SESSION: Imaging &Physiology

11:10-11:18
April27, 2019
Theater1, Level1

Vulnerable Plaque Imaging: Contrasting the Different Alternatives

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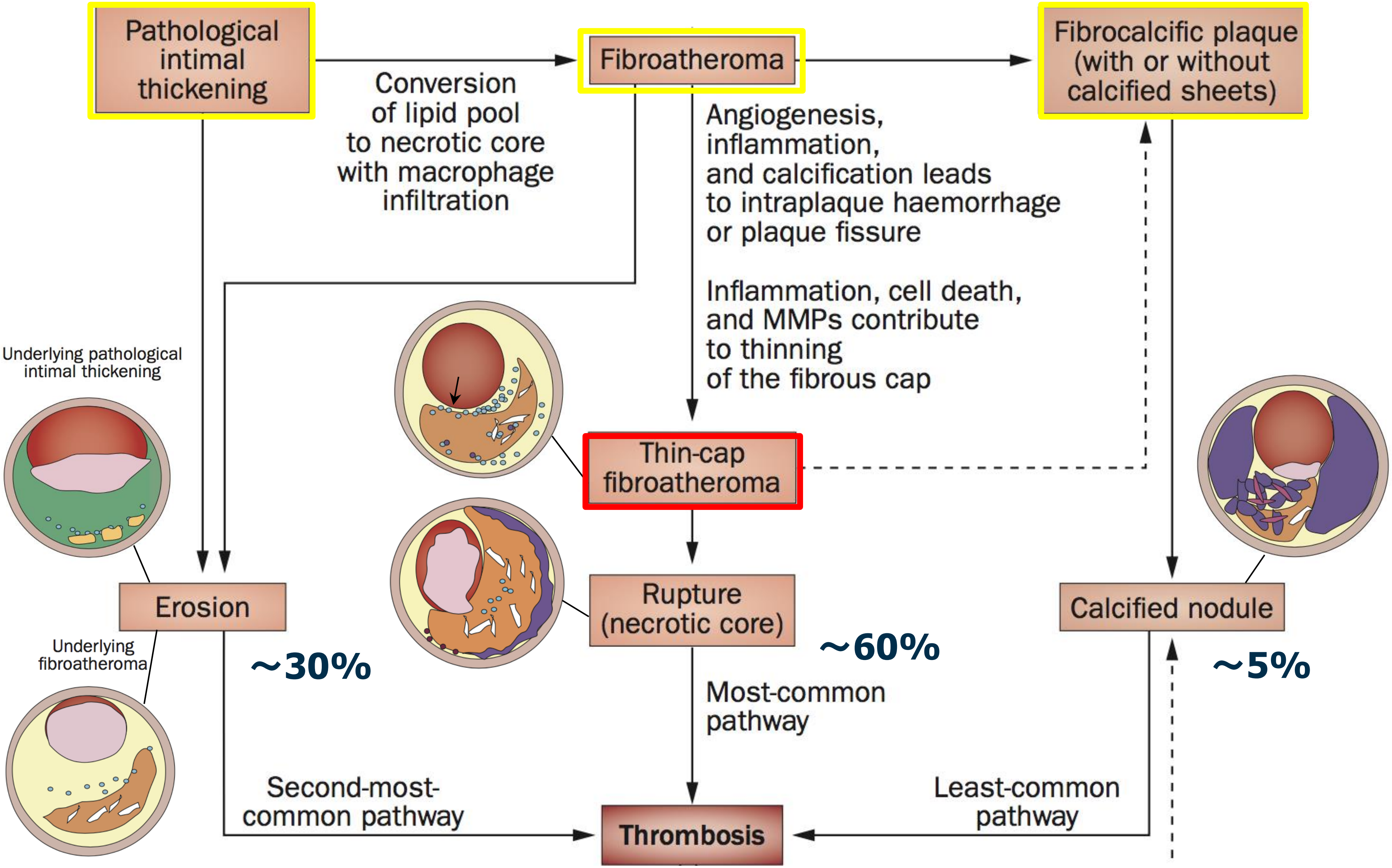
CARDIOVASCULAR SUMMIT TCTAP2019

Disclosure Statement of Financial Interest

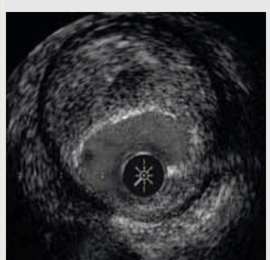
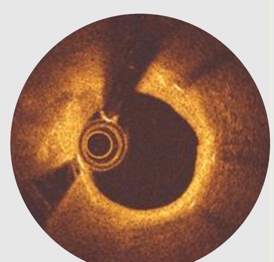
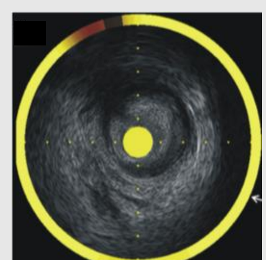
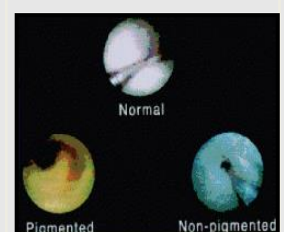
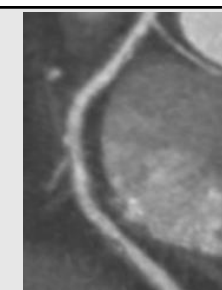
I, Yoshinobu Onuma, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Pathways causing thrombosis in coronary artery disease



Yahagi et al. Nat Rev Cardiol. 2016;13:79-98.
Yahagi et al. Atherosclerosis 2015;239:260–267

Coronary Imaging Modalities

	CAG	IVUS	OCT	NIRS-IVUS	Angio-scopy	CT
Advantages	• Resolution : 200μm • Real-time acquisition • Gold standard	• Resolution: 150-200μm • Direct imaging of coronary plaque • Calcium/ remodeling • Additional tissue typing available (VH, IB-IVUS etc)	• High Resolution: 10-20μm • Documentation of structures close to lumen • Thin cap, macrophage, NC, calcium	• Detection of lipid rich plaques • Combined with IVUS	• Resolution : 20μm • Direct assessment of plaque surface	• Non-invasive • Resolution : 200μm • Concomitant hemodynamic assessment • High Risk Plaque morphology • Total Plaque Burden • Stenosis
Shortcomings	• Contrast use • No plaque imaging	• Relatively Low tissue resolution • (:100 microns) • Slow pullback (0.5-10mm/s)	• Use of contrast medium • Tissue penetration is low (~2mm) • No complete depiction of coronary plaque	• Detection of lipid rich plaques only	Surface assessment only (color, morphology) Only available in some countries (e.g. Japan)	• Use of contrast medium
Image						

IVUS

ORIGINAL ARTICLE

A Prospective Natural-History Study of Coronary Atherosclerosis

Gregg W. Stone, M.D., Akiko Maehara, M.D., Alexandra J. Lansky, M.D., Bernard de Bruyne, M.D., Ecaterina Cristea, M.D., Gary S. Mintz, M.D., Roxana Mehran, M.D., John McPherson, M.D., Naim Farhat, M.D., Steven P. Marso, M.D., Helen Parise, Sc.D., Barry Templin, M.B.A., Roseann White, M.A., Zhen Zhang, Ph.D., and Patrick W. Serruys, M.D., Ph.D., for the PROSPECT Investigators*

The PROSPECT Trial

700 pts with ACS

UA (with ECGΔ) or NSTEMI or STEMI >24º undergoing PCI of 1 or 2 major coronary arteries at up to 40 sites in the U.S. and Europe

Metabolic S.
- Waist circum
- Fast lipids
- Fast glu
- HgbA1C
- Fast insulin
- Creatinine

PCI of culprit lesion(s)

Successful and uncomplicated

Formally enrolled

Biomarkers
- *Hs CRP*
- *IL-6*
- *sCD40L*
- *MPO*
- *TNFα*
- *MMP9*
- *Lp-PLA2*
- *others*

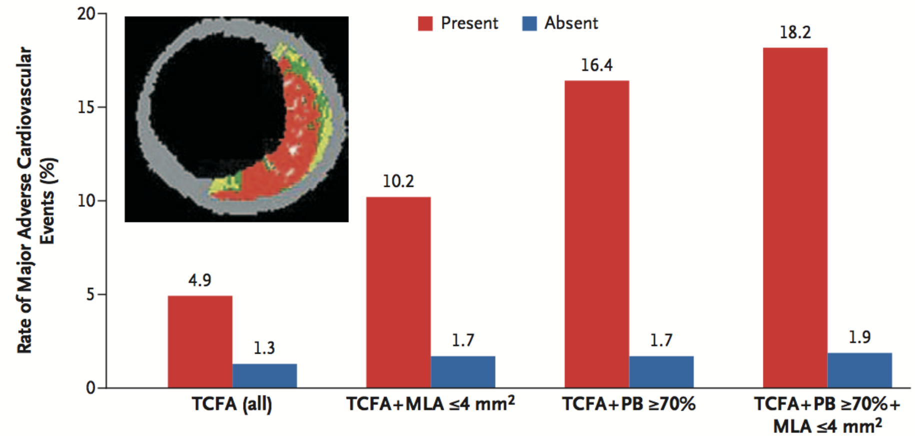
PI: Gregg W. Stone
Sponsor: Abbott Vascular; Partner: Volcano

Cardiovascular Research Foundation

Columbia University Medical Center NewYork-Presbyterian

Table 3. Independent Correlates of Major Adverse Cardiovascular Events Related to Nonculprit Lesions during Follow-up.*

Correlates	Hazard Ratio (95% CI)	P Value
Predictors of patient-level events†		
Insulin-requiring diabetes	3.32 (1.43–7.72)	0.005
Previous percutaneous coronary intervention	2.03 (1.15–3.59)	0.02
Predictors of events at individual lesion sites‡		
Plaque burden ≥70%	5.03 (2.51–10.11)	<0.001
Thin-cap fibroatheroma	3.35 (1.77–6.36)	<0.001
MLA ≤4.0 mm²	3.21 (1.61–6.42)	0.001



	TCFA (all)	TCFA+MLA ≤4 mm²	TCFA+PB ≥70%	TCFA+PB ≥70%+ MLA ≤4 mm²
Lesion hazard ratio (95% CI)	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	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

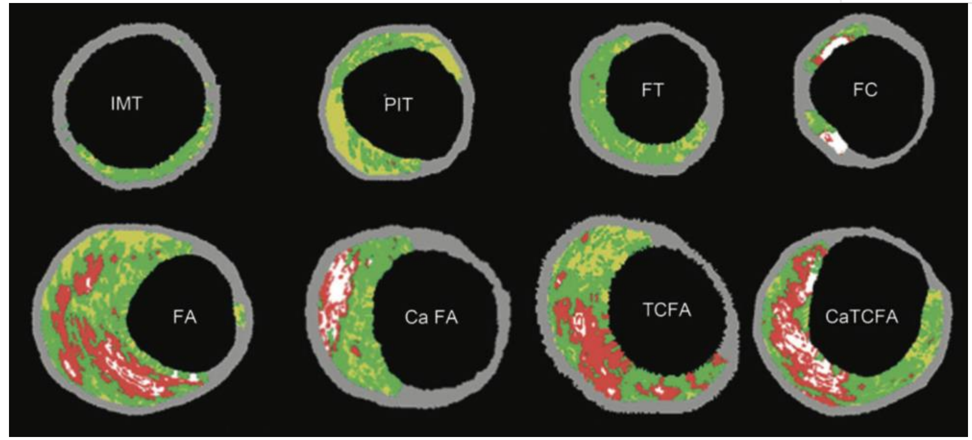
N Engl J Med. 2011 Jan 20;364(3):226-35.

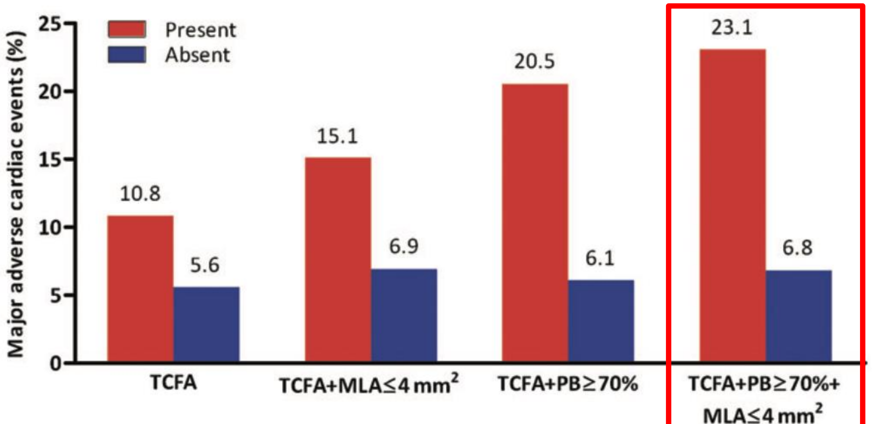
In vivo detection of high-risk coronary plaques by radiofrequency intravascular ultrasound and cardiovascular outcome: results of the ATHEROREMO-IVUS study

Jin M. Cheng†, Hector M. Garcia-Garcia†*, Sanneke P.M. de Boer, Isabella Kardys, Jung Ho Heo, K. Martijn Akkerhuis, Rohit M. Oemrawsingh, Ron T. van Domburg, Jurgen Ligthart, Karen T. Witberg, Evelyn Regar, Patrick W. Serruys, Robert-Jan van Geuns, and Eric Boersma

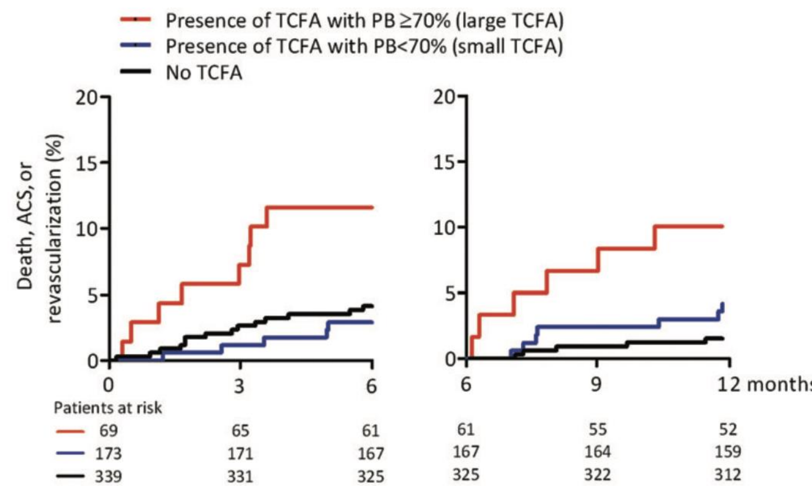
IVUS

- IVUS of a non-culprit coronary artery was performed in 581 patients who underwent coronary angiography for ACS and SAP.





	TCFA		TCFA+MLA≤4 mm²		TCFA+PB≥70%		TCFA+PB≥70%+ MLA≤4 mm²	
95% CI lower limit (%)	6.9	3.1	6.1	4.7	10.9	3.9	9.0	4.6
95% CI upper limit (%)	14.7	8.1	24.1	9.1	30.1	8.3	37.2	9.0
Prevalence (%)	41.7	58.3	10.5	89.5	11.9	88.1	6.0	94.0
No. at risk at 1 year (n)	211	312	50	473	52	471	52	471
Hazard ratio (95% CI)	1.96 (1.08-3.53)		2.26 (1.09-4.69)		3.47 (1.86-6.49)		3.70 (1.72-7.95)	
P-value	0.024		0.025		<0.001		<0.001	



Large TCFA vs. no TCFA *P*=0.011
Small TCFA vs. no TCFA *P*=0.49

Large TCFA vs. no TCFA *P*<0.001
Small TCFA vs. no TCFA *P*=0.033

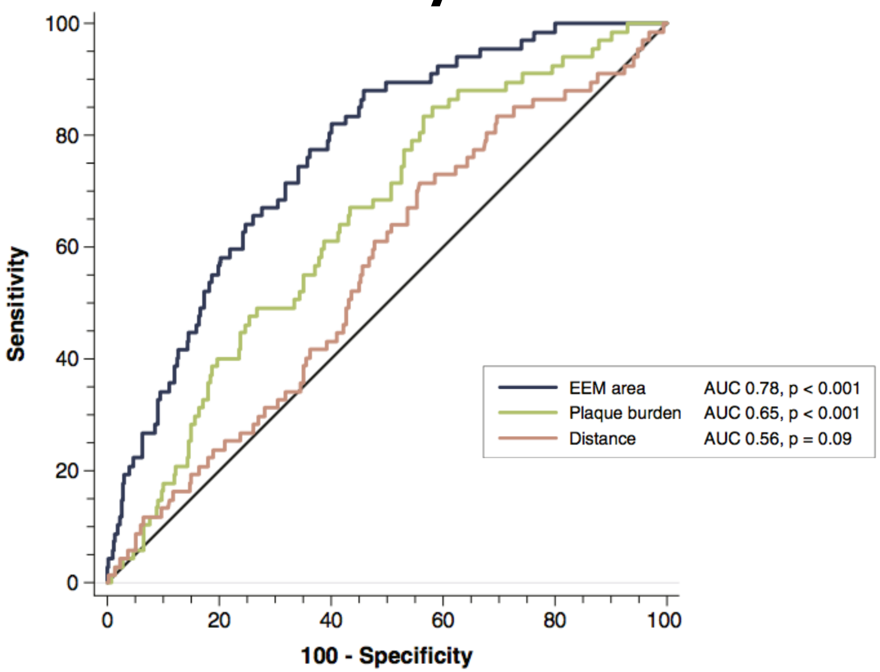
Eur Heart J. 2014 Mar;35(10):639-47.

Predictors of Plaque Rupture Within Nonculprit Fibroatheromas in Patients With Acute Coronary Syndromes

The PROSPECT Study

Bo Zheng, MD,*†‡ Gary S. Mintz, MD,† John A. McPherson, MD,§ Bernard De Bruyne, MD, PhD,|| Naim Z. Farhat, MD,¶ Steven P. Marso, MD,# Patrick W. Serruys, MD, PhD,** Gregg W. Stone, MD,*† Akiko Maehara, MD*†

ROC analysis



Vessel area may be the strongest predictor of plaque rupture among non-left main coronary arteries

JACC Cardiovasc Imaging. 2015 Oct;8(10):1180-7.

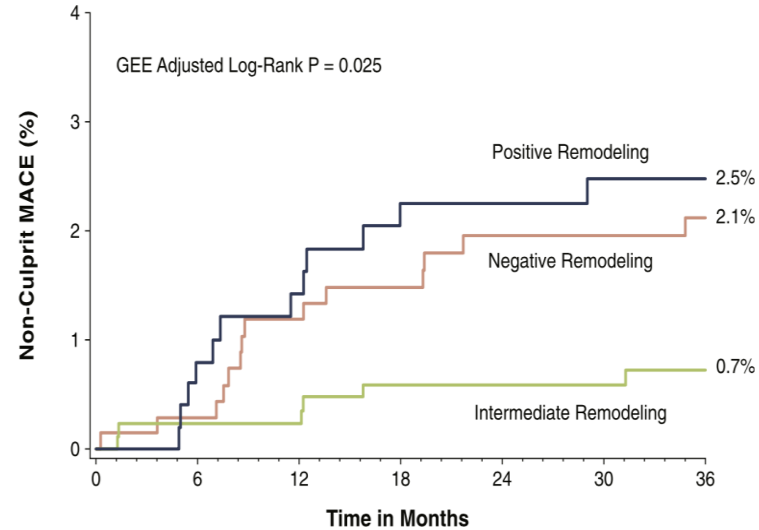
Impact of Positive and Negative Lesion Site Remodeling on Clinical Outcomes

IVUS

Insights From PROSPECT

Shinji Inaba, MD,*† Gary S. Mintz, MD,* Naim Z. Farhat, MD,‡ Jean Fajadet, MD,§ Dariusz Dudek, MD,|| Antonio Marzocchi, MD,¶ Barry Templin, MBA,# Giora Weisz, MD,*† Ke Xu, PhD,* Bernard de Bruyne, MD, PhD,** Patrick W. Serruys, MD, PhD,†† Gregg W. Stone, MD,*† Akiko Maehara, MD*†

New York, New York; Elyria, Ohio; Toulouse, France; Krakow, Poland; Bologna, Italy; Santa Clara, California; Aalst, Belgium; and Rotterdam, the Netherlands

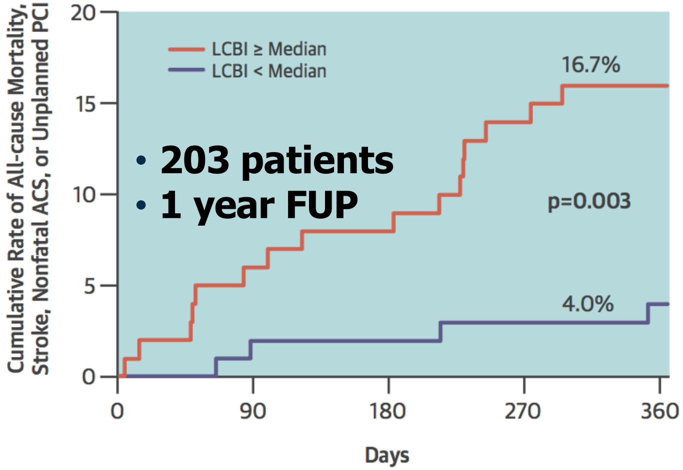


Number at Risk	0	6	12	18	24	30	36
Negative R.	734	671	657	643	629	607	391
Intermediate R.	911	841	832	807	798	775	482
Positive R.	537	488	484	460	451	435	286

Positive and negative lesion site remodeling was associated with unanticipated non-culprit lesion MACE in the PROSPECT study.

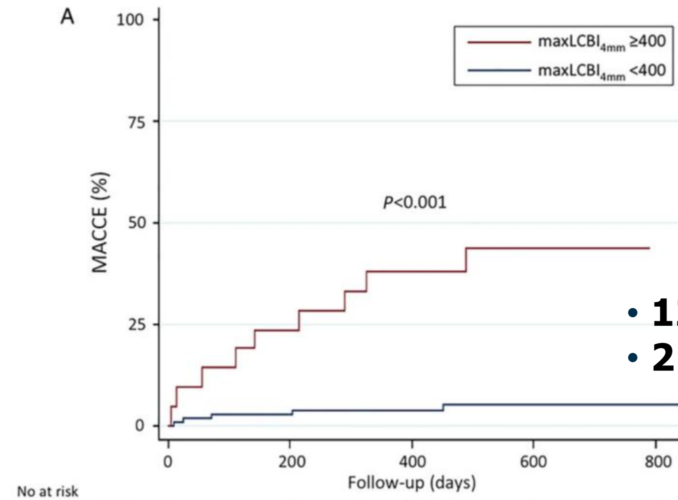
JACC Cardiovasc Imaging. 2014 Jan;7(1):70-8.

NIRS-IVUS and clinical outcomes



No. at Risk					
LCBI < Median	101	99	99	97	91
LCBI ≥ Median	102	94	92	86	83

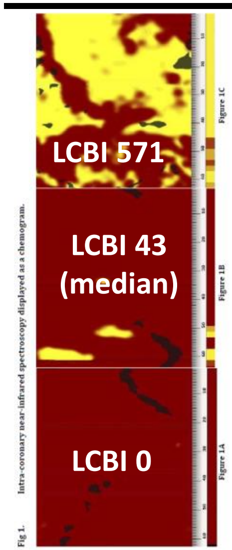
J Am Coll Cardiol. 2014 Dec 16;64(23):2510-8.

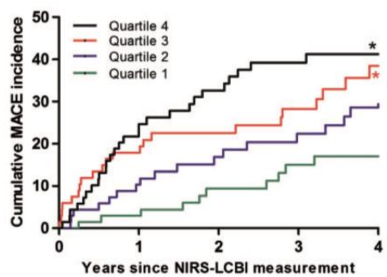


No at risk					
$maxLCBI_{4mm}$ ≥400	21	16	12	5	0
$maxLCBI_{4mm}$ <400	100	97	87	47	13

- **121 patients**
- **2 year FUP**

Madder RD, et al. Eur Heart J Cardiovasc Imaging. 2016 Apr;17(4):393-9.



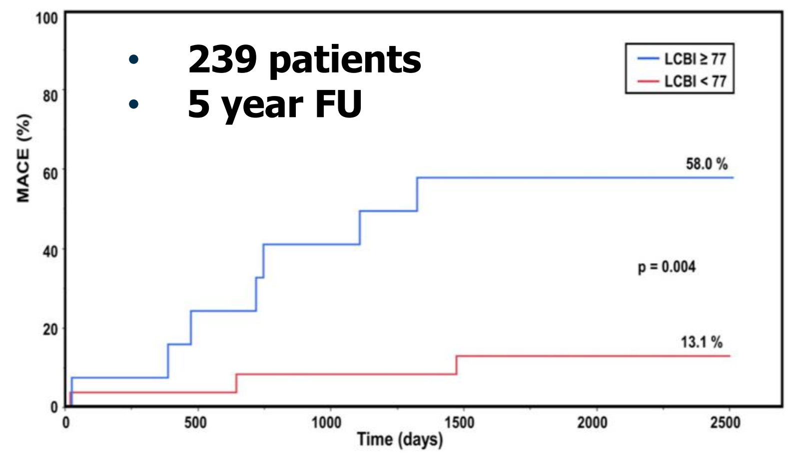


No. at risk					
LCBI Q1(<83.0)	68	66	52	43	29
LCBI Q2 (≥83.0-227.0)	68	61	47	40	31
LCBI Q3 (≥227.0-360.0)	67	55	42	35	22
LCBI Q4 (≥360.0)	70	53	41	30	25

Figure 2 Assocation between quartiles of $MaxLCBI_{4mm}$ and the occurrence of MACE. $^*P$ < 0.01 as compared with first quartile (reference).

- **275 patients**
- **4 year FUP**

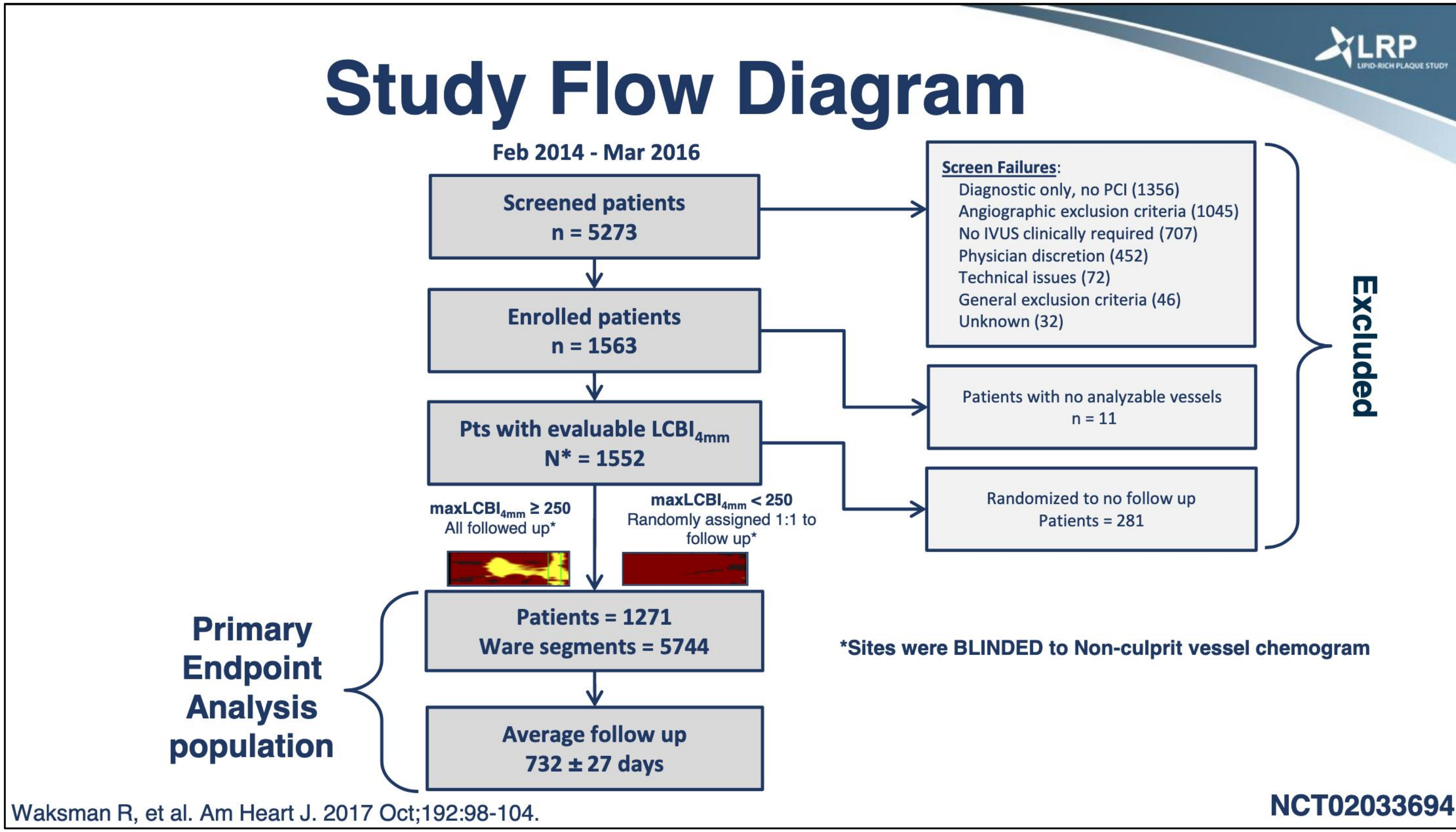
Schuurman et al.
Eur Heart J. 2017 May 20.



Number at risk						
LCBI ≥ 77	13	9	8	6	5	1
LCBI < 77	26	23	21	20	17	1

Cardiovasc Revasc Med. 2017;18:177-181.

LRP study



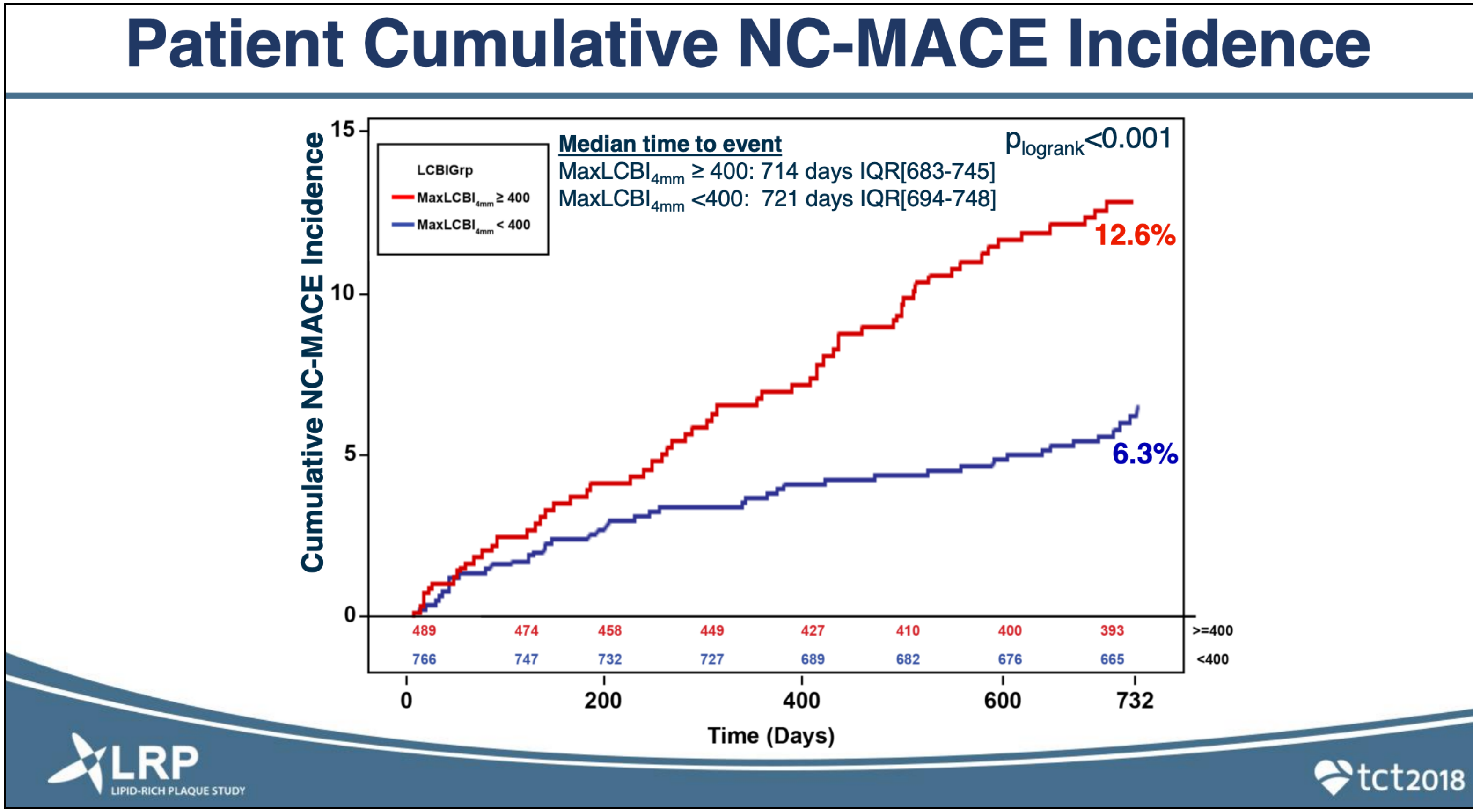
-A patient with maxLCBI4mm >400 is at 87% higher risk than lesser maxLCBI4mm >400

- In plaque-level, risk of event in vulnerable coronary segment is 45 percent higher with each 100 unit increase in $maxLCBI_{4mm}$

- Likelihood of event in segment with $maxLCBI_{4mm}$ >400 is 411% higher than a segment with a lesser $maxLCBI_{4mm}$

Ron Waxman TCT 2018

LRP study



- There was **no interaction between the maximum 4mm Lipid Core Burden Index [maxLCBI4mm] and plaque burden or minimum lumen area (MLA)** within the maxLCBI4mm by IVUS. The addition of plaque burden ≥70% did not alter the hazard ratio or have an interaction with maxLCBI4mm >400.
- The ability of NIRS to detect vulnerable plaque is independent of plaque burden or the MLA.

Ron Waxman TCT 2018

LRP study

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A Berkshire Hathaway Company

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Infraredx, a Nipro Company, Announces FDA Approval of Expanded Label Claim for the Makoto™ Intravascular Imaging System

The label claim expands usage guidelines to include identification of patients and plaques at increased risk of major adverse cardiac events (MACE)

April 22, 2019 09:00 AM Eastern Daylight Time

BURLINGTON, Mass.--(BUSINESS WIRE)--Infraredx, a Nipro Company, a pioneer in intravascular imaging for mapping coronary artery disease, announced today that it has received 510(k) clearance from the U.S. Food and Drug Administration (FDA) to expand the indications for use for its Makoto™ Intravascular Imaging System. The approval is based on the results of the landmark Lipid-Rich Plaque (LRP) Study, which demonstrated the ability of intravascular ultrasound (IVUS) and near-infrared spectroscopy (NIRS) technology to identify patients and coronary plaques at an increased risk for major adverse cardiac events (MACE).

FDA grants Infraredx, a Nipro Company, expanded indications for use of the Makoto Imaging System to include identification of patients and plaques at increased risk of major adverse cardiac events (MACE)

Tweet this

The study, which enrolled 1,563 patients from 44 sites across the U.S. and Europe, utilized IVUS+NIRS technology to assess patient and plaque lipid core burden index (LCBI) in stable and unstable patients requiring an angiogram procedure for new or ongoing cardiac symptoms. LCBI is validated as a quantitative summary metric of the lipid core in a scanned or selected region. The system utilizes NIRS to detect lipid core plaque (LCP) and automatically displays the results via a simple, color-coded map, called a chemogram. The system automatically generates LCBI calculations and the chemogram, which displays the presence of LCP in yellow and absence in red.

PROSPECT II Study (n=900)

PROSPECT ABSORB RCT

900 pts with ACS after successful PCI

3 vessel IVUS + NIRS (blinded)

≥1 IVUS lesion with ≥65% plaque burden present?

Yes → R 1:1

- **Absorb BVS + GDMT**
- **GDMT** alone

Routine angio/3V IVUS-NIRS FU at 2 years

No

Clinical FU for 15+ years

PREVENT Trial (n=1600)

All-comers, with any epicardial coronary stenosis ≤40 mm long with FFR ≥0.80 and with 2 of the following:

1. Plaque burden at the MLA >70%
2. MLA ≤4.0 mm^2
3. TCFA by OCT or VH-IVUS
4. Lipid-rich plaque on NIRS ($MaxLCBI_{4mm}$>315)

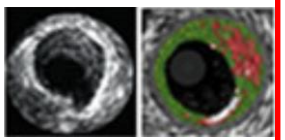
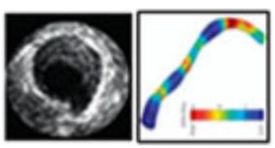
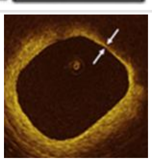
R

- DES/BVS+OMT N=800
- OMT N=800

Primary endpoint at 2 years:

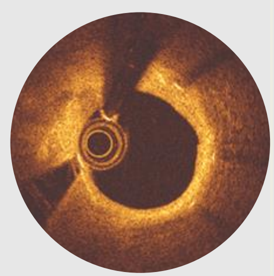
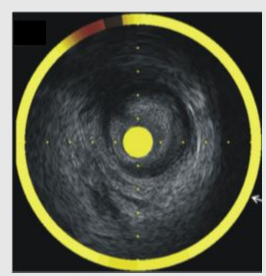
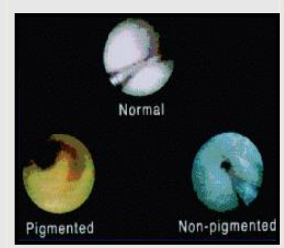
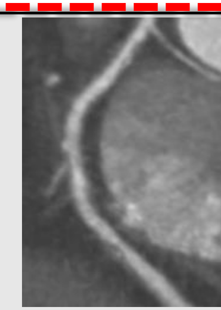
TVF: CV death, TV-MI, or ID-TVR

Summary of the positive and negative prediction values of intracoronary imaging derived variables for predication of clinical outcomes

Modality	Study	Identified parameter(s)	Endpoint	Positive Predictive value	Negative predictive value
IVUS & VH 	PROSPECT (n=697) ATHEROREMO-IVUS (n=581)	**PB ≥70%, MLA <4 mm2, VH-TCFA**	MACE	18% 23%	98% 93%
	Substudy of PROSPECT	+ Remodeling (either positive or negative)	MACE	NA	NA
	Substudy of PROSPECT	+ Longitudinal lesion location (proximal), absence of Ca	Plaque rupture	NA	NA
	PREDICTION (n=506)	**PB >58%, ESS <1.0 Pa**	PCI	41%	92%
OCT 		Cap thickness, superficial macrophages	Plaque rupture	NA	NA
NIRS 	ATHEROREMO-NIRS (n=203)	**LCBI >43%**	MACE	12%	99%
	Lipid Rich Plaque study (n=1552)	**LCBI max 4mm**	NC-MACE	For each 100 unit increase ofmaxLCBI4mm the risk of NC-MACE increases by 45%	

Adapted from Koskinas et al. EHJ 2016

Coronary Imaging Modalities

	CAG	IVUS	OCT	NIRS-IVUS	Angio-scopy	CT
Advantages	• Resolution : 200µm • Real-time acquisition • Gold standard	• Resolution: 150-200µm • Direct imaging of coronary plaque • Calcium/ remodeling • Additional tissue typing available (VH, IB-IVUS etc)	• High Resolution: 10-20µm • Documentation of structures close to lumen • Thin cap, macrophage, NC, calcium	• Detection of lipid rich plaques • Combined with IVUS	• Resolution : 20µm	• Non-invasive • Resolution : 200µm • Concomitant hemodynamic assessment • High Risk Plaque morphology • Total Plaque Burden • Stenosis
Shortcomings	• Contrast use • No plaque imaging	• Relatively Low tissue resolution • (:100 microns) • Slow pullback (0.5-10mm/s)	• Use of contrast medium • Tissue penetration is low (~2mm) • No complete depiction of coronary plaque	• Detection of lipid rich plaques only	Surface assessment only (color, morphology) Only available in some countries (e.g. Japan)	• Use of contrast medium
Image						

Long-Term Prognostic Effect of Coronary Atherosclerotic Burden Validation of the Computed Tomography-Leaman Score

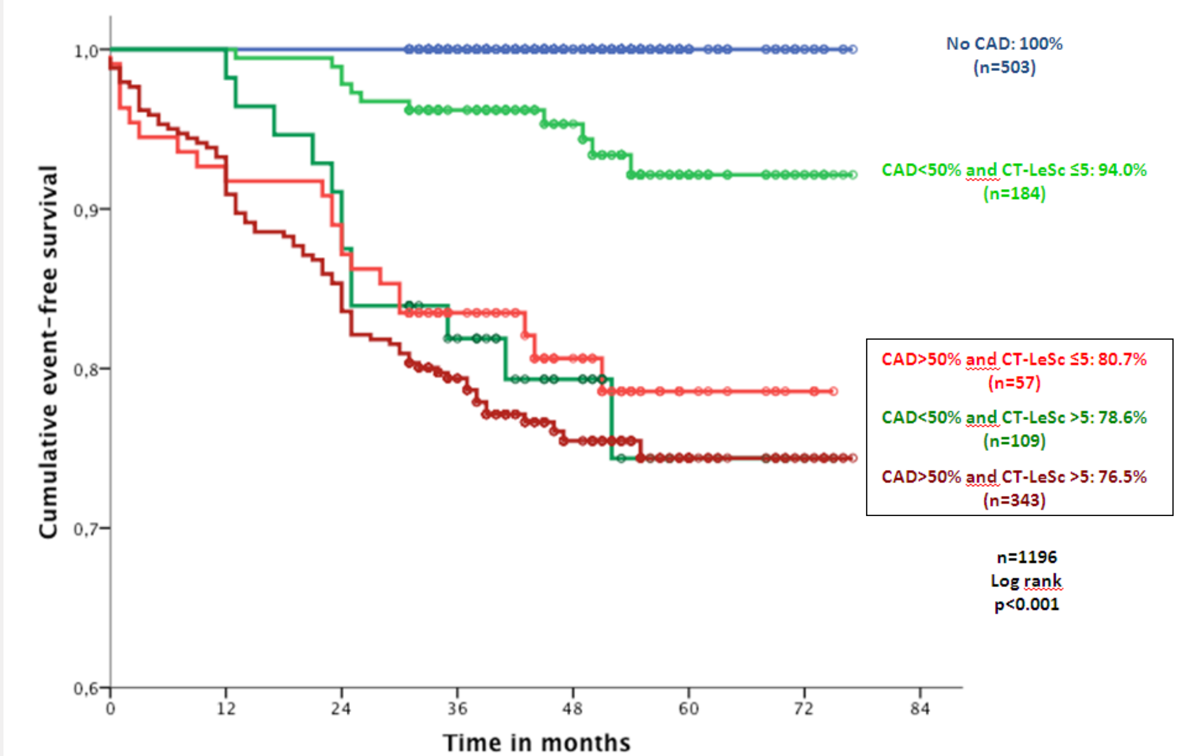
Saima Mushtaq, MD*; Pedro De Araujo Gonçalves, MD*; Hector M. Garcia-Garcia, PhD; Gianluca Pontone, MD; Antonio L. Bartorelli, MD; Erika Bertella, MD; Carlos M. Campos, MD; Mauro Pepi, MD; Patrick W. Serruys, MD, PhD; Daniele Andreini, MD, PhD

Circulation: Cardiovascular Imaging

2015 Feb;8(2):e002332.

MSCT Leaman score

1) ***Localization*** of the coronary plaques, accounting for dominance.
2) ***Type of plaque***, with a multiplication factor of 1 for calcified plaques and of **1.5 for non-calcified and mixed plaques.**
3) ***Degree of stenosis***, with a multiplication factor of 0.615 for non-obstructive (<50% stenosis) and a multiplication factor of 1 for obstructive (**≥50% stenosis**) lesions.



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http://dx.doi.org/10.1016/j.jacc.2015.05.069

ORIGINAL INVESTIGATIONS

Plaque Characterization by Coronary Computed Tomography Angiography and the Likelihood of Acute Coronary Events in Mid-Term Follow-Up

Sadako Motoyama, MD, PhD,*† Hajime Ito, MD, PhD,* Masayoshi Sarai, MD, PhD,* Takeshi Kondo, MD, PhD,* Hideki Kawai, MD, PhD,* Yasuomi Nagahara, MD,* Hiroto Harigaya, MD, PhD,*‡ Shino Kan, MD,*‡ Hirofumi Anno, MD, PhD,§ Hiroshi Takahashi, BSc,|| Hiroyuki Naruse, MD, PhD,* Junichi Ishii, MD, PhD,* Harvey Hecht, MD,† Leslee J. Shaw, PhD,¶ Yukio Ozaki, MD, PhD,* Jagat Narula, MD, PhD†

3,158 patients undergoing CTA
FUP: mean 3.9 ± 2.4 years

CTA-verified HRP was an independent predictor of ACS.

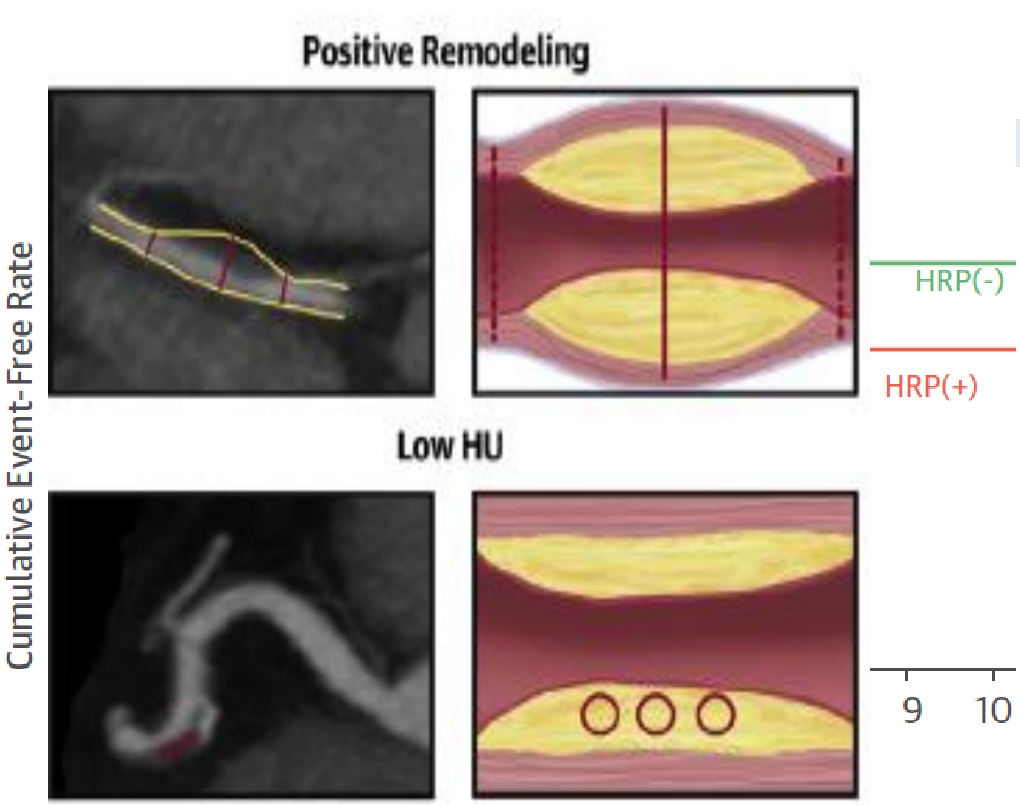
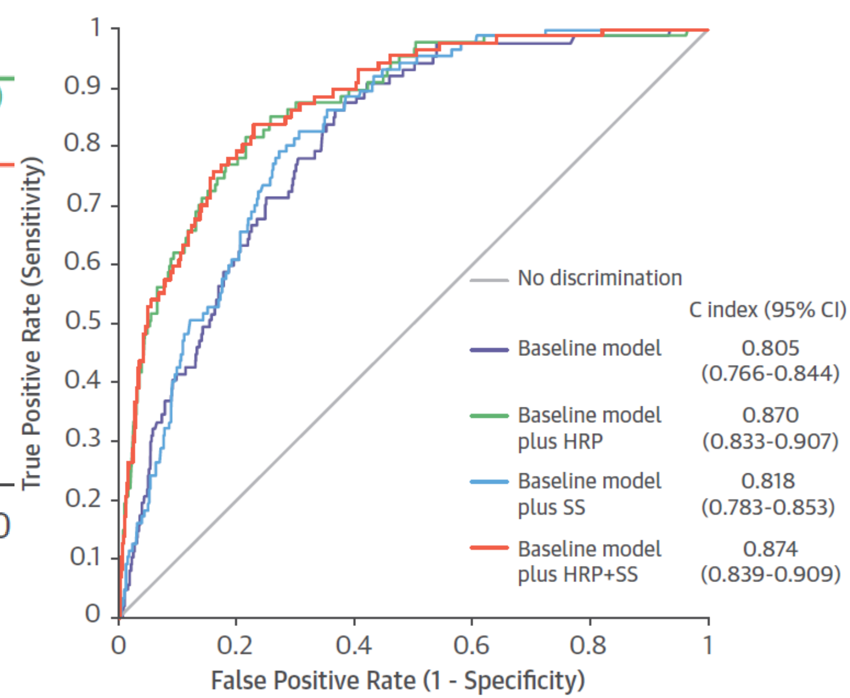


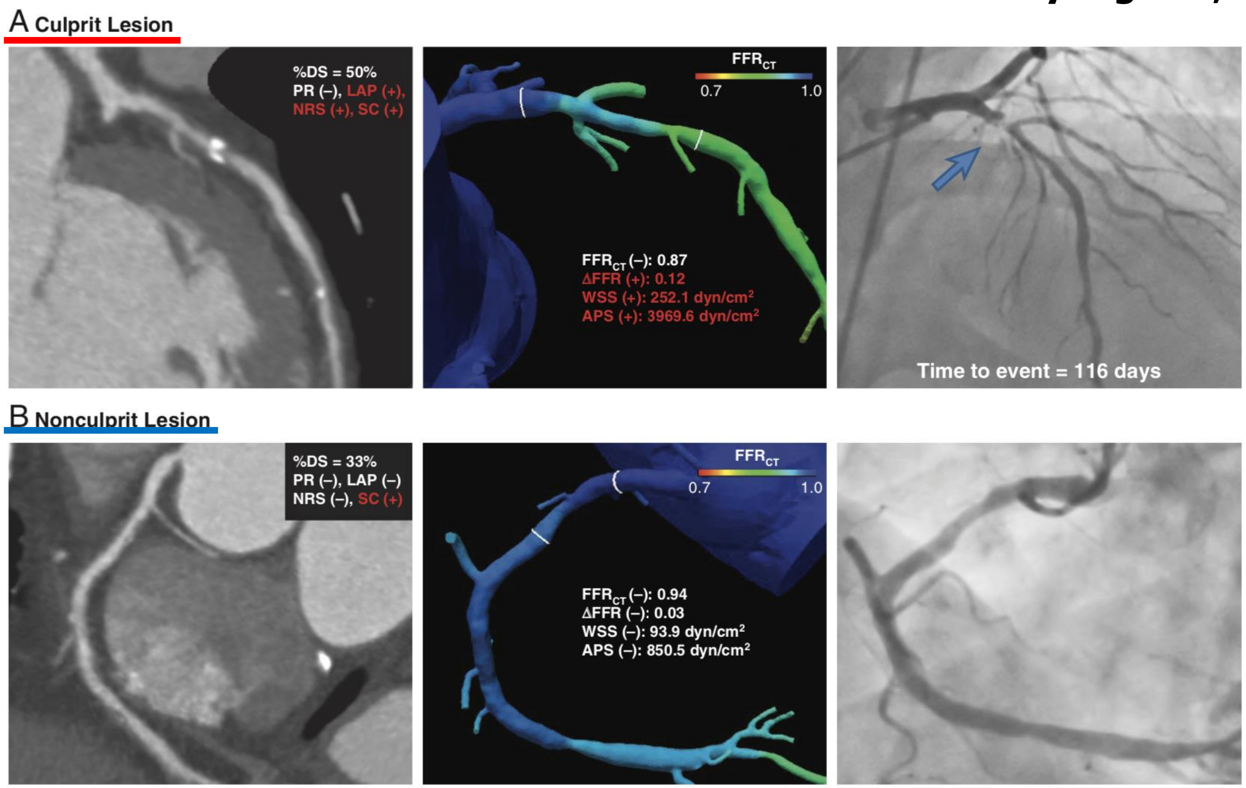
FIGURE 3 Incremental Value of CTA to Detect ACS



Identification of High-Risk Plaques Destined to Cause Acute Coronary Syndrome Using Coronary Computed Tomographic Angiography and Computational Fluid Dynamics : [EMERALD]

JACC: Cardiovascular Imaging
Available online 14 March 2018

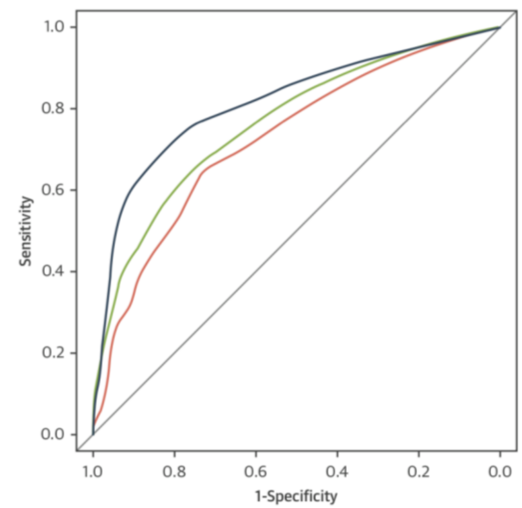
Joo Myung Lee, Gilwoo Choi, Bon-Kwon Koo, et.al



Model1: %DS and lesion length

Model2: Model1+APC (adverse plaque characteristics)

Model3: Model2+AHC (adverse hemodynamic characteristics)



- 72 pts with clearly documented ACS and available CTA
- 66 culprit and 150 nonculprit lesions
- Adverse plaque characteristics (APC)
- **Adverse hemodynamic characteristics** (FFR_{CT}, change in FFR_{CT} across the lesion [ΔFFR_{CT}], wall shear stress [WSS], and axial plaque stress)

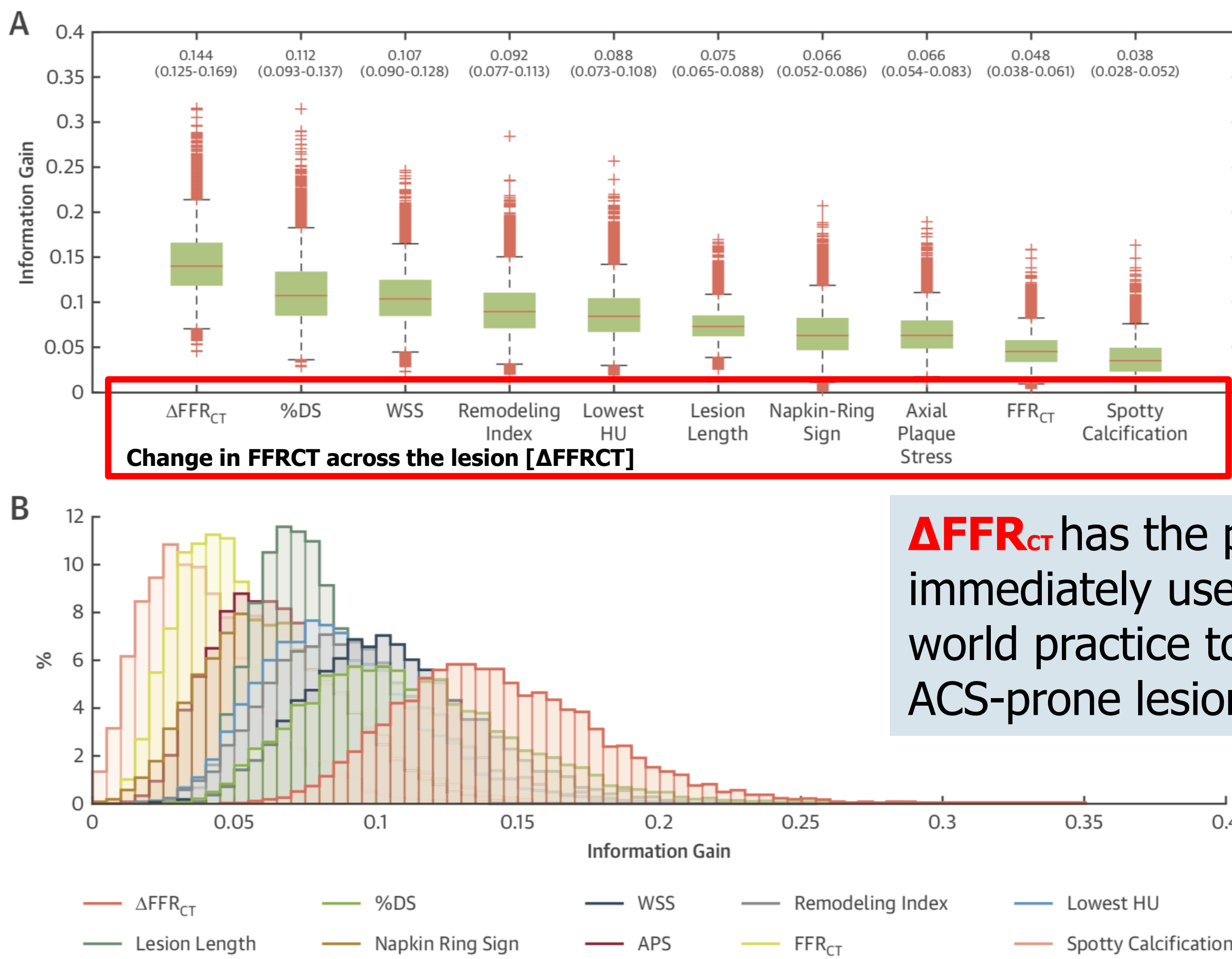
The incremental discriminant and reclassification abilities of APC/AHC to stenosis/lesion length were assessed.

Identification of High-Risk Plaques Destined to Cause Acute Coronary Syndrome Using Coronary Computed Tomographic Angiography and Computational Fluid Dynamics : [EMERALD]

JACC: Cardiovascular Imaging
Available online 14 March 2018

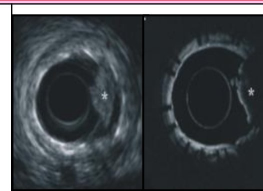
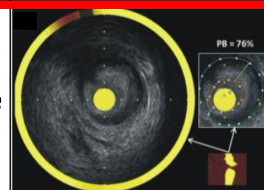
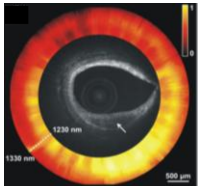
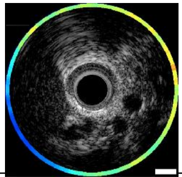
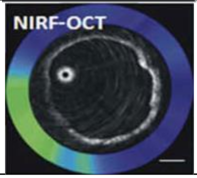
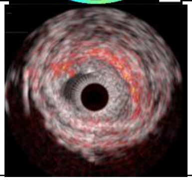
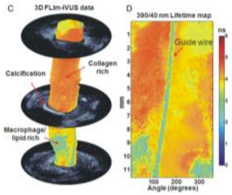
Joo Myung Lee, Gilwoo Choi, Bon-Kwon Koo, et.al

Comparison of Information Gain Among Included Parameters in Prediction Models



ΔFFR$_{CT}$ has the potential to be immediately used in real-world practice to discriminate ACS-prone lesions.

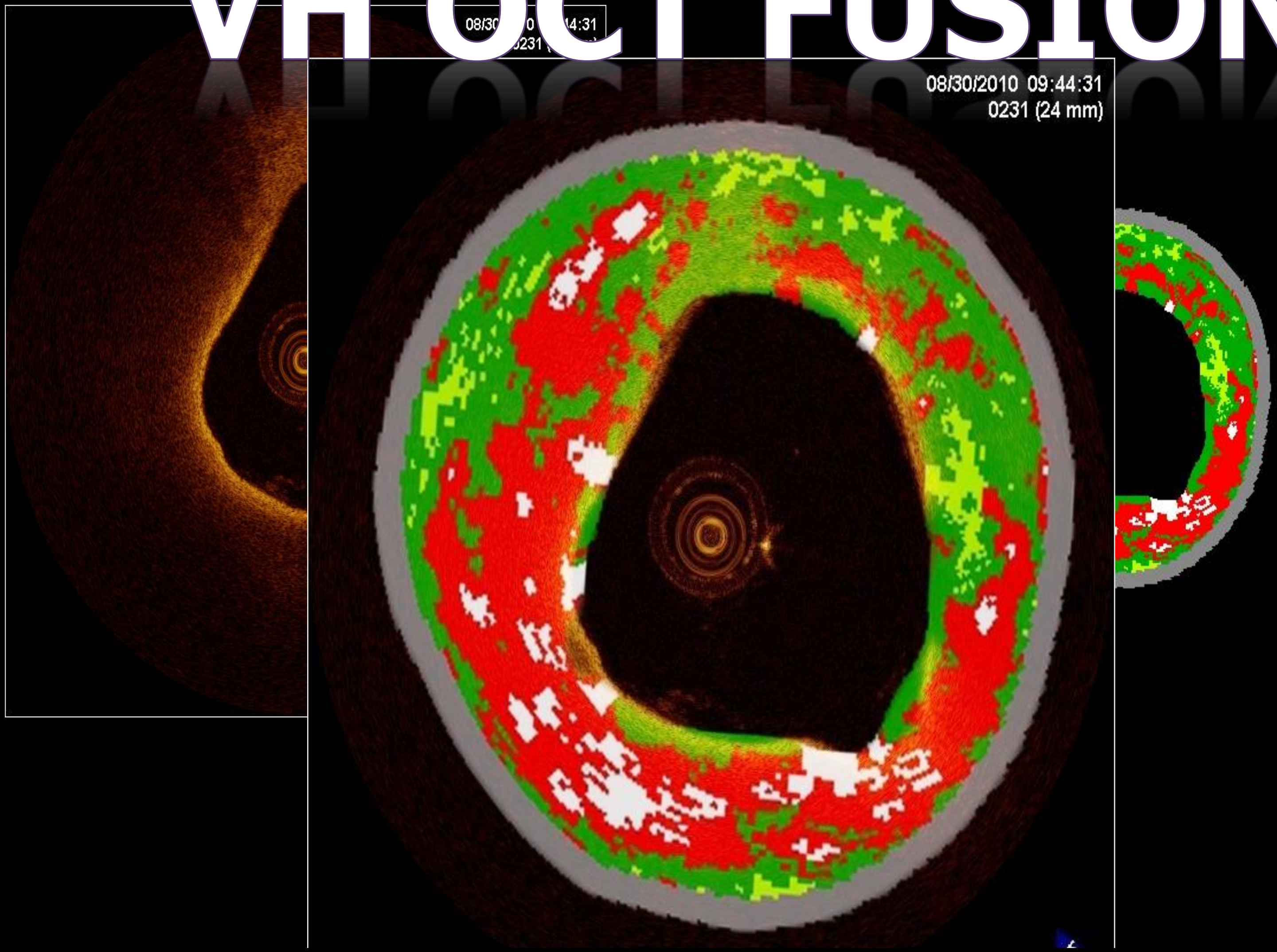
The combined intravascular imaging catheters

	Axial Resolution	IVUS		OCT	
		20 µm		8 µm	
OCT	8 µm	IVUS-OCT: Detailed plaque characterization with vessel size (remodeling) assessment.			
NIRS	NA	**NIRS-IVUS:** **Simultaneous assessment of lipid component and vessel structure (plaque burden, remodeling).** **only combined catheter clinically applied**		NIRS-OCT: Differentiating deep tissue (I.e. deeply embedded calcific tissue and lipid tissue).	
NIRF	NA	NIRF-IVUS: Simultaneous assessment of Inflammation and vessel structure.		NIRF-OCT: Correlates inflammation and detailed morphological assessment.	
IVPA	100 µm	IVPA-IVUS: Simultaneous assessment of chemical composition (i.e., lipid, inflammation, stent) and structural information.			
TRFS (FLIm)	160 µm	TRFS-IVUS: Simultaneous assessment of compositional characteristics (i.e., lipid, collagen, elastin) of the superficial plaque and vessel structure.			

Katagiri, Serruys, Onuma et al.
Expert Rev Med Devices. 2017 Dec;14(12):985-999.

NIRF = near infrared fluorescence, IVPA = intravascular photoacoustic,
TRFS = time resolved fluorescence spectroscopy, FLIm = fluorescence life time imaging.

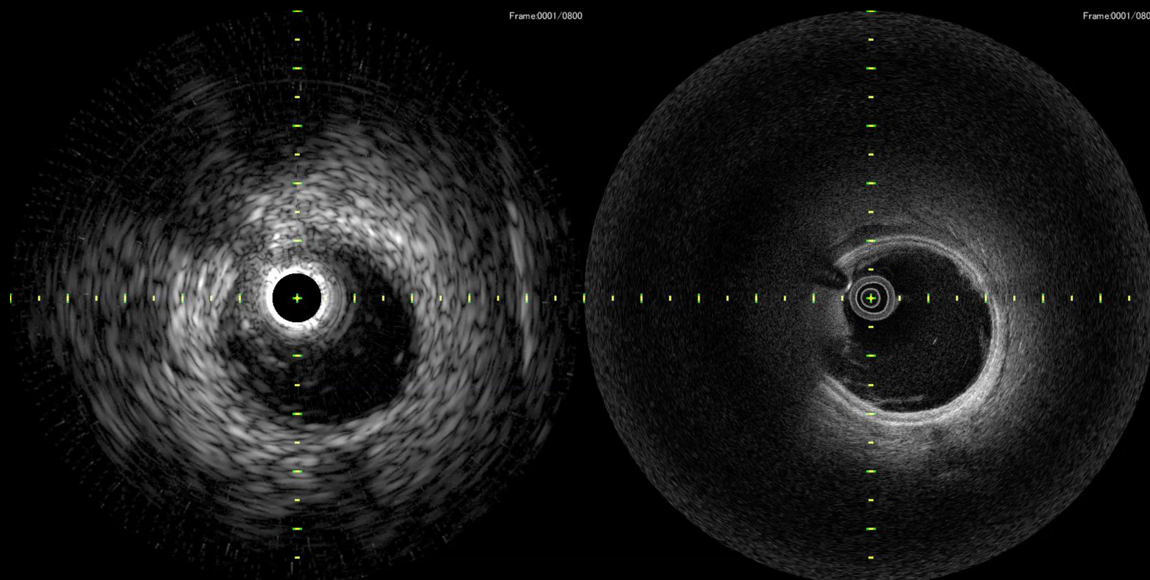
VH OCT FUSION



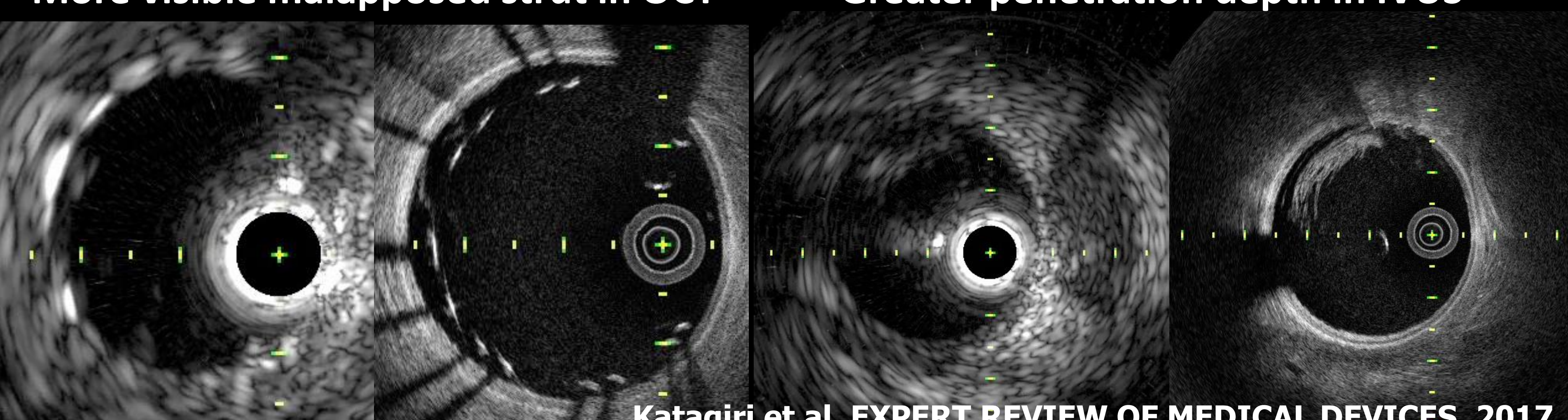
Fusion methodology, the most conventional but advanced merging technique of the 3 established intra imaging modalities (OCT, VH and IVUS) already belongs to the past.

Next generation IVUS-OCT hybrid catheter

IVUS-OCT hybrid catheter is under development (TERUMO).



More visible malapposed strut in OCT **Greater penetration depth in IVUS**



Katagiri et al. EXPERT REVIEW OF MEDICAL DEVICES, 2017

Summary and Conclusions

- **Among intravascular and non-invasive imaging clinically available (IVUS, OCT-NIRS and MSCT), several parameters were identified to be associated with future clinical event.**

Imaging modality	Predictors of future events
IVUS	Large PB, Small MLA, VH-TCFA, remodeling, longitudinal position of plaque, (absence of) calcification
OCT	Cap thickness*, Superficial macrophages*
NIRS(-IVUS)	**maxLCBI4mm**
Other combined catheters	No clinical data available
MSCT	Plaque burden (Leaman score), High risk plaque characteristics, adverse hemodynamic characteristics

*As a marker of plaque rupture. Not yet prospectively investigated in natural history studies.

- **Further development in intravascular imaging catheters and future natural history studies will elucidate other predictors of vulnerable plaque, while synergistic effect with other is also expected.**