;77:1975-1983)



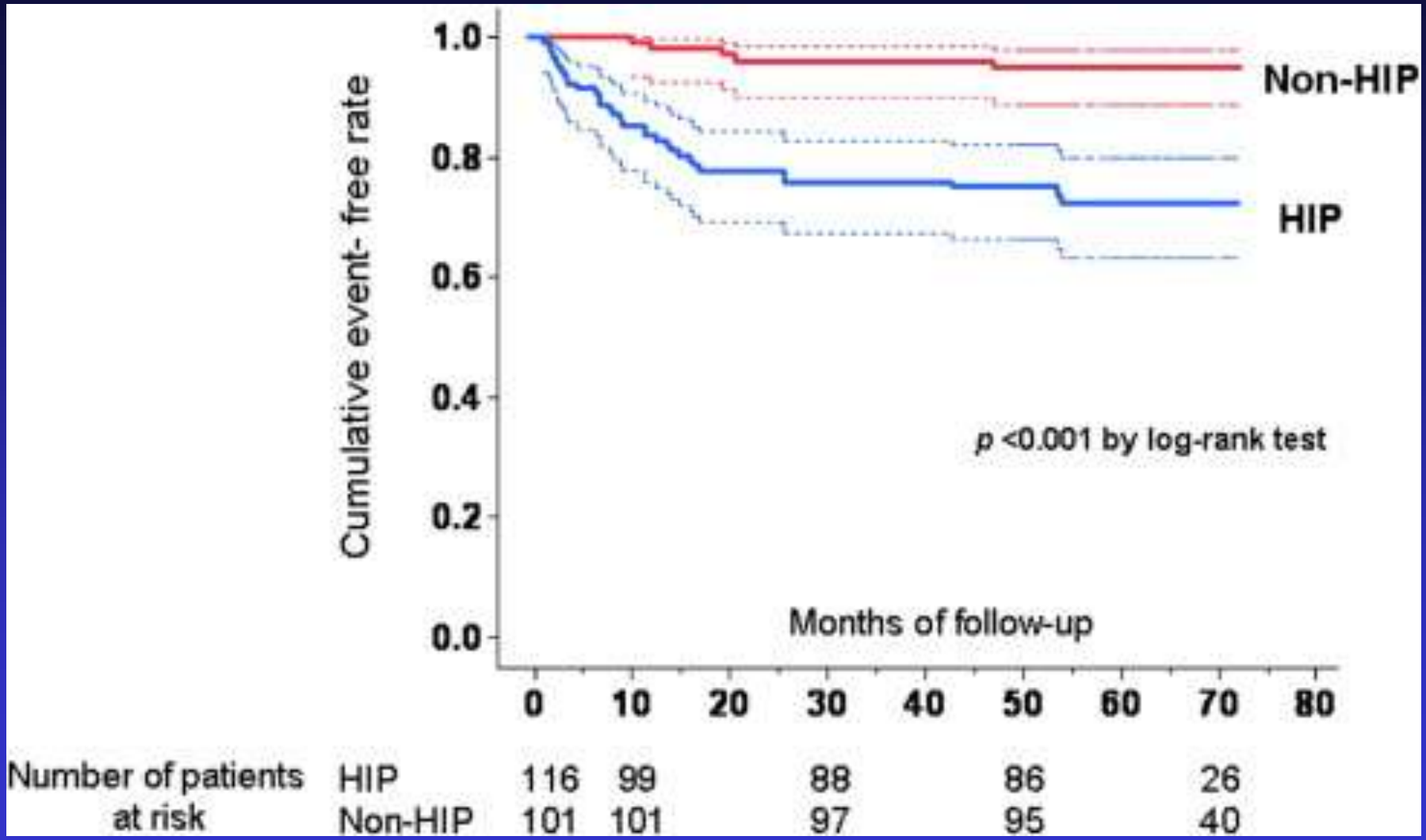
HIP by T1-enhanced MRI



(Noguchi T, et al. Circ J 2013;77:1975-1983) Wakayama Medical University

Coronary Event during 72 months f/u

217 pts with stable coronary artery disease



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- EPA
- Other vascular protective agents (aspirin, β-blocker, ACE-I, ARB, etc.)

Local approach (Plaque sealing) to vulnerable plaque

- Bio-absorbable scaffold (BVS) = PREVENT study, PROSPECT II
- DEB
- Others

Summary

Recurrent Event After ACS: Why It Happen & How to Stop IT?

- Recurrent events represent one fourth of ACS because plaque instability would be a pan-vascular process of vulnerable plaques.
- To reduce the recurrent events after ACS, there are two approaches including systemic and/or local therapies.
- By using various imaging modalities, there are many evidences demonstrated the effectiveness of high dose statin for reducing the recurrent event after ACS as a systemic therapy.
- To promote local treatment by plaque sealing, prediction of future events should be very important, and various imaging modalities in addition to bio-markers would be a promising method.
- Randamized prospective trials such as PREVENT study and PROSPECT II trials would be planning to confirm the advantage of local therapy by plaque sealing for preventing recurrent events after PCI.