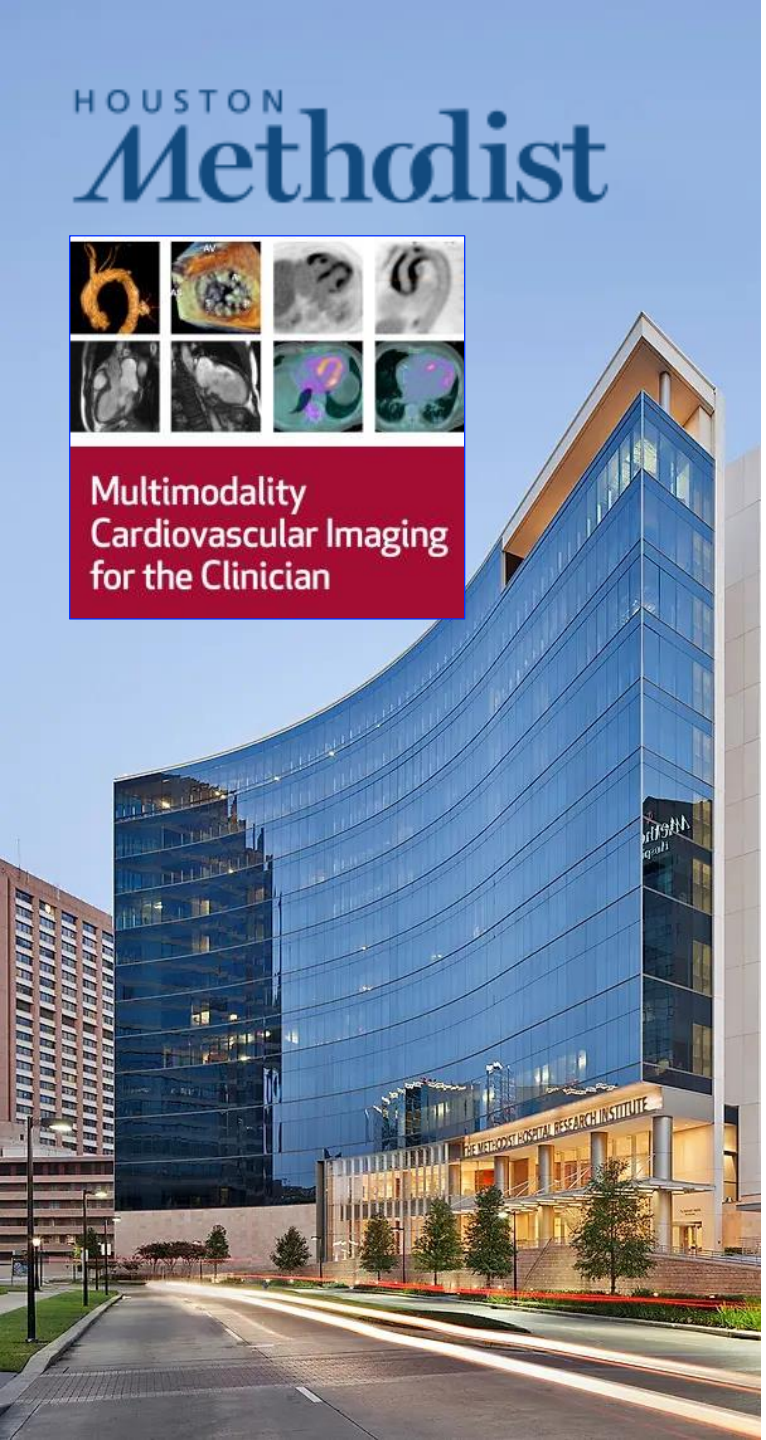


The Vulnerable Plaque:

What is the Most Predictive of Coronary Events?

Jagat Narula MD, PhD, MACC
Executive Vice President and Chief Academic Officer
K. Lance Gould Distinguished University Chair for Coronary Pathophysiology

UTHealth
The University of Texas
Health Science Center at Houston

"Of course it's empty!

DISCLOSURES

No financial conflicts of interest, but
do admit to a major perceptible conflict: I am a diehard fan and proponent of CT Angiography Imaging, esp. for high-risk plaque.

Revascularization in Chronic Coronary Disease

DOGMA (noun) ['dȯg-mə]
- Statement of ideas accepted uncritically.
- A doctrine authoritatively affirmed.
- Doctrines, tenets, or beliefs, collectively.
- Rules that cannot be questioned.

MANAGEMENT OF CCS:

CAD is Bad

[It causes hard events]

Progressive Atheroma

↓

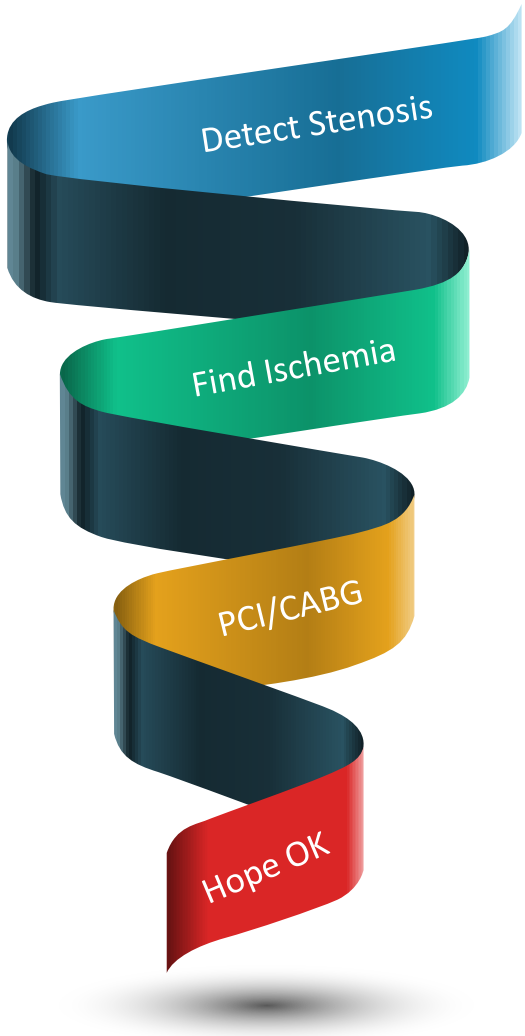
Significant Stenosis

↓

Reduces Flow [so, Ischemia]

↓

Causes Events



Find Coronary Stenosis

Since it Causes Ischemia

Find Ischemia

Since it Causes Events

Treat Stenosis

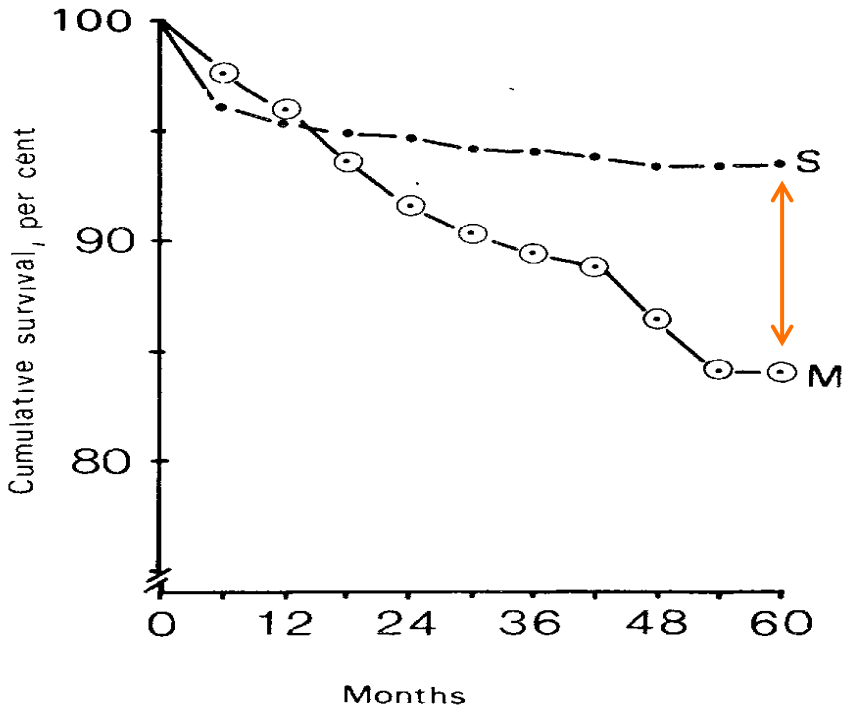
This Will Reduce Ischemia

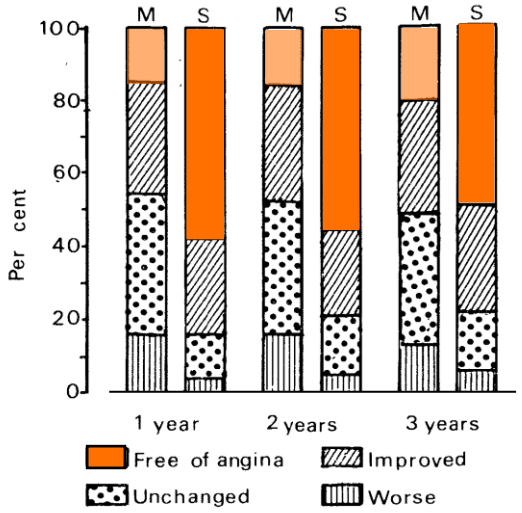
Improve Outcomes

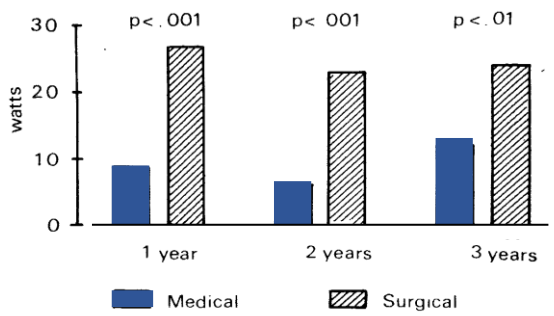
Fixing Stenosis & Reducing Ischemia will automatically mean less MI & Deaths

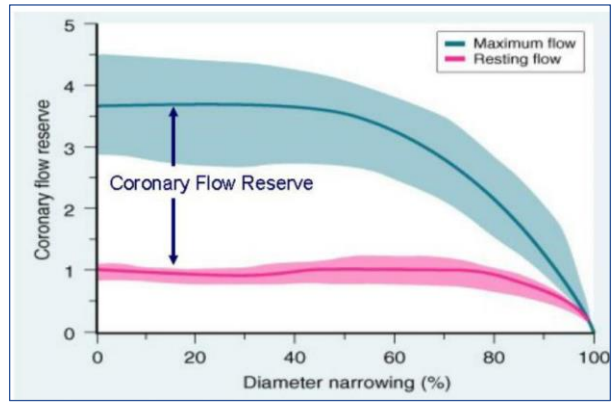
PROSPECTIVE RANDOMISED STUDY OF CABG IN STABLE ANGINA PECTORIS

The European Coronary Surgery Study Group



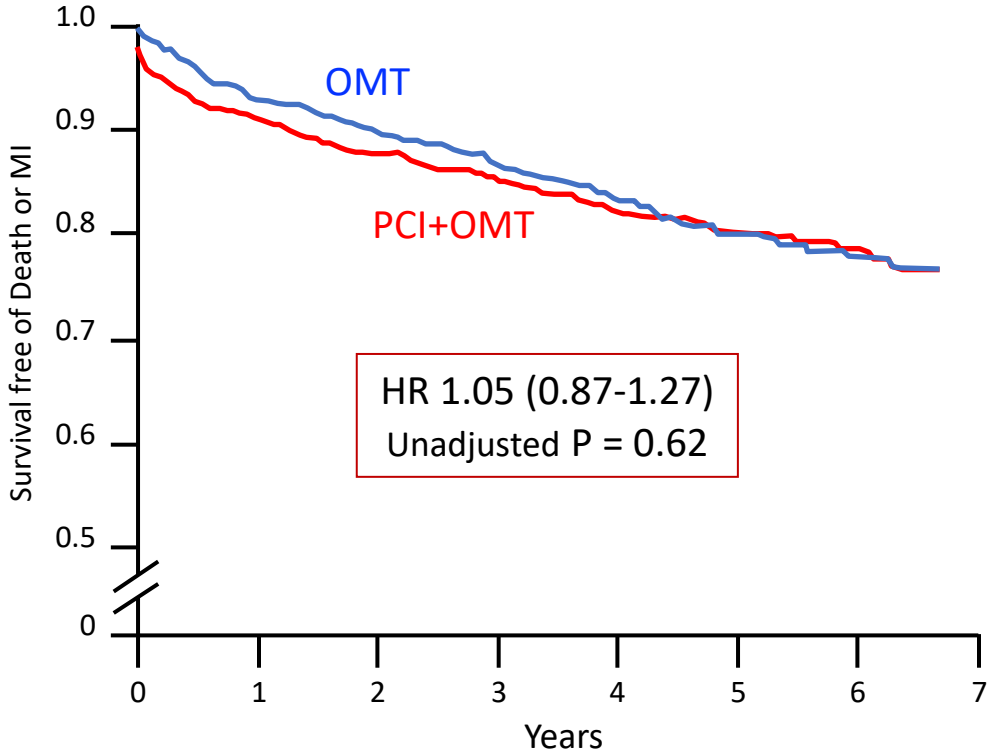




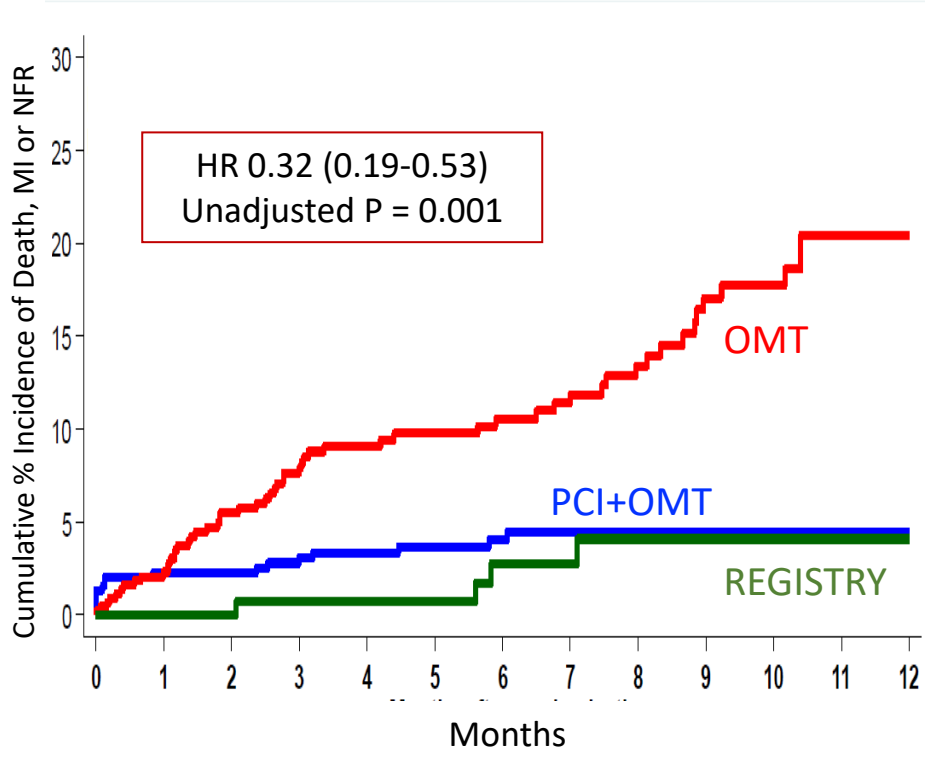


Lancet, 6 Sep.1980

COURAGE: Treatment effect on primary outcome



FAME 2: FFR-Guided PCI vs. OMT in Stable CAD

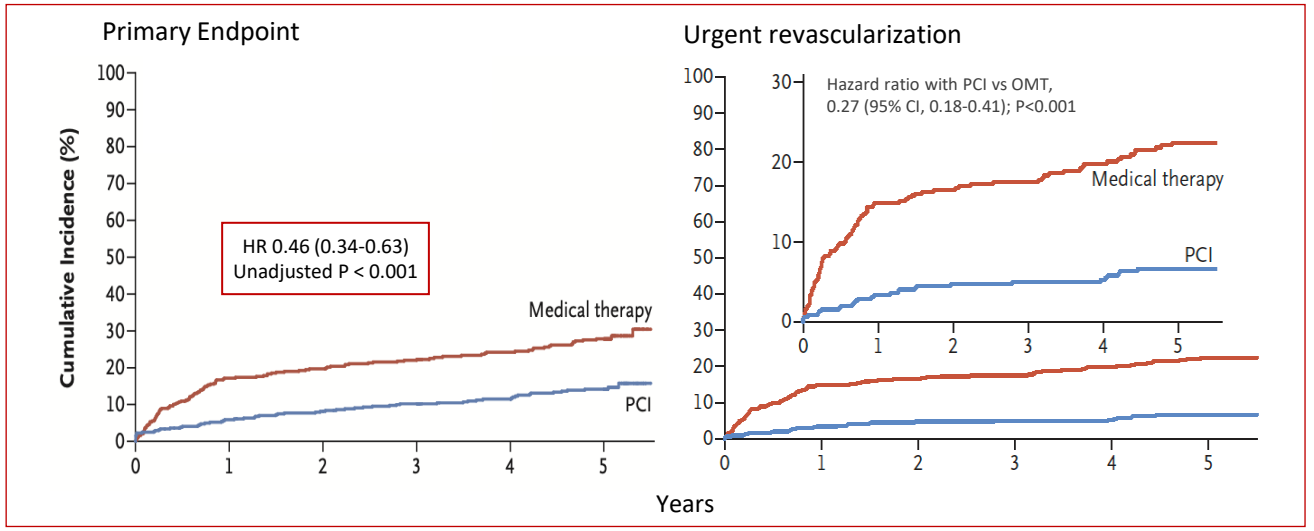


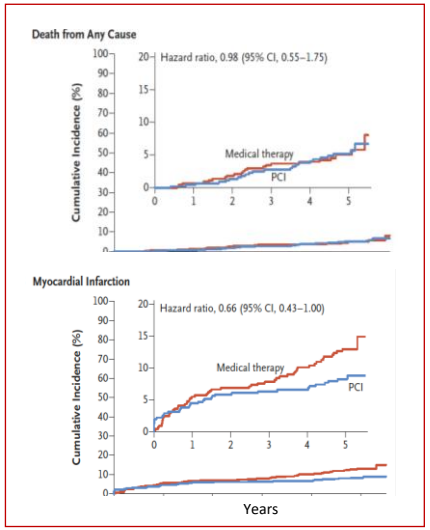
New data were needed. And a courageous trial refined our views!
And then the famous study of functional significance of disease arrived

Boden WE et al. *NEJM.* 2007;356:1503-16; Bruyne et al. NEJM 2012;367:991-1001

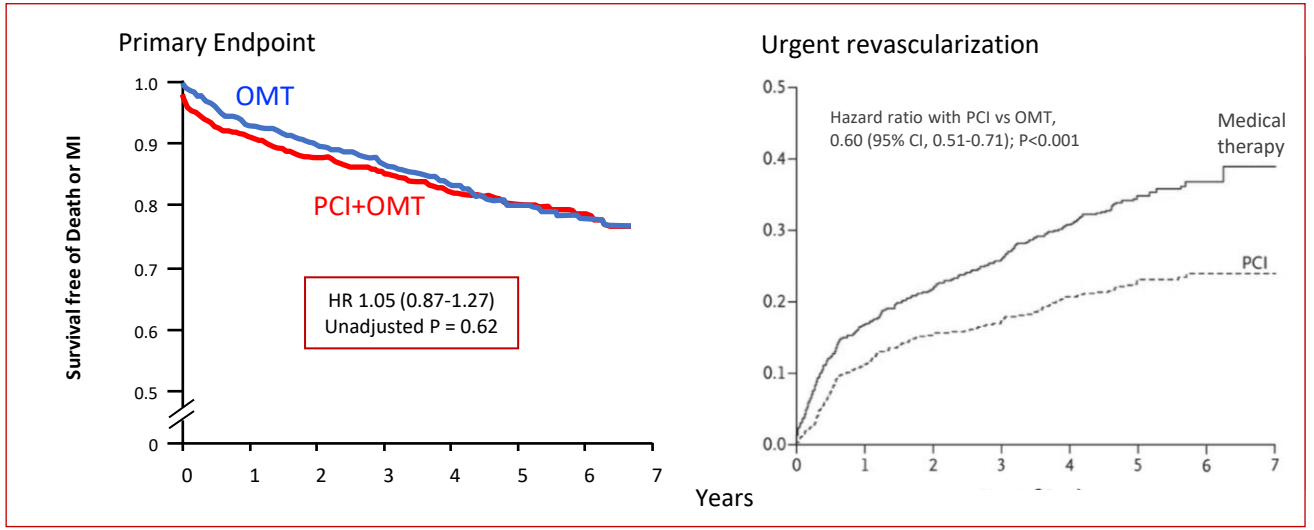
What is more enduring: COURAGE Or FAME?

FAME 2: FFR-Guided PCI vs OMT in CAD

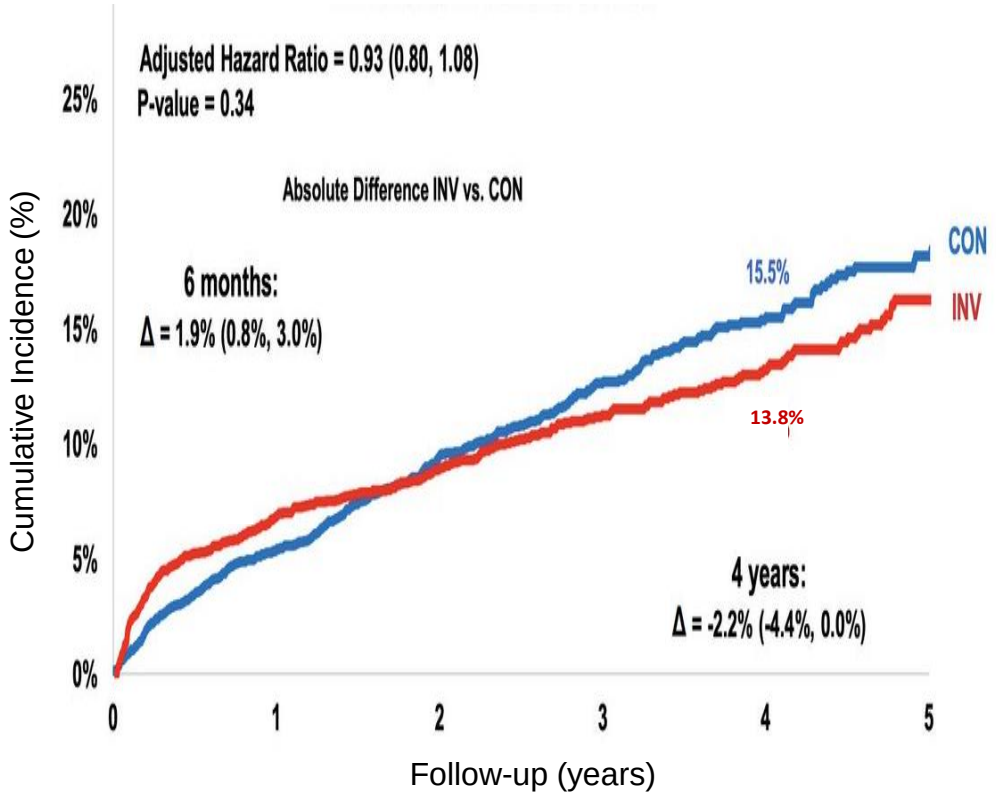




COURAGE

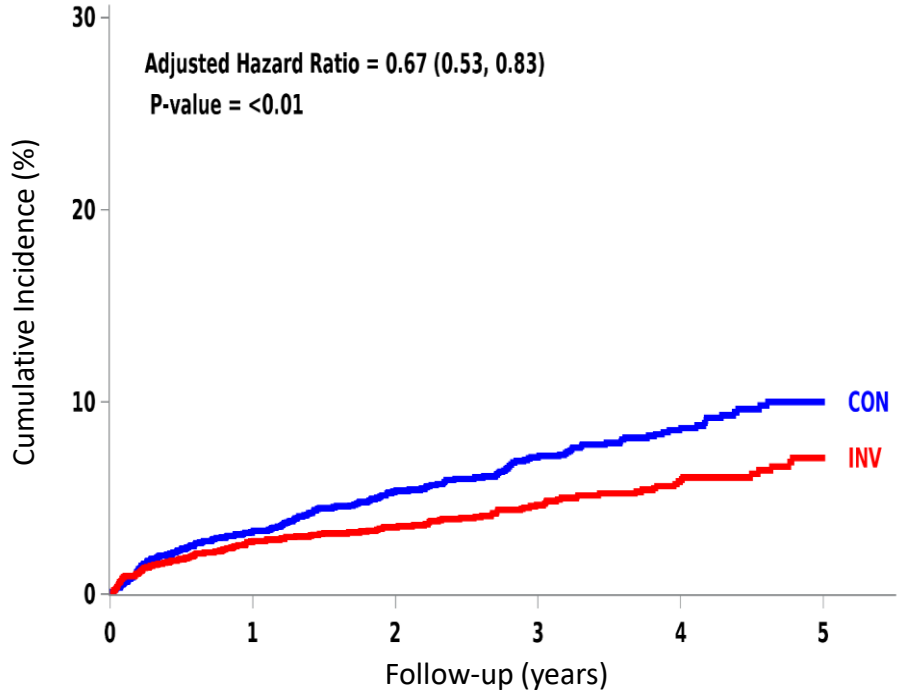


ISCHEMIA: PRIMARY OUTCOME: CV DEATH, MI, hUA, hHF or rCA



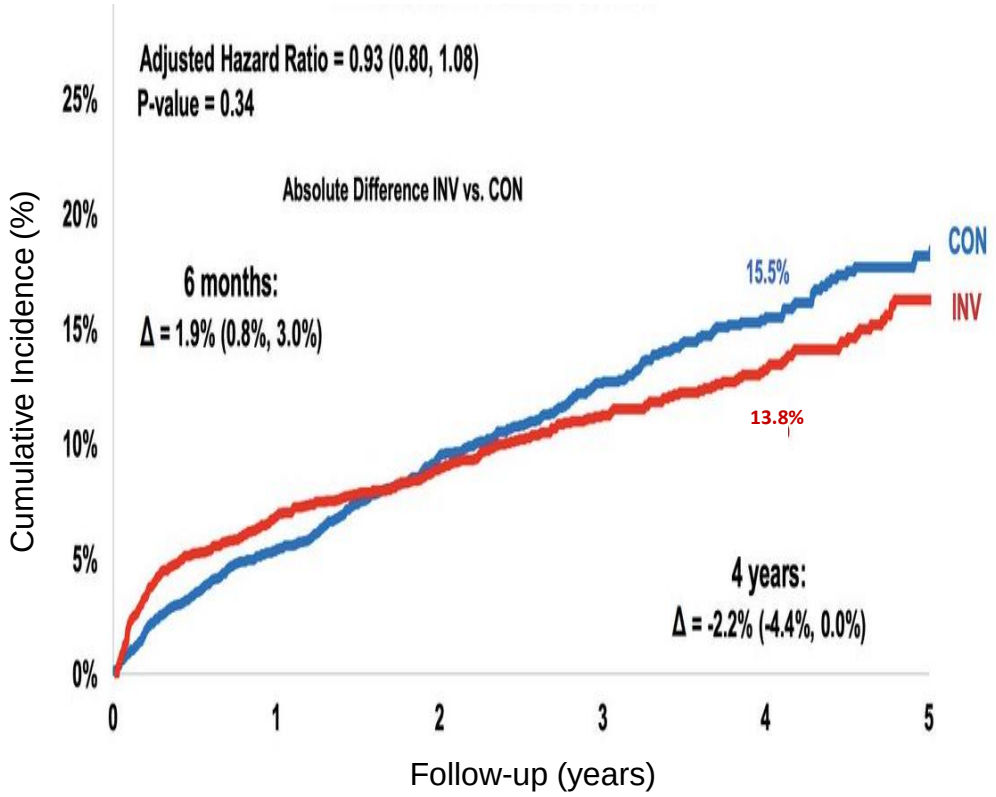
Maron et al. NEJM 2020; 382:1395-1407

Spontaneous MI Types 1, 2, 4b, or 4c



Spontaneous MI rate: Conservative (5.8%); Invasive (2.8%); ARR (3%), RRR (52%)
DID ISCHEMIA DEMONSTRATE FAILURE OF REVASCULARIZATION TO REDOCE MI,
OR FAILURE OF ISCHEMIA TESTING TO GUIDE REVASCULARIZATION

ISCHEMIA: PRIMARY OUTCOME: CV DEATH, MI, hUA, hHF or rCA



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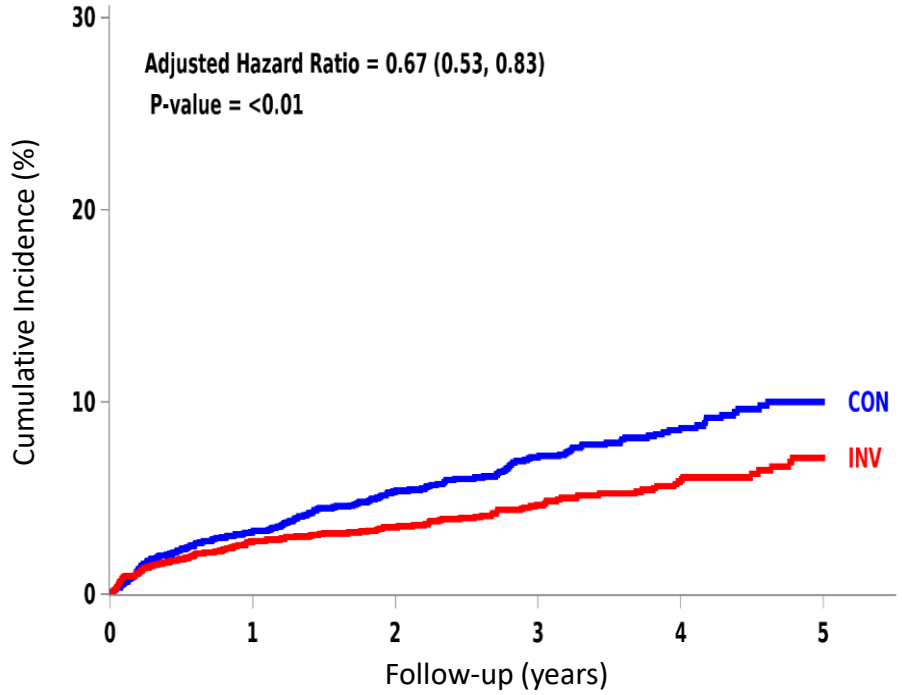
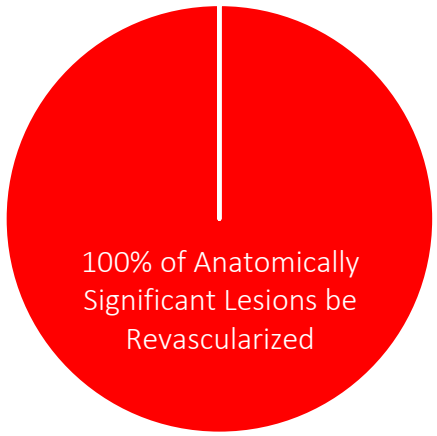


Spontaneous MI rate: Conservative (5.8%); Invasive (2.8%); ARR (3%), RRR (52%)
DID ISCHEMIA DEMONSTRATE FAILURE OF REVASCULARIZATION TO REDUCE MI,
OR FAILURE OF ISCHEMIA TESTING TO GUIDE REVASCULARIZATION

EVOLVING PARADIGMS…

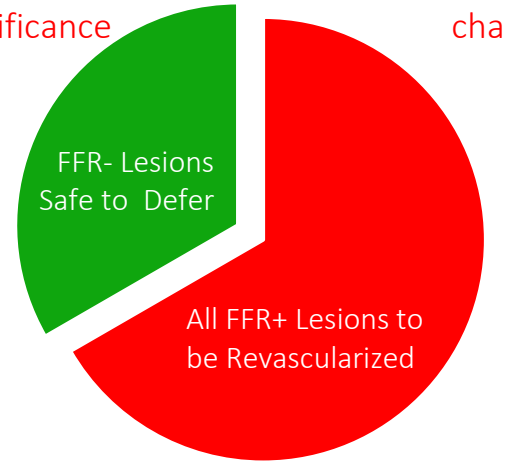


What Did We Think?

CASS and other mega-surgical trials of revascularization suggested relevance anatomical stenosis

FIRST Deferral: FFR- lesions

FFR assessment of functional significance



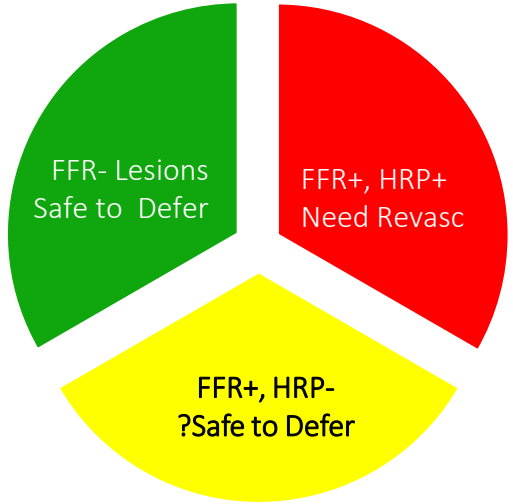
What Do We Think?

COURAGE suggested revascularization based on anatomical stenosis alone is NOT indicated

FAME Trial demonstrated safety of deferral of FFR- lesion, regardless of the degree of luminal stenosis

SECOND Deferral: FFR+ but HRP-

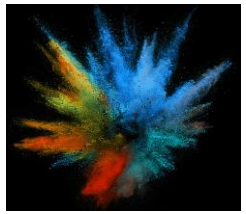
CT assessment of HRP characteristics



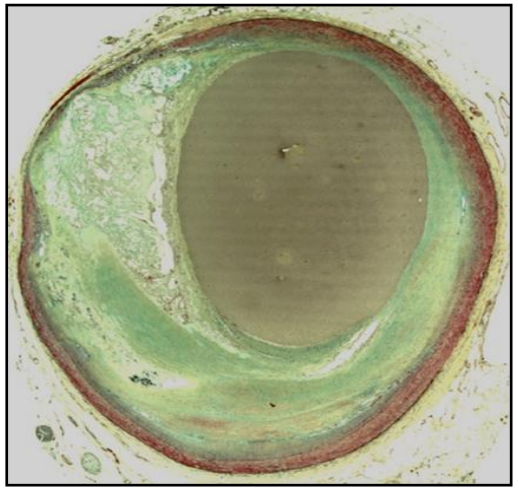
What Should We Think?

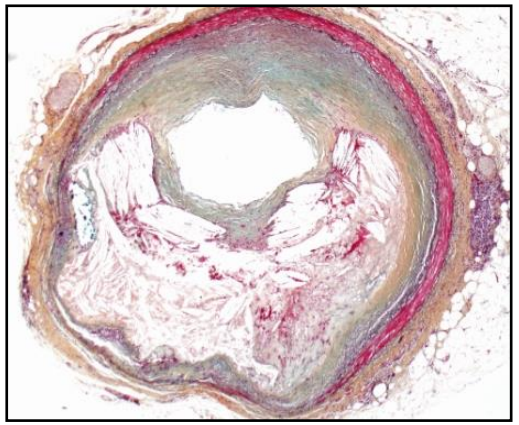
FAME-2: 50% of FFR+ on OMT remain event-free with no difference in rate of death and MI, revascularization, angina

Ahmadi, Narula. JACC. 2019:74:1608-17



Eventful and event-prone plaques: Histopathological Characteristics

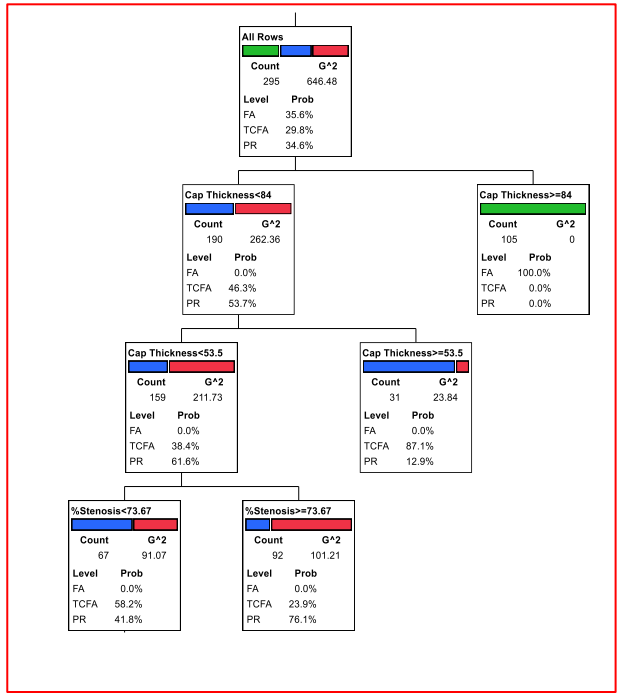




Narula, Virmani et al. JACC 2013

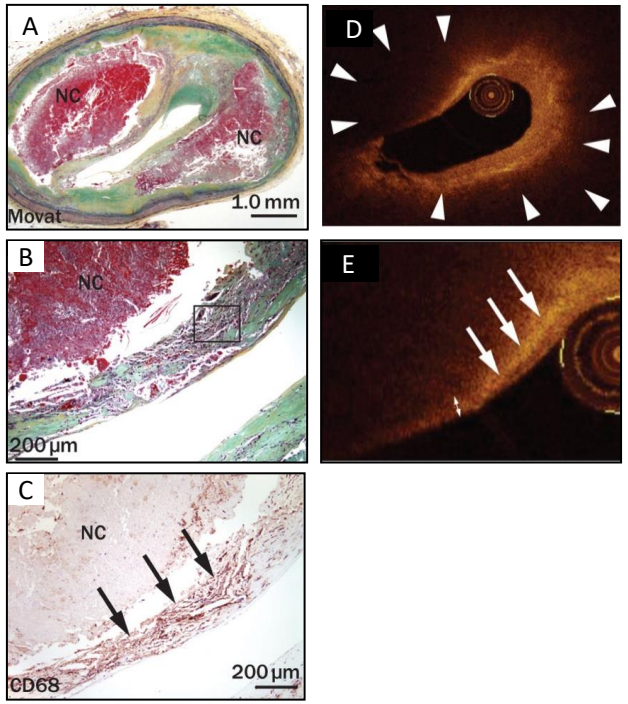
The HIGH-RISK Plaques…

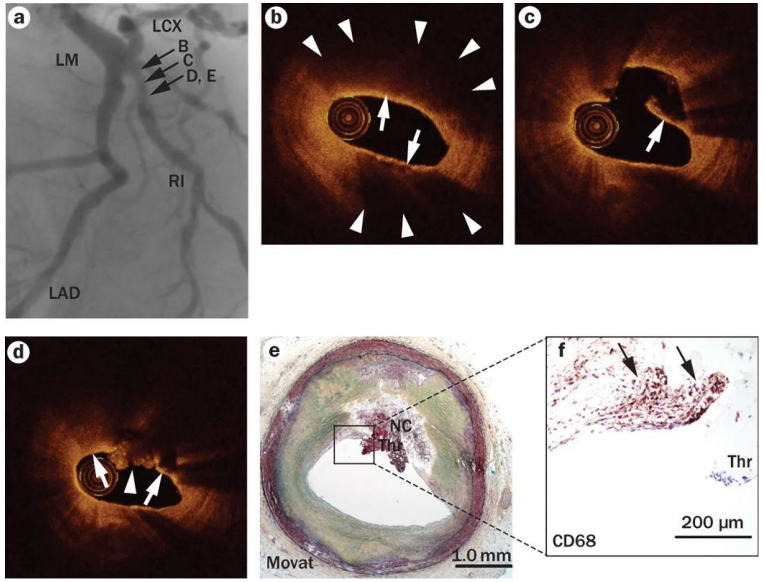
Recursive Partitioning Analyses



Narula et al. JACC 2013

Post-mortem

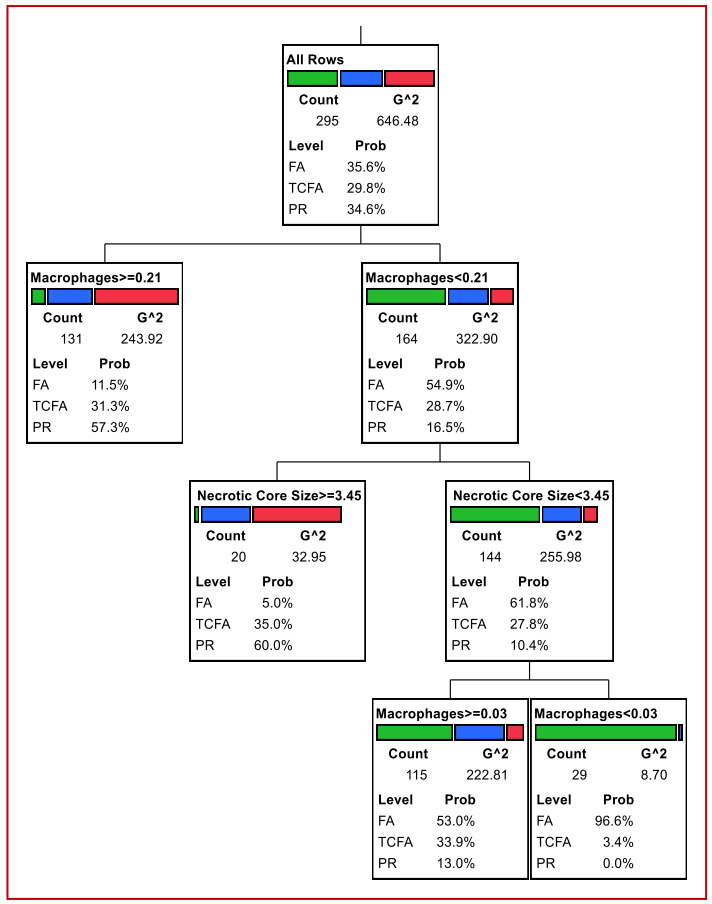




Narula et al. Nature Rev Cardiol 2015

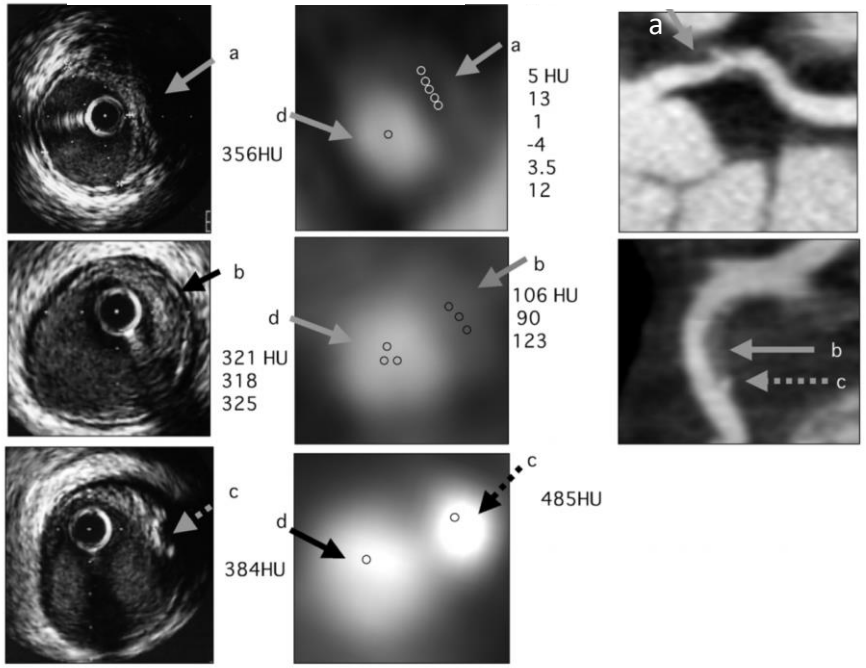
Morphology of event-prone plaques and CTA-based adverse plaque characteristics

Recursive Partitioning Analyses



Narula et al. JACC 2013

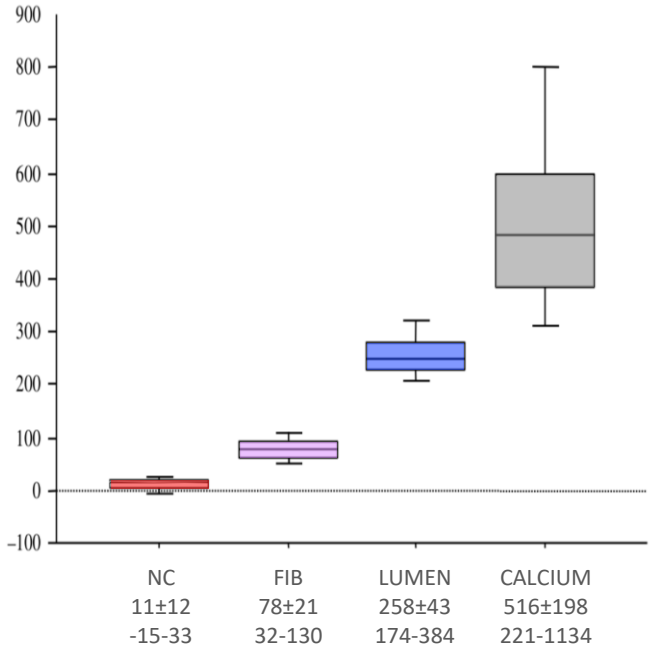
IVUS | CT: X-sectional | CT: Curved MPR



Motoyama, Narula et al. Circulation J 2007

CT Angiographic Characteristics, and Intravascular Ultrasound

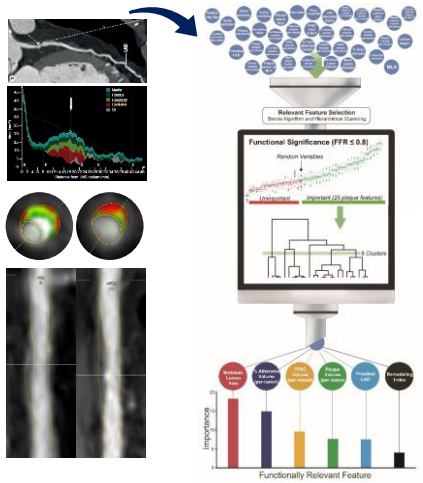
CTA [HU]



<0.0001, Nonparametric Kruskal-Wallis Tests

Motoyama, Narula et al. JACC 2007

Prognostic Implications of Selected Plaque Features

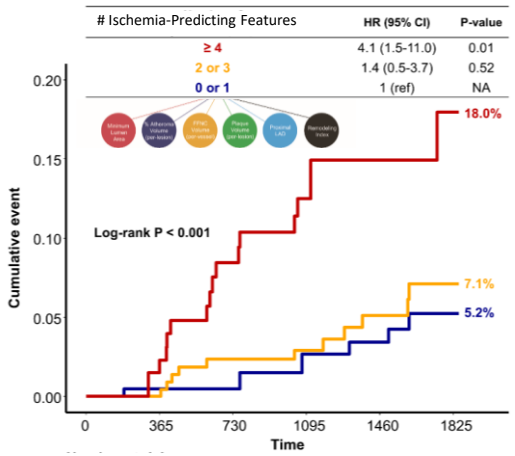


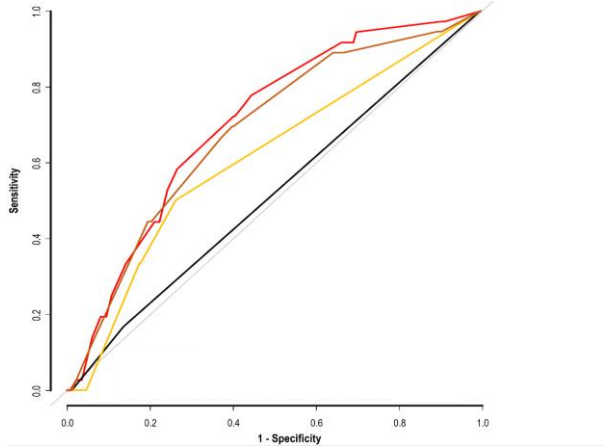
Ischemia-Predicting
Plaque Features

MLA, PAV, NCV, PV, pLAD, RI

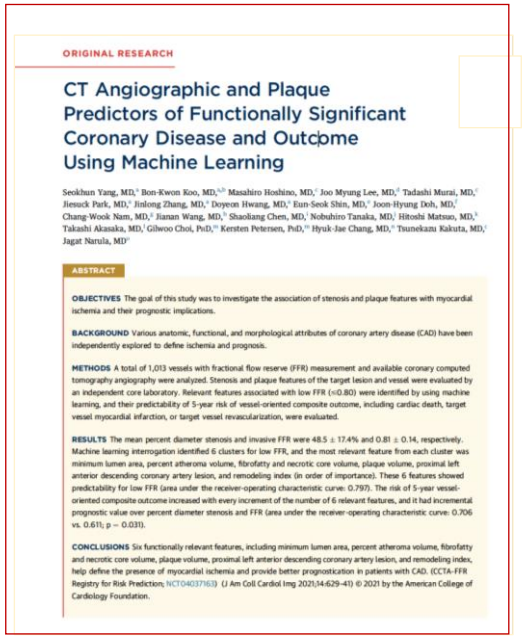
OMT GROUP

# Ischemia-Predicting Features	HR (95% CI)	P-value
≥ 4	4.1 (1.5-11.0)	0.01
2 or 3	1.4 (0.5-3.7)	0.52
0 or 1	1 (ref)	NA





Model	AUC	P-value
Model 1: % Diameter stenosis	0.515	0.030
Model 2: % Diameter stenosis + FFR ≤ 0.80	0.611	0.226
Model 3: % Diameter stenosis + No. of six features	0.681	0.202
Model 4: % Diameter stenosis + FFR ≤ 0.80 + No. of six features	0.706	0.031 <0.001



ORIGINAL RESEARCH

CT Angiographic and Plaque Predictors of Functionally Significant Coronary Disease and Outcome Using Machine Learning

Seokhun Yang, MD,[1] Bon-Kwon Koo, MD,[1,2] Masahiro Hoshino, MD,[1] Joo Myung Lee, MD,[2] Tadashi Murai, MD,[2] Jiesuck Park, MD,[2] Jinlong Zhang, MD,[3] Doyeon Hwang, MD,[4] Eun-Seok Shin, MD,[2] Joon-Hyung Doh, MD,[2] Chang-Wook Nam, MD,[5] Jianan Wang, MD,[6] Shaoliang Chen, MD,[7] Nobuhiro Tanaka, MD,[8] Hitoshi Matsuo, MD,[9] Takashi Akasaka, MD,[9] Gilwoo Choi, PhD,[10] Kersten Petersen, PhD,[10] Hyuk-Jae Chang, MD,[1] Tsunekazu Kakuta, MD,[2] Jagat Narula, MD[11]

ABSTRACT

OBJECTIVES The goal of this study was to investigate the association of stenosis and plaque features with myocardial ischemia and their prognostic implications.

BACKGROUND Various anatomic, functional, and morphological attributes of coronary artery disease (CAD) have been independently explored to define ischemia and prognosis.

METHODS A total of 1,013 vessels with fractional flow reserve (FFR) measurement and available coronary computed tomography angiography were analyzed. Stenosis and plaque features of the target lesion and vessel were evaluated by an independent core laboratory. Relevant features associated with low FFR (≤0.80) were identified by using machine learning, and their predictability of 5-year risk of vessel-oriented composite outcome, including cardiac death, target vessel myocardial infarction, or target vessel revascularization, were evaluated.

RESULTS The mean percent diameter stenosis and invasive FFR were 48.5 ± 17.4% and 0.81 ± 0.14, respectively. Machine learning interrogation identified 6 clusters for low FFR, and the most relevant feature from each cluster was minimum lumen area, percent atheroma volume, fibrofatty and necrotic core volume, plaque volume, proximal left anterior descending coronary artery lesion, and remodeling index (in order of importance). These 6 features showed predictability for low FFR (area under the receiver-operating characteristic curve: 0.797). The risk of 5-year vessel-oriented composite outcome increased with every increment of the number of 6 relevant features, and it had incremental prognostic value over percent diameter stenosis and FFR (area under the receiver-operating characteristic curve: 0.706 vs. 0.611; p = 0.031).

CONCLUSIONS Six functionally relevant features, including minimum lumen area, percent atheroma volume, fibrofatty and necrotic core volume, plaque volume, proximal left anterior descending coronary artery lesion, and remodeling index, help define the presence of myocardial ischemia and provide better prognostication in patients with CAD. (CCTA-FFR Registry for Risk Prediction; NCT04037163) (J Am Coll Cardiol Img 2021;14:629-41) © 2021 by the American College of Cardiology Foundation.

NEW RESEARCH PAPER

High-Risk Morphological and Physiological Coronary Disease Attributes as Outcome Markers After Medical Treatment and Revascularization

Seokhun Yang, MD,[1] Bon-Kwon Koo, MD,[1,2] Doyeon Hwang, MD,[3] Jinlong Zhang, MD,[4] Masahiro Hoshino, MD,[1] Joo Myung Lee, MD,[2] Tadashi Murai, MD,[2] Jiesuck Park, MD,[2] Eun-Seok Shin, MD,[2] Joon-Hyung Doh, MD,[2] Chang-Wook Nam, MD,[5] Jianan Wang, MD,[6] Shaoliang Chen, MD,[7] Nobuhiro Tanaka, MD,[8] Hitoshi Matsuo, MD,[9] Takashi Akasaka, MD,[10] Hyuk-Jae Chang, MD,[1] Tsunekazu Kakuta, MD,[2] Jagat Narula, MD[11]

ABSTRACT

OBJECTIVES This study sought to evaluate the prognostic impact of plaque morphology and coronary physiology on outcomes after medical treatment or percutaneous coronary intervention (PCI).

BACKGROUND Although fractional flow reserve (FFR) is currently best practice, morphological characteristics of coronary artery disease also contribute to outcomes.

METHODS A total of 872 vessels in 538 patients were evaluated by invasive FFR and coronary computed tomography angiography. High-risk attributes (HRA) were defined as high-risk physiological attribute (invasive FFR ≤0.8) and high-risk morphological attributes including: 1) local plaque burden (minimum lumen area <4 mm² and plaque burden ≥70%); 2) adverse plaque characteristics ≥2; and 3) global plaque burden (total plaque volume ≥306.5 mm³ and percent atheroma volume ≥32.2%). The primary outcome was the composite of revascularization, myocardial infarction, or cardiac death at 5 years.

RESULTS The mean FFR was 0.88 ± 0.08, and PCI was performed in 239 vessels. The primary outcome occurred in 54 vessels (6.2%). All high-risk morphological attributes were associated with the increased risk of adverse outcomes after adjustment for FFR ≤0.8 and demonstrated direct prognostic effect not mediated by FFR ≤0.8. The 5-year event risk proportionally increased as the number of HRA increased (p for trend <0.001) with lower risk in the PCI group than the medical treatment group in vessels with 1 or 2 HRA (9.7% vs. 14.7%), but not in vessels with either 0 or ≥3 HRA. Of the vessels with pre-procedural FFR ≤0.8, ischemia relief by PCI (pre-PCI FFR ≤0.8 and post-PCI FFR >0.8) significantly reduced vessel-oriented composite outcome risk compared with medical treatment alone in vessels with 0 or 1 high-risk morphological attributes (hazard ratio: 0.33; 95% confidence interval: 0.12 to 0.93; p = 0.035), but the risk reduction was attenuated in vessels with ≥2 high-risk morphological attributes.

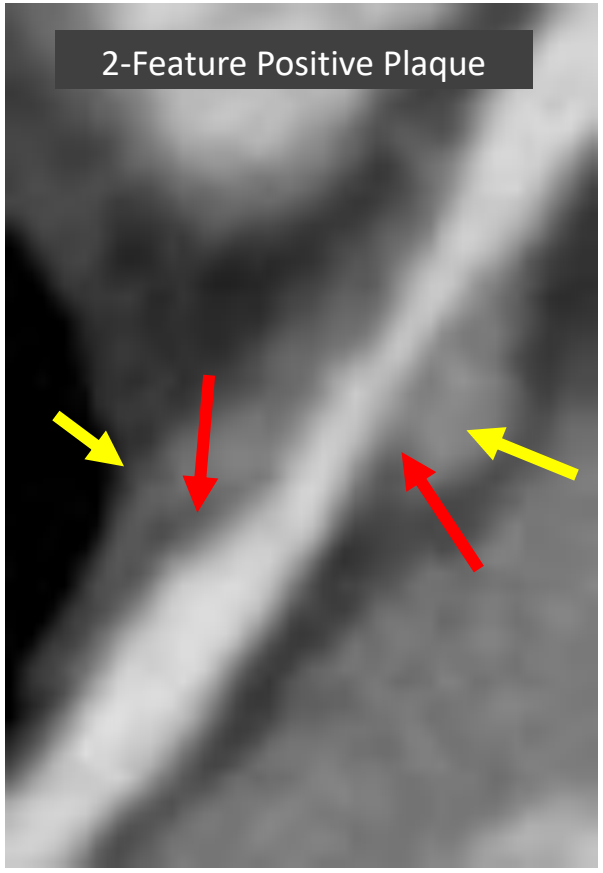
CONCLUSIONS High-risk morphological attributes offered additive prognostic value to coronary physiology and may optimize selection of treatment strategies by adding to FFR-based risk predictions (CCTA-FFR Registry for Development of Comprehensive Risk Prediction Model; NCT04037163) (J Am Coll Cardiol Img 2021;■:■-■) © 2021 by the American College of Cardiology Foundation.

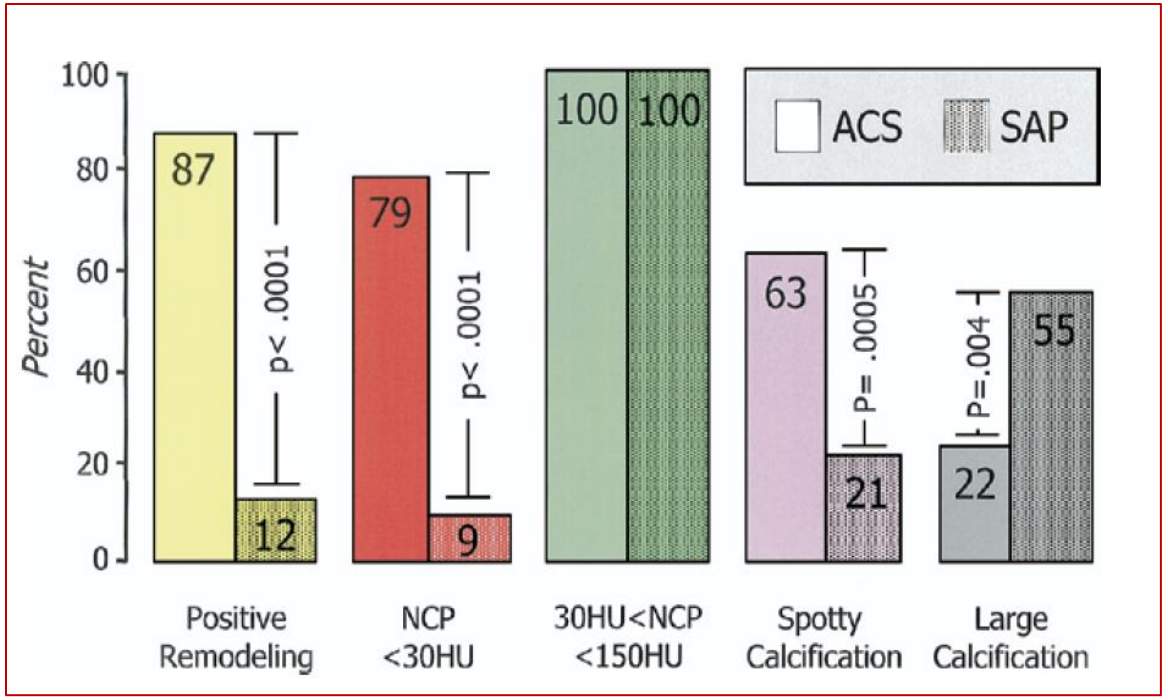
REVEALPLAQUE Study

SCCT, BOSTON | July 2023

ACS, Plaque Morphology & APC

Prospective Single Center; N=1000+, F/U at least 2 years; Endpoint: MACE



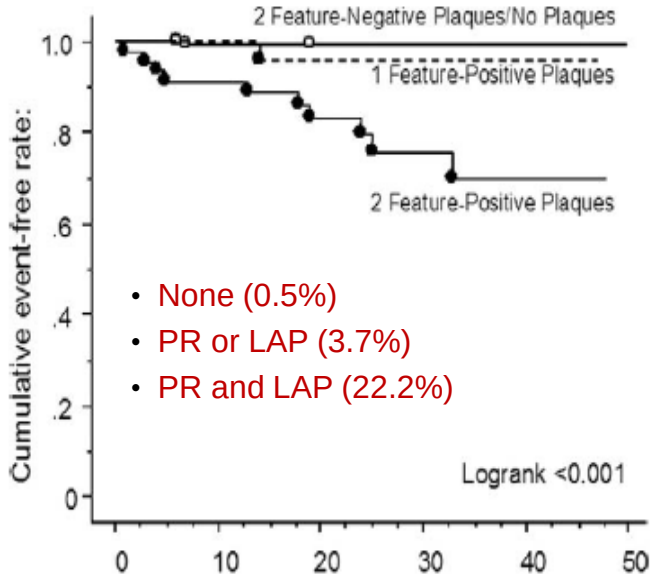


Motoyama, Narula et al. Circ J 2005, JACC 2007, 2009, 2013, 2015

ACS and adverse plaque characteristics

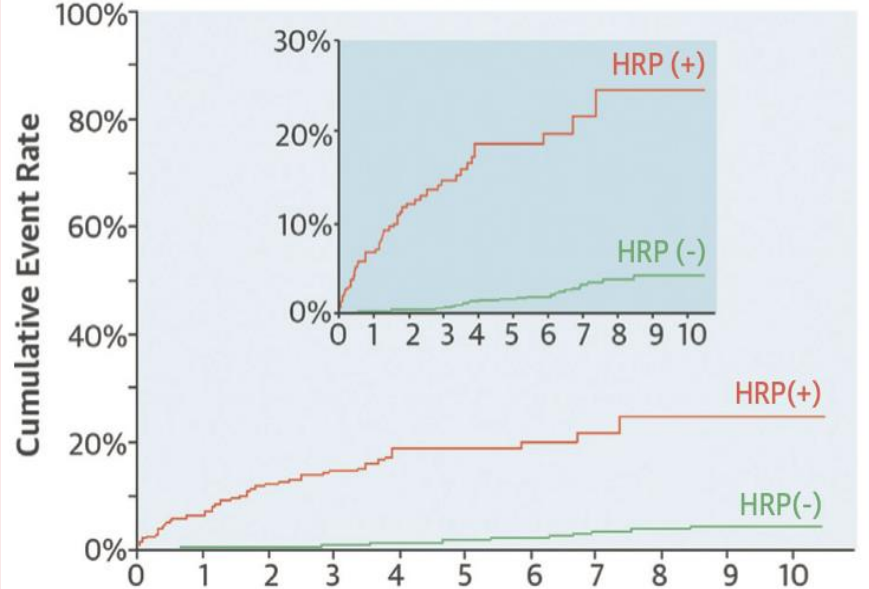
Prospective Single Center; N=1000+, F/U at least 2 years; Endpoint: MACE
Prospective Single Center; N=3000+, F/U up to 10 years; Endpoint: MACE





- None (0.5%)
- PR or LAP (3.7%)
- PR and LAP (22.2%)

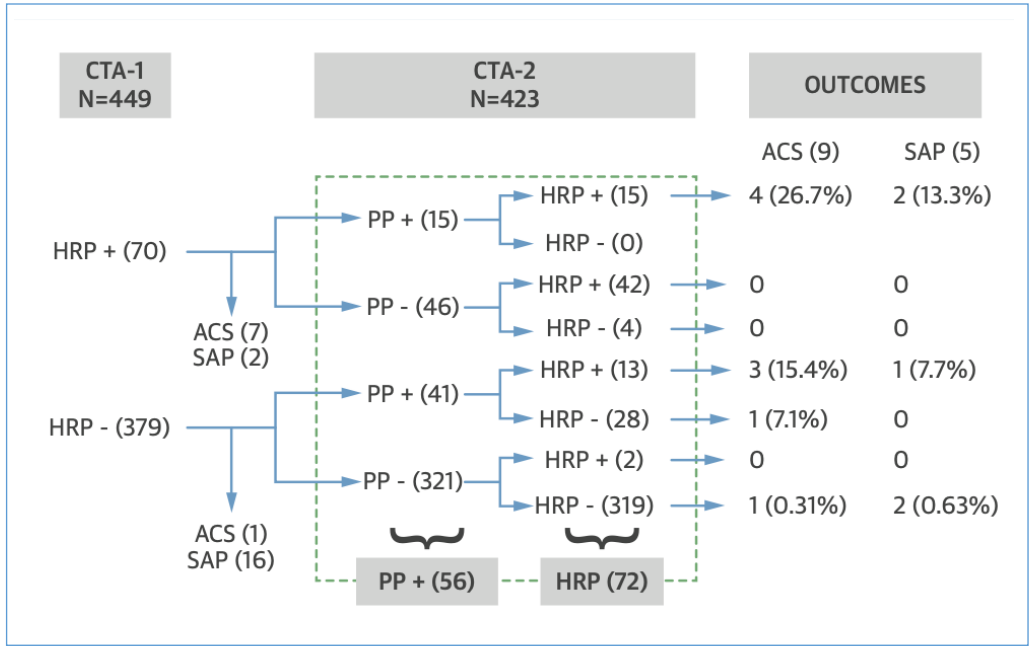
	2-Feature Positive Plaques		
	ACS (n = 11)	No ACS (n = 63)	p Value
Remodeling index (%)			0.003
Mean ± SE	126.7 ± 3.9	113.4 ± 1.6	
95% confidence interval	(118.9 to 134.5)	(110.2 to 116.6)	
Total plaque volume (mm^3)			<0.001
Mean ± SE	134.9 ± 14.1	57.8 ± 5.7	
95% confidence interval	(106.8 to 162.9)	(46.3 to 69.2)	
LAP volume (mm^3)			<0.001
Mean ± SE	20.4 ± 3.4	1.1 ± 1.4	
95% confidence interval	(13.58 to 27.21)	(−1.7 to 3.9)	
Maximum LAP area (mm^2)			<0.001
Mean ± SE	3.2 ± 0.5	0.5 ± 0.2	
95% confidence interval	(2.3 to 4.1)	(0.2 to 0.9)	
Maximum LAP area/plaque area (%)			0.001
Mean ± SE	21.4 ± 3.7	7.7 ± 1.5	
95% confidence interval	(14.1 to 28.7)	(4.7 to 10.6)	

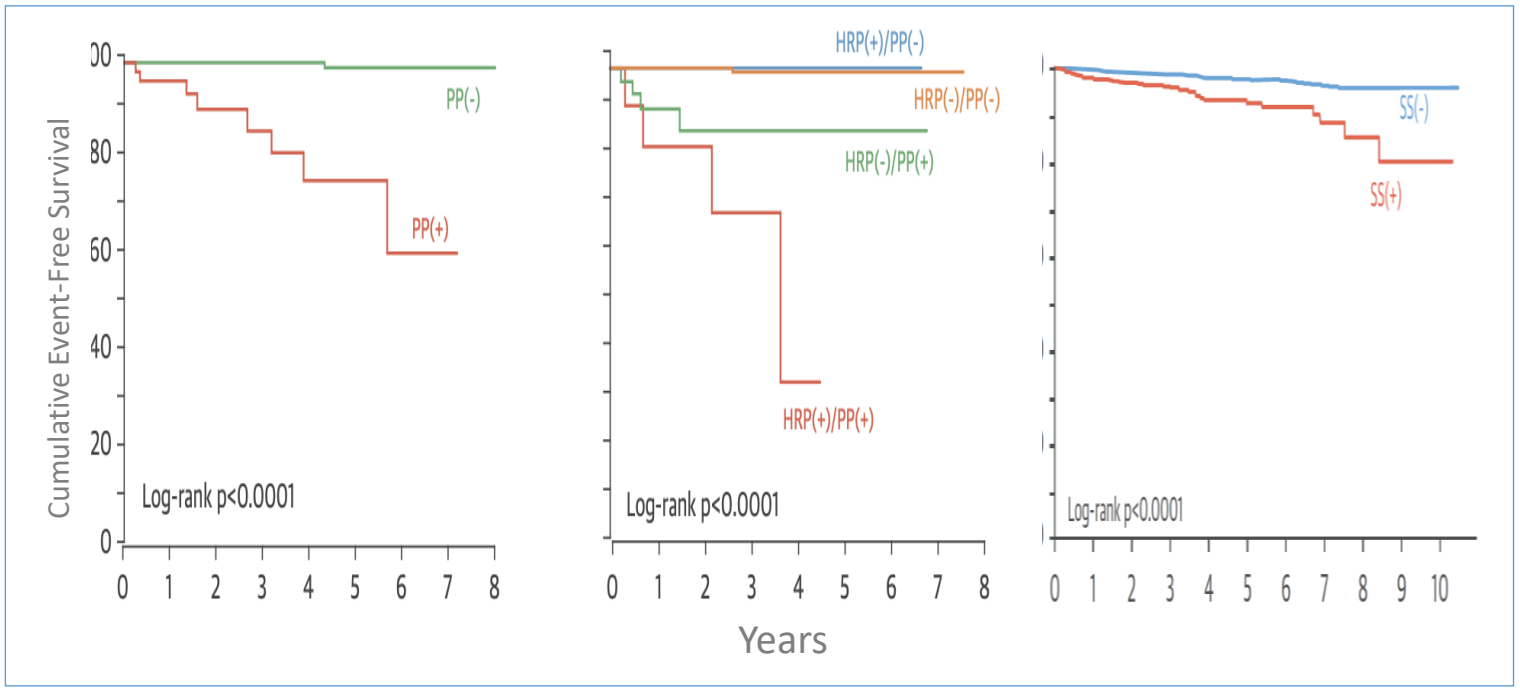


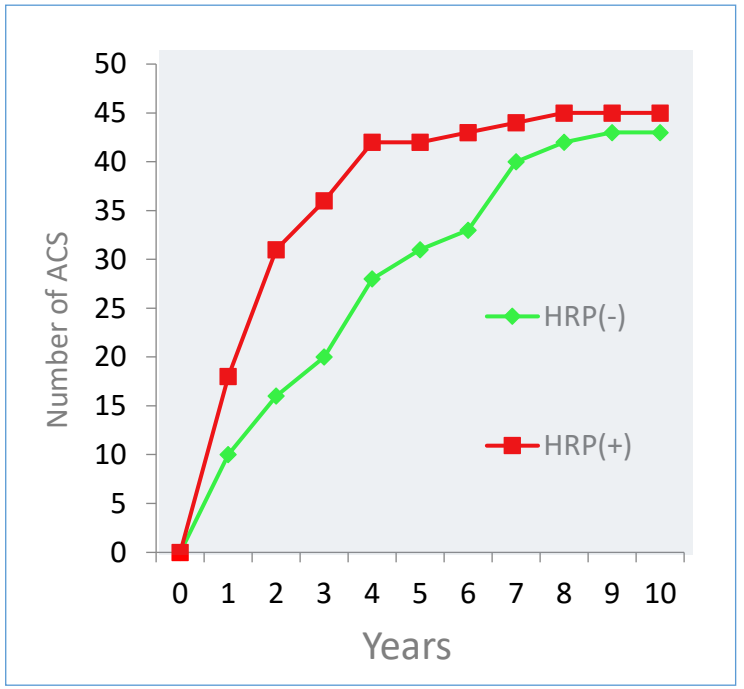
The burden of imaging is to find out who will live without events and who will die of preventable events and when

Motoyama, Narula et al. JACC. 2009;54:49
Motoyama, Narula et al. JACC. 2015;66:337

Plaque Progression as a Necessary Feature of Vulnerability







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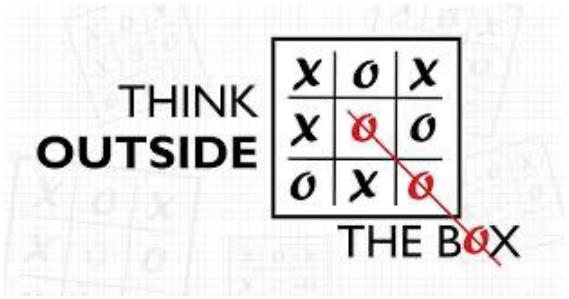
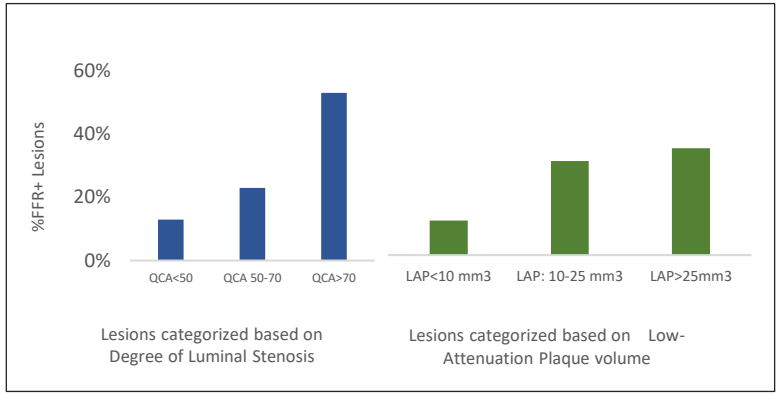
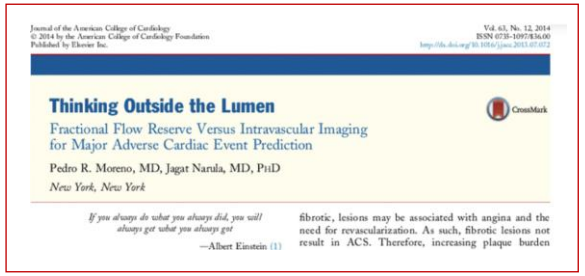


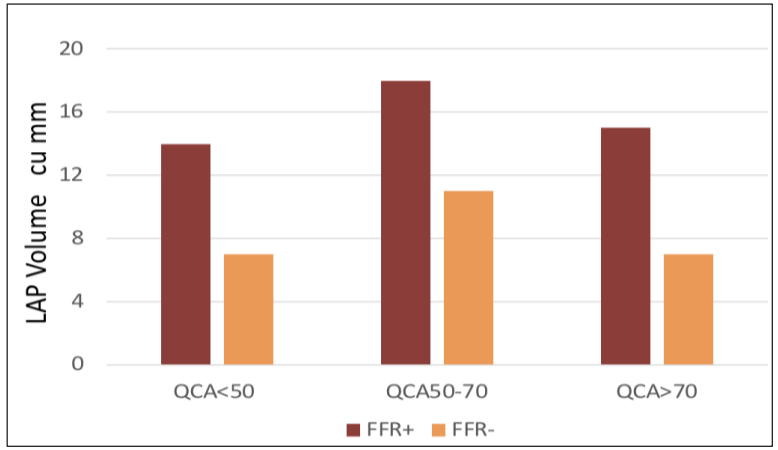
FFR:

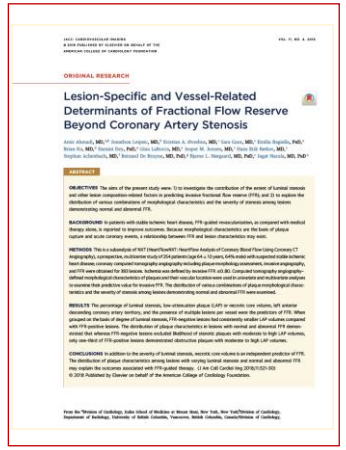
Lesion-Specific and Vessel-Related Determinants

Effect	Model: All Vessels		
	Estimate	SE	P
Intercept	1.044	0.020	<0.0001
QCA	-0.002	0.0002	<0.0001
LAP Volume	-0.001	0.0003	0.0006
Vessel Territory (LAD vs. RCA/LCX)	-0.065	0.011	<0.0001
Lesion Location (Proximal vs. Mid/Distal)	-0.024	0.010	0.0174
Number of segments	-0.019	0.006	0.0020
Lesion Length (mm)	0.0002	0.001	<0.7762

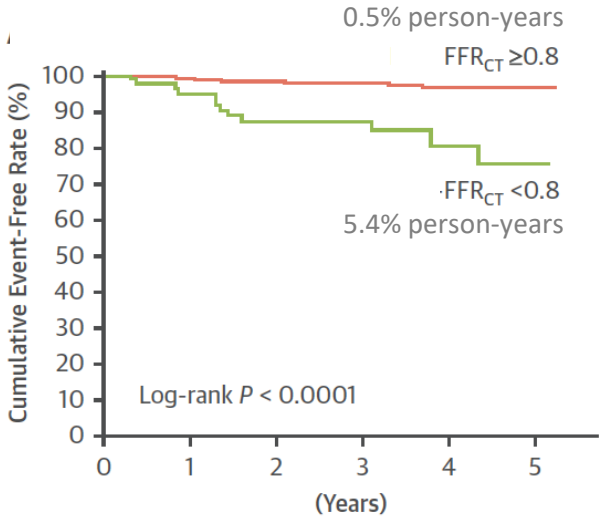






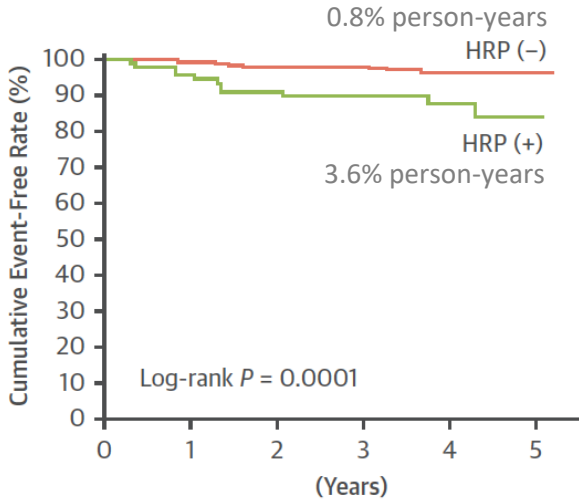


Kaplan-Meier Estimator for Cardiac Event Rate Based on FFRCT and HRP



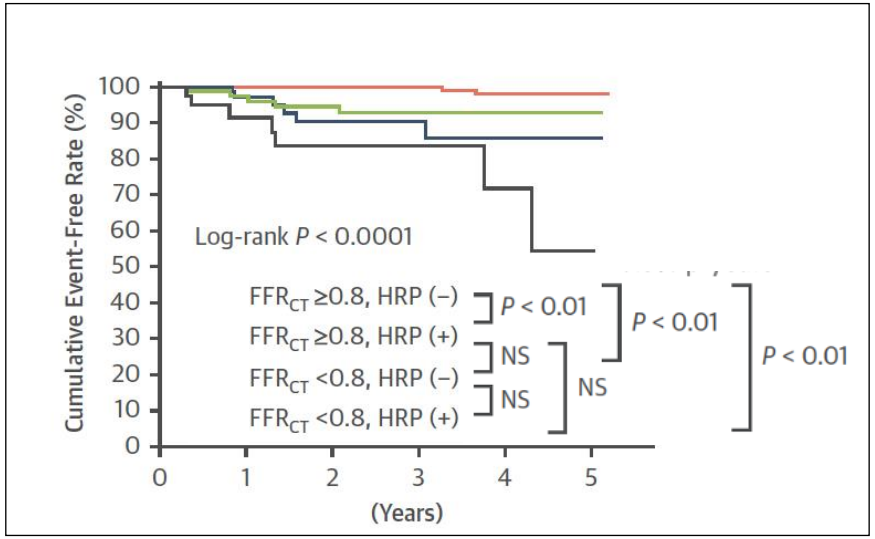
Patients at risk

FFR$_{CT}$ ≥0.8	629	402	300	201	107	9
FFR$_{CT}$ <0.8	116	85	47	31	20	4



Patients at risk

HRP (–)	618	393	277	179	97	10
HRP (+)	127	94	70	53	29	3



Patients at risk

FFR$_{CT}$ ≥0.8, HRP (–)	538	335	250	160	83	8
FFR$_{CT}$ ≥0.8, HRP (+)	91	68	51	42	24	2
FFR$_{CT}$ <0.8, HRP (–)	80	59	28	20	15	3
FFR$_{CT}$ <0.8, HRP (+)	36	27	20	12	6	2

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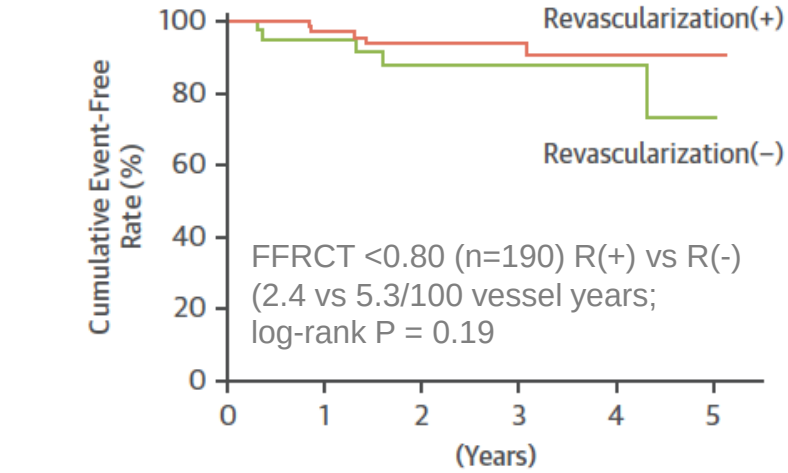
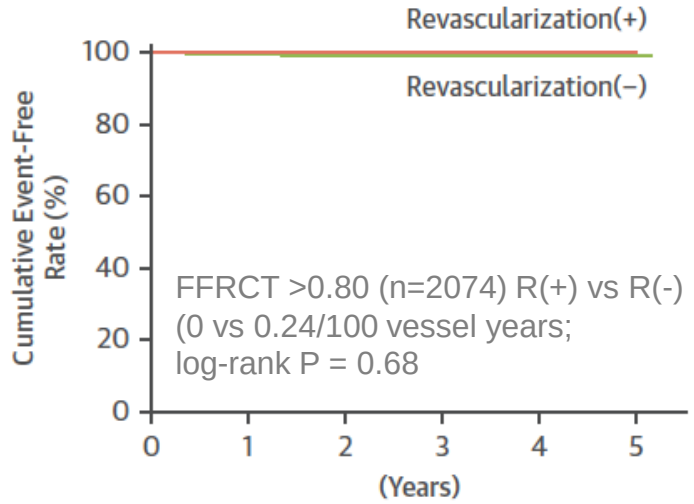
Kaplan-Meier Estimator for Effect of Revascularization on CTA-FFR (+) vs (-) Vessels on Cumulative Event Free Rate (%)

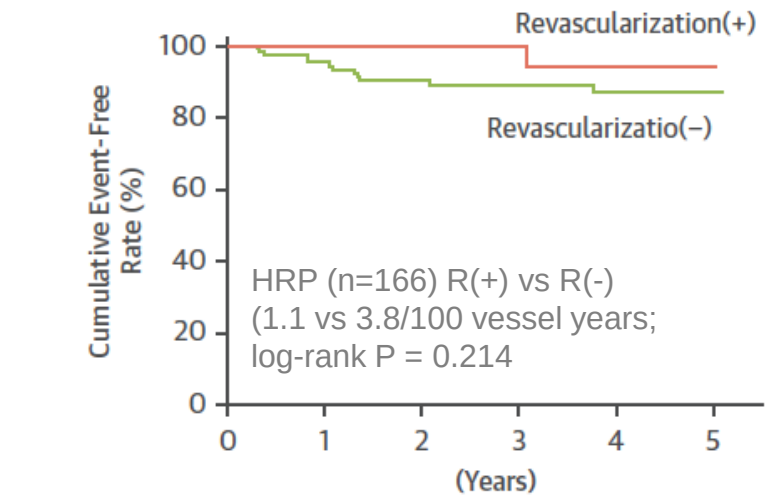


Vessels at risk						
Revasc(+)	95	74	41	30	21	3
Revasc(−)	45	33	21	12	8	2

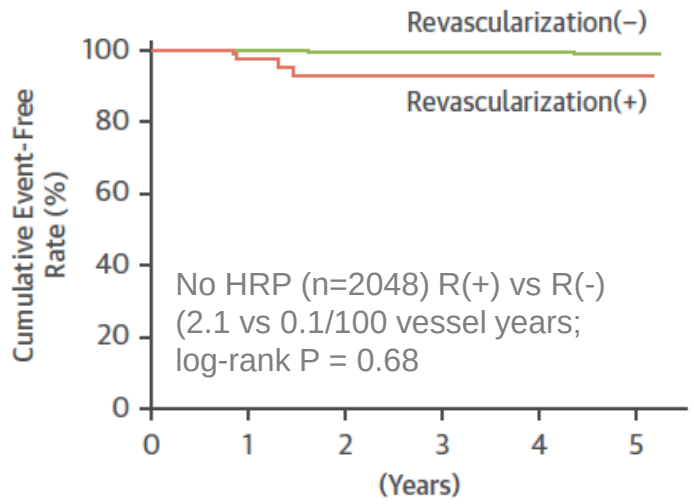


Vessels at risk						
Revasc(+)	25	22	14	12	9	4
Revasc(−)	2,049	1,326	968	656	352	31

Kaplan-Meier Estimator for Effect of Revascularization in CTA-HRP (+) vs (-) Vessels on Cumulative Event Free Rate (%)



Vessels at risk						
Revasc(+)	32	29	20	17	12	3
Revasc(−)	131	97	72	54	30	2



Vessels at risk						
Revasc(+)	88	67	35	25	18	4
Revasc(−)	1,963	1,262	917	614	330	31

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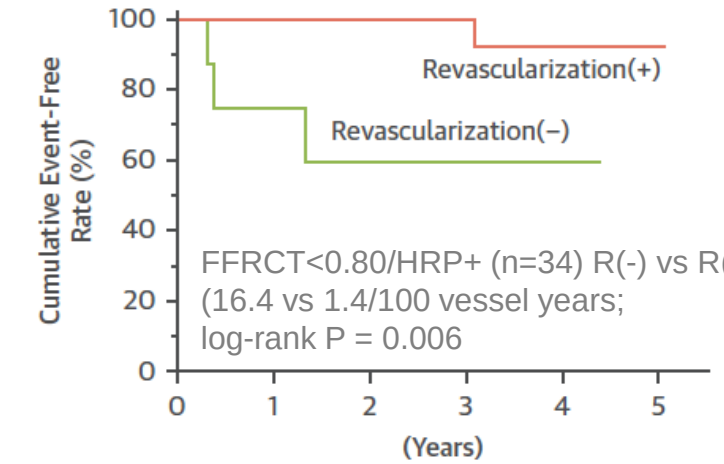
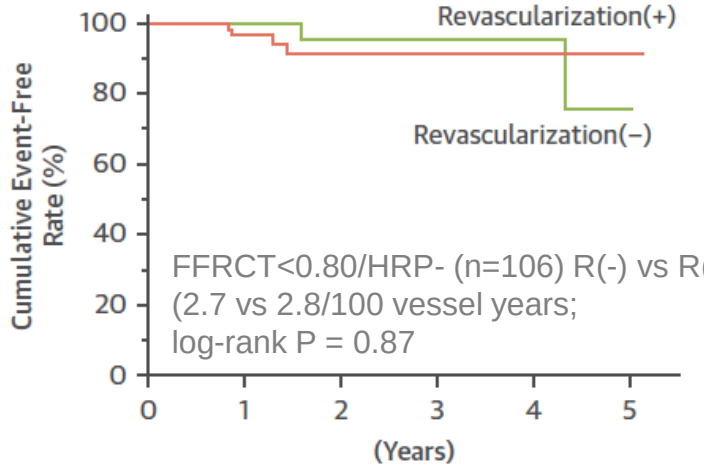
Kaplan-Meier Estimator for Effect of Revascularization in Combination of FFRCT & HRP on Cumulative Event Free Rate (%)



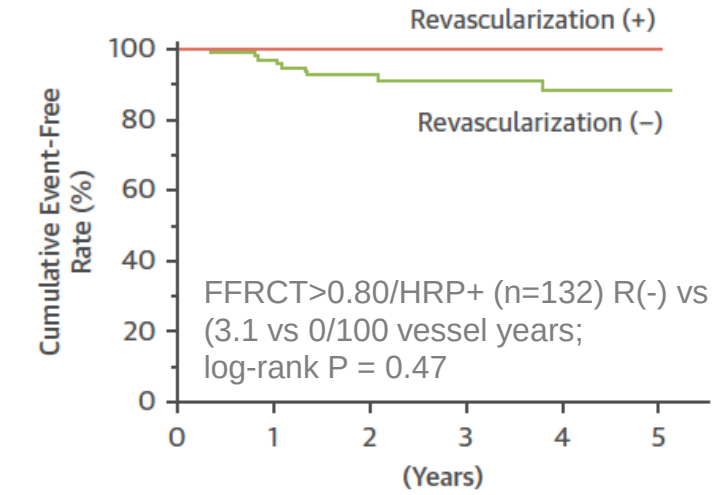
Vessels at risk

Revasc(+)	25	23	17	14	10	3
Revasc(–)	9	6	5	3	2	



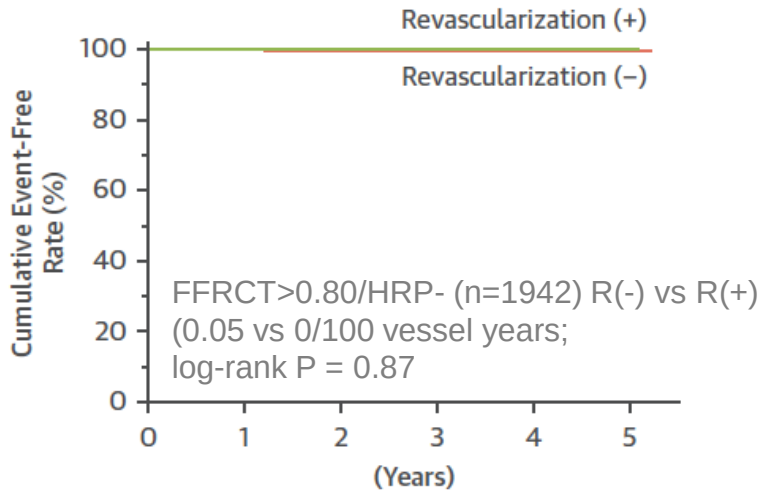
Vessels at risk

Revasc(+)	70	52	25	17	12	2
Revasc(–)	36	28	17	10	7	2



Vessels at risk

Revasc(+)	7	7	4	4	3	1
Revasc(–)	122	92	68	52	29	2



Vessels at risk

Revasc(+)	18	16	11	9	7	4
Revasc(–)	1,927	1,235	901	605	323	30

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PIECING IT ALL TOGETHER [PLAIN PATTERNS]....

	FFR <0.80	FFR ≥0.80
HRP(+)	Revascularization 1.4 vs no revascularization 16.4 per 100 vessel-years, Log-rank *P* = 0.006 1. Could this represent unsafely deferred group in COURAGE and ISCHEMIA? 2. Could this represent appropriately chosen group for FAME-2 study? 3. Could this have been an alternative population for PROSPECT-II study?	Revascularization 0 vs no revascularization 3.1 per 100 vessel-years, Log-rank *P* = 0.47 1. This represents the PROSPECT-II population. 2. Could this group be treated with aggressive lipid-lowering Rx instead? 3. Do plaques imminently at danger of rupture need better identification?
HRP(–)	Revascularization 2.8 vs no revascularization 2.7 per 100 vessel-years, Log-rank *P* = 0.87 1. Does this goup represent true COURAGE or ISCHEMIA proposal? 2. Could this population be safely deferred from the FAME-2 indication?	Revascularization 0 vs no revascularization 0.05 per 100 vessel-years, Log-rank *P* = 0.87 1. Revascularization is unjustified in these patients. 2. Only preventive Rx should be recommended.

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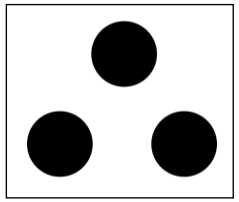

1. Eligibility for revascularization in chronic coronary disease based on anatomic significance of lesions is debated and made way for establishing the functional importance of luminal stenosis.
2. FAME-2 demonstrated that not all hemodynamically significant lesions require intervention (possibly true COURAGE-type patients); it is important to identify lesions that could be deferred.
3. The possibility of role played by plaque composition has been suggested to be responsible for the hard endpoints. CTA-verified LAP and PR best describe high-risk plaques. Novel methods have suggested the feasibility of detection of plaque inflammation by CTA.
4. Prospective studies are needed to define the role of plaque pathology in management of chronic coronary disease (ie. to define imminently event-prone population of ISCHEMIA).
5. Our entire experience has been based on subjectively binary interpretation of CTA, and AI-supported strategies for automated quantitative plaque assessment at both lesion and vessel levels are currently being investigated.