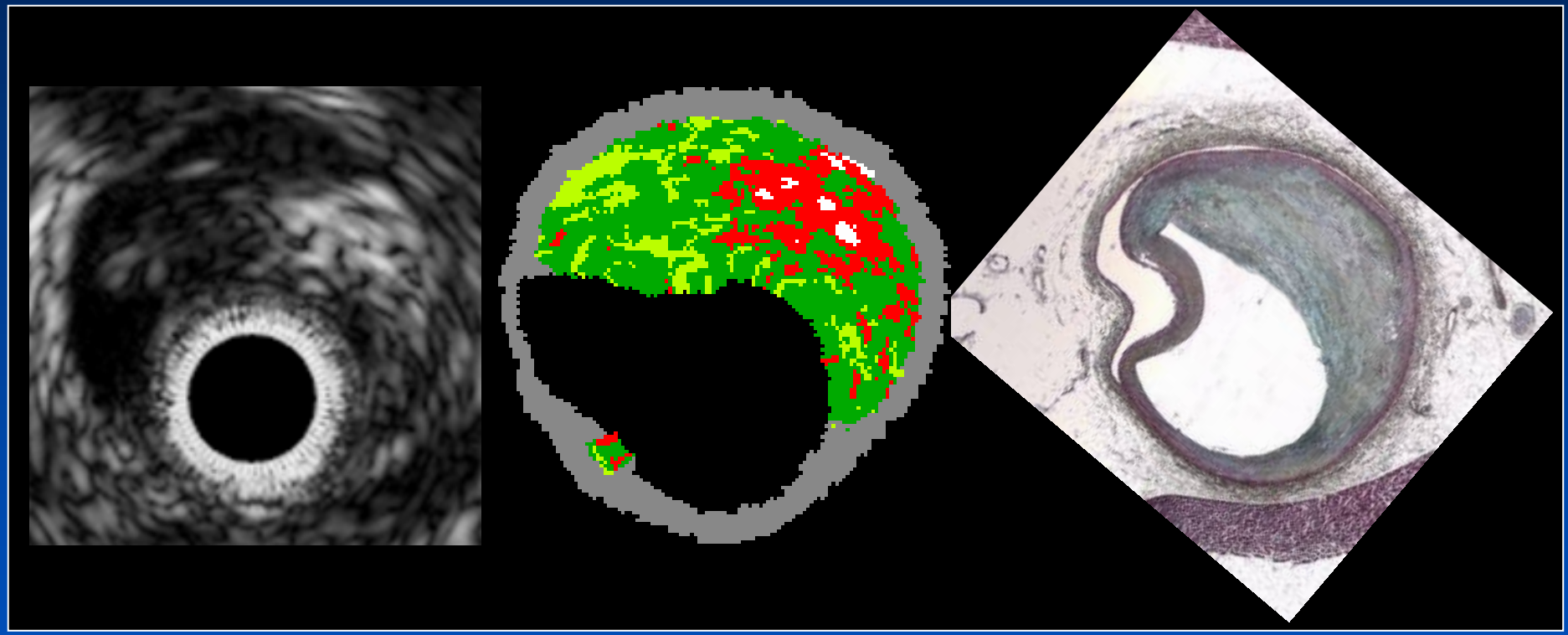
Use of VH-IVUS Findings as Surrogate Marker for Anti-Atherosclerotic Drug

Duk-Woo Park, MD, PhD

University of Ulsan College of Medicine
Asan Medical Center, *Seoul, Korea*

Virtual Histology -IVUS

In-vivo characterization of plaque composition via advanced spectral analysis



Fibrous; Fibrofatty; Necrotic core; Dense calcium

Potential VH-IVUS Applicability in Clinical Field

- Risk stratification
- PCI outcomes: acute and long-term
- Plaque Vulnerability
- Surrogate marker for Atherosclerotic Drug

Usefulness of VH-IVUS for risk stratification

"VH findings are well correlated with established risk factors predicting cardiovascular events"

- Known risk factors
  - each of established risk factors for CAD
  - established risk score system (Framingham and Score)
- Abnormal lipid profiles
- Multiple biomarkers (hs-CRP, tPA, etc)

Potential VH-IVUS Application improving PCI outcomes

- Find the origin of the problem (the culprit of the culprit) and large NC area
- Assess the risk of plaque protrusion
- Assess the risk of distal embolization or need for appropriate lesion preparation (dense calcified necrotic core and fibrofatty rich lesions)

Potential VH-IVUS Application to detect vulnerable plaques

- Plaque vulnerability assessed by VH-IVUS correlated well with clinical vulnerability (AMI>UA>SA)
- VH IVUS data correlates with known sites for plaque accumulation and ruptures.
- More data are needed to assess the relationship between current vulnerability by VH-findings and future coronary events.

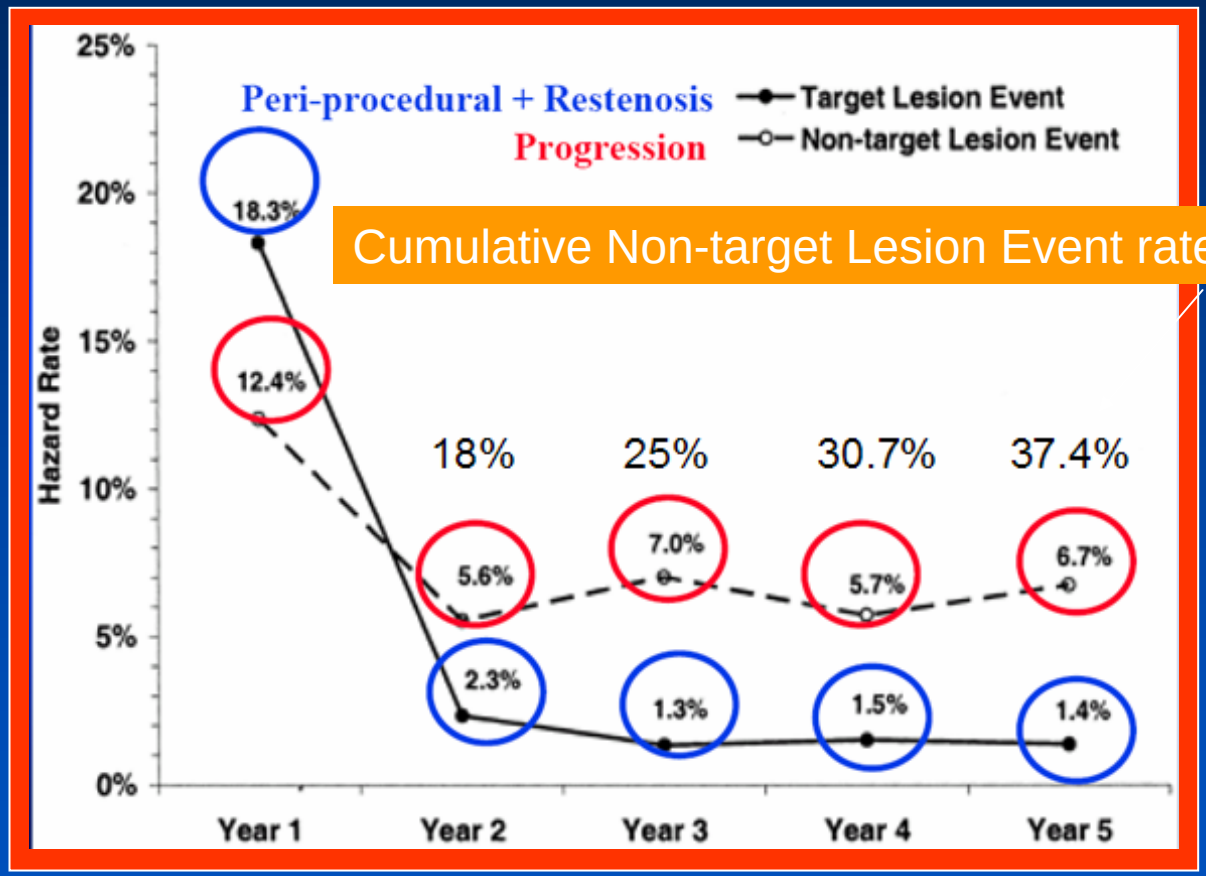
Potential VH-IVUS Applicability in Clinical Field

- Risk stratification
- PCI outcomes: acute and long-term
- Plaque Vulnerability
- ***Surrogate marker for Atherosclerotic Drug***

Cumulative non-target lesion event rate is higher than target lesion event rate after stenting

Optimal PCI

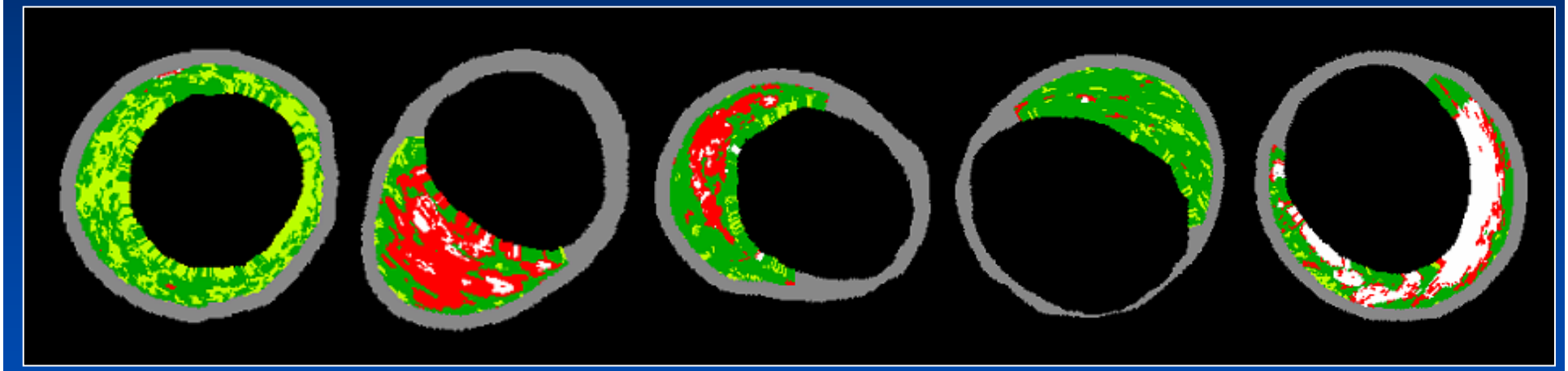
5-year outcomes after stenting: HCRI database



Cutlip et al. Circulation 2004; 110: 1226–1230.

Serial Change in Plaque Type assessed VH-IVUS

Non-culprit lesion phenotype in 106 patients (201 lesions with plaque burden >40%) from the Global VH Registry with baseline and 8-month follow-up VH analysis



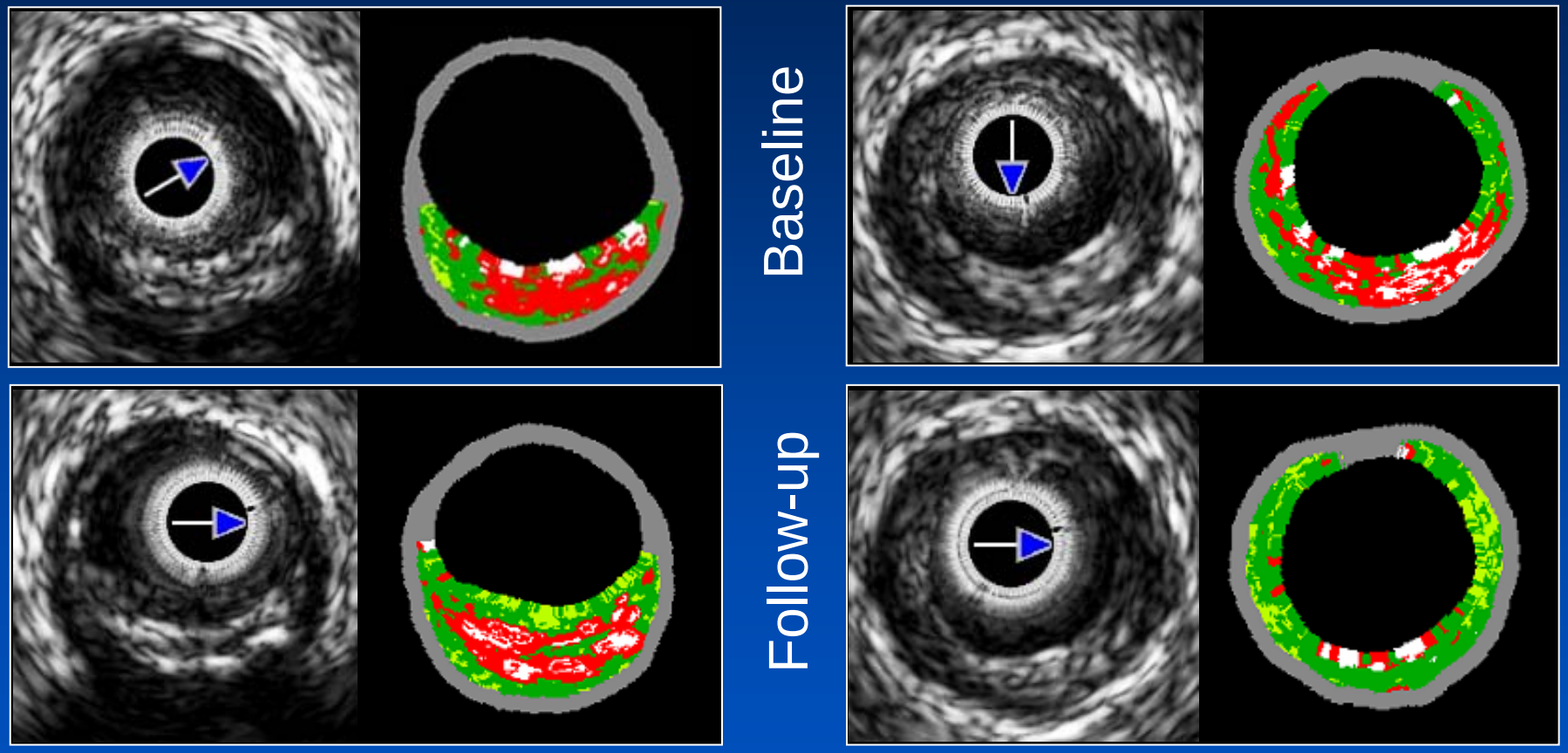
Pathological intimal thickening (PIT)	Thin-cap fibroatheroma (TCFA)	Thick-cap fibroatheroma (ThFA)	Fibrotic	Fibrocalcific

Kubo et al. AHA 2008

Serial Change in Plaque Type assessed VH-IVUS

Baseline (n=201)	Follow-up (n=201)					
		PIT (n=52)	TCFA (n=15)	ThFA (n=109)	Fibrotic (n=24)	Fibrcalcific (n=21)
	PIT (n=64)	48	6	10	0	0
	TCFA (n=21)	0	5	14	2	0
	ThFA (n=94)	0	4	85	4	1
	Fibrotic (n=22)	4	0	0	18	0
	Fibrocalcific (n=20)	0	0	0	0	20

Serial Change in Plaque Type assessed VH-IVUS

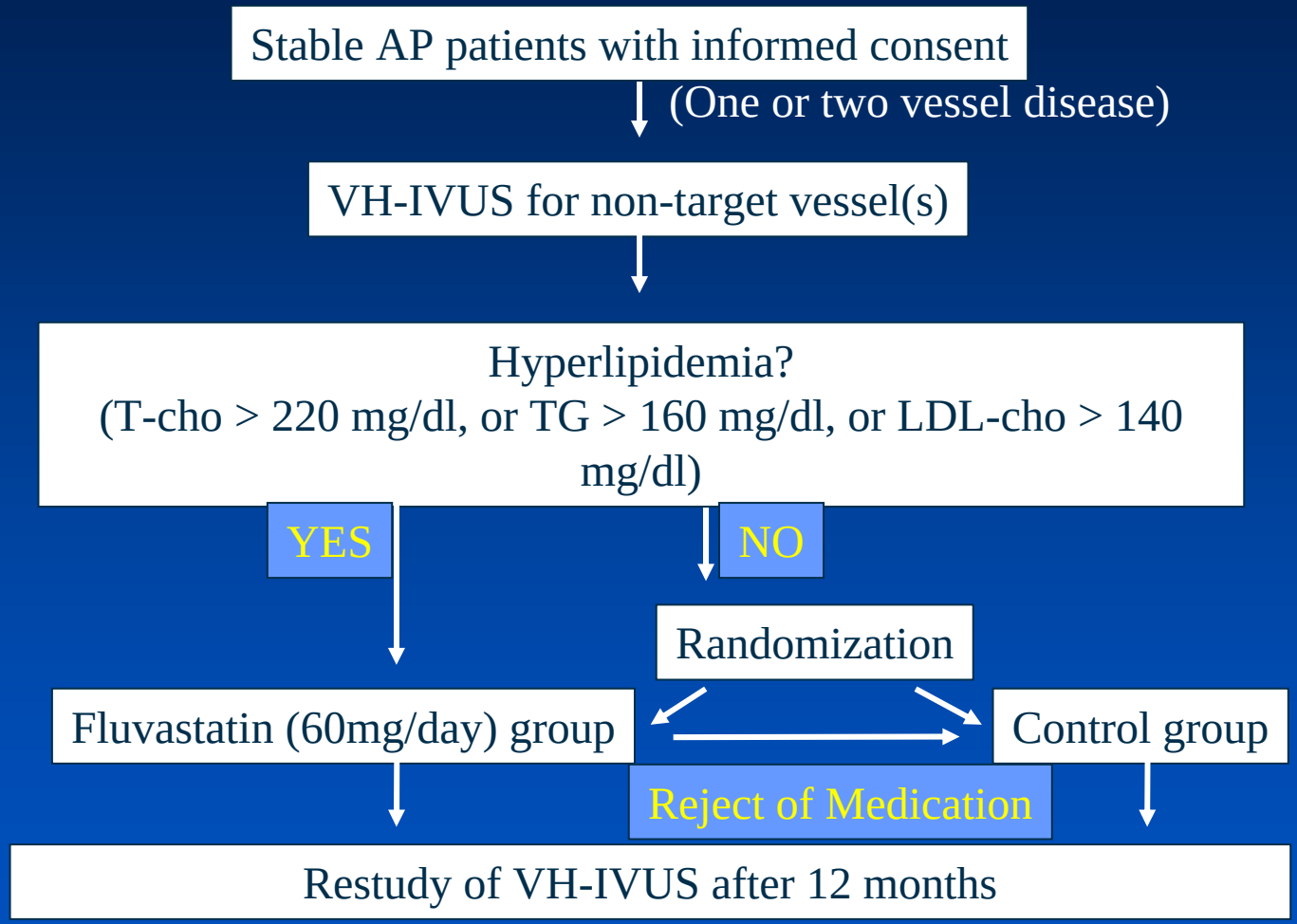


TCFA → ThFA

TCFA → Fibrocalcific

Serial Plaque Change Studies Using VH-IVUS Findings as Surrogate Marker for Anti-Atherosclerotic Drug

Effect of Fluvastatin on progression of coronary atherosclerotic plaque evaluated by VH-IVUS



Kenya Nasu, M.D., Toyohashi Heart Center, AHA 2007

Serial VH IVUS FU

	Fluvastatin	Control	P value
Ave. Fibrous CSA, mm^2			
Baseline	3.18±1.50	2.46±1.20	0.04
Follow-up	2.38±1.30*	3.34±1.41*	0.008
Ave. Fibro-fatty CSA, mm^2			
Baseline	1.51±0.83	0.97±0.44	0.004
Follow-up	0.68±0.52*	1.32±0.84*	0.0008
Ave. Necrotic CSA, mm^2			
Baseline	0.50±0.45	0.43±0.28	0.04
Follow-up	0.51±0.33	0.65±0.51*	0.24
Ave.Dense calcium CSA, mm^2			
Baseline	0.18±0.16	0.24±0.20	0.24
Follow-up	0.24±0.20	0.37±0.31*	0.07

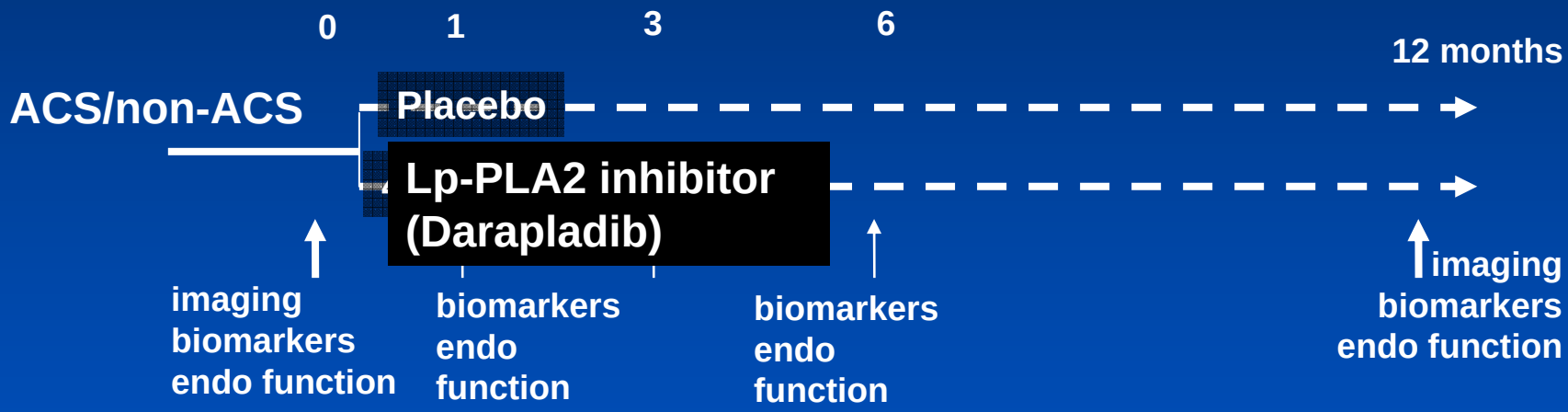
"Fluvastatin may halt the progression of coronary atherosclerosis by the reduction of fibro-fatty."

IBIS 2 (Europe)

(Integrated Biomarkers and Imaging Study)

Overall Design

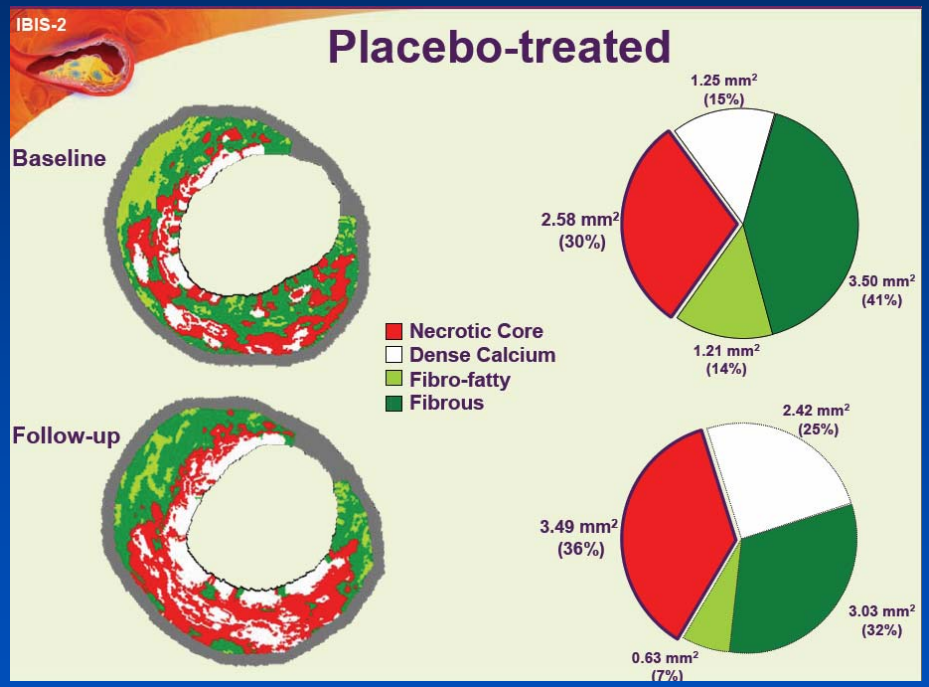
Multicenter, randomized, double-blind, parallel-group, placebo-controlled treatment trial in 330 patients with non-culprit CAD

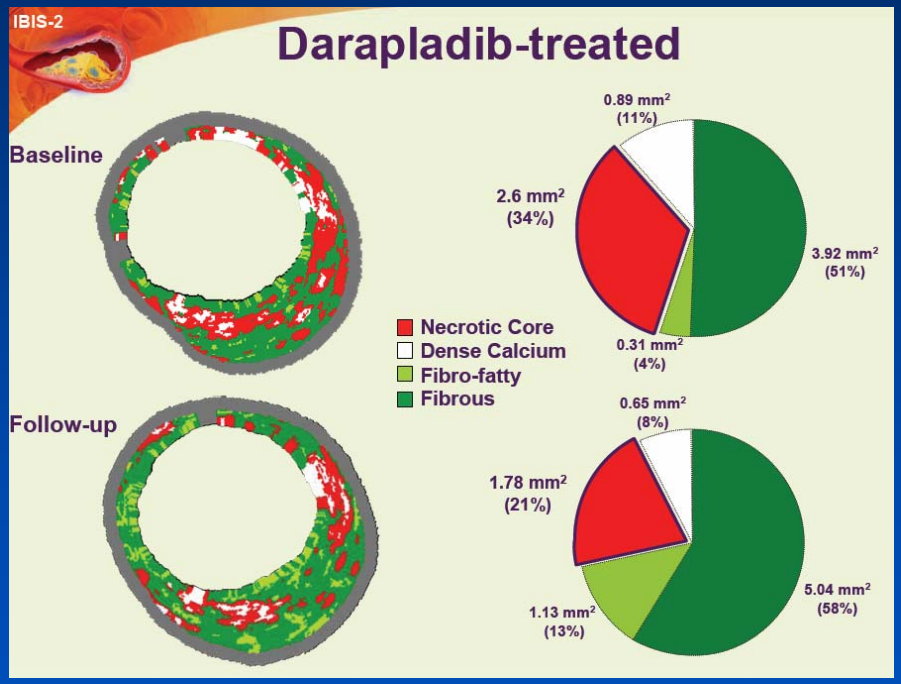


All patients on standard medical therapy !!!

Serruys PW et al. Circulation 2008; 118: 1172–82.

IBIS-2: Effects of the direct Lp-PLA$_2$ inhibitor darapladib vs placebo on human coronary atherosclerotic plaque.

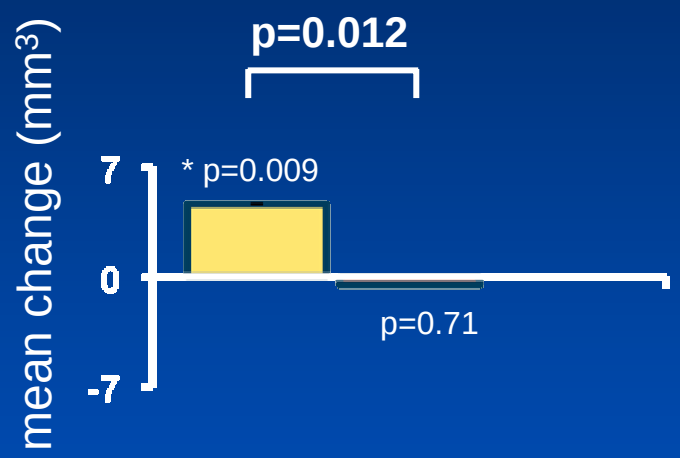




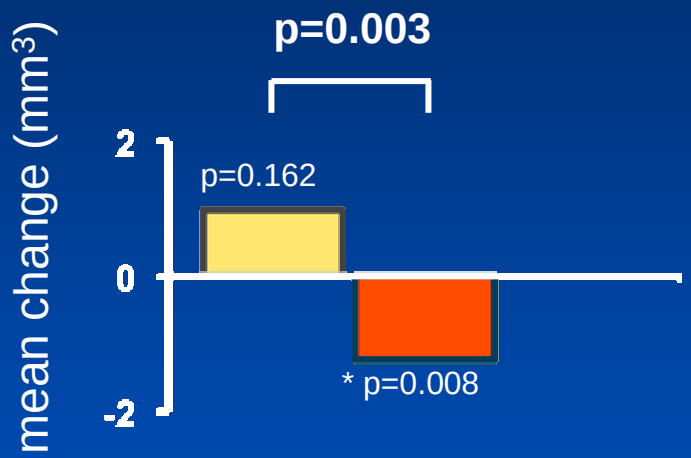
Serruys PW et al. Circulation 2008; 118: 1172–82.

Plaque Composition
by IVUS - VH
change from baseline in necrotic core volume

Entire region of interest
[mean 48 mm]



The worst 10 mm subsegment

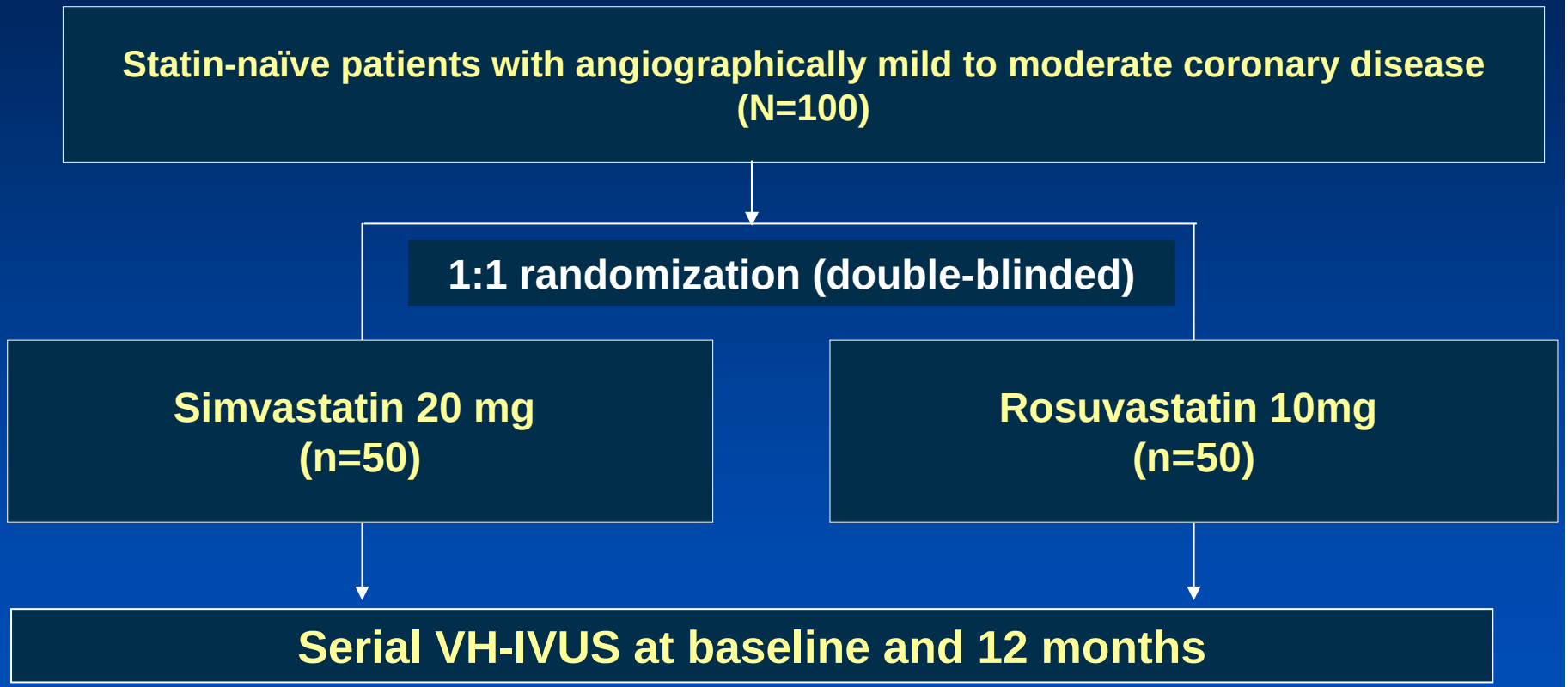


placebo (plus standard of care) n=110
darapladib 160 mg (plus standard of care) n=129

"Despite standard-of-care medical Treatment, NC continued to expand in placebo group, but darapladib prevented NC expansion"

AMC Data

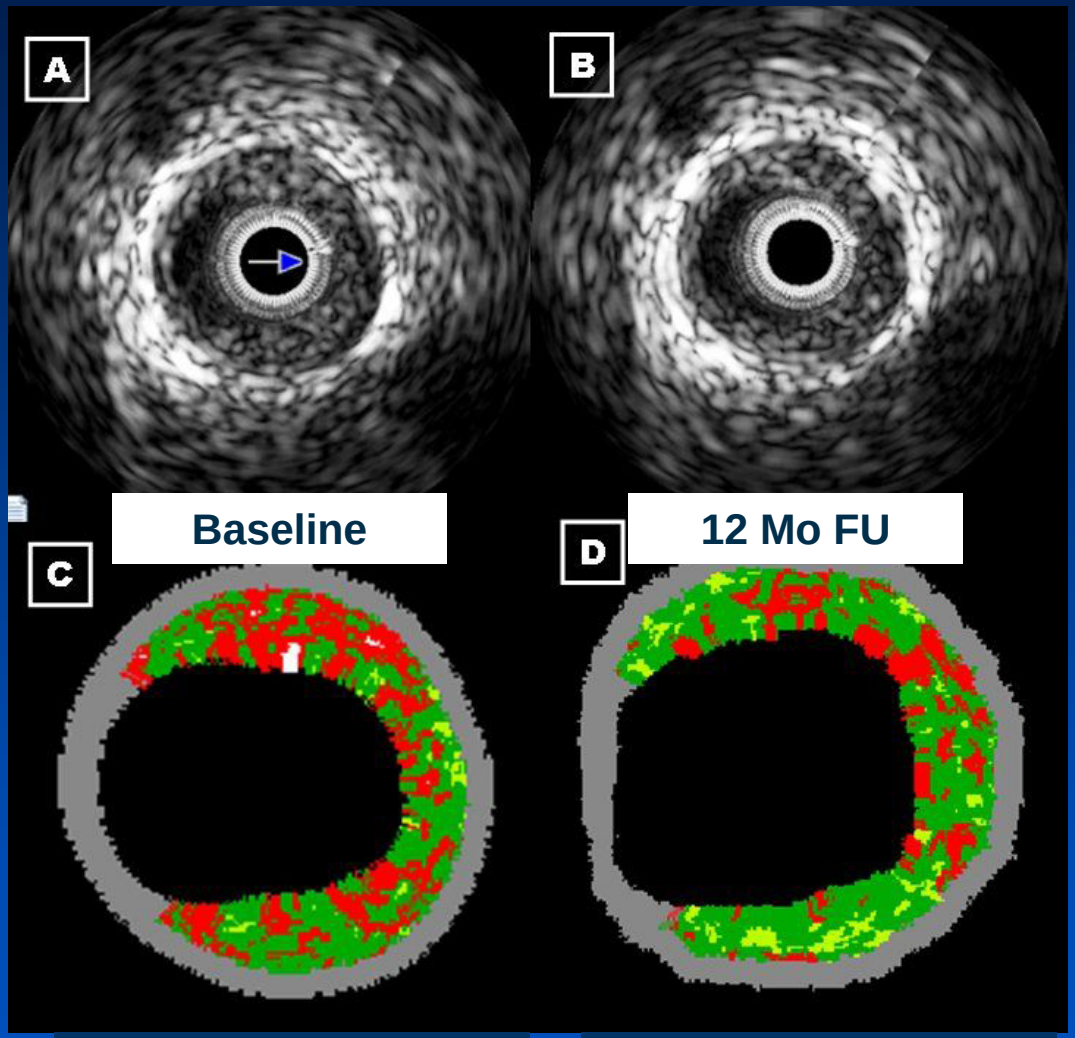
Effects of Statin Treatments on Coronary Plaque Stabilization Assessed by Volumetric VH-IVUS



Hong et al. JACC Interv 2009, In press

AMC Data

Representative Case: Rosuvastatin group



Hong et al. JACC Interv 2009, In press

Baseline characteristics

AMC Data

	Simvastatin (N=50)	Rosuvastatin (N=50)	P
Age (years)	58 ± 10	59 ± 9	0.7
Male gender	40 (80)	37 (74)	0.5
Hypertension	22 (44)	24 (48)	0.7
Diabetes mellitus	13 (26)	11 (22)	0.6
Cigarette smoking	19 (38)	19 (38)	1.0
Acute coronary syndrome	20 (40)	23 (46)	0.5
C-reactive protein (mg/dL)			
Baseline	0.17 ± 0.22	0.21 ± 0.20	0.4
12-month follow-up	0.12 ± 0.12	0.09 ± 0.07	0.22
Changes	-0.05 ± 0.22	-0.12 ± 0.19	0.12

Hong et al. JACC Interv 2009, In press

Baseline characteristics

AMC Data

	Simvastatin (N=50)	Rosuvastatin (N=50)	P-value
Lipid profiles at baseline			
Total cholesterol (mg/dL)	191 ± 34	189 ± 27	0.7
LDL cholesterol (mg/dL)	119 ± 30	116 ± 28	0.6
HDL cholesterol (mg/dL)	43 ± 10	43 ± 11	0.8
Triglycerides (mg/dL)	149 ± 69	152 ± 75	0.9
Lipid profiles at 12-month follow-up			
Total cholesterol (mg/dL)	142± 22	128 ± 20	0.002
LDL cholesterol (mg/dL)	78 ± 20	64 ± 21	0.002
HDL cholesterol (mg/dL)	48 ± 12	52 ± 14	0.127
Triglycerides (mg/dL)	115 ± 50	107 ± 96	0.6

Hong et al. JACC Interv 2009, In press

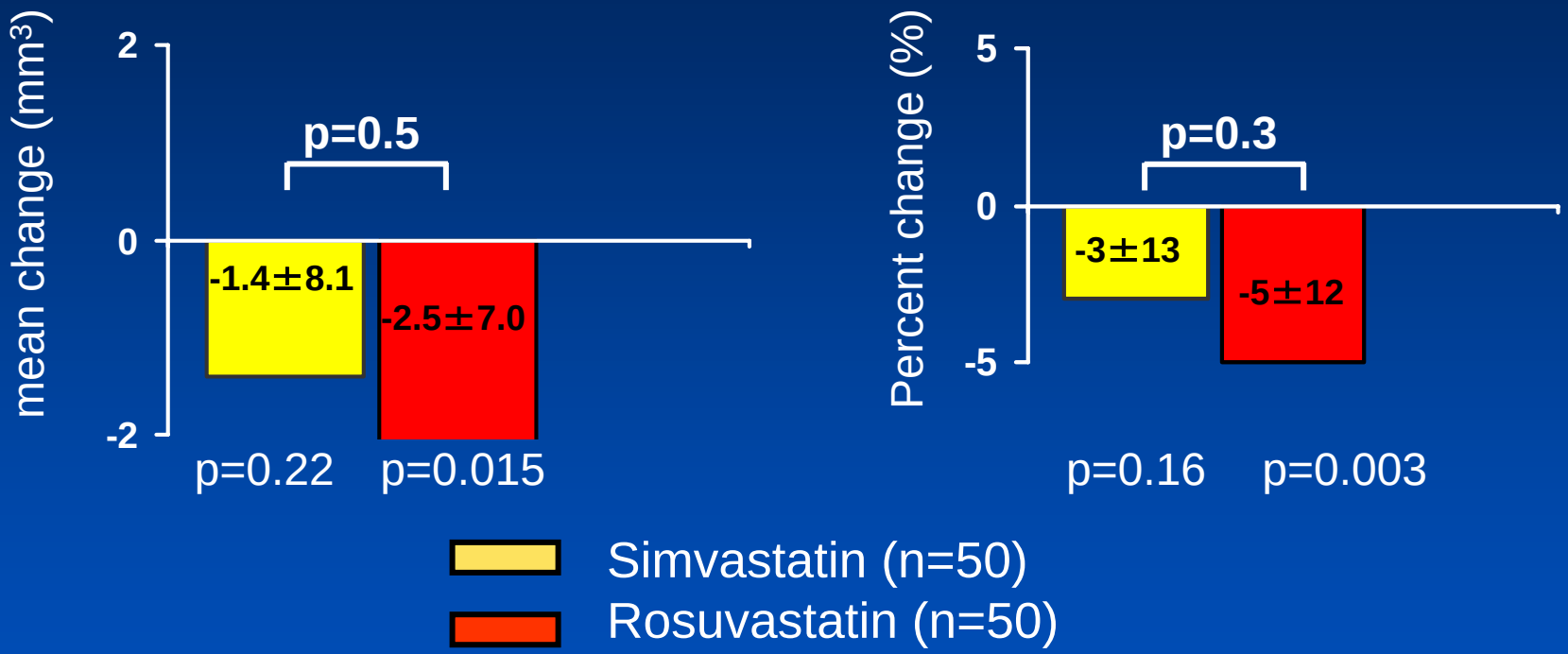
Plaque Composition

AMC Data

by IVUS - VH

change from baseline in necrotic core volume

The worst 10 mm Segment

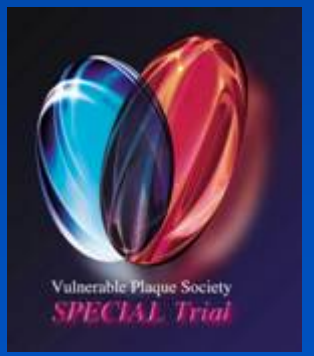


There was no significant treatment effect among statin groups. However, by intra-group serial analysis, there was significant reduction of NC in the rosuvastatin group.

Hong et al. JACC Interv 2009, In press

SPECIAL
: clinically silent plaque progression

- **PIs: Dr Tadanori Aizawa and Dr Etsuo Tsuchikane**
- Multicenter study on the safety of **3-vessel VH-IVUS interrogation, clinical event rate and silent plaque progression of angiographically intermediate lesions in ACS patients**
- Angiographic and IVUS follow-up at 1 year
- All sites: Japan
- n=300



ATLANTA

Assessment of Tissue characteristics, Lesion morphology and hemodynamics by Angiography with fractional flow reserve, intravascular ultrasound and virtual histology and Non-invasive computed Tomography in Atherosclerotic plaques

the correlation with VH IVUS and FFR with a non-invasive MSCT

- PI Dr S Voros
- Single center registry with one year clinical outcome (MACE) of intermediate lesions by angiogram and diagnostic correlation with further assessment by FFR, MSCT and grayscale and VH IVUS
- N=300

JUPITOR Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 20, 2008 VOL. 359 NO. 21

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

Paul M Ridker, M.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Robert J. Glynn, Sc.D., for the JUPITER Study Group*

"Suggested Plausible Mechanism of Statin to Reduce Major Cardiovascular Events was Plaque Stabilization"

The STABLE trial

(***ST***atin and ***A***theroma Vulnera***B***i***L***ity ***E***valuation)

: Double-blinded, Prospective, Randomized, Controlled Trial

Statin-naïve patients with angiographically documented mild to moderate coronary disease (Total 312 patients needed)

2:1 randomization (double-blinded)

Rosuvastatin 40mg (n=208)

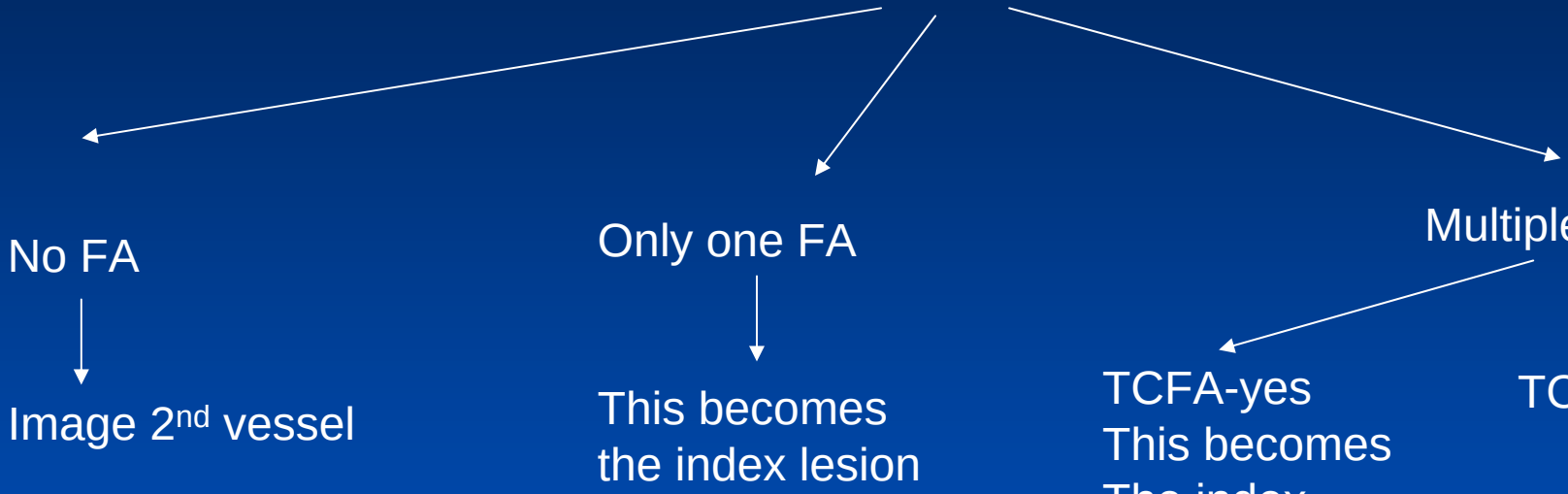
Rosuvastatin 10mg (n=104)

VH-IVUS, Conventional IVUS, and OCT follow-up at 12 months
Clinical follow-up at 12 months

****Primary end point:** % compositional change of coronary plaque from baseline to 12-months follow-up.

STABLE Trial; PI SJ Park, Seoul: Basic concept for Lesion Selection

1. Perform IVUS with VH of "index" vessel - at least prox 50 mm
2. Perform on-site VH IVUS analysis of "index" vessel
3. Identify all FibroAtheromas



4. VH IVUS study sent to core lab to see if index lesion meets enrollment criteria (FA)
   a. If yes, patient is followed for 12 mos and imaging repeated
   b. if no, patient is de-enrolled and a replacement patient sought

- Additional secondary end-points:
  - Delta % NC volume of entire pullback length
  - Analysis of all other lesions (plaque burden >40% in 3 consecutive frames)

Overall Summary

Current Clinical Study Results and Future Study Perspective

- VH Findings showed good correlation with known risk factors, blood biomarker, clinical presentation, and pathologic plaque composition suggested in previous literatures.
- Ongoing clinical study will provide the information regarding the impact of VH-findings on future clinical outcomes (PROSPECT, SPECIAL, ATLANTA)
- VH-IVUS plaque vulnerability can also be used as good surrogate marker for plaque stabilization or regression (IBIS-1, IBIS-2, STABLE trial)