Coronary Imaging and Physiology

Association and prognostic implication of "Hemodynamics" and "Plaque vulnerability"

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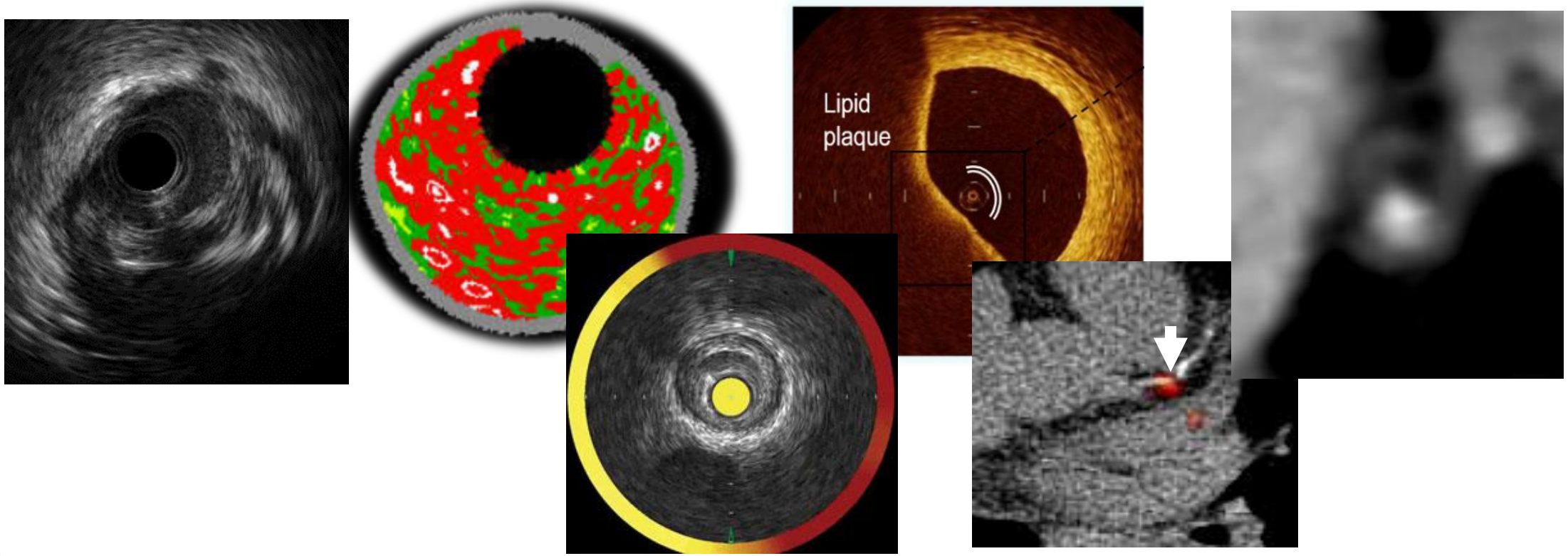
How to define vulnerable patients?

Plaque characteristics

Positive remodeling, posterior attenuation, lipid, cap thickness, TcFA, calcium, napkin ring, low density,…….



Why do we need a "better ap

TABLE 2 Prognostic Performance of Plaque Characteristics

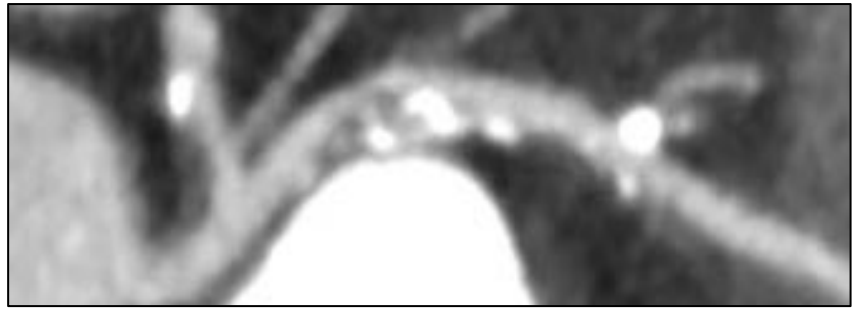
Trial (Ref. #), Follow-Up	Cohort	Endpoint	Lesion Variable	Event Rate % (n/N) + Lesion Variable	Event Rate % (n/N) − Lesion Variable	OR/HR	PPV	NPV	AUC (95% CI)
Intravascular Imaging Studies									
PROSPECT(3), 3.4 yrs (lesion-specific risk)	ACS	MACE	TCFA	4.4 (26/595)	1.2 (25/2,114)	3.8	0.04	0.99	0.71 (0.62-0.79)
			PB ≥70%	8.7 (25/288)	1.0 (30/2,941)	9.6	0.09	0.99	0.82 (0.76-0.87)
			MLA ≤4 mm^2	4.9 (30/616)	1.0 (25/2,522)	5.11	0.05	0.91	0.75 (0.67-0.82)
			All 3	18.2 (8/44)	1.6 (44/2,665)	13.6	0.18	0.98	0.86 (0.76-0.92)
PROSPECT (3), 3.4 yrs (patient-specific risk)	ACS	MACE	PB ≥70%	19.1 (42/220)	7.0 (31/440)	3.1	0.19	0.93	0.68 (0.60-0.75)
VIVA (4), 1.8 yrs (lesion-specific risk)*	ACS + SCAD	MACE	NC-VHTCFA	2.9 (5/175)	1.1 (8/756)	7.53†			NA
			PB ≥70%	NA	NA	8.13	NA	NA	NA
VIVA (4), 1.8 yrs (patient-specific risk)*	ACS + SCAD	MACE	NC-VHTCFA	NA	NA	1.79			NA
ATHEROREMO-IVUS (6), 1 yr (patient-specific risk)	ACS + SCAD	MACE	TCFA	10.8 (23/211)	5.6 (17/312)	1.98	NA	NA	0.62 (0.51-0.72)
			PB ≥70%	16.2 (20/124)	5.5 (21/384)	2.90			0.69 (0.55-0.80)
			MLA ≤4 mm^2	9.4 (16/182)	7.1 (23/326)	1.23‡	NA	NA	0.55 (0.38-0.72)
			All 3	23.1 (12/52)	6.8 (32/471)	3.70			0.72 (0.61-0.82)
ATHEROREMO-NIRS (2), 1 yr (patient-specific risk)	ACS + SCAD	MACE	LCP ($LCBI_{4mm}$ ≥43)	16.7 (17/102)	4.0 (4/101)	4.20			0.74 (0.56-0.87)
		ACM/ACS		8.8 (9/102)	1.0 (1/101)	9.36	0.11	0.94	0.82 (0.52-0.97)
		ACM/ACS/Stroke		11.8 (12/102)	1.0 (1/101)	11.9			0.85 (0.57-0.97)
PREDICTION (5), 1 yr (patient-specific risk)	ACS	PCI	PB ≥58%	22	2	17.6			0.85 (0.67-0.94)
			Low ESS	25	9	3.18	0.16	0.95	0.69 (0.56-0.79)
			Both	41	8	NA			0.80 (0.68-0.88)
Noninvasive Imaging Study							0.10	0.93	
CTA (7), 2 yrs (patient-specific risk)	SCAD	ACS	Positive remodeling + low attenuation plaque	22.2 (10/45)	0.49 (4/820)	45.6	0.23	0.93	0.95 (0.87-0.98)
Invasive Hemodynamic Assessment							0.17	0.96	
FAME-2 (8), 30 days (patient-specific risk)§	SCAD	MACE (D/MI/UR)	FFR ≤0.80	12.7 (56/441)	3.0 (5/166)	4.22			0.74 (0.59-0.85)
		D/MI		3.9 (17/441)	1.8 (3/166)	2.13‡	0.09	0.99	0.63 (0.41-0.81)
							0.12	0.99	
							0.22	0.98	

Kaul S & Narula J. JACC 2014;64:2519-14

FFR/iFR-guided clinical decision: Standard approach for CAD

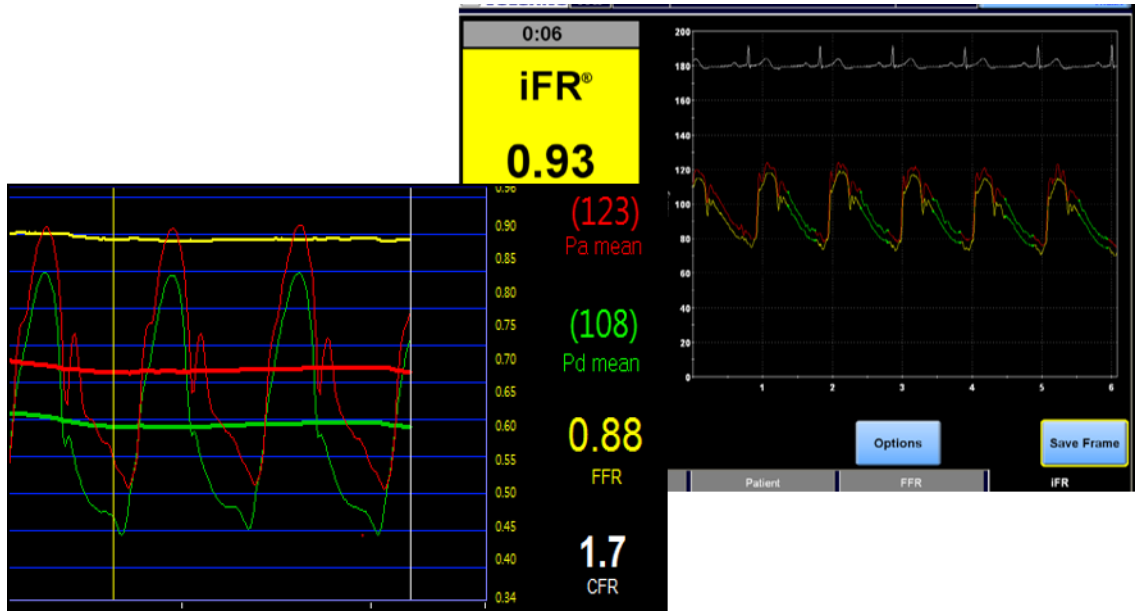
2018 ESC/EACTS Guidelines on myocardial revascularization.

Non-invasive imaging



- 70% stenosis

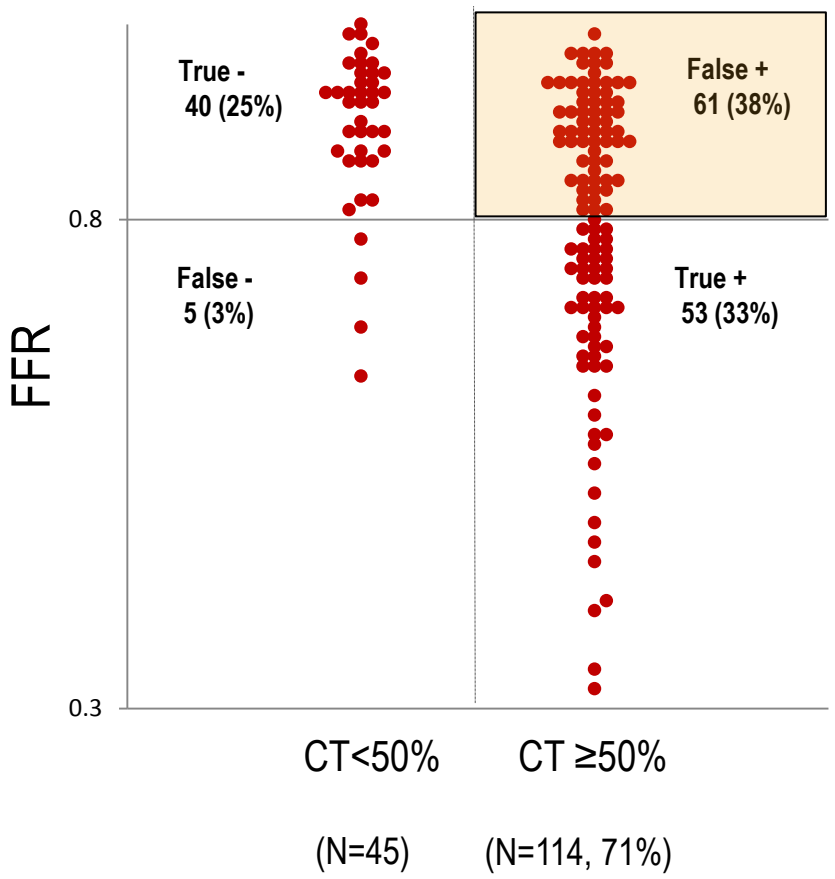
Invasive physiology

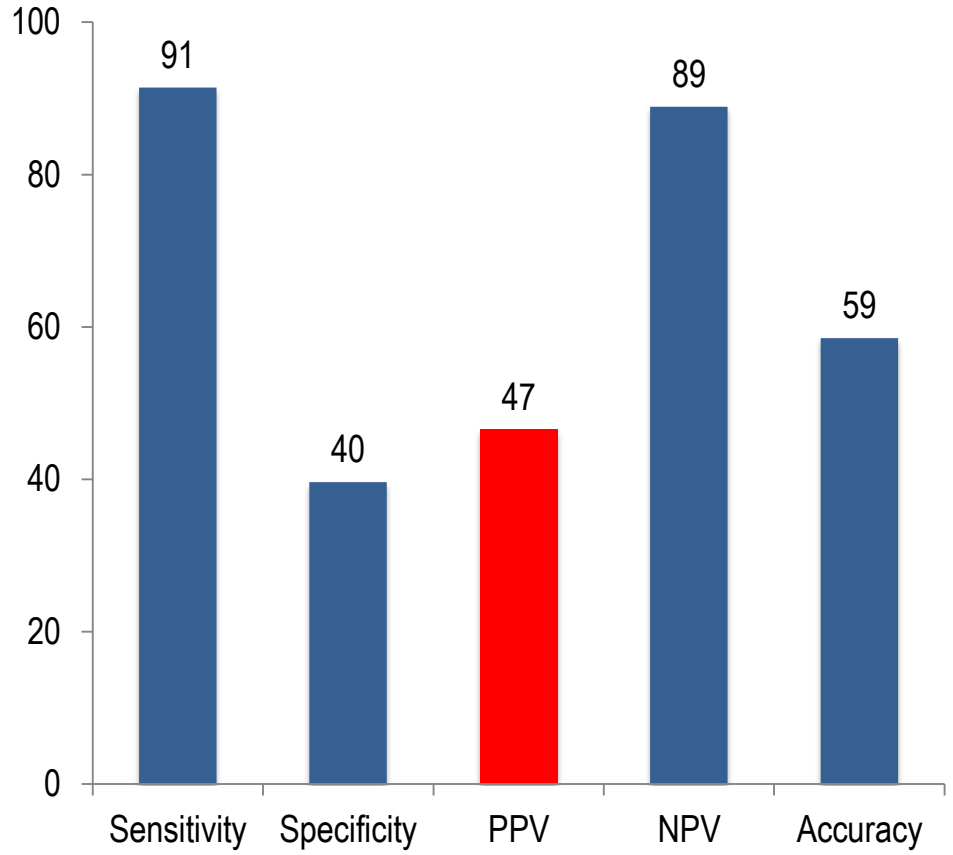


- No ischemia → Medical treatment

This happens quite frequently….

DISCOVER FLOW study: Per-vessel analysis (n=159)





PPV: positive predictive value, NPV: negative predictive value

Koo BK, et al, J Am Coll Cardiol, 2011

FFR-guided clinical decision: Standard approach for CAD

2018 ESC/EACTS Guidelines on myocardial revascularization.

Non-invasive imaging

Invasive physiology

Inside the catheterization laboratory

“No ischemia

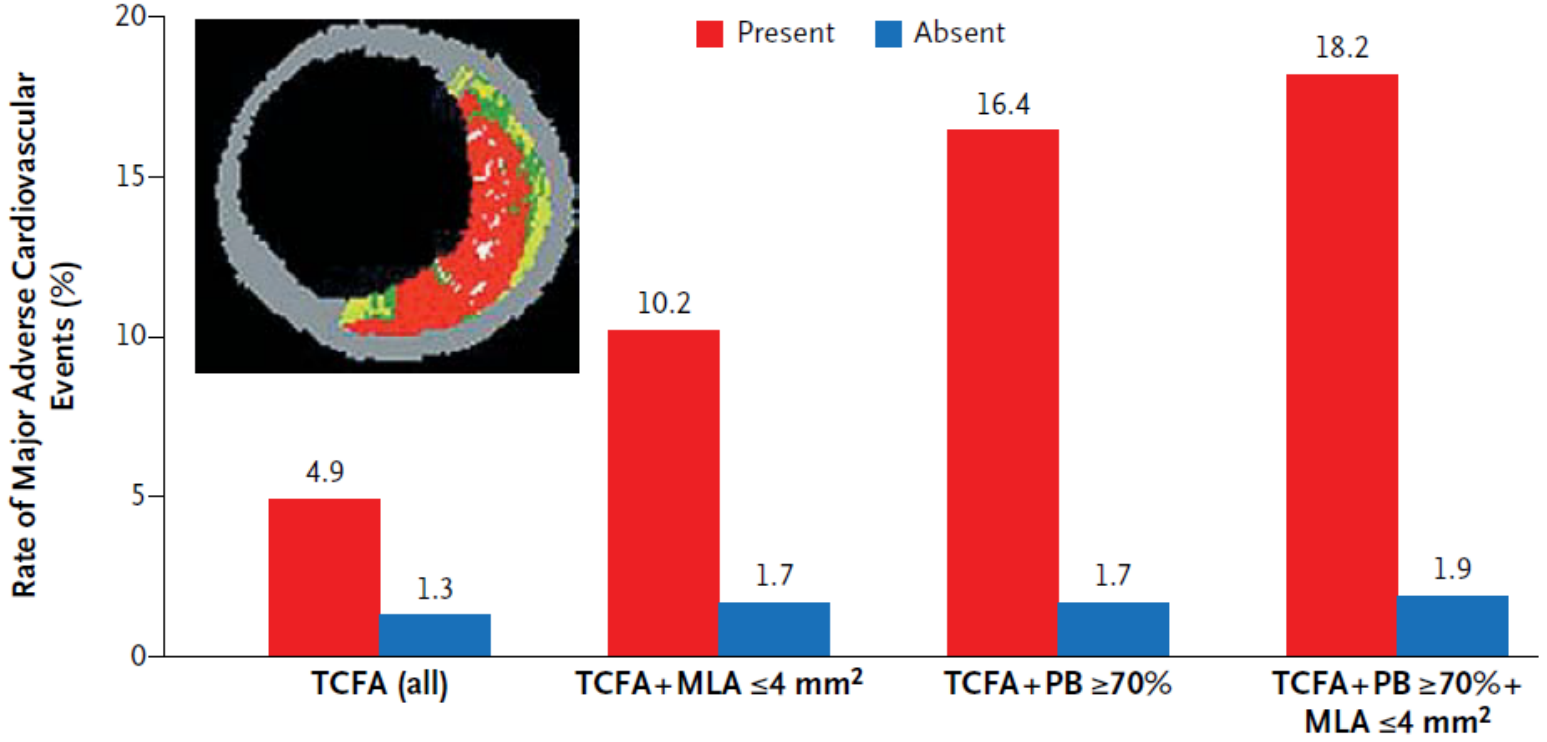
→ No PCI and Forget about it !”

- 70% stenosis

Is there any other way to make it better?

Value of invasive/non-invasive imaging
Anatomical severity + Plaque character

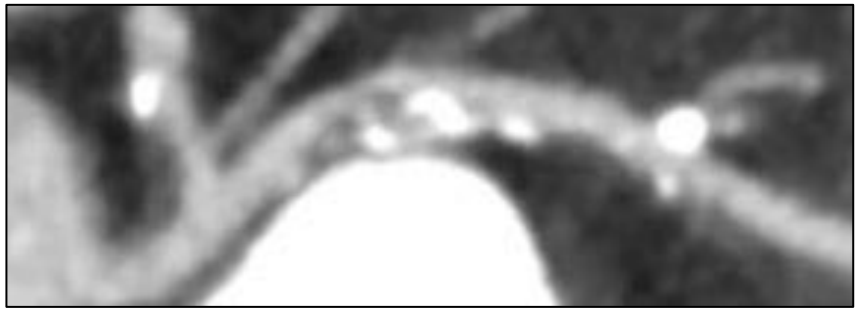
PROSPECT study



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

Stone G, et al., NEJM 2011;364:226

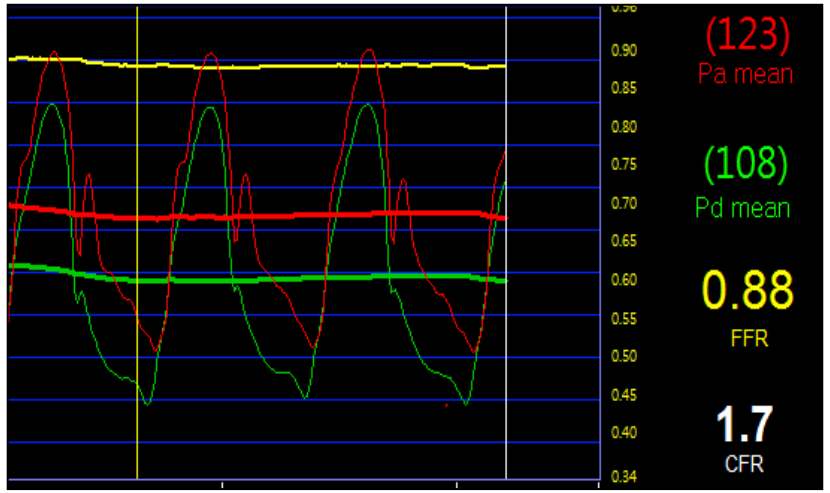
Non-invasive imaging



- 50-70% stenosis
- Mixed plaque, Plaque burden>70%
- Spotty calcification+
- Positive remodeling+

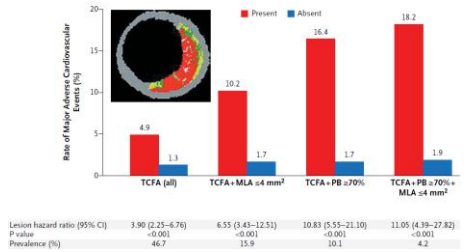
+

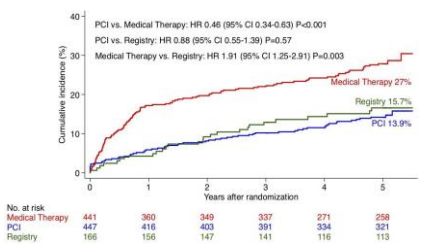
Invasive physiology



We can enjoy both “PROSPECT” and “FAME”!

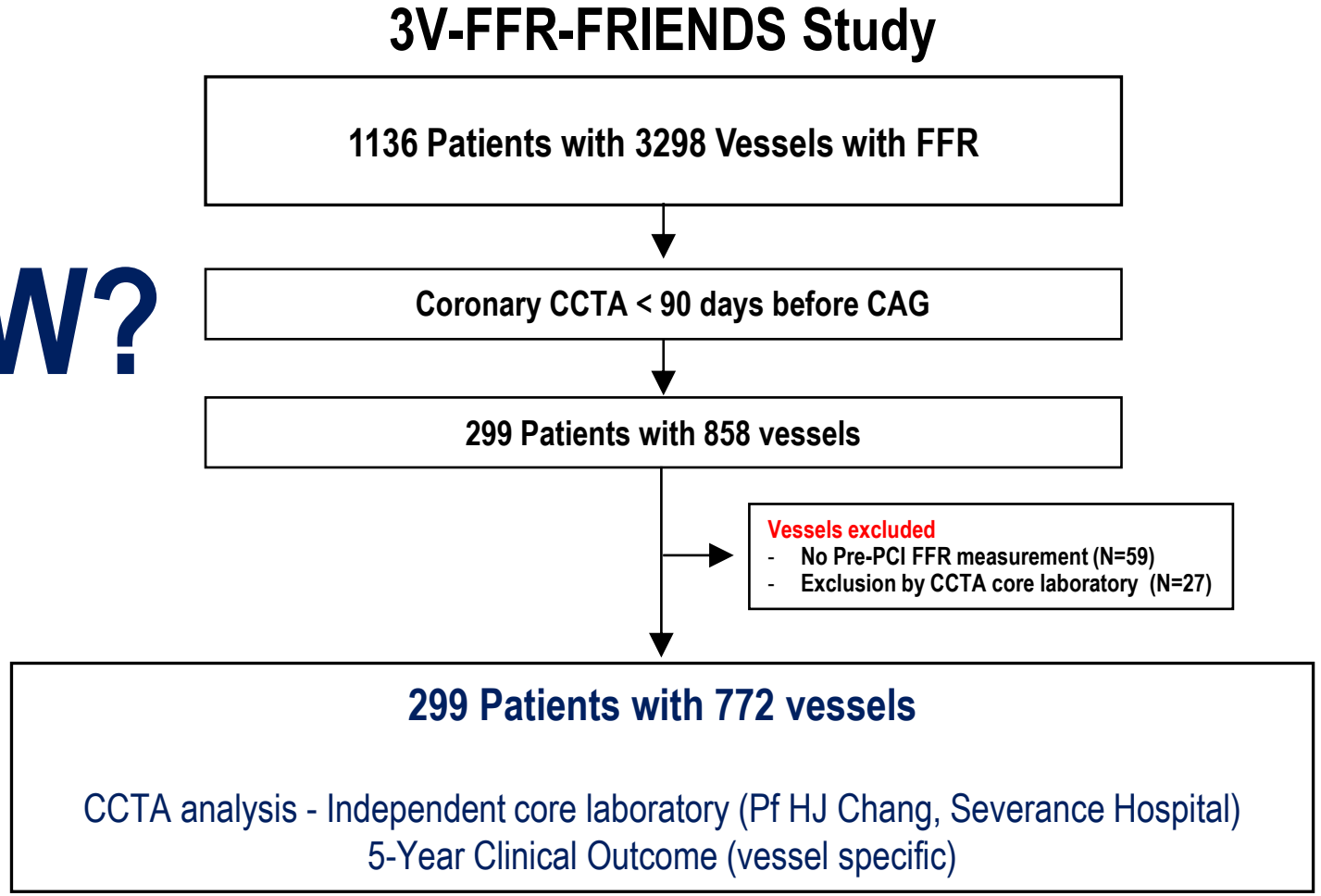
PROSPECT FOR SUCCESS





Prognostic Implication of CCTA-defined High Risk Plaque Characteristics and FFR

HOW?

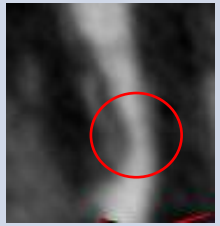
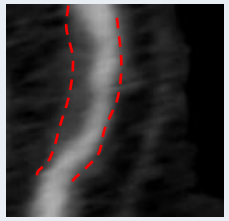
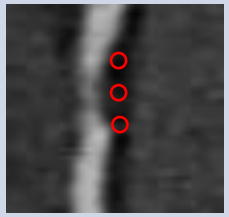


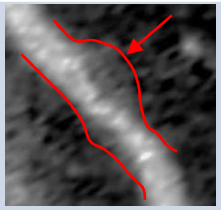
Lee JM, Koo BK et al. Eur Heart J. 2018 Mar 14;39(11):945-951.

CCTA-defined HRPC

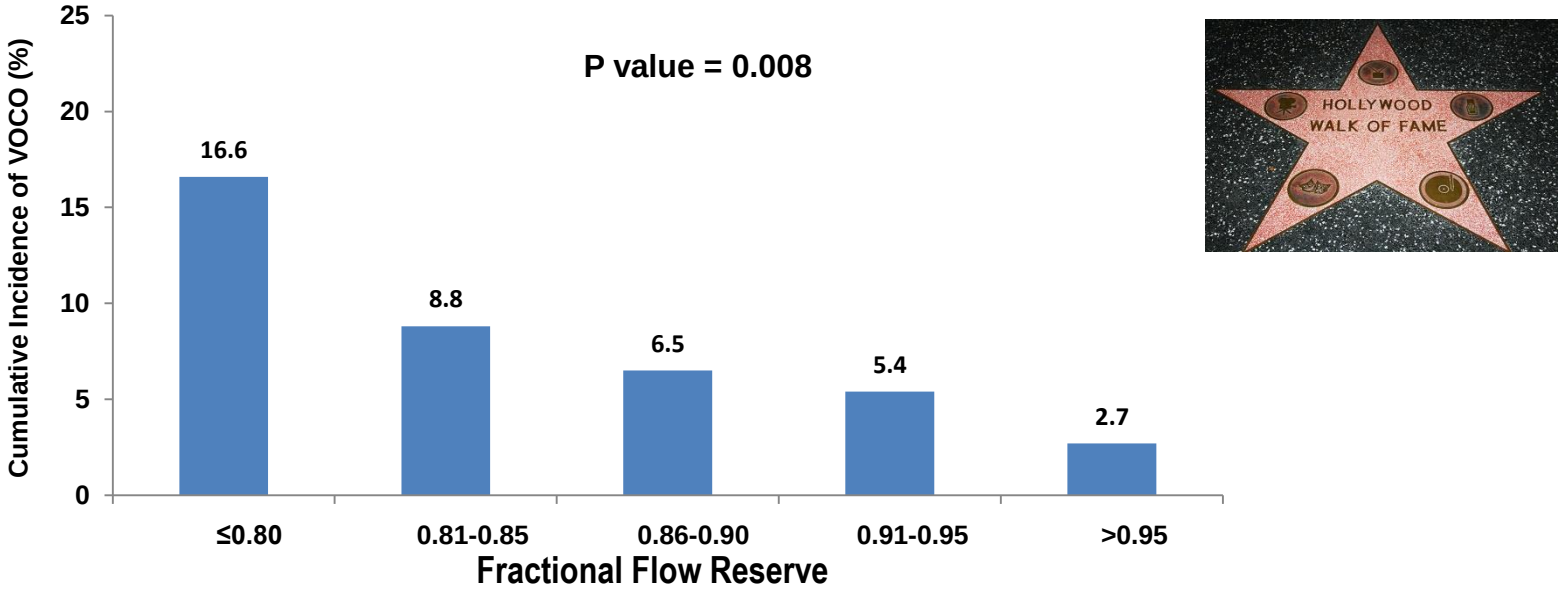
Quantitative and Qualitative high risk plaque characteristics

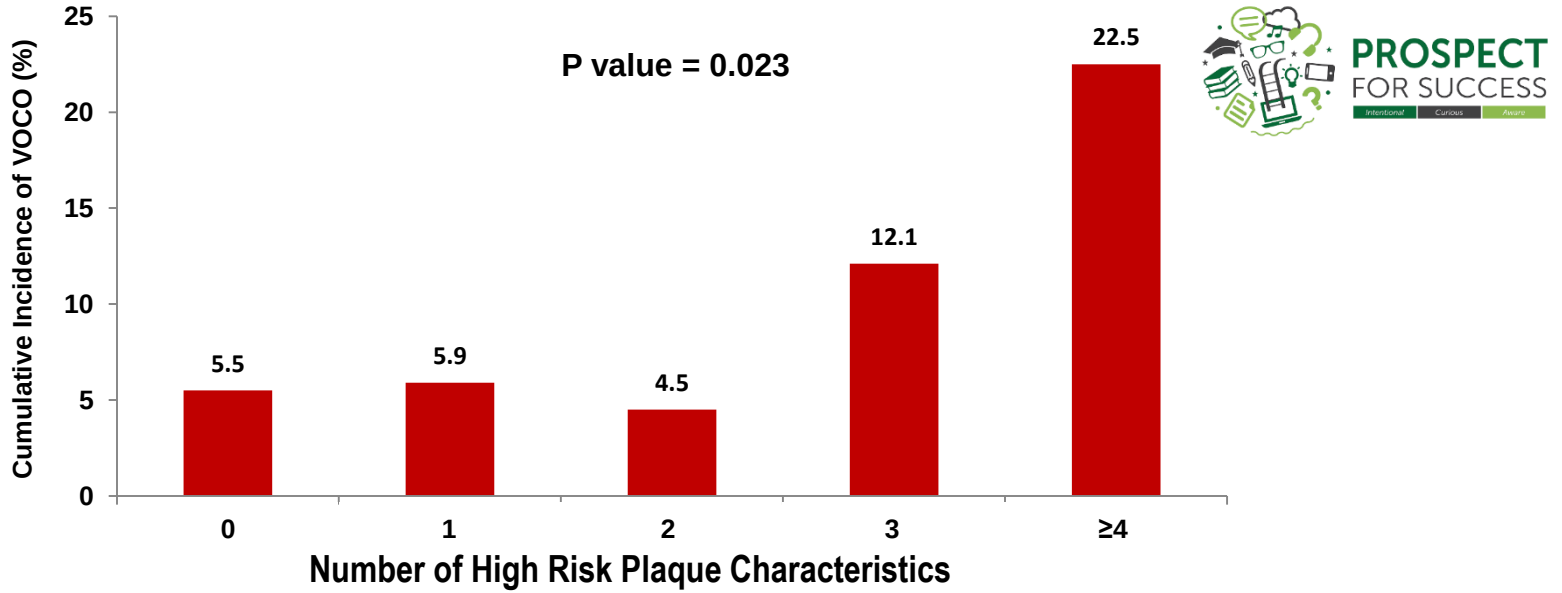
(from PROSPECT, ATHEROREMO-IVUS, ROMICAT, Motoyama et al.)

	CCTA definition	Harrell's C-index 5-Year Events
MLA<4mm^2		0.687 [95% CI 0.499-0.875]
Plaque Burden≥70%		0.764 [95% CI 0.615-0.913]
Low attenuation		0.517 [95% CI 0.423-0.589]

	CCTA definition	Harrell's C-index 5-Year Events
Positive remodeling		0.590 [95% CI 0.479-0.700]
Napkin-ring sign		0.513 [95% CI 0.480-0.551]
Spot calcification		0.529 [95% CI 0.476-0.583]

Prognostic Implications of FFR and High-Risk Plaque Characteristics

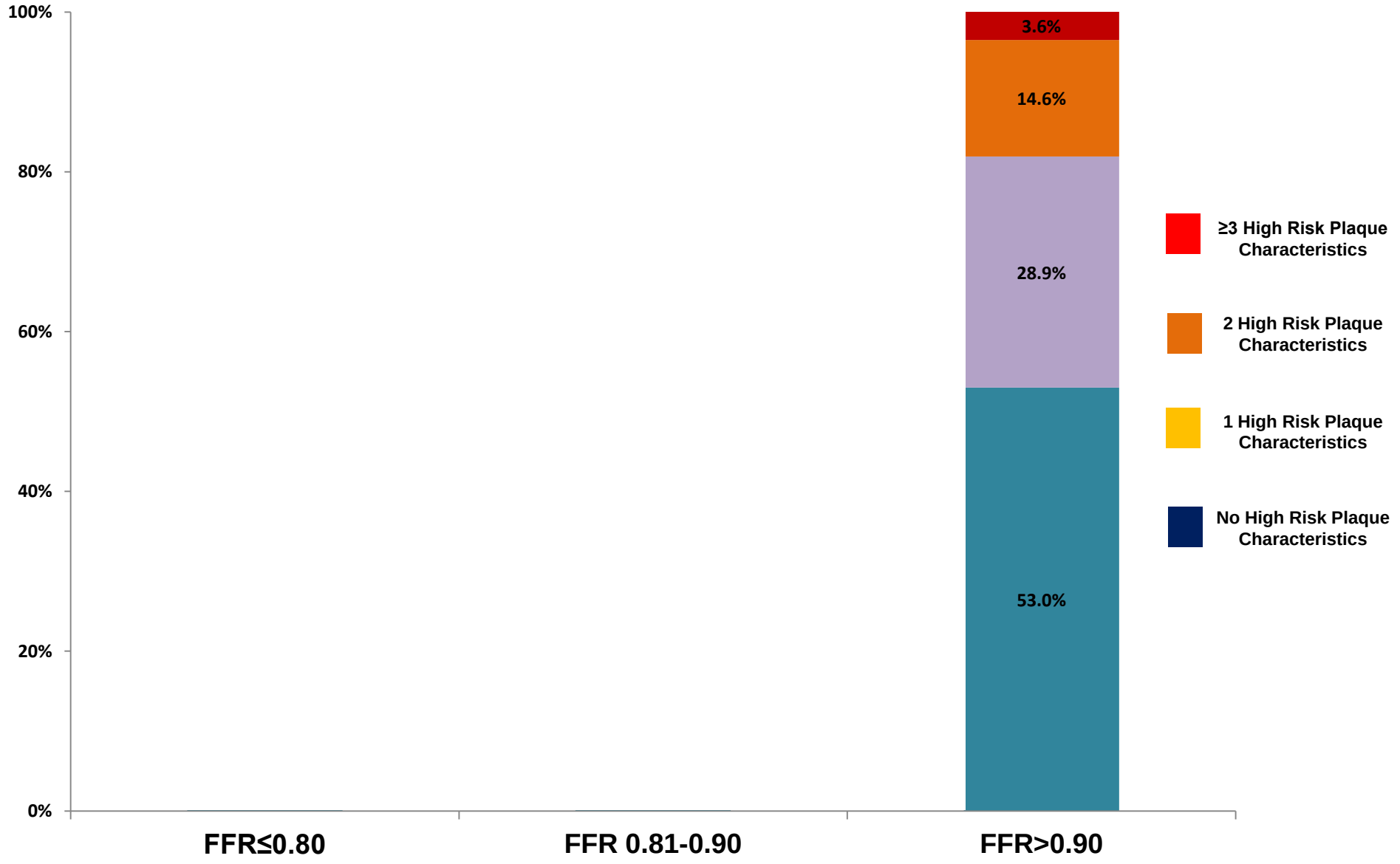




PROSPECT FOR SUCCESS

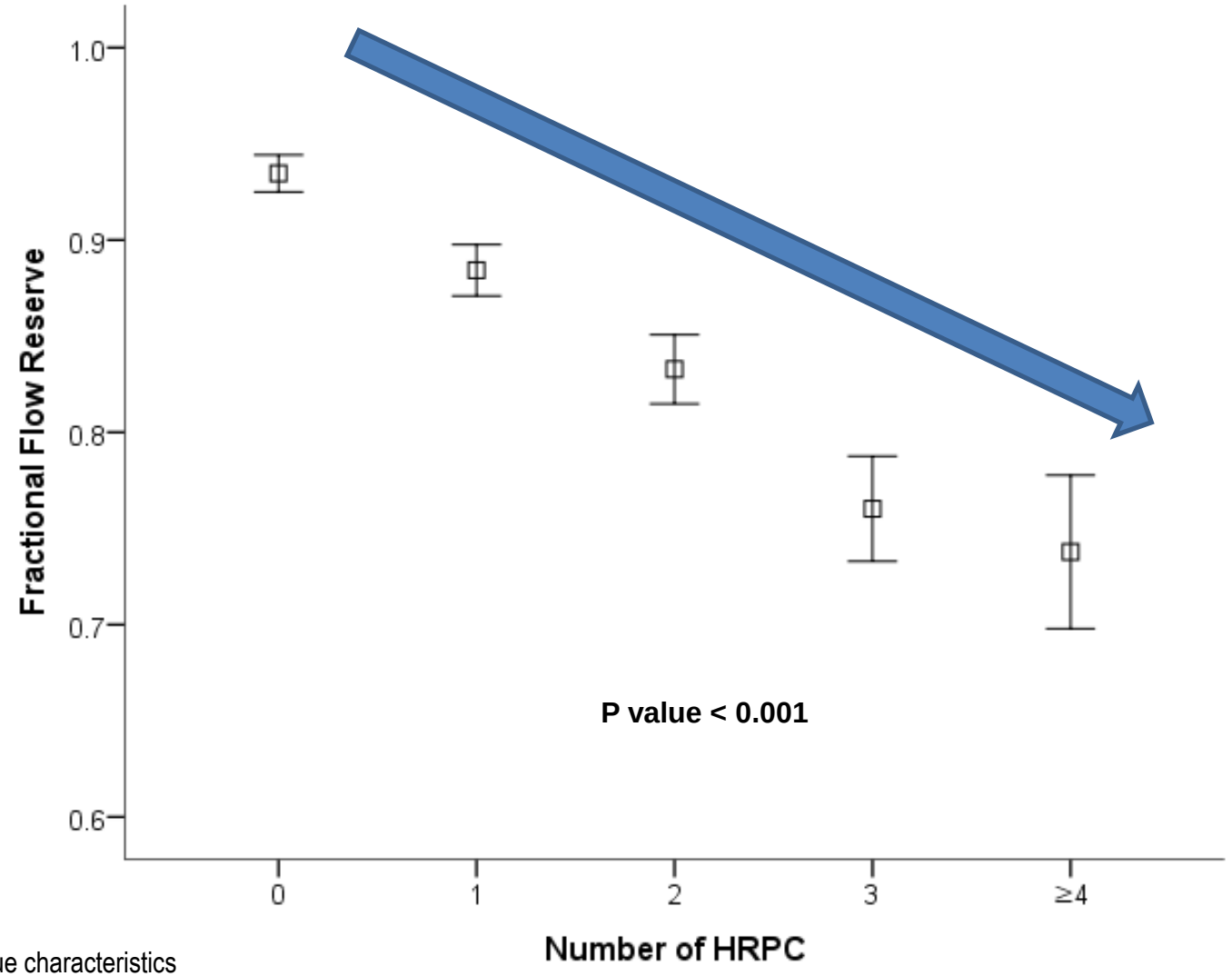
Lee JM, Koo BK et al, JACC 2019

FFR and Plaque vulnerability: Friends or Foes?



Lee JM, Koo BK et al, JACC 2019

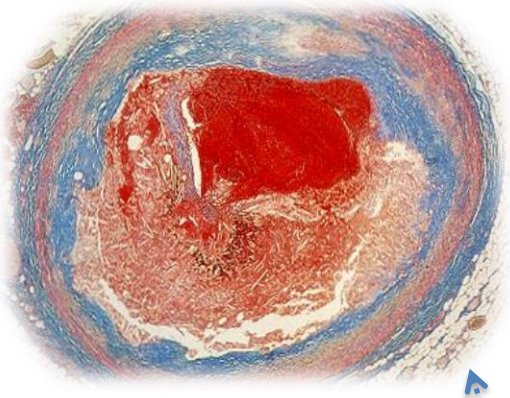
FFR and Plaque vulnerability: Friends or Foes?



HRPC: high risk plaque characteristics

Lee JM, Koo BK et al, JACC 2019

Association between FFR and Plaque vulnerability



ACS (with rupture)

Plaque Stress

Platelet activation
Thrombosis

High external force
High axial plaque stress

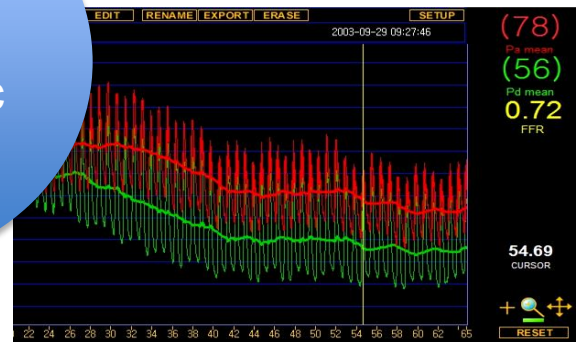
High WSS
High WSS gradient

Plaque vulnerability

High WSS
High WSS gradient

Stenosis and Local hemodynamic derangement

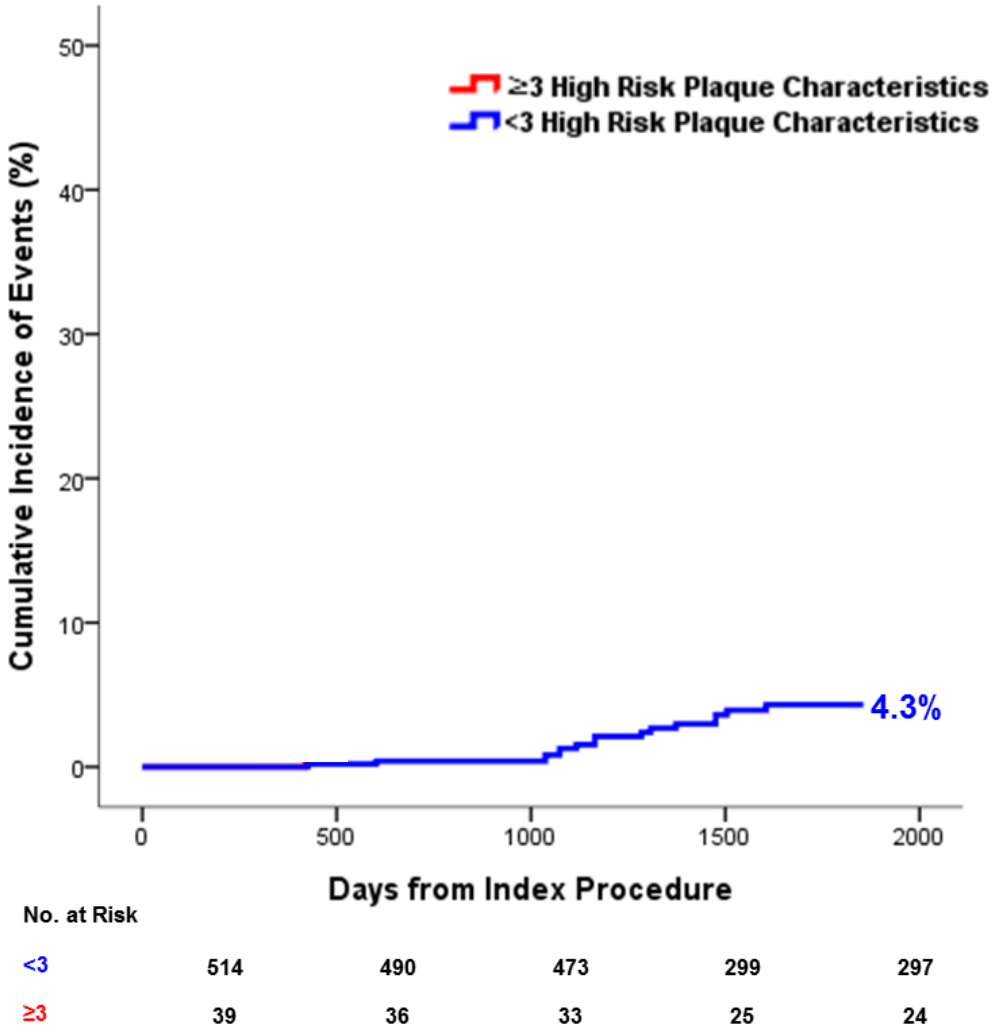
Mechanism?



Slager, et al. Nature Clin Pract 2005
Samady H, et al. Circulation 2011
Park JB, Koo BK, et al. Heart 2016
Choi GW, Lee JM…Koo BK. JACC imaging 2015
Lee JM, Koo BK, et al. JACC imaging 2017
Lee JM, Choi GW…Koo BK. JACC imaging 2019

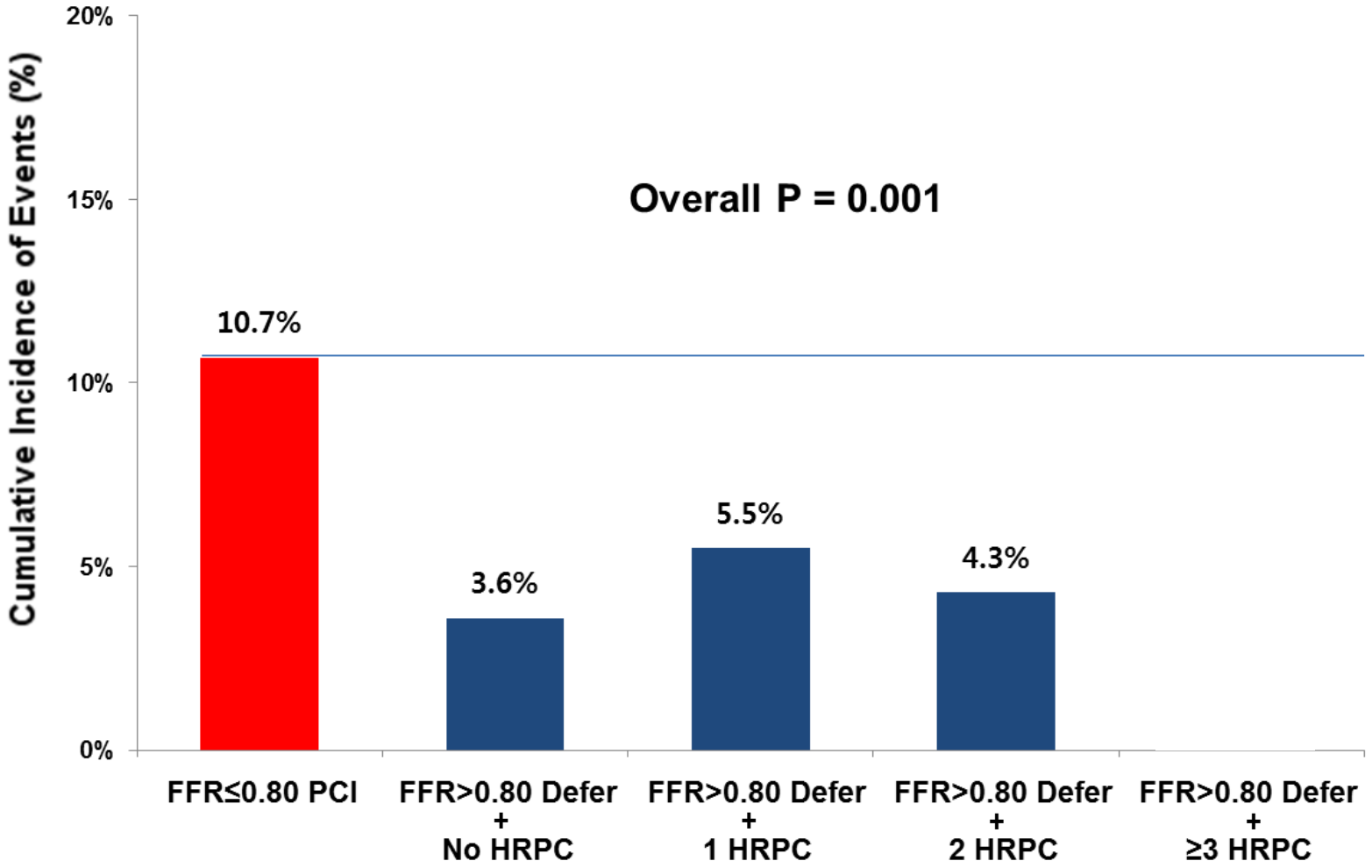
Differential Prognostic Implications of HRPC and FFR

Vessel-Oriented Composite Outcomes in High FFR and Deferred Vessels



Lee JM, Koo BK et al, JACC 2019

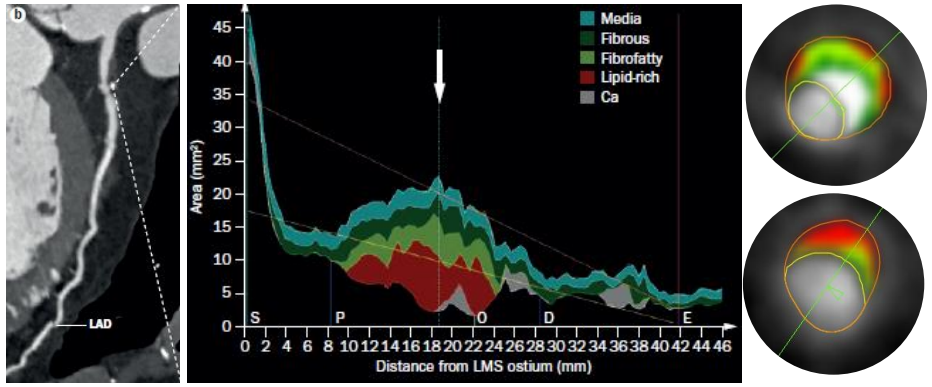
Outcomes according to Tx strategy, FFR and HRPC



Lee JM, Koo BK et al, JACC 2019

Application of 3D CCTA analysis and Machine learning technique

Comprehensive Plaque Assessment with CCTA

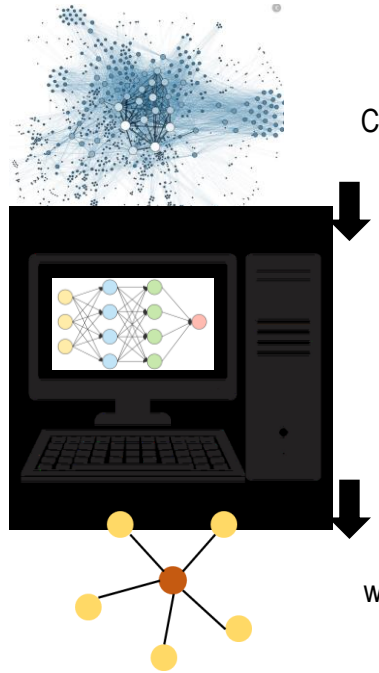


Cross-sectional and Volumetric Quantification For Whole Coronary Tree

- High risk plaque character (LAP/SC/PR/NRS)
- Maximal plaque thickness
- Lumen area stenosis / Lumen diameter stenosis
- Bifurcation tortuosity
- Ostium to MLD/Lesion length
- Plaque eccentricity/Plaque burden/Plaque thickness maximal
- Plaque composition
- Plaque Volume/Percent atheroma volume
- Vessel volume/Lumen Volume
- Compositional Plaque volume (Fibrous/Fibrous-fatty/Necrotic Core/Dense calcium Volume)

Feature Selection by Machine Learning

- Evolving computational method in the classification and regression of variables.
- Relevant features can be extracted from the complex dataset based on a data-driven approach.



Comprehensive CCTA Analysis

Feature Selection
Using **Boruta Algorithm** or
Information Gain

Risk Prediction
with Relevant Plaque Features

Study Population and Data Analysis

Multi-center CCTA-FFR registry (NCT04037163) from 9 centers, 3 countries

1,013 vessels (643 patients) with suspected CAD who underwent both CCTA and FFR (≤ 90 days)

Seoul National University Hospital, Korea

Tsuchiura Kyodo General Hospital, Japan

Ulsan University Hospital, Korea

Keimyung University Dongsan Medical Center, Korea

Inje University Ilsan Paik Hospital, Korea

Samsung Medical Center, Korea

The Second Affiliated Hospital of Zhejiang University, China

Gifu Heart Center, Japan

Wakayama Medical University, Japan

Data Analysis by Independent Core Lab

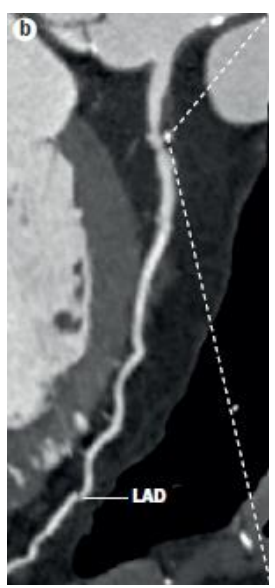
Invasive Coronary Angiography Core Lab
Seoul National University Hospital, Korea

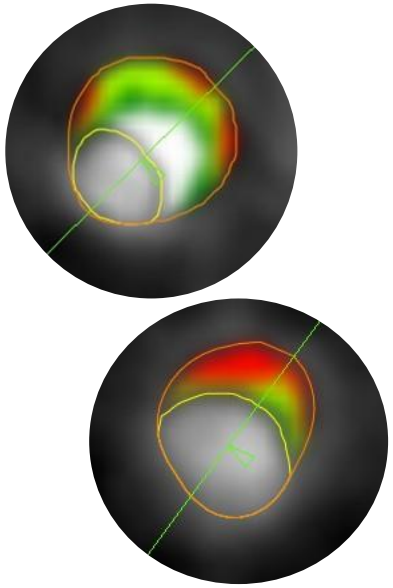
Physiologic Index Core Lab
Seoul National University Hospital, Korea

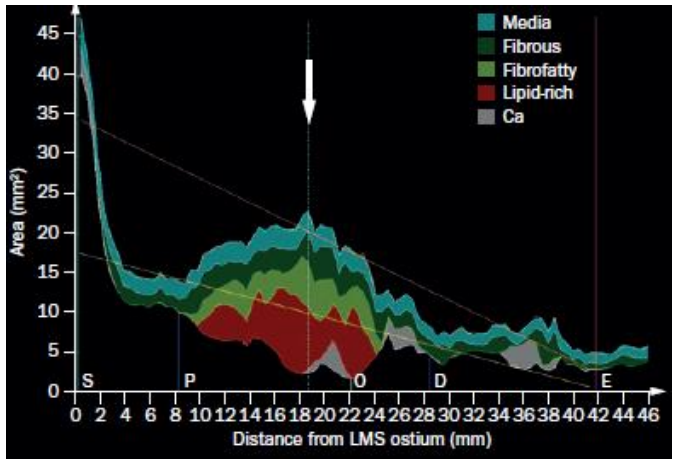
CCTA Analysis Core Lab
Severance Cardiovascular Hospital, Korea

Clinical Outcome Adjudication
Independent Clinical Event Committee

Comprehensive Lumen and Plaque Assessment







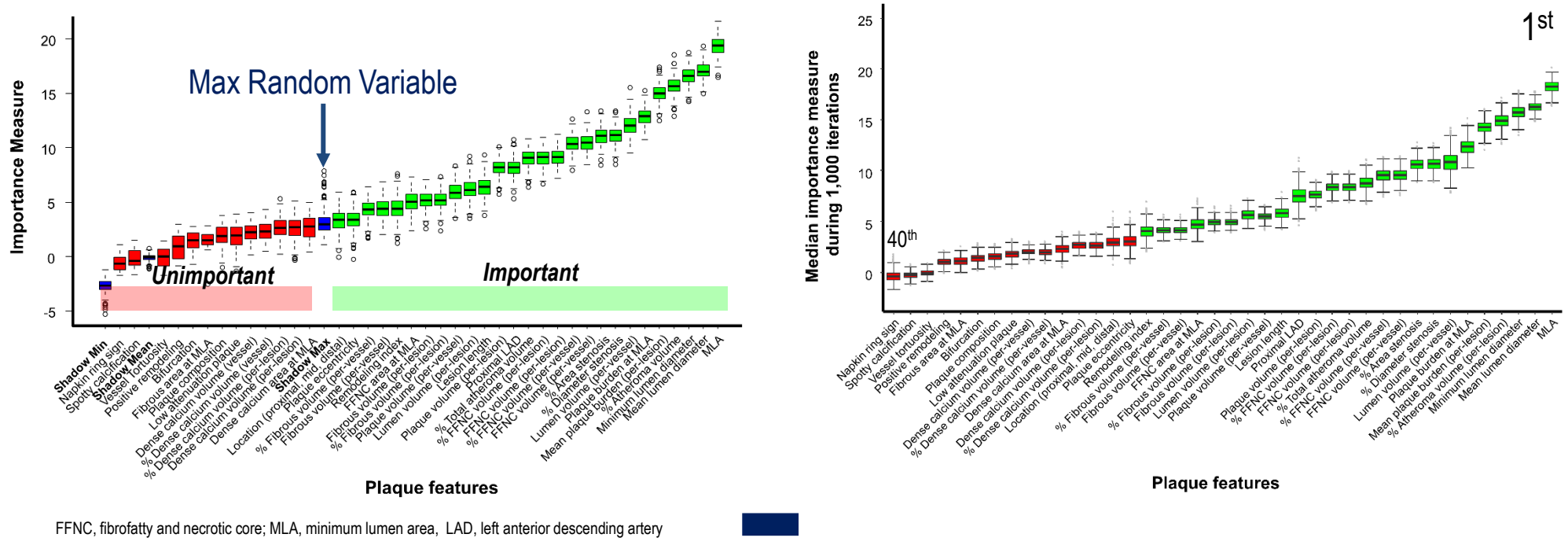
"40" plaque features from CCTA

Lesion Characteristics
Vessels
Location (Proximal/Mid/Distal)
Vessel Tortuosity
Bifurcation
Plaque characteristics
Plaque composition (NCP/CCP/MCP)
Low-attenuation plaque
Positive remodeling
Spotty calcification
Napkin ring sign
Remodeling index
Plaque Eccentricity
Quantitative CT angiographic parameters
% Diameter stenosis
Lesion length (mm)
Minimal lumen diameter (mm)
Mean lumen diameter (mm)
Cross-sectional parameters
MLA (mm^2)
Plaque burden at MLA (%)
Mean plaque burden (per-lesion)
% Area stenosis
Composition
Dense calcium area (mm^2)
Fibrous area (mm^2)
FFNC area (mm^2)

Volumetric quantification (per-lesion)
Plaque volume (mm^3)
Lumen volume (mm^3)
% Atheroma volume
Composition
Dense calcium volume (mm^3)
Fibrous volume (mm^3)
FFNC volume (mm^3)
Normalized by vessel volume
% Dense calcium volume
% Fibrous volume
% FFNC volume
Volumetric quantification (per-vessel)
Plaque volume (mm^3)
Lumen volume (mm^3)
% Total atheroma volume
Composition
Dense calcium volume (mm^3)
Fibrous volume (mm^3)
FFNC volume (mm^3)
Normalized by vessel volume
% Dense calcium volume
% Fibrous volume
% FFNC volume

Boruta Algorithm for Relevant Feature Selection

- Boruta algorithm is one of the most powerful feature selection methods.
- It classified all features as important or unimportant with assigned numeric ranking based on comparison with random variables



FFNC, fibrofatty and necrotic core; MLA, minimum lumen area, LAD, left anterior descending artery

Validation by 10-fold cross-validation with 100 permutation (1,000 iterations)

Yang SH, et al. Unpublished data

Selected 25 Plaque Features After Boruta Algorithm

Comprehensive Plaque Assessment on CCTA

↓

40 Plaque Features

↓

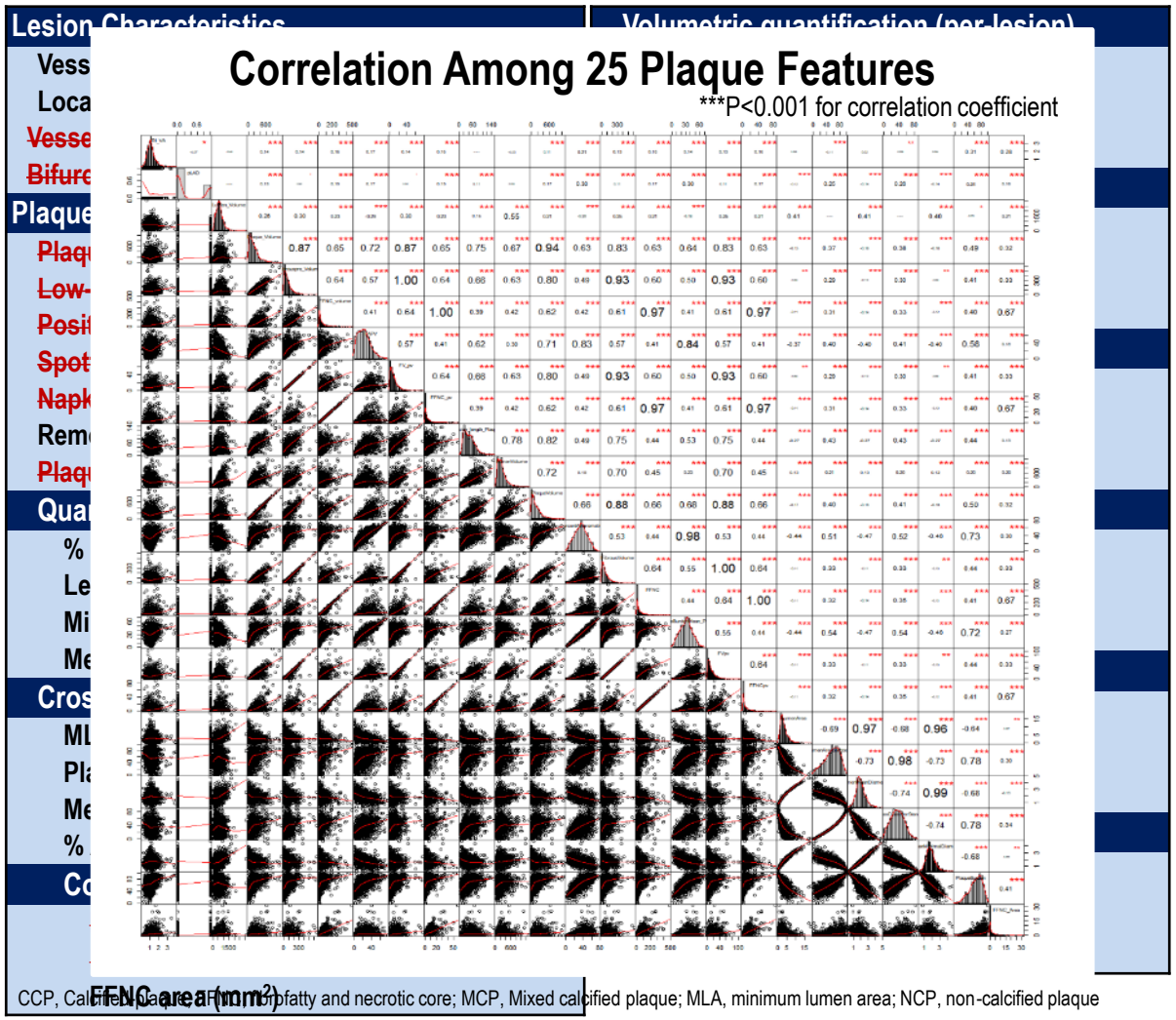
Boruta algorithm
1,000 iterations

↓

25 Plaque Features

Still too many and Need to solve collinearity

For 1,013 vessels

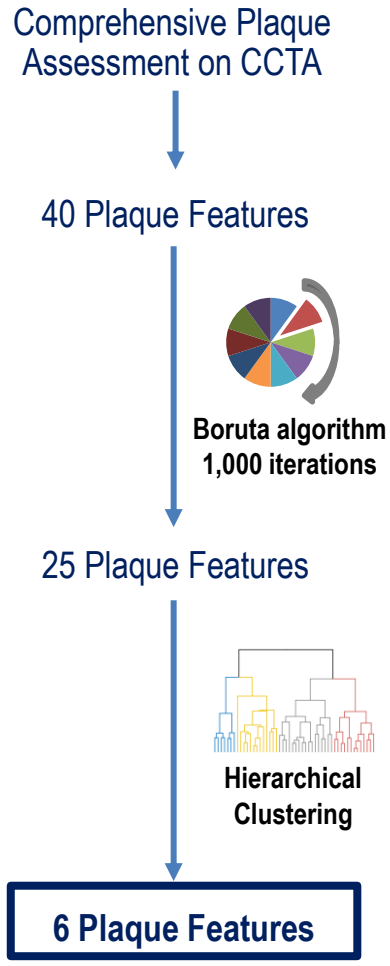


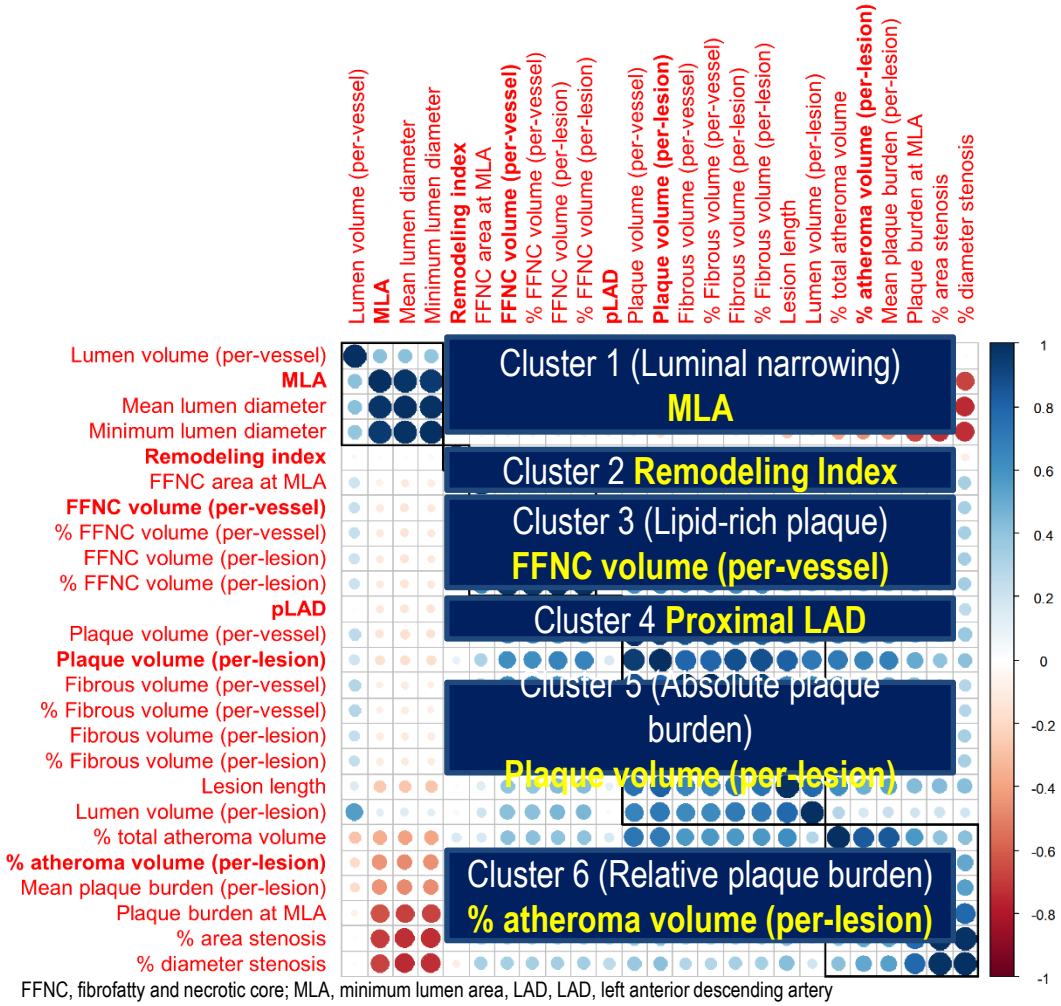
CCP, Calcified plaque; FFNC, fibrofatty and necrotic core; MCP, Mixed calcified plaque; MLA, minimum lumen area; NCP, non-calcified plaque

Yang SH, et al. Unpublished data

Hierarchical Clustering for 25 Plaque Features

- An approach for grouping objects based on their similarity (correlation).
- After hierarchical clustering, only one feature with the highest ranking was finally selected from each cluster.

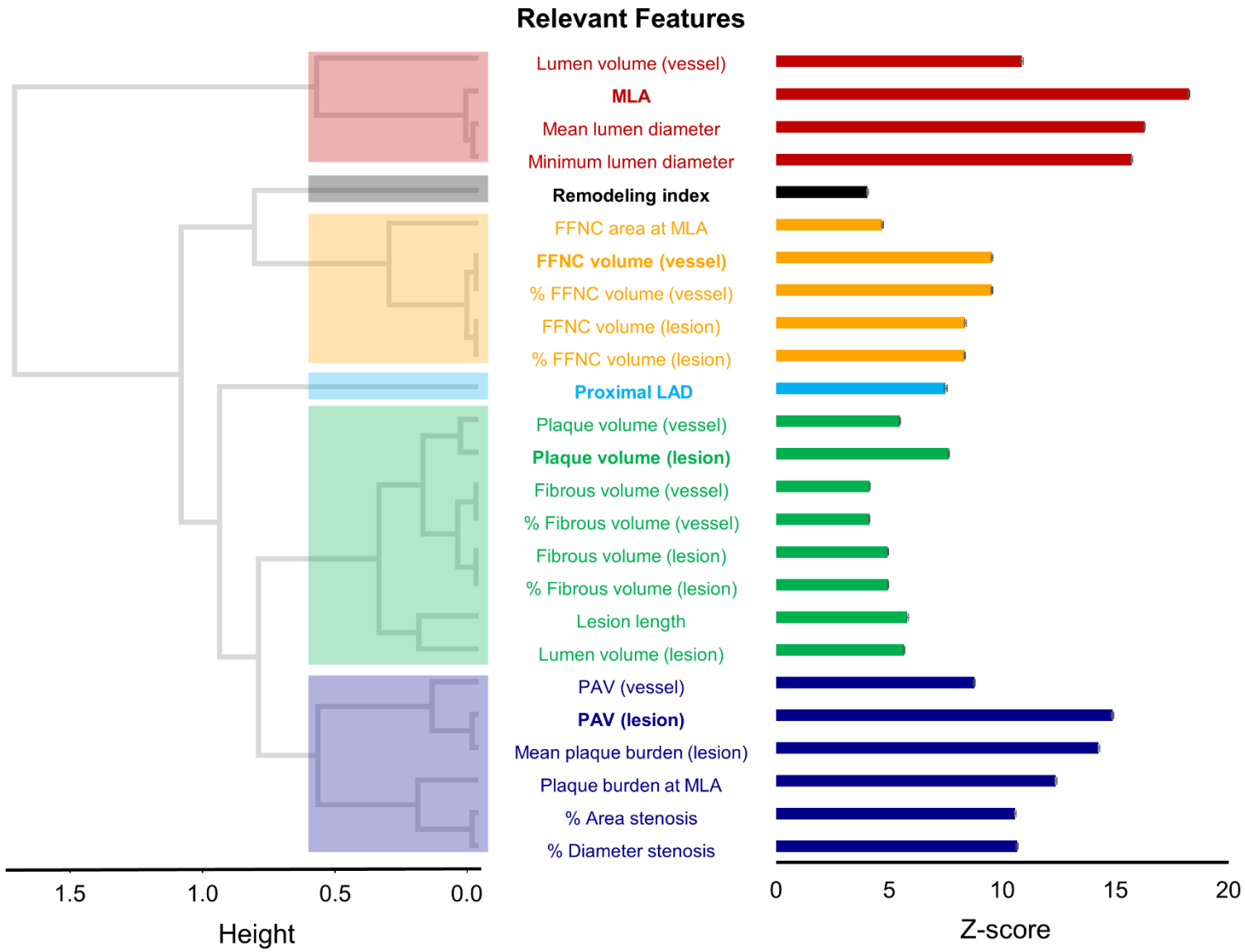




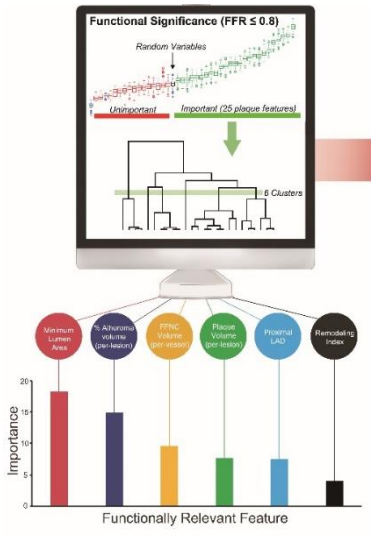
FFNC, fibrofatty and necrotic core; MLA, minimum lumen area, LAD, LAD, left anterior descending artery

Yang SH, et al. Unpublished data

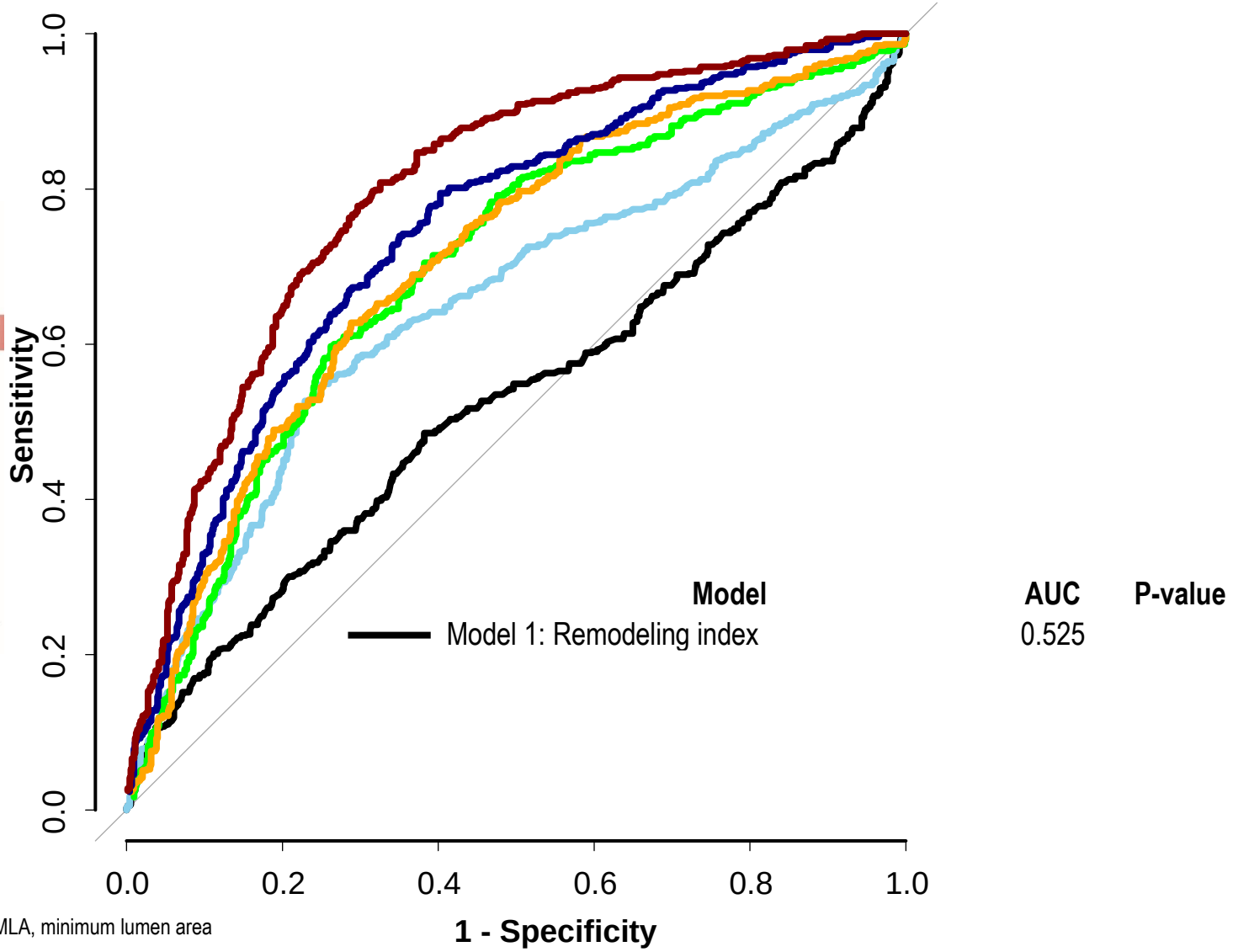
Dendrogram created by hierarchical clustering and importance of features



Performance of new features for prediction of “ISCHEMIA”



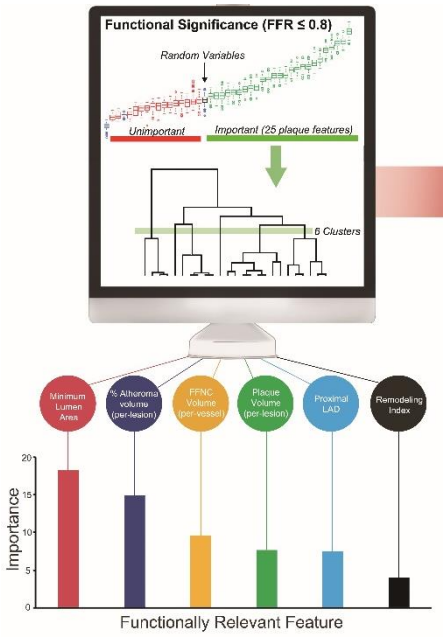
New features



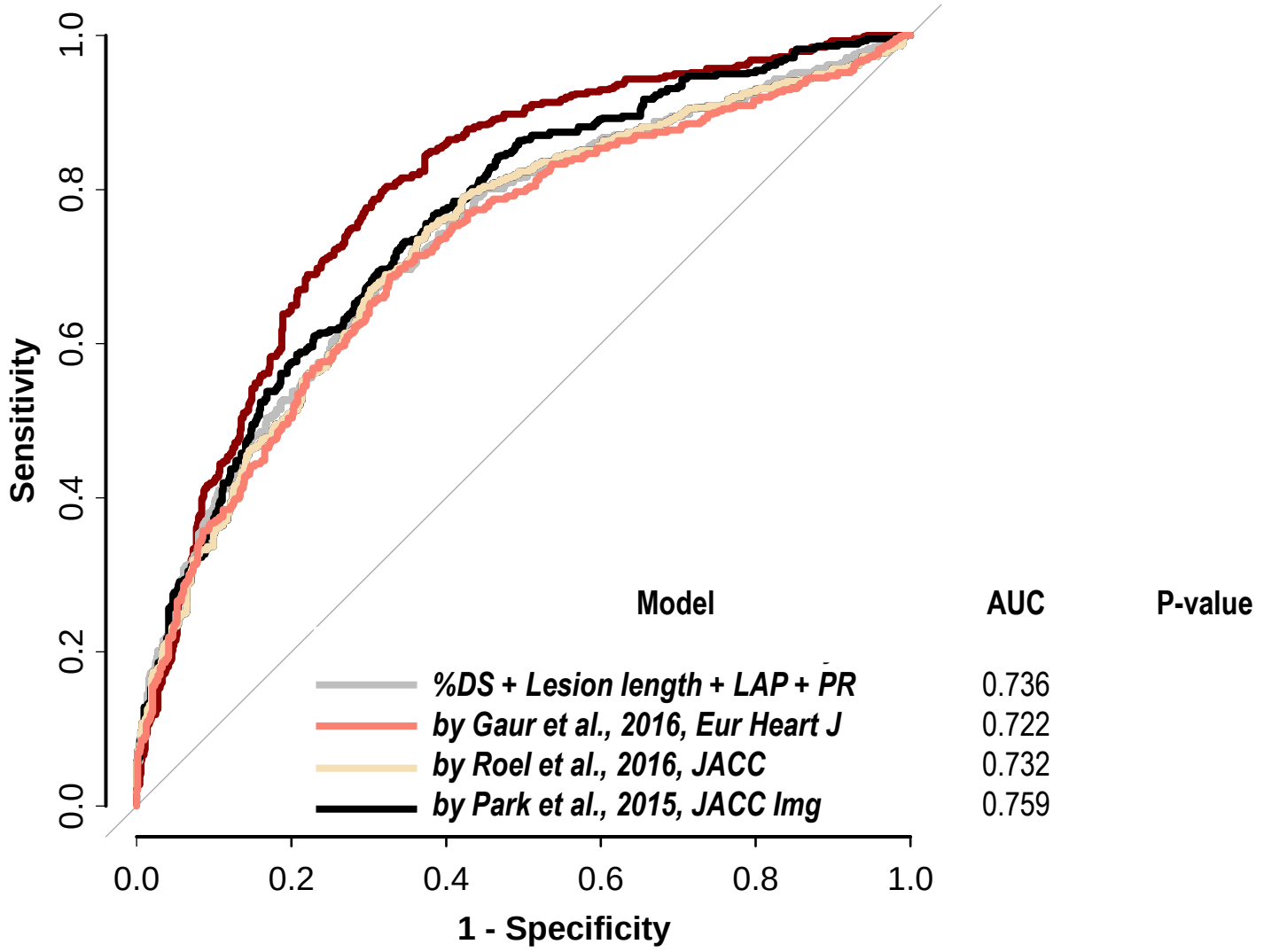
FFNC, fibrofatty and necrotic core; MLA, minimum lumen area

Yang SH, et al. Unpublished data

Performance of new features for prediction of “ISCHEMIA”



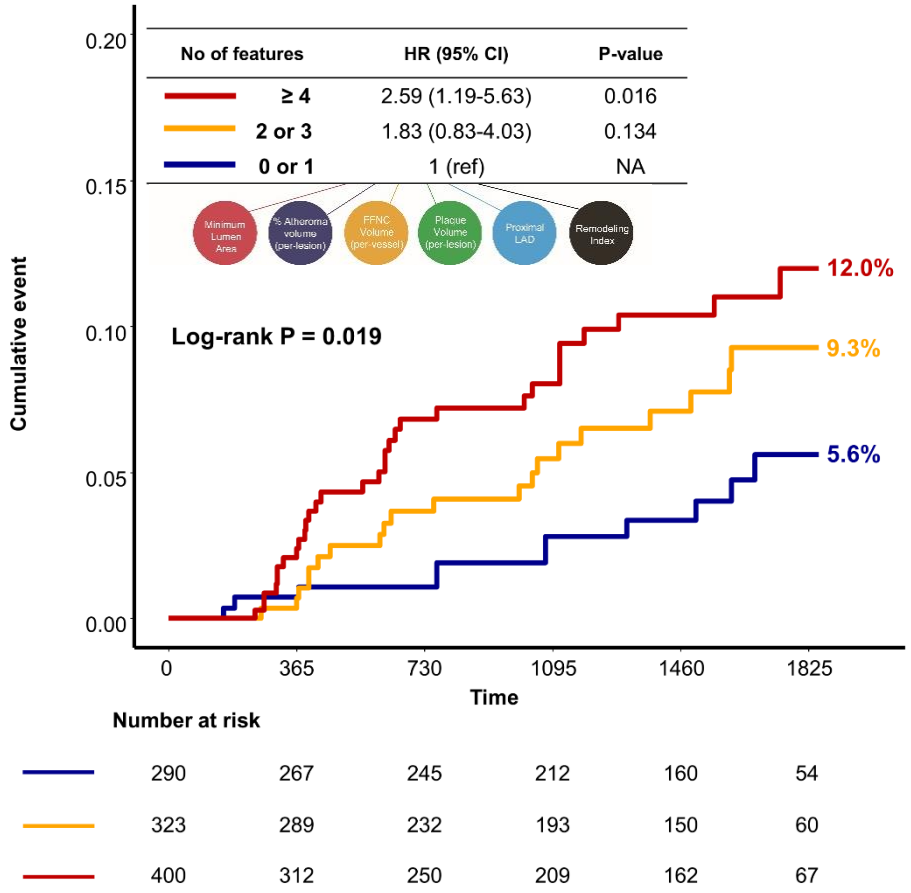
New features



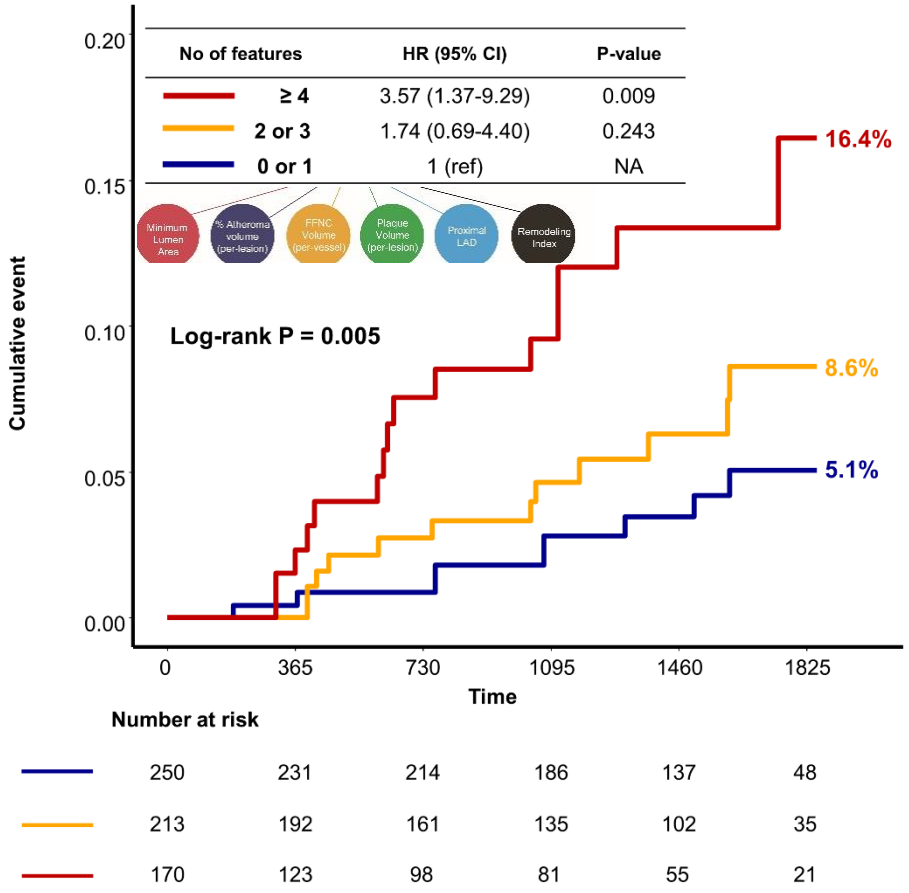
Yang SH, et al. Unpublished data

Performance of new features for prediction of “Clinical Events”

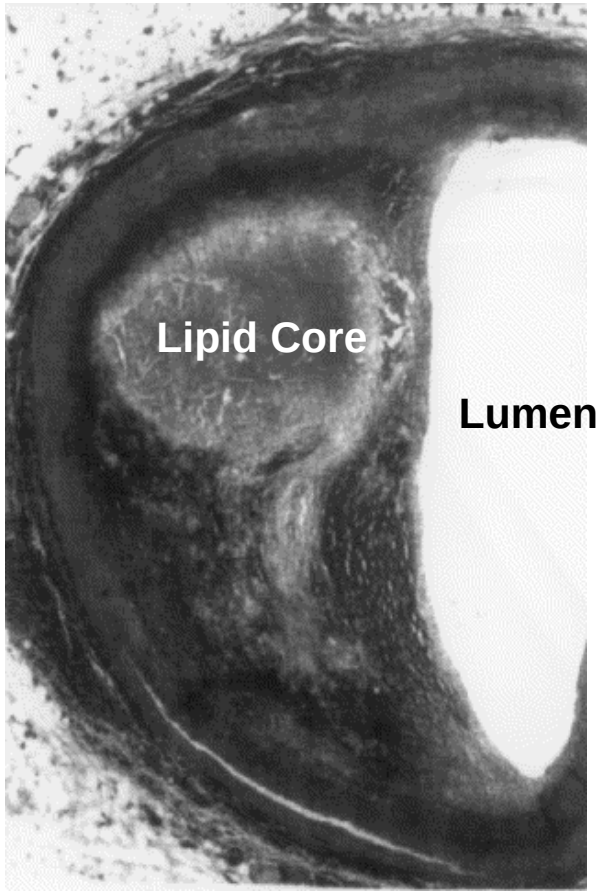
5-year outcomes in Whole population

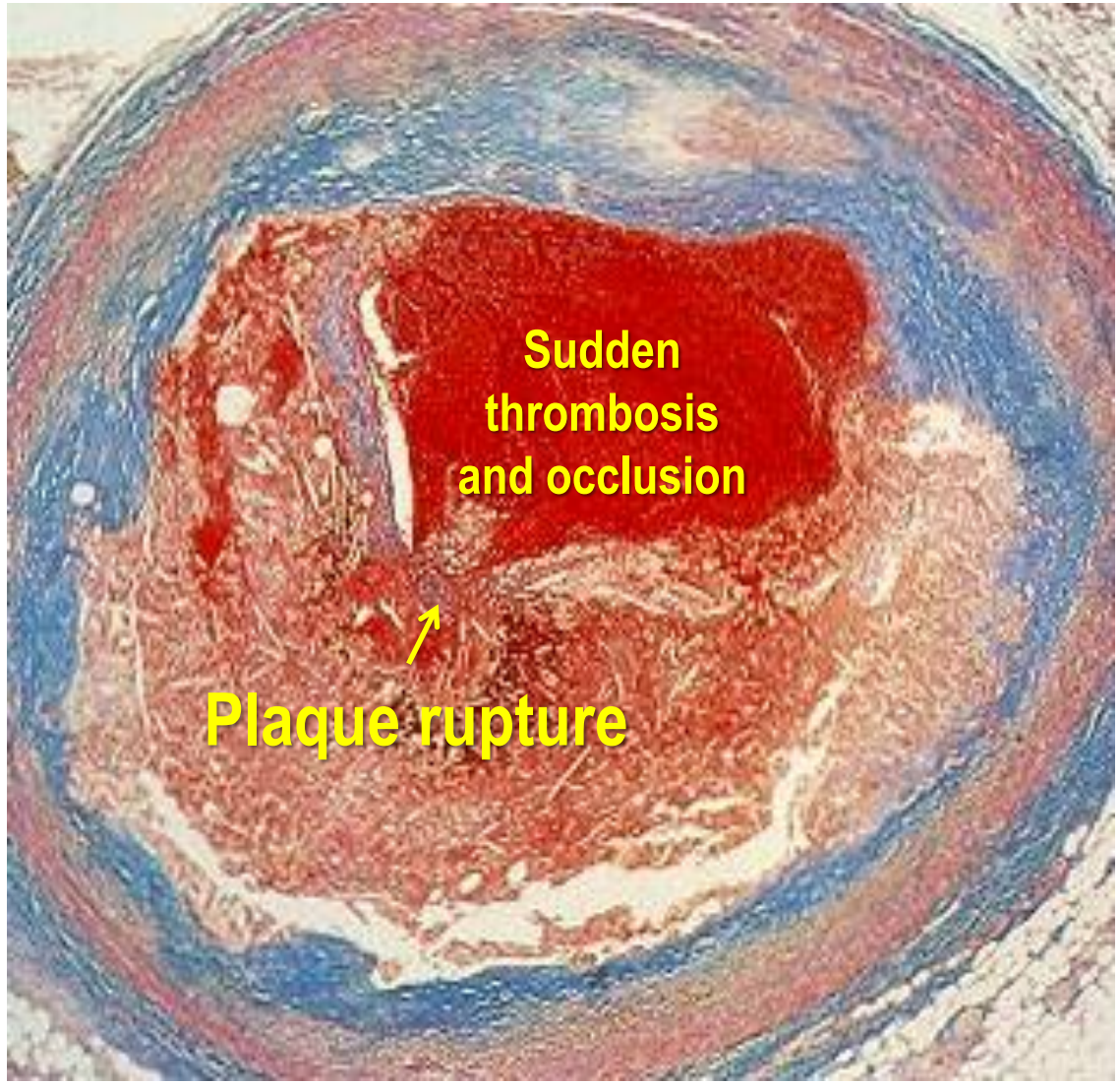


5-year outcomes in Defer group



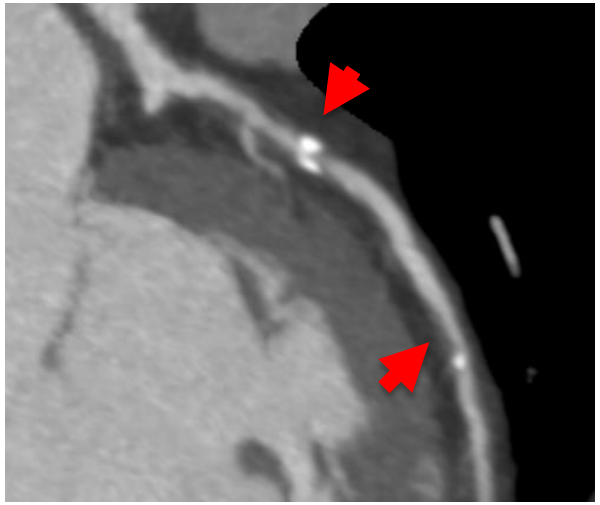
Ischemia is bad, but plaque rupture is fatal!

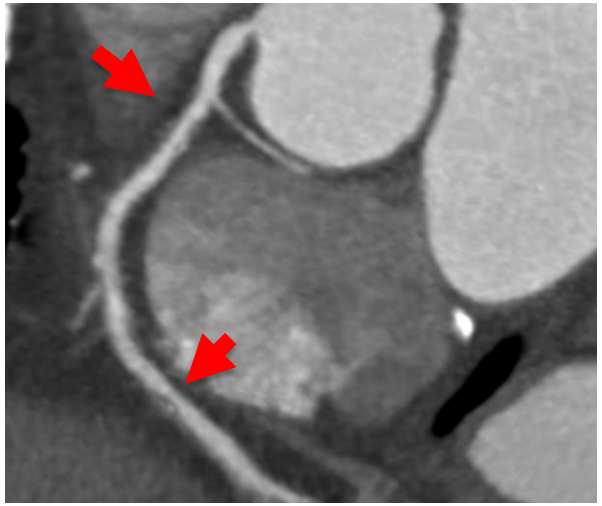




How can we identify the vulnerable plaque?

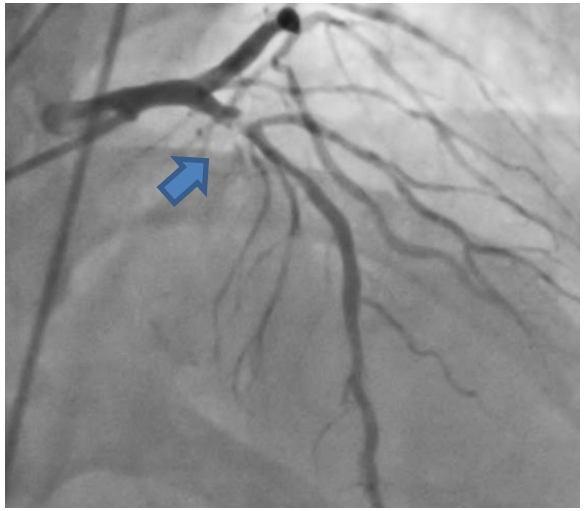
M/69, Asymptomatic

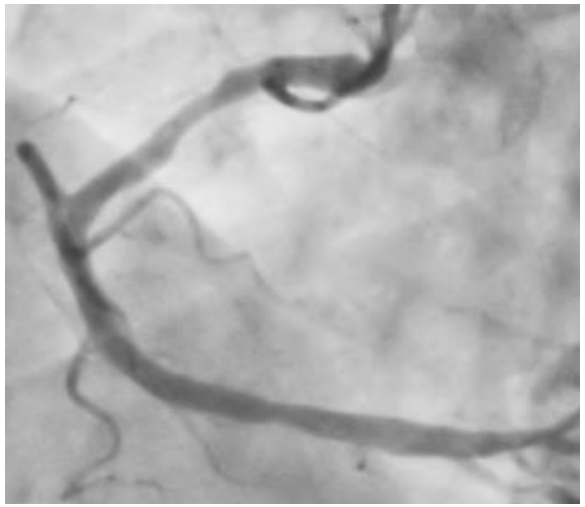




116 days later, the patient visited ER.

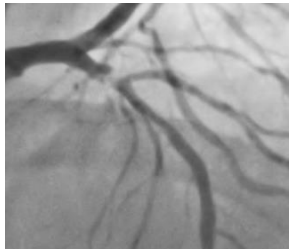
M/70, Myocardial Infarction





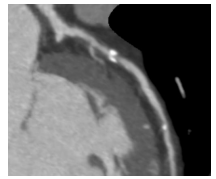
EMERALD study

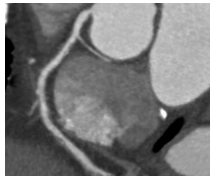
Exploring the **ME**chanism of the Plaque **R**upture in **A**cute Coronary Syndrome using Coronary CT Angiography and Computational**L** Fluid **D**ynamics



Patients with Acute Coronary Syndrome
From 11 International Cardiovascular Centers
(Korea, Japan, Belgium, Denmark, the Netherlands)

Patients who underwent Coronary CT angiography
before ACS event (1 month – 2 year before the event)
(N=120)



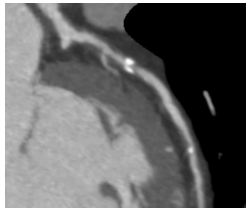


Validation with clinical data, cCTA and coronary angiography (3 independent core labs)

Exclusion (N=41)
- No adequate CT image: 27
- Unclear diagnosis or No definite culprit lesion on Angiography: 10
- No definite lesion on cCTA: 4

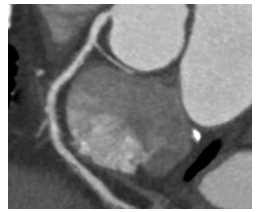
Exclusion by CFD core lab due to CT image quality (N=7)

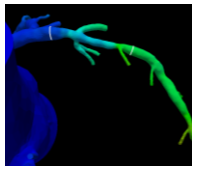
Final Enrollment for cCTA and CFD analysis
(72 patients, 216 lesions)



CASE
Culprit for subsequent ACS (N=66)

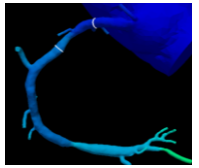
CONTROL
Non- Culprit Lesion (N=150)





cCTA analysis
adverse plaque characteristics
(Core Lab – SNU Bundang Hospital)

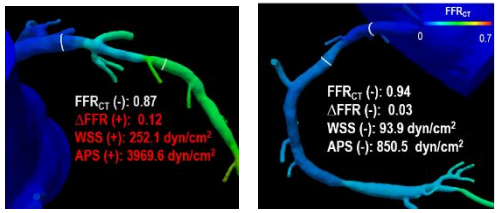
CFD analysis
Non-invasive hemodynamics
(Core Lab - HeartFlow Inc.)



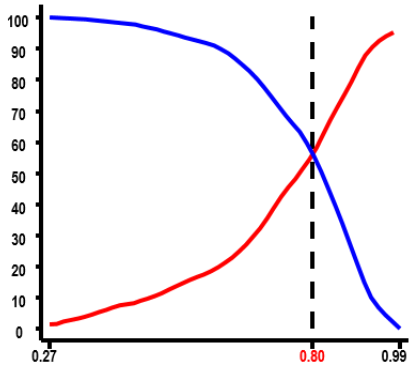
Koo BK. EuroPCR 2016

From FFR to "Adverse Hemodynamic Characteristics (AHC)"

EMERALD study

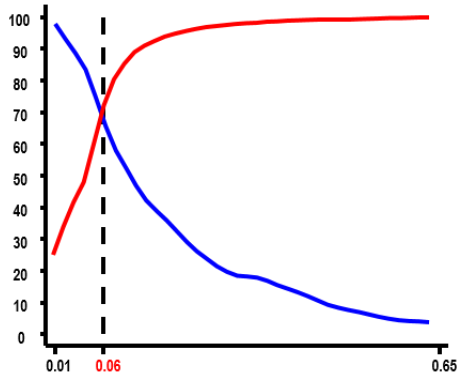


FFR$_{CT}$: 0.80



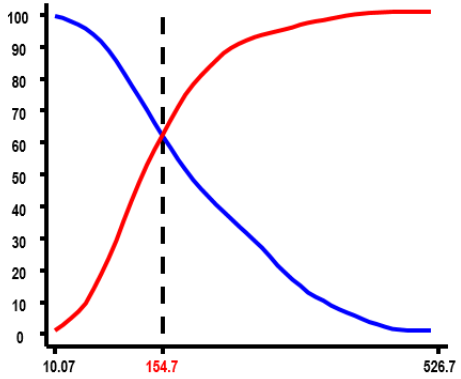
FFR$_{CT}$	
BCV	0.80
Sensitivity	54.6%
Specificity	58.0%
PPV	40.0%
NPV	71.3%
Accuracy	56.8%

△FFR$_{CT}$: 0.06



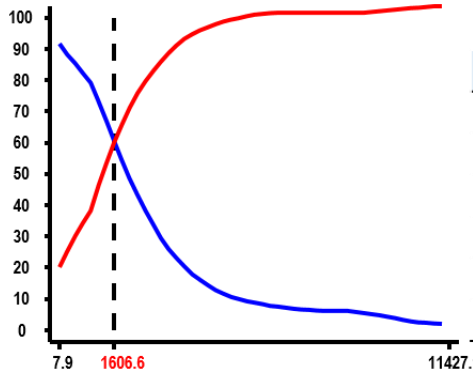
Delta FFR$_{CT}$	
BCV	0.06
Sensitivity	62.3%
Specificity	71.3%
PPV	52.8%
NPV	78.7%
Accuracy	68.2%

Wall Shear Stress (dyn/cm^2): 154.7



Wall Shear Stress	
BCV	154.7
Sensitivity	64.9%
Specificity	61.3%
PPV	46.3%
NPV	77.3%
Accuracy	62.6%

Axial Plaque Stress (dyn/cm^2): 1606.6

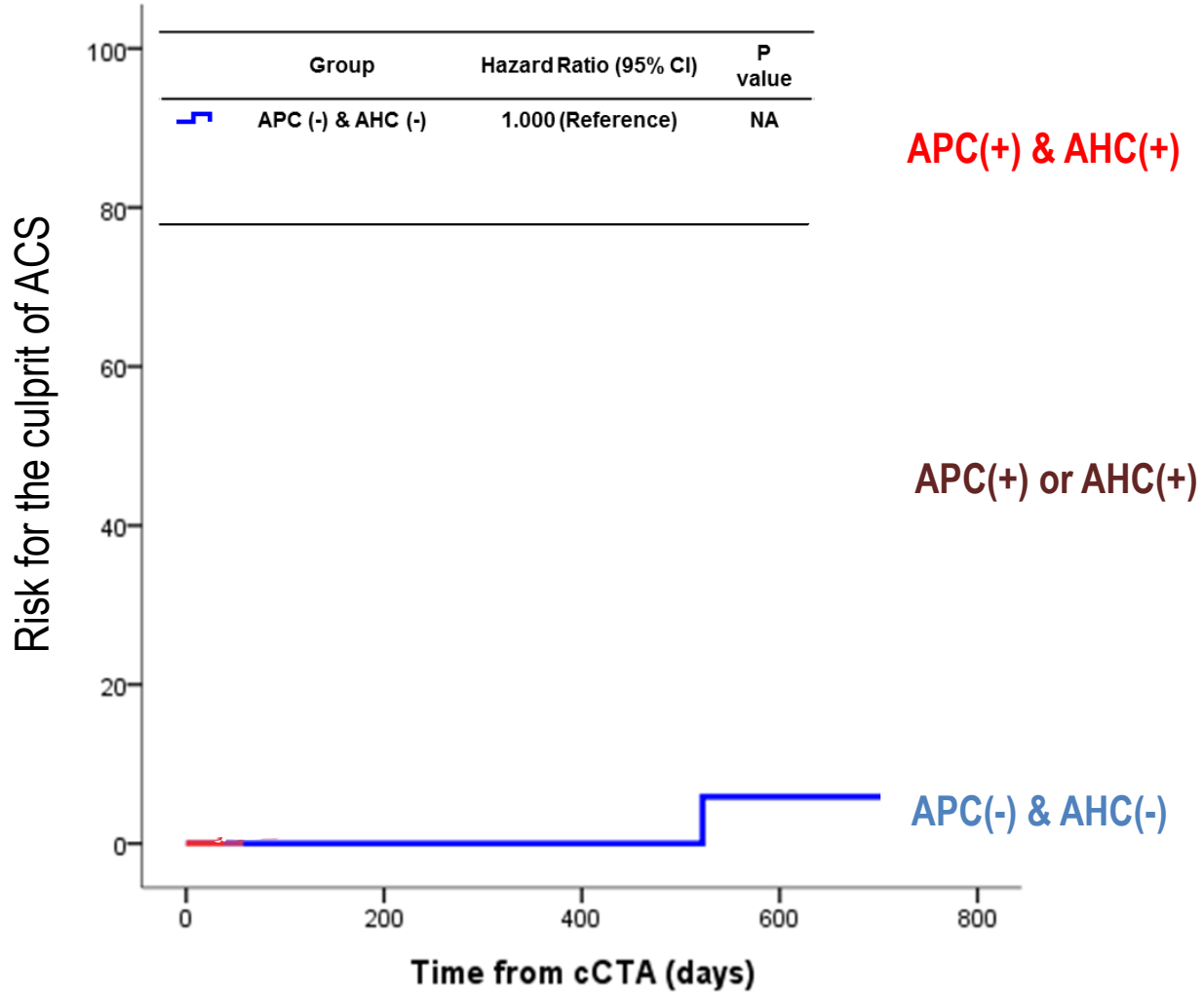


| Raw APS |	
BCV	1606.6
Sensitivity	59.7%
Specificity	62.0%
PPV	41.2%
NPV	77.5%
Accuracy	61.3%

Lee JM & Choi GW, Koo BK….. JACC imaging 2018

Risk for ACS according to

Adverse plaque characteristics (APC) and Adverse hemodynamic characteristics (AHC)



Lee JM & Choi GW, Koo BK….. JACC imaging 2018

Association and prognostic implication of hemodynamics and plaque vulnerability

- Physiologic stenosis severity and the vulnerable plaque features are closely related.
- Both components are associated with the risk of clinical events.
- Integration of coronary hemodynamics and plaque imaging can provide better prognostic information and more appropriate treatment.
- Application of non-invasive comprehensive hemodynamics/3D-plaque assessment and advanced machine learning technique will maximize the benefit of coronary imaging and physiologic assessment