Imaging of Coronary Lipid Rich Plaque and its Clinical Implications

Gary S. Mintz, MD

Cardiovascular Research Foundation

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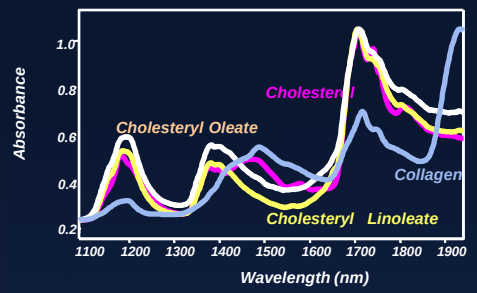
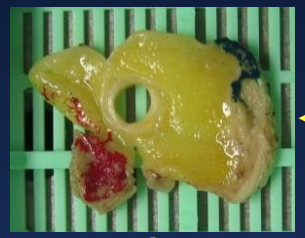
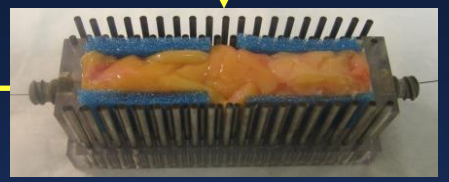
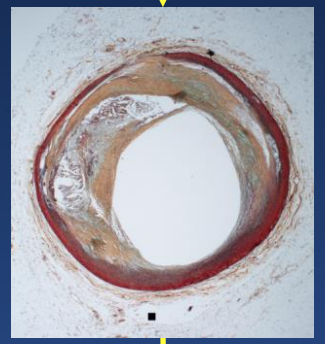
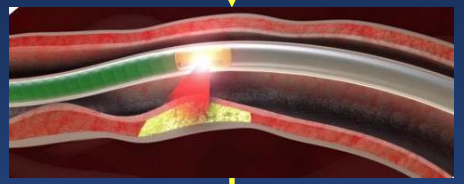
Ex vivo validation of NIRS for detection of confluent [>0.2mm thick & >60° in circumference] LRP that is relatively superficial [overlying fibrous cap thickness <0.45mm]).

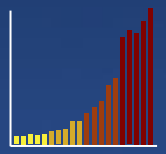


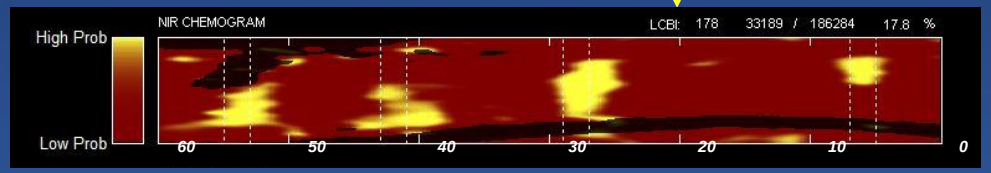












Circulation
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https://doi.org/10.1161/hc0802.104291

CLINICAL INVESTIGATION AND REPORTS

Detection of Lipid Pool, Thin Fibrous Cap, and Inflammatory Cells in Human Aortic Atherosclerotic Plaques by Near-Infrared Spectroscopy

Pedro R. Moreno, MD, Robert A. Lodder, PhD, K. Raman Purushothaman, MD, William E. Charash, MD, PhD, William N. O'Connor, MD, and James E. Muller, MD

ABSTRACT: ***Background*—** A method is needed to identify nonstenotic, lipid-rich coronary plaques that are likely to cause acute coronary events. Near-infrared (NIR) spectroscopy can provide information on the chemical composition of tissue. We tested the hypothesis that NIR spectroscopy can identify plaque composition and features associated with plaque vulnerability in human aortic atherosclerotic plaques obtained at the time of autopsy. ***Methods and Results*—** A total of 199 samples from 5 human aortic specimens were analyzed by NIR spectroscopy. Features of plaque vulnerability were defined by histology as presence of lipid pool, thin fibrous cap (<65 μm by ocular micrometry), and inflammatory cell infiltration. An InfraAlyzer 500 spectrophotometer was used. Spectral absorbance values were obtained as log (1/R) data from 1100 to 2200 nm at 10-nm intervals. Principal component regression was used for analysis. An algorithm was constructed with 50% of the samples used as a reference set; blinded predictions of plaque composition were then performed on the remaining samples. NIR spectroscopy sensitivity and specificity for histological features of plaque vulnerability were 90% and 93% for lipid pool, 77% and 93% for thin cap, and 84% and 89% for inflammatory cells, respectively. ***Conclusions*—** NIR spectroscopy can identify plaque composition and features associated with plaque vulnerability in postmortem human aortic specimens. These results support efforts to develop an NIR spectroscopy catheter system to detect vulnerable coronary plaques in living patients.

Key Words: atherosclerosis ■ plaque ■ tissue ■ spectroscopy

There is widespread agreement that new diagnostic techniques are required to identify coronary plaques that are prone to disruption.[1–3] The type of plaque considered to be most vulnerable to disruption is a thin-capped fibroatheroma with increased inflammatory cell content.[4–6] Multiple techniques are being tested to identify such plaques before they disrupt and cause thrombosis.[7–14] Identification of these potentially lethal plaques before they disrupt will facilitate the development of therapeutic strategies to prevent acute coronary events.

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Detection of Lipid Core Coronary Plaques in Autopsy Specimens With a Novel Catheter-Based Near-Infrared Spectroscopy System

Craig M. Gardner, PhD,* Huwei Tan, PhD,* Edward L. Hull, PhD,*
Jennifer B. Lisauskas, MS,* Stephen T. Sum, PhD,* Thomas M. Meese, BS,*
Chunsheng Jiang, PhD,* Sean P. Madden, PhD,* Jay D. Caplan, BS, MBA,*
Allen P. Burke, MD,† Renu Virmani, MD,‡ James Goldstein, MD,§ James E. Muller, MD*
Burlington, Massachusetts; Washington, DC; Gaithersburg, Maryland; and Royal Oak, Michigan

OBJECTIVES This study sought to assess agreement between an intravascular near-infrared spectroscopy (NIRS) system and histology in coronary autopsy specimens.

BACKGROUND Lipid core plaques cannot be detected by conventional tests, yet are suspected to be the cause of most acute coronary syndromes. Near-infrared spectroscopy is widely used to determine the chemical content of substances. A NIRS system has been developed and used successfully in 99 patients.

METHODS Scanning NIRS was performed through blood in 212 coronary segments from 84 autopsy hearts. One histologic section was analyzed for every 2 mm of artery. Lipid core plaque of interest (LCP) was defined as a lipid core >60° in circumferential extent, >200-μm thick, with a mean fibrous cap thickness <450 μm. The first 33 hearts were used to develop the algorithm; the subsequent 51 validation hearts were used in a prospective, double-blind manner to evaluate the accuracy of NIRS in detecting LCP. A NIRS-derived lipid core burden index for an entire artery was also validated by comparison to histologic findings.

RESULTS The LCPs were present in 115 of 2,649 (4.3%) sections from the 51 validation hearts. The algorithm prospectively identified LCP with a receiver-operator characteristic area of 0.80 (95% confidence interval [CI]: 0.76 to 0.85). The lipid core burden index detected the presence or absence of any fibroatheroma with an area under the curve of 0.86 (95% CI: 0.81 to 0.91). A retrospective analysis of lipid core burden index conducted in extreme artery segments with either no or extensive fibroatheroma yielded an area under the curve of 0.96 (95% CI: 0.92 to 1.00), confirming the accuracy of spectroscopy in identifying plaques with markedly different lipid content under ideal circumstances.

CONCLUSIONS This novel catheter-based NIRS system accurately identified lipid core plaques through blood in a prospective study in coronary autopsy specimens. It is expected that this novel capability will be of assistance in the management of patients with coronary artery disease. (J Am Coll Cardiol Img 2008;1:638–48) © 2008 by the American College of Cardiology Foundation

From *InfraReDx, Inc., Burlington, Massachusetts; †Division of Cardiovascular Pathology, Armed Forces Institute of Pathology, Washington, DC; ‡CVPath Institute, Gaithersburg, Maryland; and the §Division of Cardiology, William Beaumont Hospital, Royal Oak, Michigan.

InfraReDx was the sole source of financing for this study. Drs. Gardner, Tan, Hull, Sum, Jiang, Madden, and Muller, and Ms. Lisauskas, Mr. Meese, and Mr. Caplan are current employees of InfraReDx or were employees at the time of this study. Dr. Goldstein is an InfraReDx consultant and equity owner. Drs. Burke and Virmani were consultants to InfraReDx for histologic studies.
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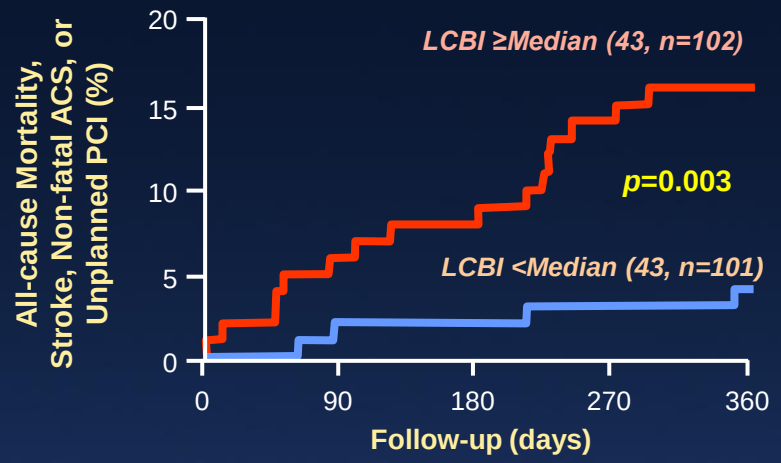
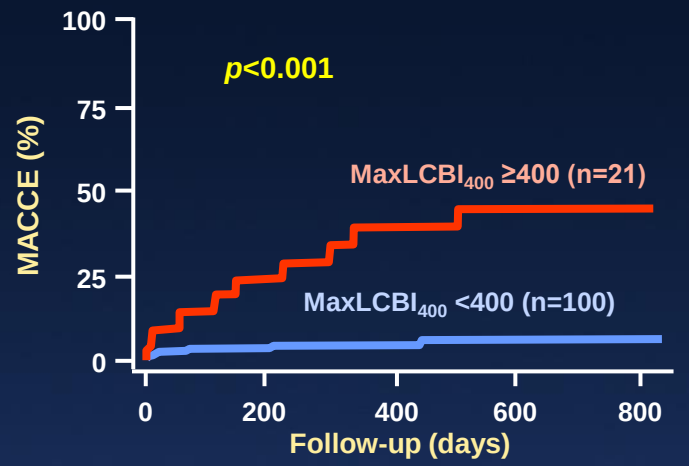
Moreno et al. Circulation 2002;105:923-7
Gardner et al. JACC Cardiovasc Imaging 2008;1:638-48

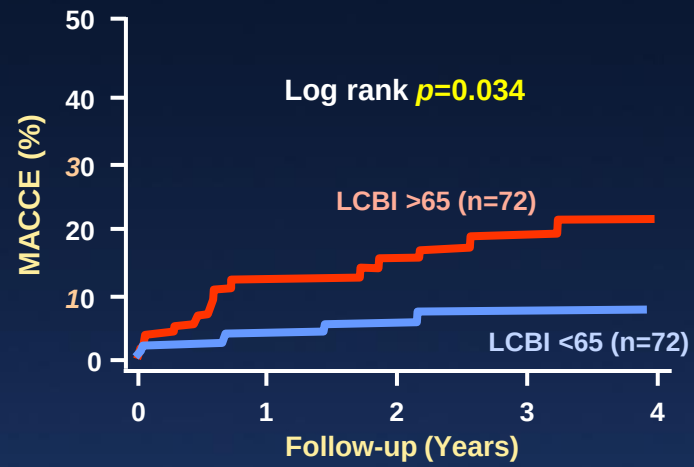
Early Studies of NIRS Predicting Patient-Level NC-MACE

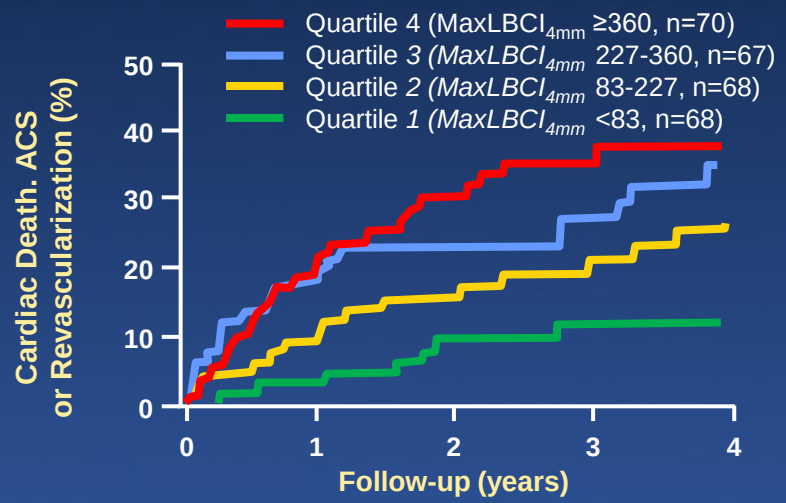


Oemrawsingh et al *J Am Coll Cardiol*. 2014;64:2510-8

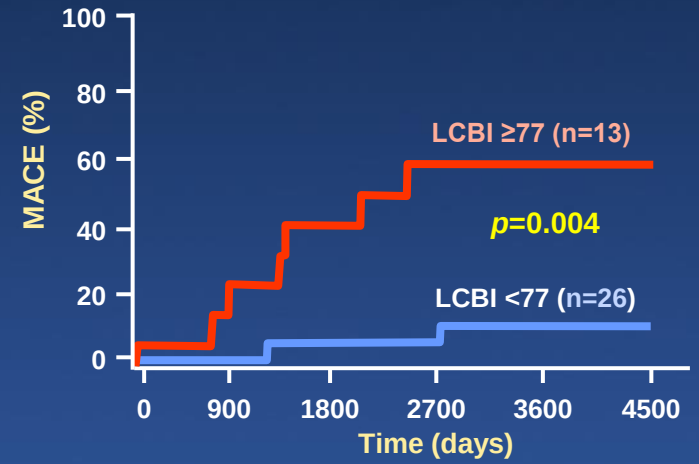


Madder et al. *Eur Heart J Cardiovasc Imaging*. 2016;17:393-9

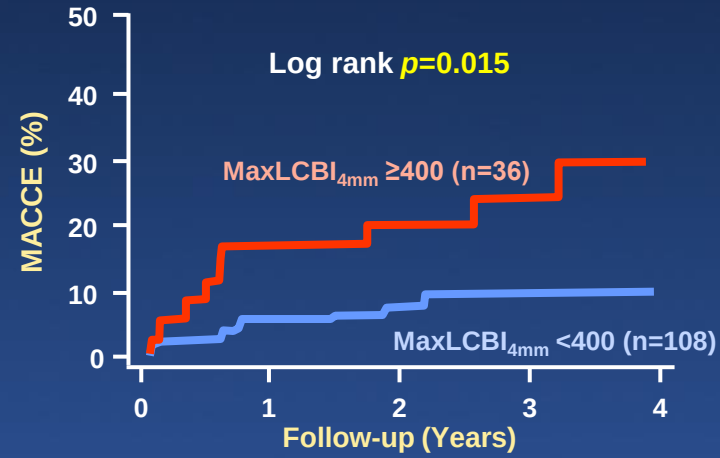




Schuurman et al. *Eur Heart J.* 2018;39:295-302



Danek et al. *Cardiovasc Revasc Med.* 2017;18:177-81.



Karlsson et al. *Open Heart* 2019;6. doi:10.1136/openhrt-2018-000917

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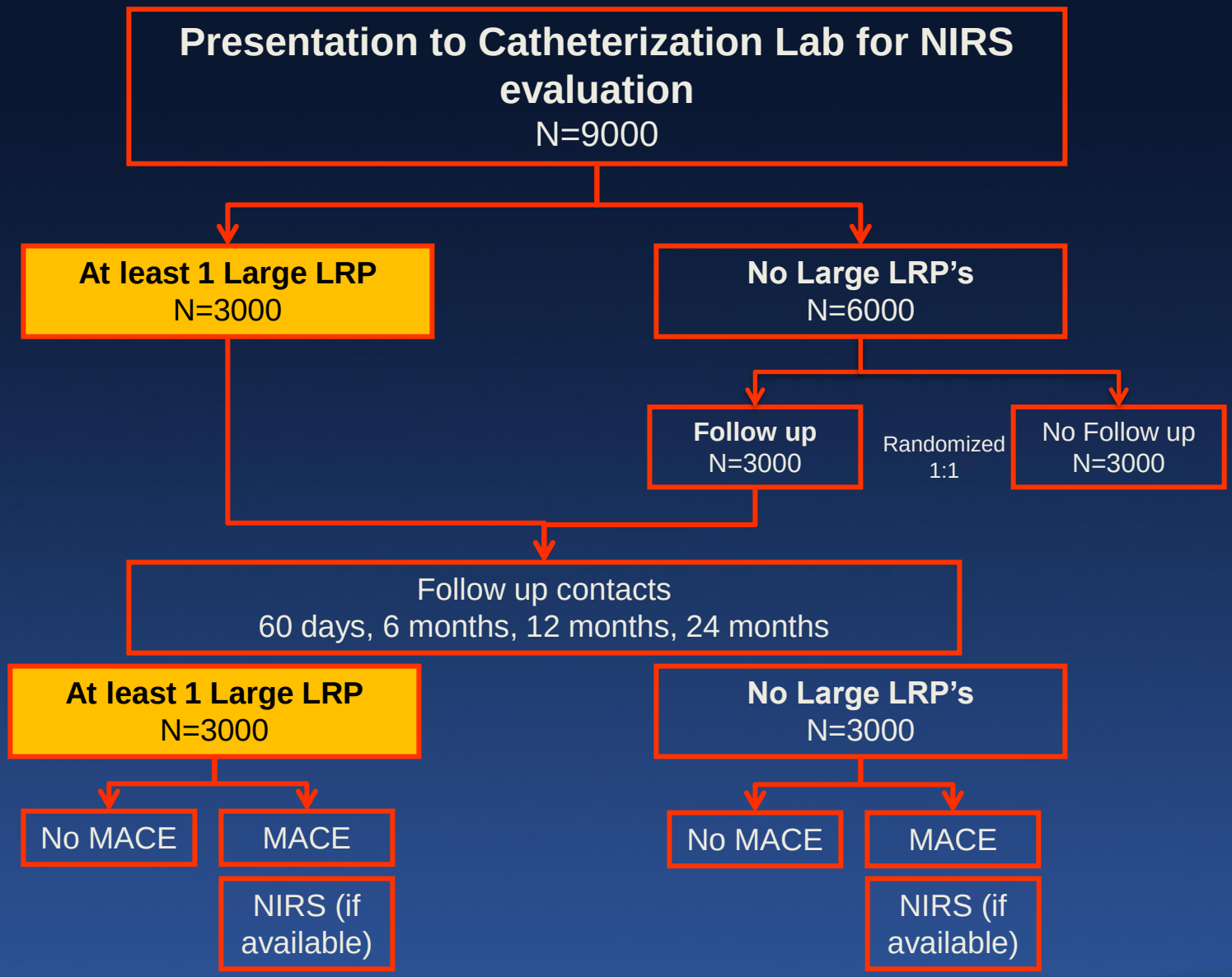
LRP Study Flow

Two hypotheses were tested for plaques at non-stenotic sites that have not undergone PCI:

- The Vulnerable Patient Hypothesis: Pts with increased max 4mm LCBI in all scanned arteries are more likely to experience Non Culprit-MACE than those without increased max 4mm LCBI
- The Vulnerable Plaque Hypothesis: Coronary artery segments with increased max 4mm LCBI (within the segment) are more likely than segments without increased max 4mm LCBI to cause Non Culprit - MACE



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Waksman et al. Lancet. 2019;394:1629-37

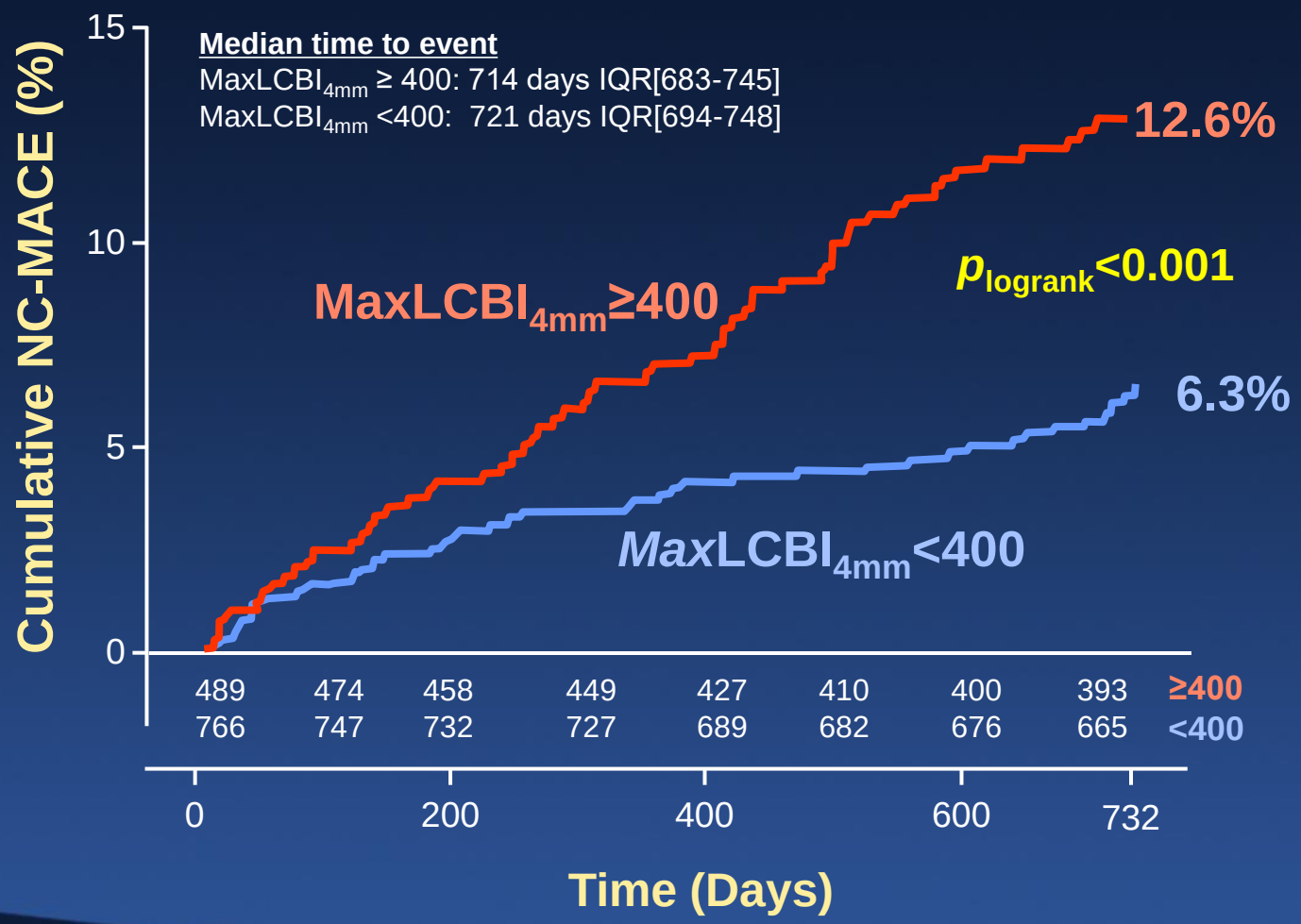
Multivariable Model of Lesion-level NCL-MACE

Lesion-level predictors	OR (95% CI)
MaxLCBI$_{4mm}$ ≥400	3.39 (1.85–6.20)
Plaque burden ≥70%	3.99 (1.38–11.56)
Minimum lumen area ≤4.0mm^2	1.79 (1.02–3.16)

Interaction between maxLCBI4mm >400 and plaque burden within maxLCBI$_{4mm}$ ≥70%, p=0.822.
Interaction between maxLCBI4mm >400 and MLA within maxLCBI4mm ≤$_{4mm}$, p=0.512.

Waksman et al. Lancet. 2019;394:1629-37

Patient-level Cumulative NC-MACE



	HR [95% CI]	p Value	
Primary Endpoint: maxLCBI$_{4mm}$ as a continuous variable	1.18 [1.05-1.32]	0.005	For each 100 increase of maxLCBI$_{4mm}$ NC-MACE risk increased by 18%
Secondary Endpoint: maxLCBI$_{4mm}$ >400	1.87 [1.25-2.80]	0.003	Pt with maxLCBI$_{4mm}$ >400 is at 87% higher risk of NC-MACE

Adjusted by age, male gender, diabetes, hypertension, smoking history, prior PCI, ACS, and renal insufficiency

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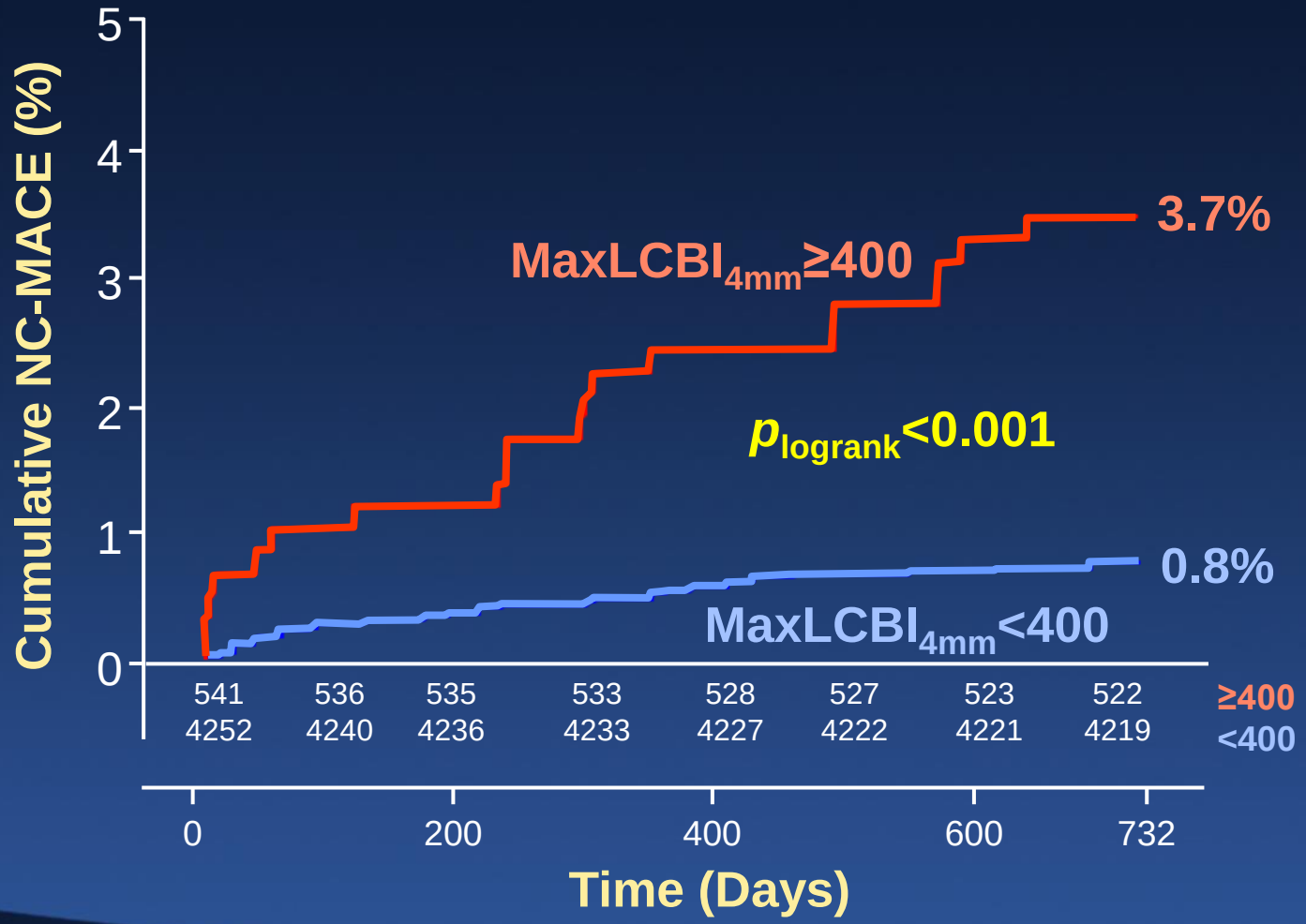
Waksman et al. Lancet. 2019;394:1629-37

Segment-level Cumulative NC-MACE (n=56)



	HR [95% CI]	p Value	
Primary Endpoint: $maxLCBI_{4mm}$ as a continuous variable	1.45 [1.28-1.64]	<0.001	For each 100 increase of $maxLCBI_{4mm}$ NC-MACE risk increased by 45%
Secondary Endpoint: $maxLCBI_{4mm}$ >400	4.11 [2.3-7.34]	<0.001	Coronary segment with $maxLCBI_{4mm}$ >400 is at 411% higher risk of NC-MACE

Patient cluster adjusted via WLW methodology

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Waksman et al. Lancet. 2019;394:1629-37

PROSPECT II Natural History Study

(PROSPECT ABSORB RCT)

902 pts with troponin(+) ACS had 3 vessel NIRS-IVUS after successful PCI

4 pts were not followed beyond 30 days because NCL imaging data was not acquired; these pts remained in the safety cohort

898 pts: ≥1 non-flow limiting lesion with ≥65% plaque burden?

Yes (N=182)

R 1:1

ABSORB BVS + GDMT (N=93)

GDMT (N=89)

No (n=716)

Routine angio/3V IVUS-NIRS FU at 25 months

Clinical FU in PROSPECT II: Median 3.7 years

The primary outcome was a composite of cardiac death, MI, unstable angina or progressive angina either requiring revascularization or with rapid lesion progression, attributed to originally untreated NCLs

The primary safety outcome of intravascular imaging-related major complications requiring treatment occurred in 2/902 pts (0.2%)

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Erlinge et al. Lancet. 2021;397:985-95

Multivariable Model of Lesion-level NCL-MACE with all 3 High Risk Plaque Characteristics

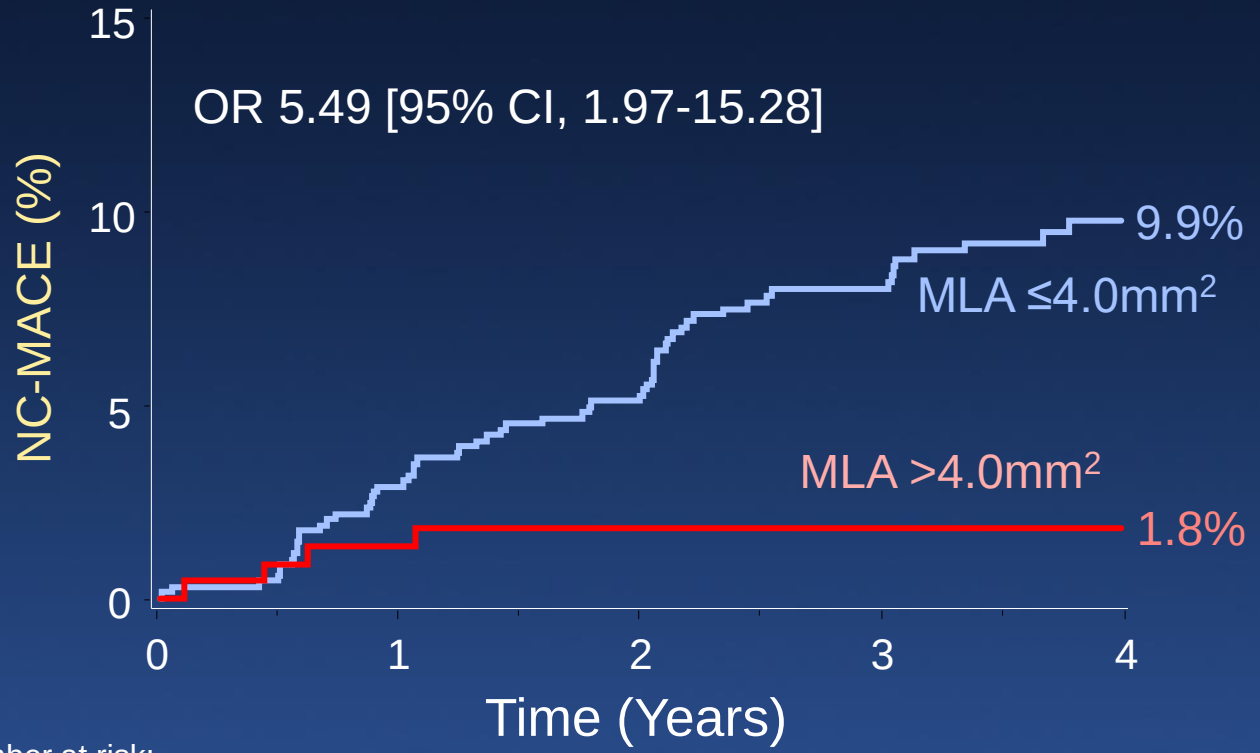
Lesion-level predictors*	OR (95% CI)
$MaxLCBI_{4mm}$ ≥324.7	3.80 (1.87-7.70)
Plaque burden ≥70%	5.37 (2.42-11.89)
Minimum lumen area ≤4.0mm^2	1.85 (0.95-3.61)

Covariate adjusted for age, sex, prior PCI, HTN, diabetes, use of high-dose statin at discharge, total non-culprit segment length analyzed

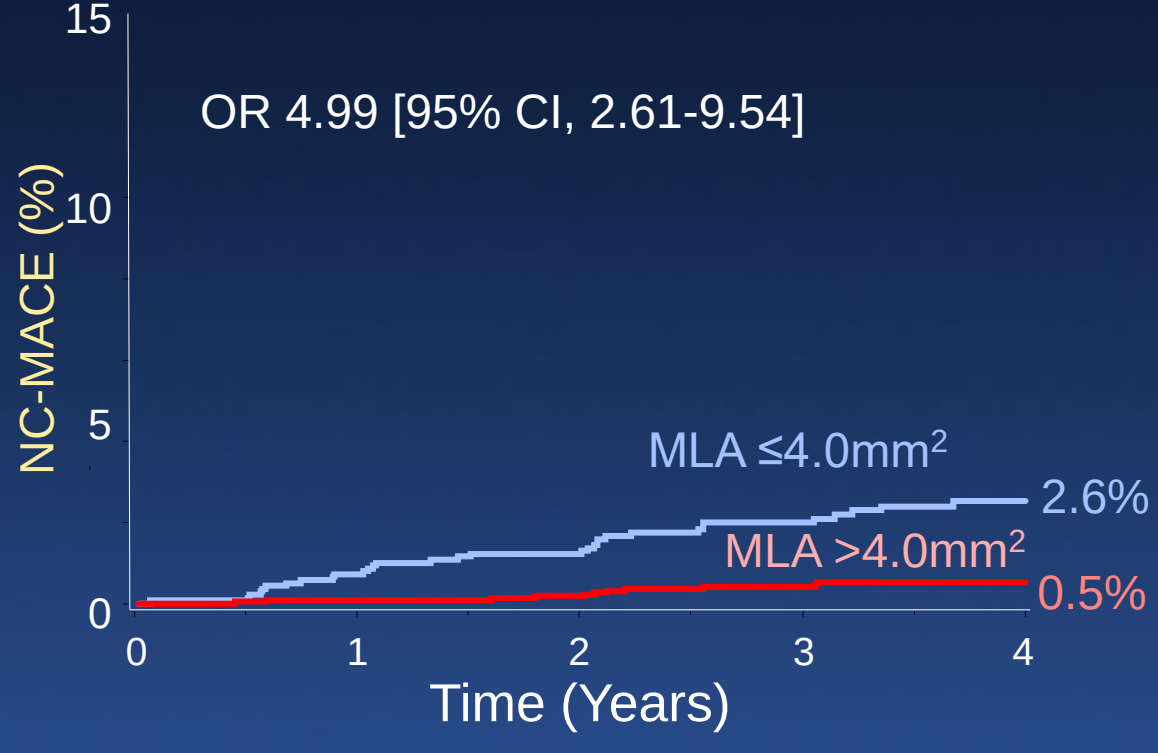
Erlinge et al. Lancet. 2021;397:985-95

NCL-related MACE According to the Presence of MLA ≤4.0 mm²

Patient-level events



Lesion-level events



Number at risk:

≤4.0 mm²	679	654	636	465	259	1,375	1,354	1,340	1,108	593
>4.0 mm²	219	215	212	158	72	2,254	2,235	2,228	1,665	907

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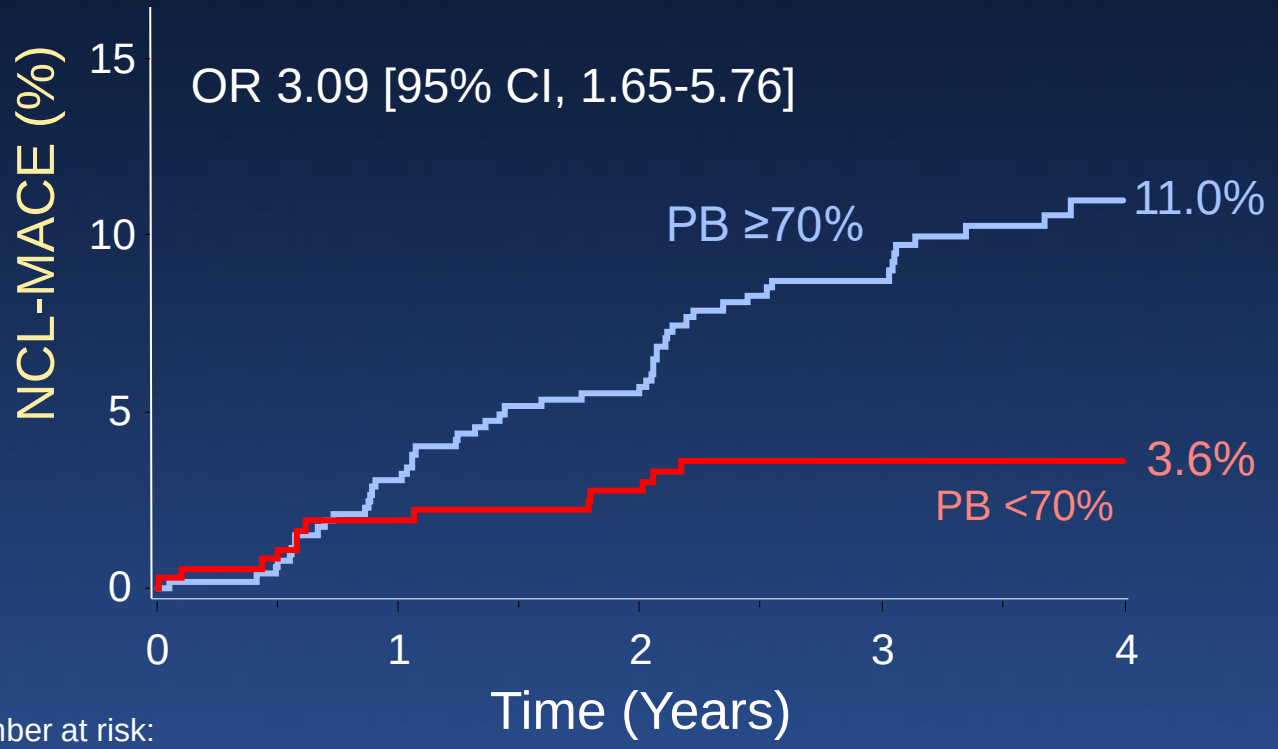
Erlinge et al. Lancet. 2021;397:985-95

NCL-related MACE According to the Presence of Plaque Burden ≥70%

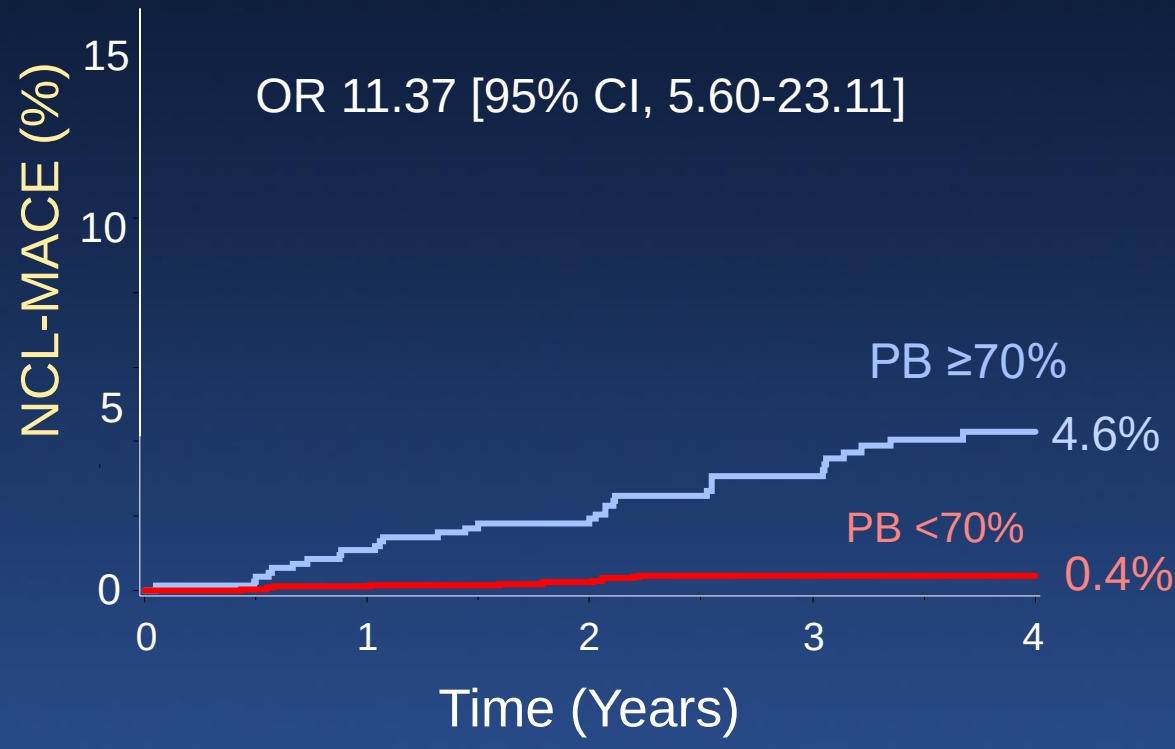
Patient-level events



Number at risk:

PB ≥70%	530	510	494	367	199
PB <70%	368	359	354	256	132

Lesion-level events



PB ≥70%	787	773	764	576	338
PB <70%	2,842	2,816	2,804	2,107	1,162

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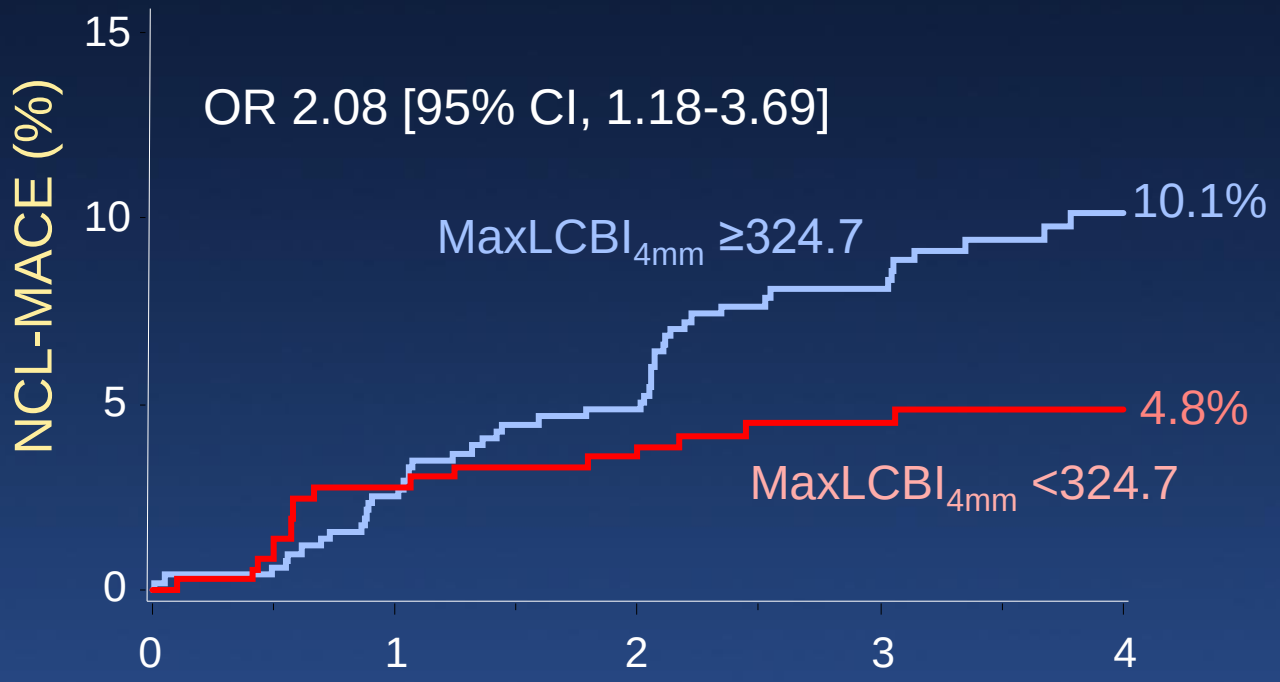
NCL-related MACE According to the Presence of HR Plaque Defined by MaxLCBI$_{4mm}$ ≥324.7

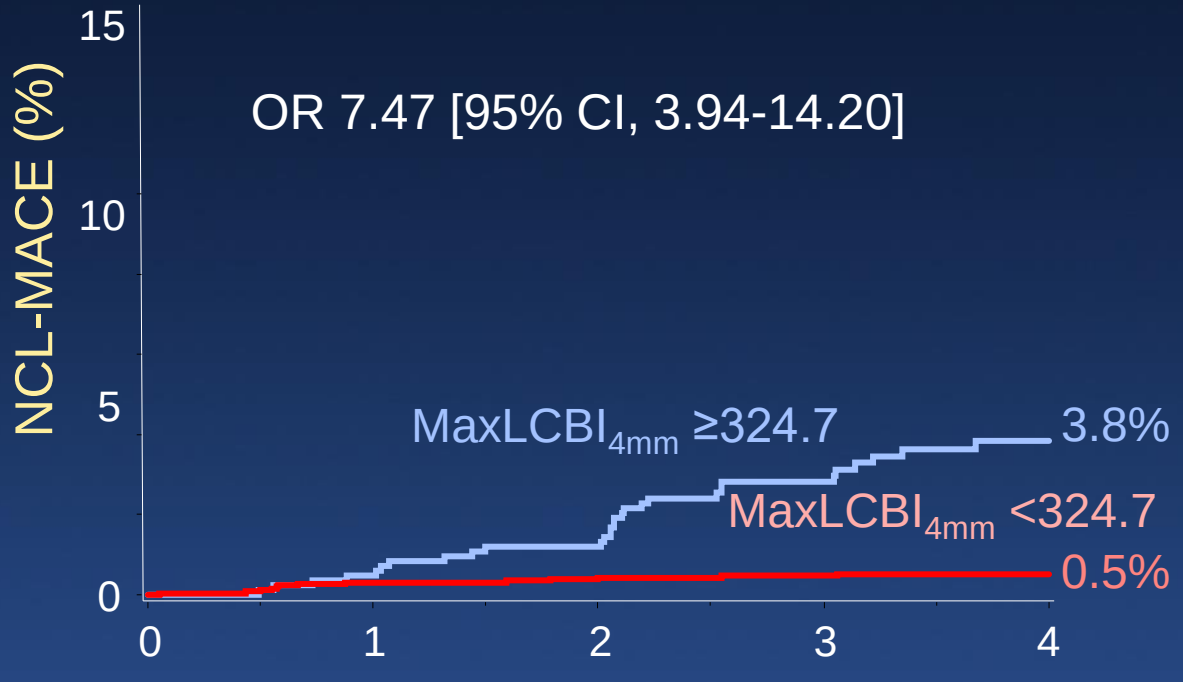
Patient-level events



Number at risk:

≥324.7	520	503	490	359	202
<324.7	364	352	345	255	127

Lesion-level events



	851	837	830	621	359
	2,649	2,623	2,610	1,976	1,092

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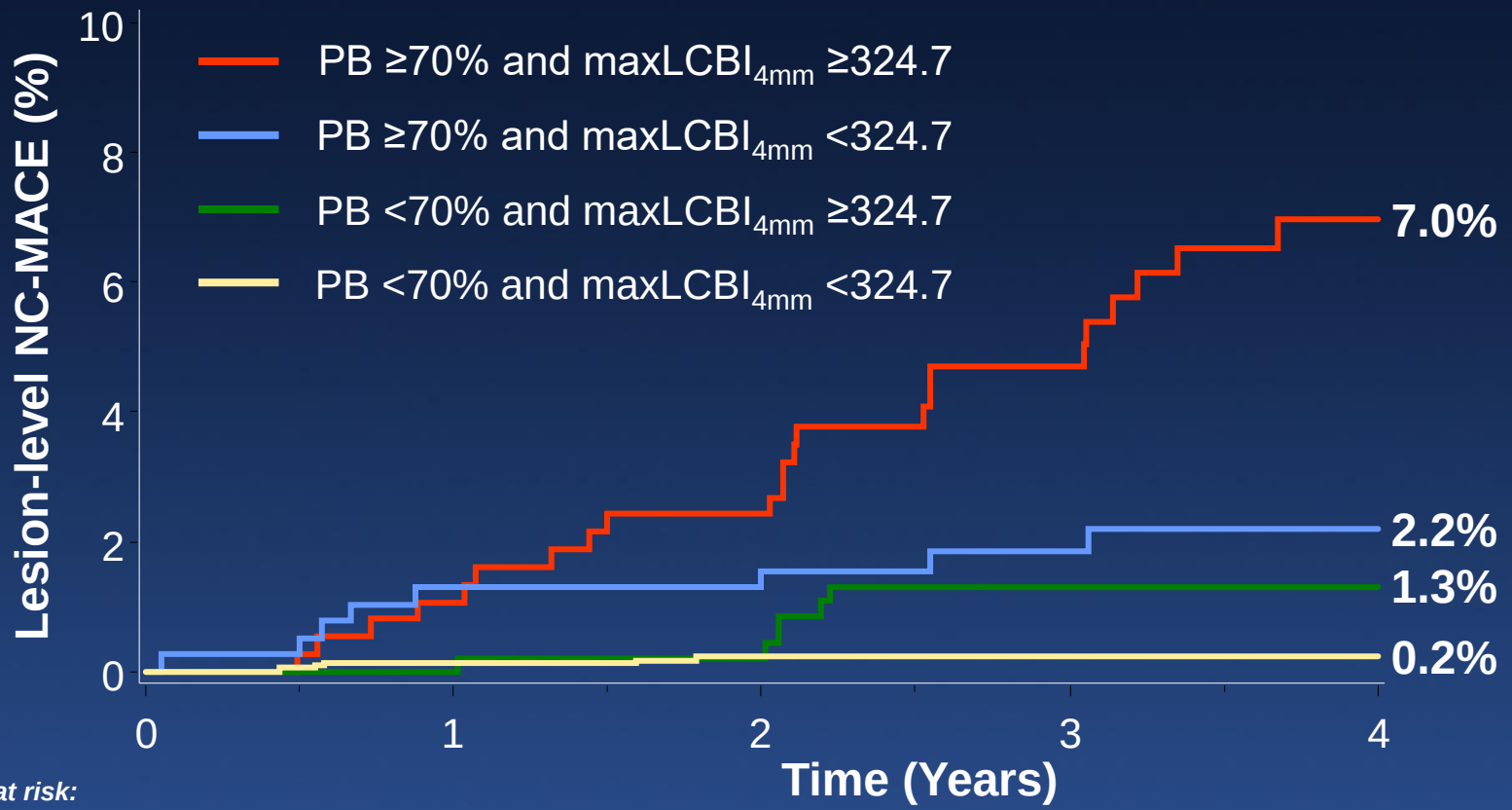
Lesion-level NCL-MACE According to the Presence of MaxLCBI$_{4mm}$ ≥324.7 and PB ≥70%

OR 11.33 [95% CI, 6.10-21.03]
PB ≥70% and maxLCBI$_{4mm}$ ≥324.7 vs. others

OR 36.73 [95% CI, 13.59-99.28]
PB ≥70% and maxLCBI$_{4mm}$ ≥324.7 vs. PB <70% and maxLCBI$_{4mm}$ <324.7



Number at risk:

10% of lesions → **PB ≥70% and maxLCBI$_{4mm}$ ≥324.7**	**374**	**368**	**362**	**271**	**162**
PB ≥70% and maxLCBI$_{4mm}$ <324.7	391	383	381	293	168
PB <70% and maxLCBI$_{4mm}$ ≥324.7	477	469	468	350	197
PB <70% and maxLCBI$_{4mm}$ <324.7	2,258	2,240	2,229	1,683	924

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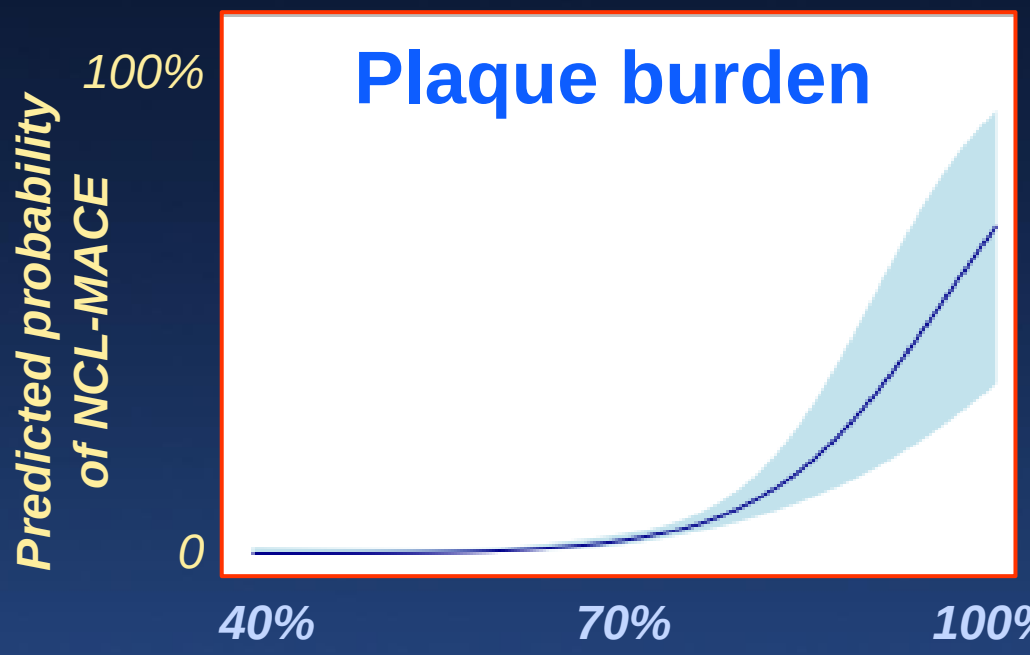
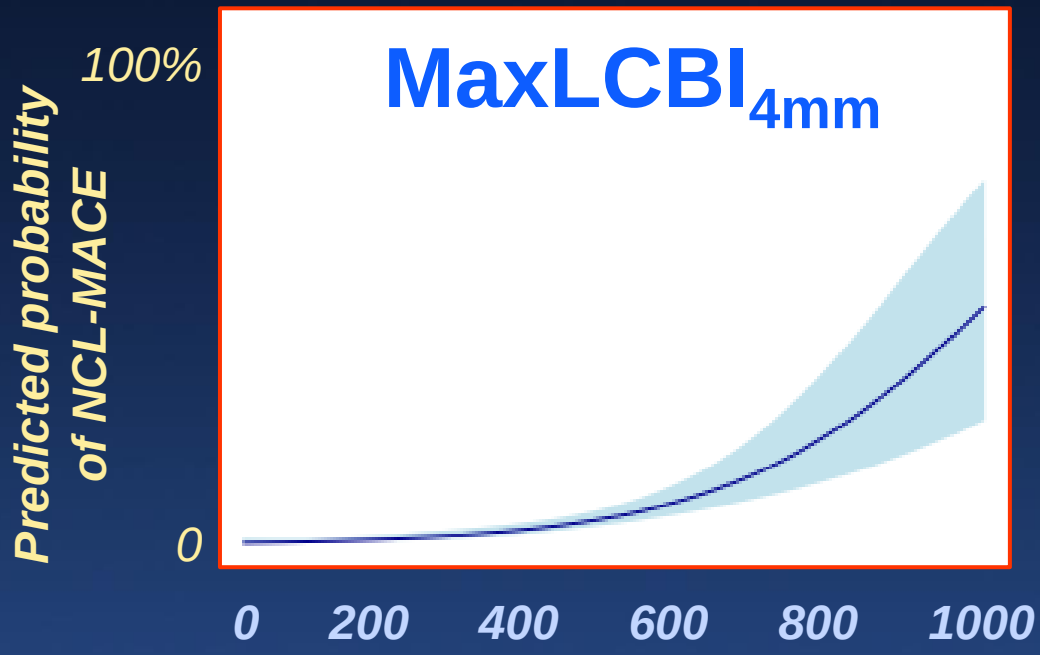
Spline and ROC analyses of the continuous relationship between probability of lesion-level NCL-MACE and plaque burden and $MaxLCBI_{4mm}$



AUC (95% CI)	0.84 (0.79, 0.89)
Optimal cutoff (95% CI)	**69.8% (66.7, 70.7)**
Sensitivity	0.82
Specificity	0.78
Accuracy	0.79



AUC (95% CI)	0.79 (0.72, 0.86)
Optimal cutoff (95% CI)	**324.6 (129.7, 473.6)**
Sensitivity	0.70
Specificity	0.76
Accuracy	0.76

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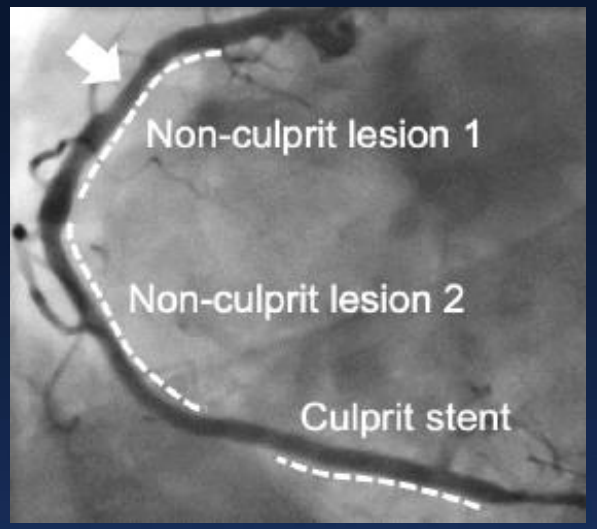

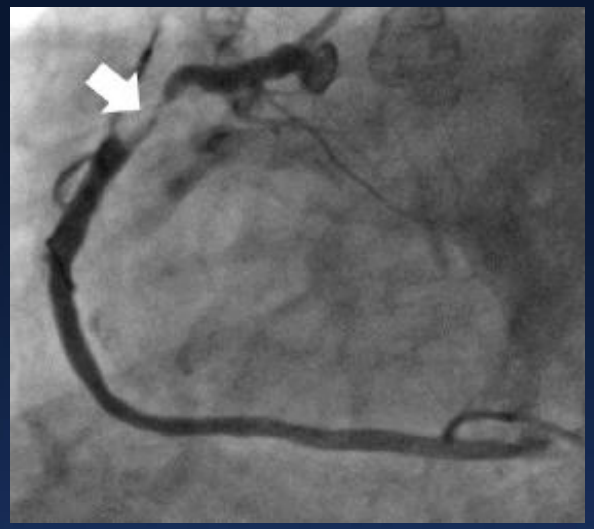

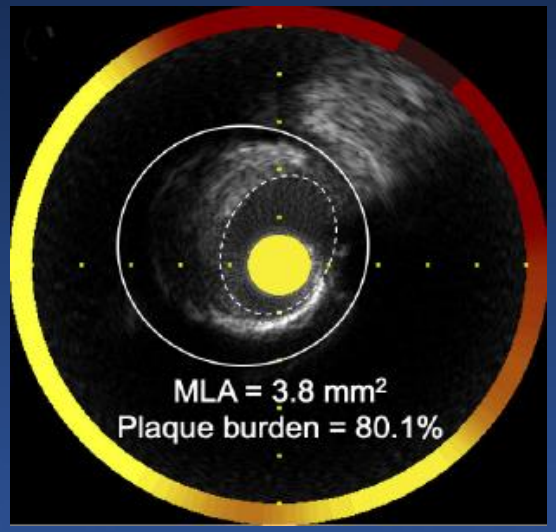

Non-culprit lesion 1

Non-culprit lesion 1 Non-culprit lesion 2 Culprit stent

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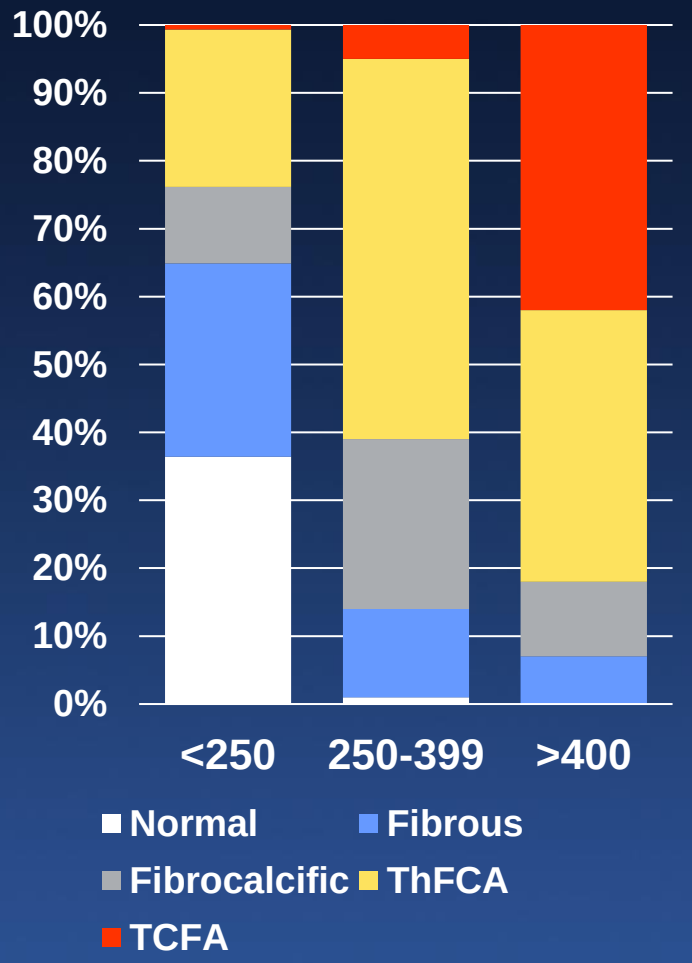
Predicting OCT-TCFA

	MaxLCBI$_{4mm}$				vs OCT-TCFA	
	<250	250-399	≥400	P-value	AUC	Cut-off
#	124	118	57			
OCT						
Lumen area, mm^2	8.4±3.9	7.6±3.2	7.9±3.5	0.3		
Min FC thickness, μ	119±38	110±51	78±33	<0.001		
Mean lipid angle, °	126±33	137±32	162±54	<0.001	0.752	>178°
IVUS						
Vessel area, mm^2	15.0±6.4	16.2±5.9	16.9±7.1	0.13		
Lumen area, mm^2	8.4±3.9	7.6±3.2	7.9±3.5	0.3		
Atheroma volume, %	44±12	53±10	53±11	<0.001	0.699	>55%
Remodeling index	1.01±0.10	1.02±0.10	1.08±0.10	<0.001	0.564	>1.053
NIRS						
maxLCBI$_{4mm}$	174±43	322±43	524±12	<0.001	0.882	>401
Mean lipid angle, °	11±13	50±28	94±44	<0.001	0.809	>98°

OCT Plaque Types vs Max LCBI$_{4mm}$



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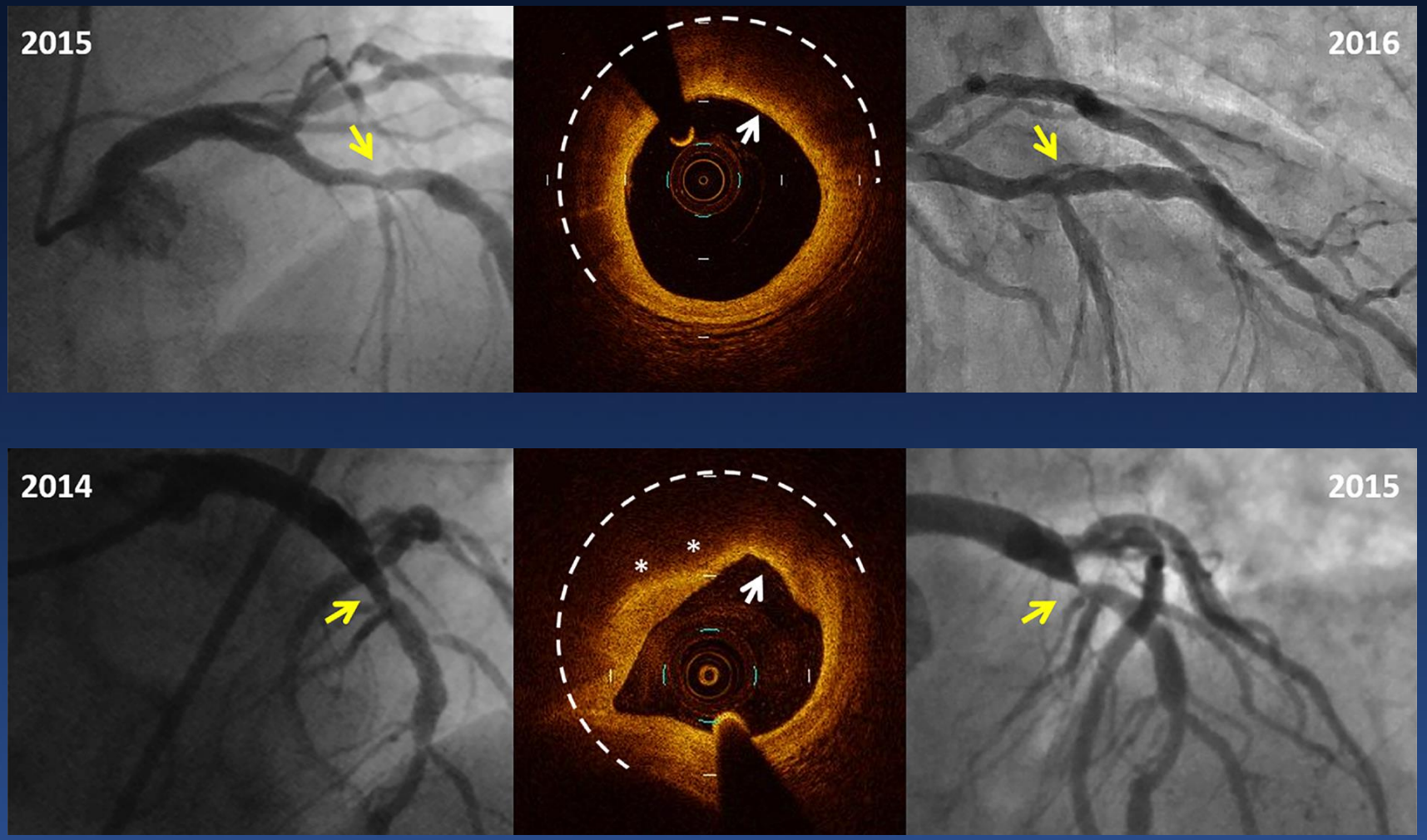
Zanchin et al. Eur Heart J Cardiovasc Imaging 2021;22:824-834.

CLIMA Study

- In 1003 pts undergoing OCT evaluation of the untreated proximal LAD, markers of high-risk plaques
  - MLA <3.5 mm^2
  - Minimum FCT <75µm overlying a lipid core and measured at the thinnest point
  - Lipid plaque with lipid arc >180°
  - Macrophage clusters
- Primary Endpoint -- Composite of cardiac death and target segment MI -- observed in 37 pts (3.7%)

Prati et al. Eur Heart J 2020;41:383-91

Pre-specified simultaneous presence of the four OCT criteria in the same plaque was observed in 18.9% of pts experiencing the primary endpoint and was an independent predictor of events (HR 7.54, 3.1–18.6).



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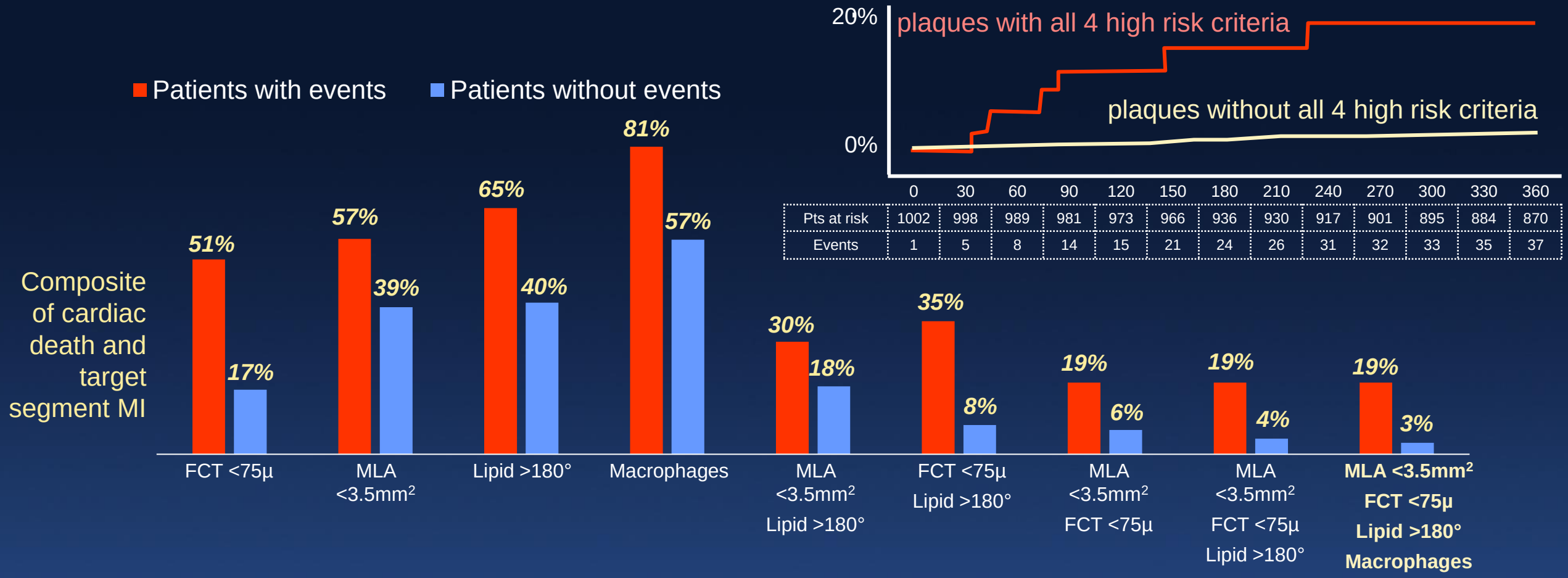
Prati et al. Eur Heart J 2020;41:383-91



Hazard ratio	4.65	2.07	2.40	2.66	1.94	6.53	3.40	5.40	**7.54**
p-value	<0.001	0.032	0.013	0.021	0.07	<0.01	<0.01	<0.01	**<0.01**
Prevalence	19.8%	39.5%	44.4%	62.4%	18.3%	8.7%	6.9%	4.7%	**3.6%**
PPV	5.3%	10.4%	5.9%	5.2%	5.7%	5.6%	4.1%	3.4%	**19.4%**
NPV	97.4%	97.6%	97.5%	98.0%	96.5%	96.7%	96.7%	96.3%	**96.9%**

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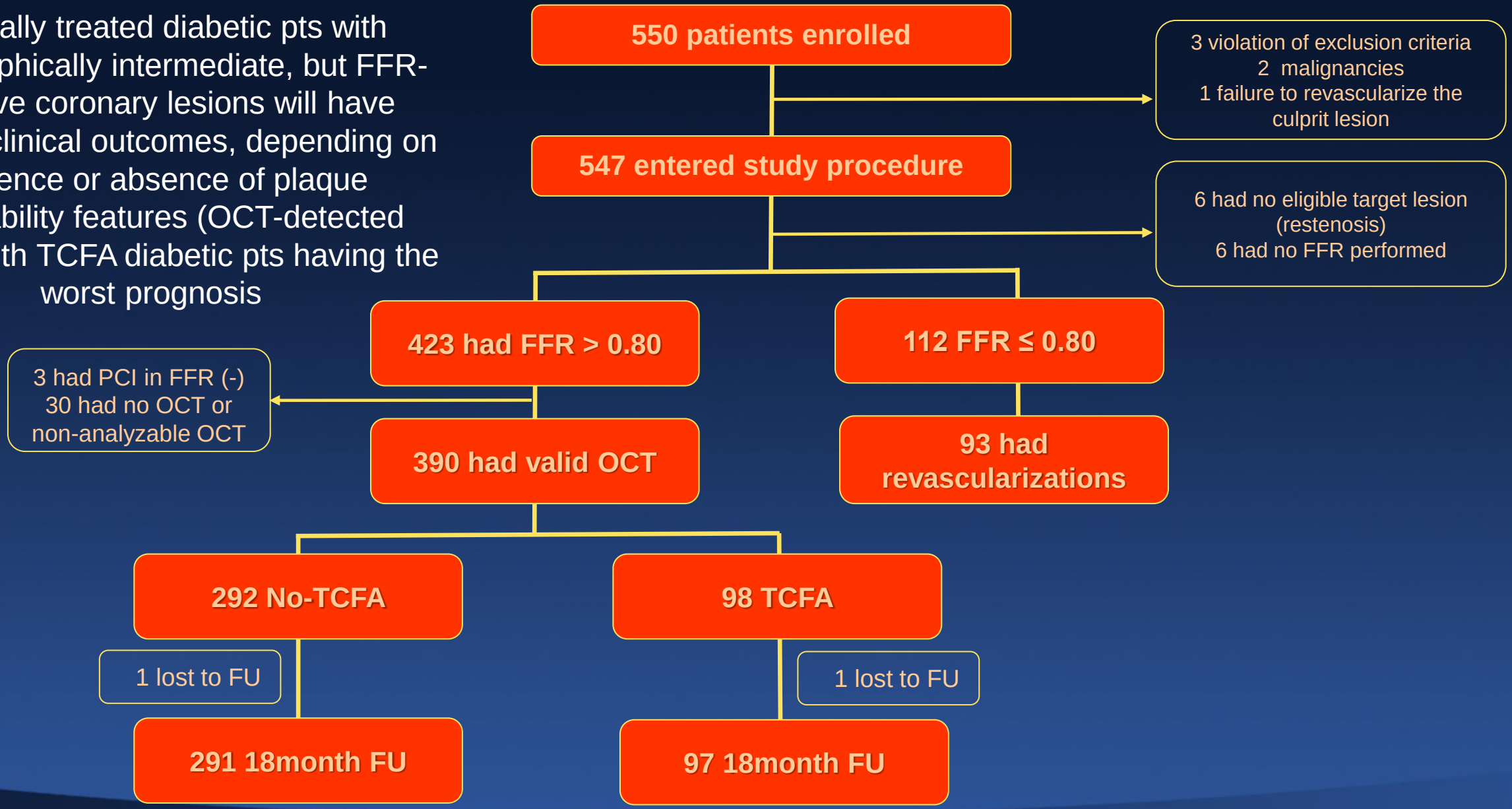
Prati et al. Eur Heart J 2020;41:383-91

COMBINE

Medically treated diabetic pts with angiographically intermediate, but FFR-negative coronary lesions will have different clinical outcomes, depending on presence or absence of plaque vulnerability features (OCT-detected TCFA), with TCFA diabetic pts having the worst prognosis



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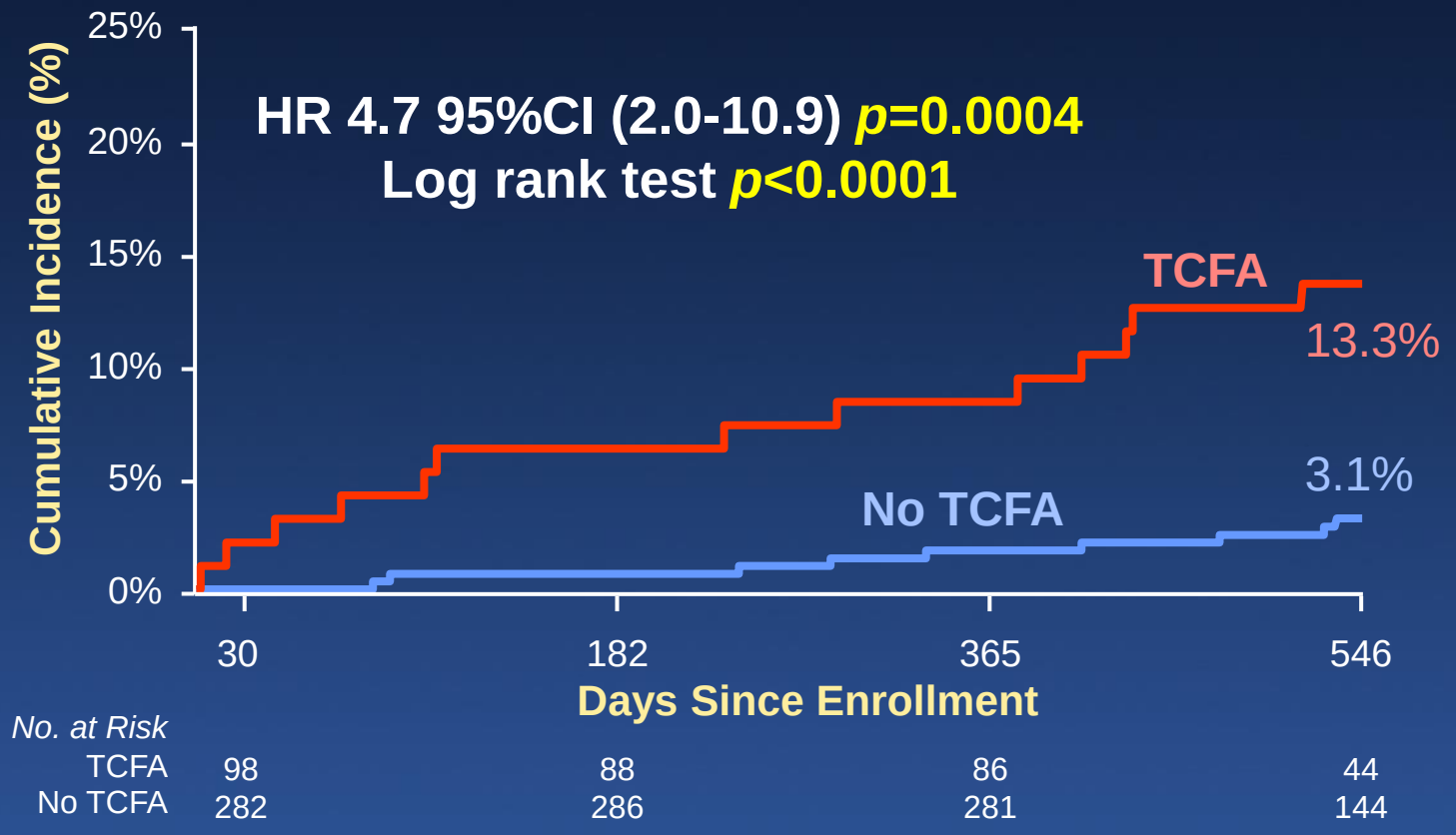
Kedhi et al. Eur Heart J. 2021:ehab433. doi: 10.1093/eurheartj/ehab433

COMBINE: OCT-TCFA vs no OCT-TCFA in FFR negative lesions in diabetic pts

Primary Endpoint: Cardiac death, TV-MI, CD-TLR, or Hospitalization for USA



	TCFA	No TCFA	P-value
Cardiac death	0%	0.3%	0.6
TV-MI	4.1%	0%	<0.001
CD-TLR	11.2%	1.4%	<0.001
Hospitalization for USA	6.2%	1.7%	0.002

TCFA (HR 4.6, p<0.001) and MLA per 1mm² decrease (HR 1.6, p=0.04) were independent predictors of the primary endpoint

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Kedhi et al. Eur Heart J. 2021:ehab433. doi: 10.1093/eurheartj/ehab433

What is the likelihood of distal embolization or peri-procedural MI during stent implantation?

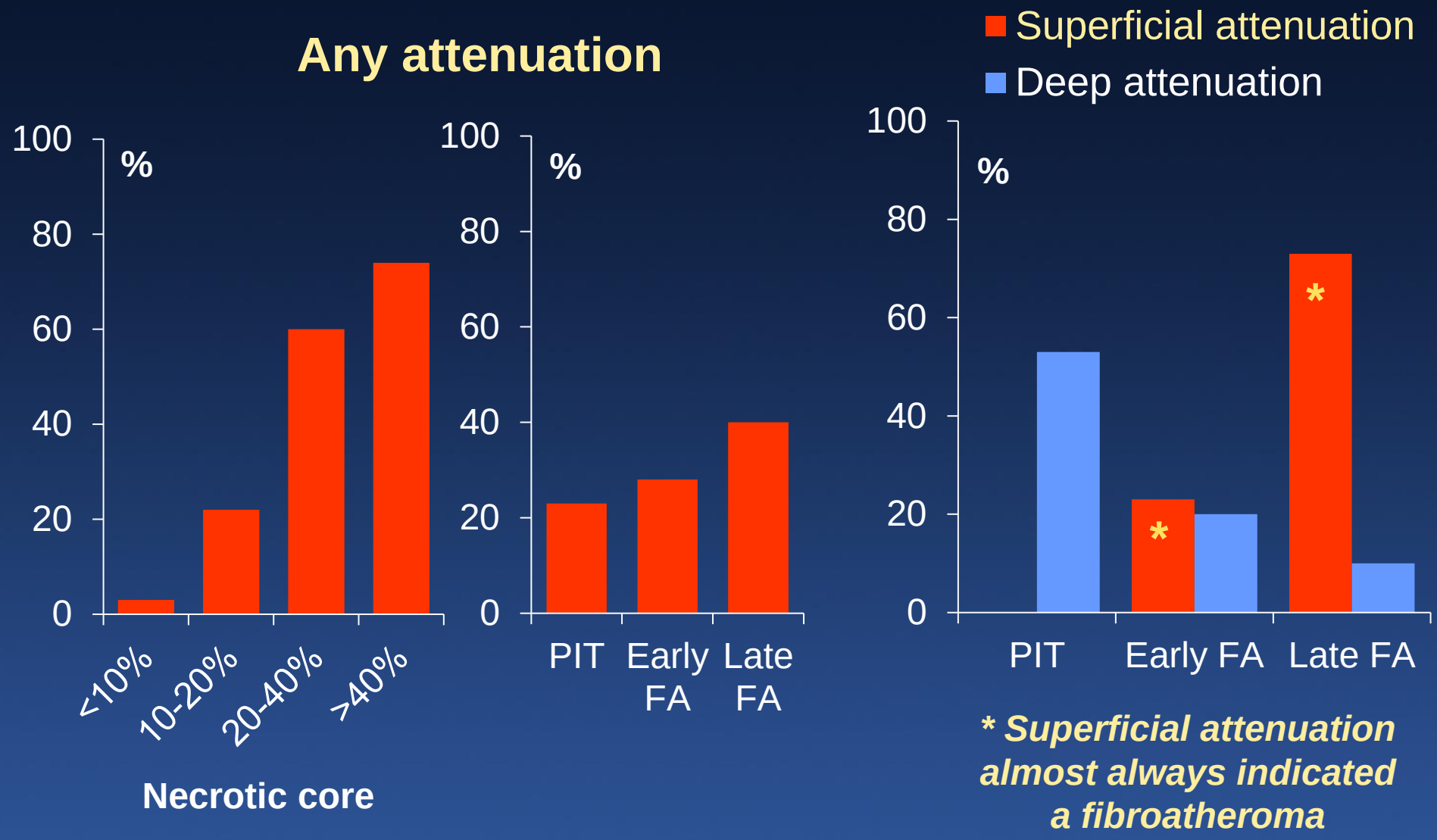
Peri-procedural CK-MB elevation occurred in 20.4%

Peri-procedure CK-MB >3xULN occurred in 16.9%

An ACC National Cardiovascular Data Registry (NCDR) report indicated that no-reflow occurred in 2.3% of primary PCI and was associated with greater in-hospital mortality (12.6% vs. 3.8%, p<0.001)

Jeremias et al. J Am Coll Cardiol. 2004;44:1210-14
Stone et al Circulation 2001;104:642-7
Harrison et al. Am J Cardiol 2013;111:178-84

Prevalence of echoattenuated plaque



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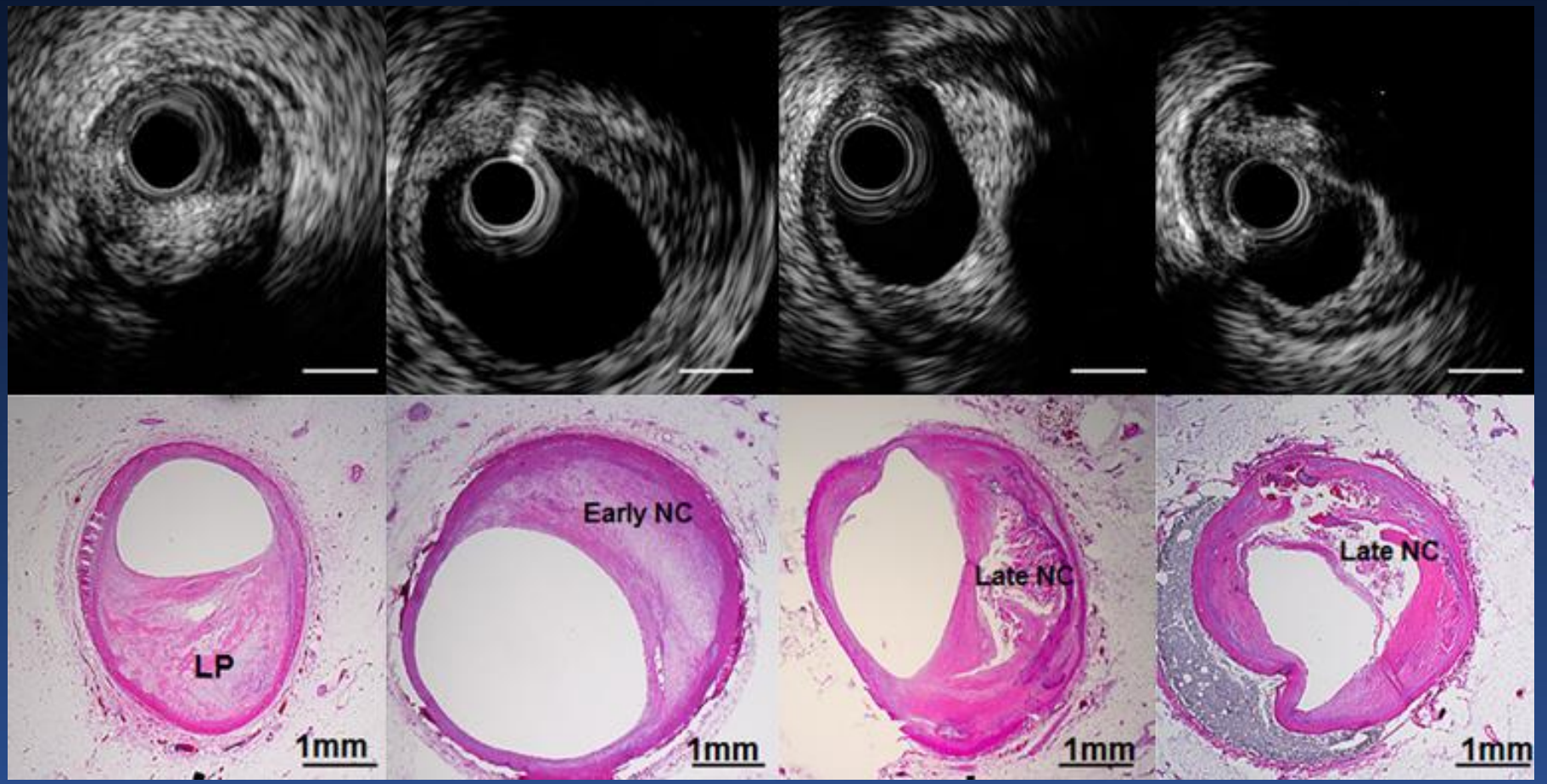
Pu et al. J Am Coll Cardiol 2014;63:2220-33

Echoattenuated plaque



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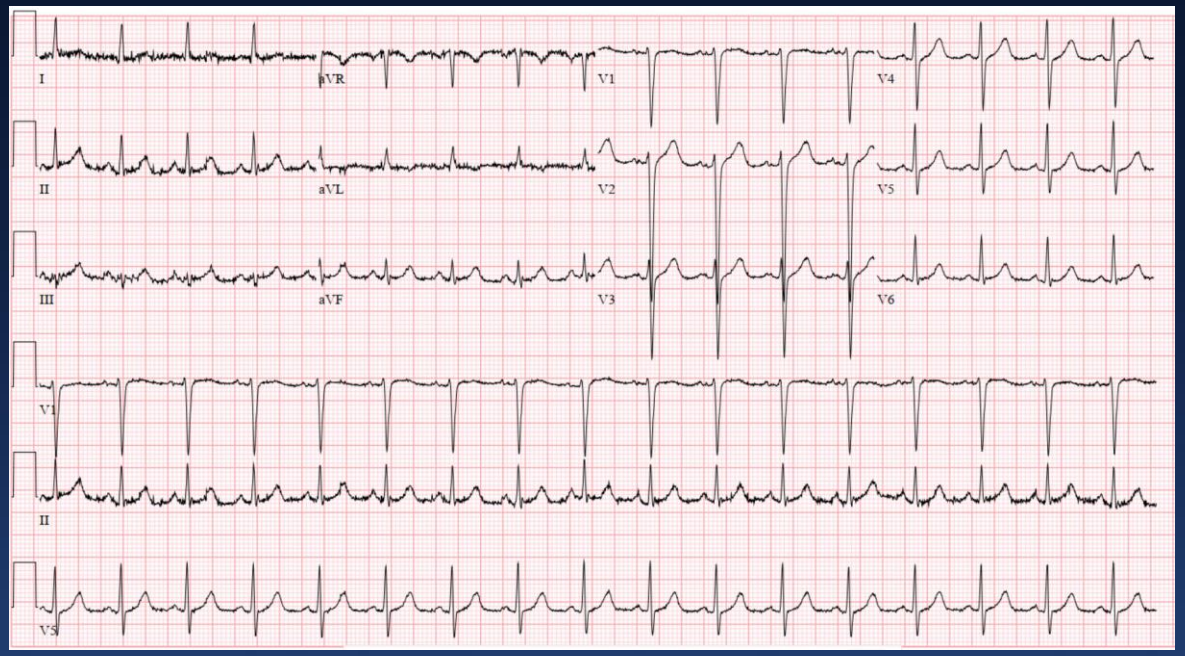
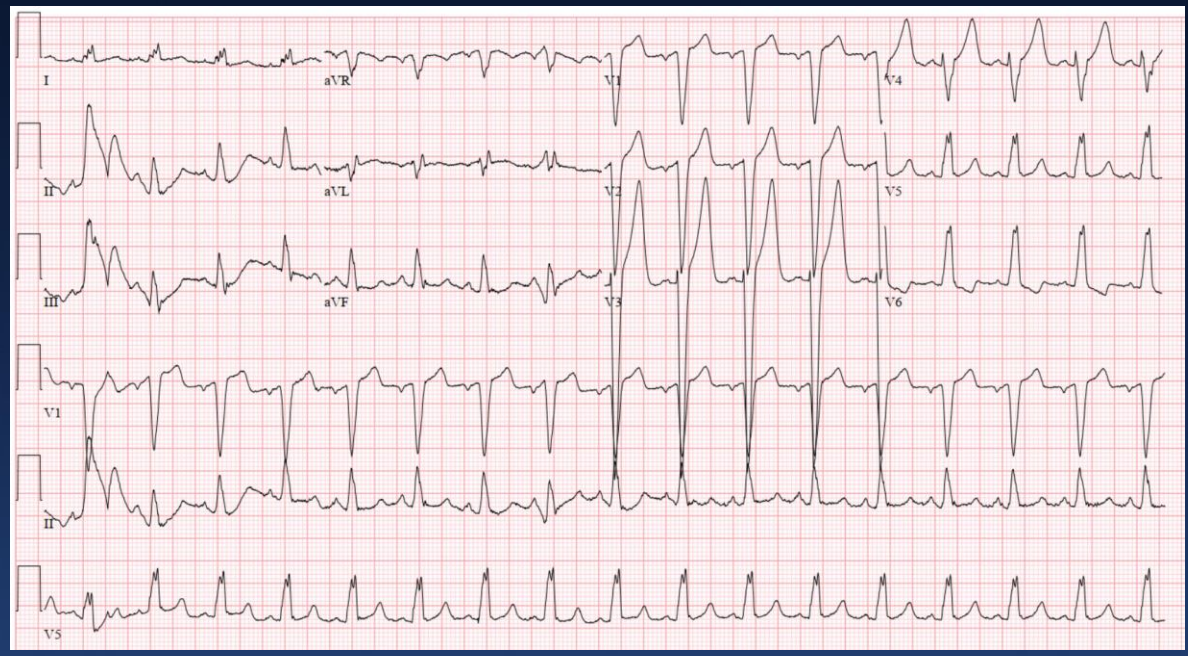
Pu et al. J Am Coll Cardiol 2014;63:2220-33

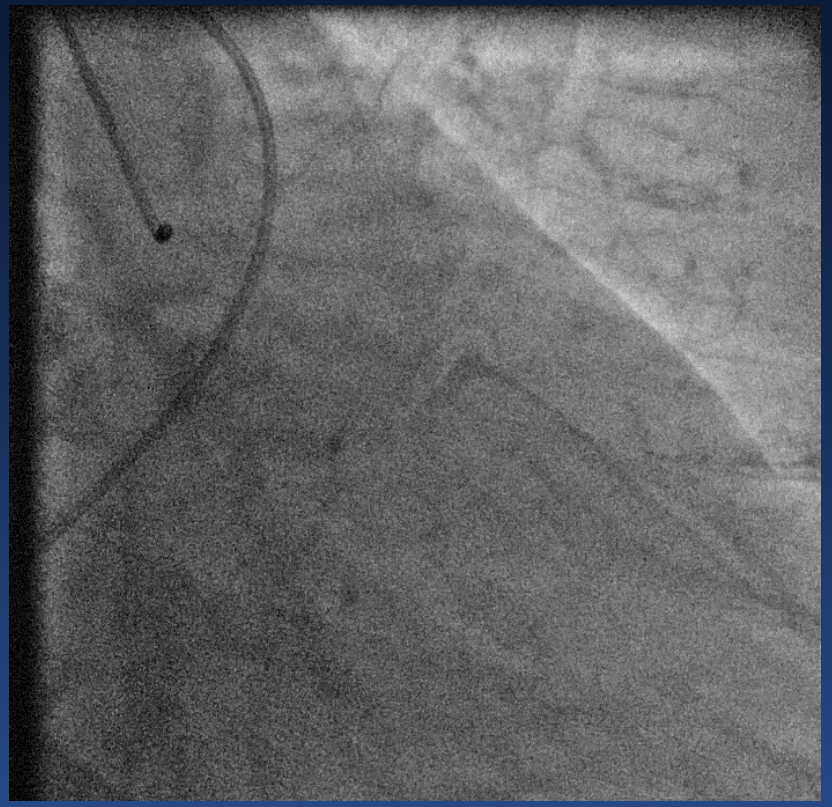
62y/o man with HTN, DM, and PAD s/p R-BKA complaining of chest discomfort. High sensitivity Troponin 41 ng/L. ECG with new LBBB.

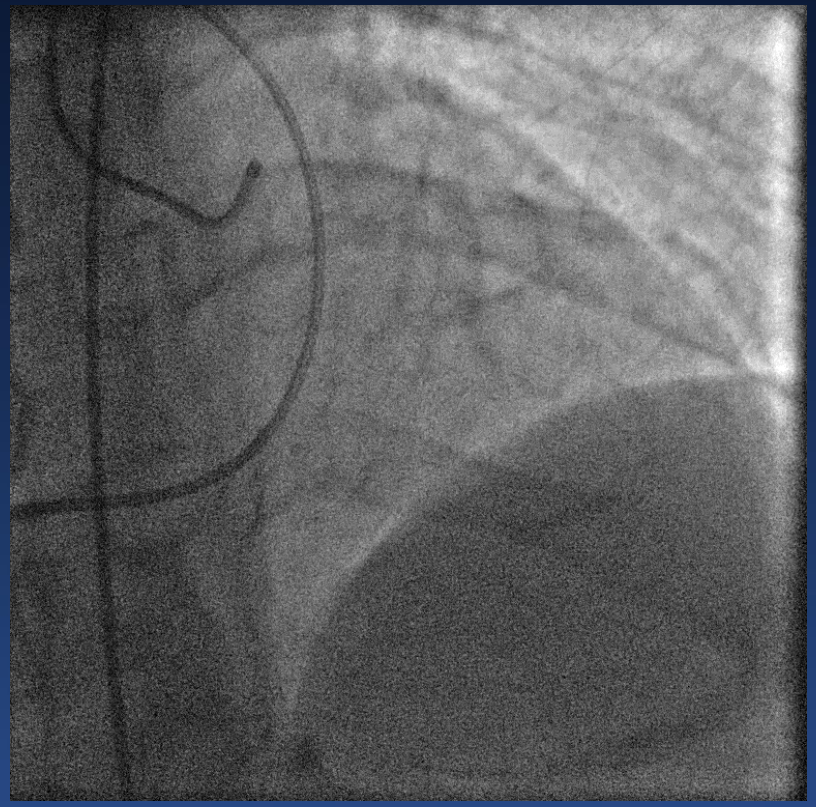


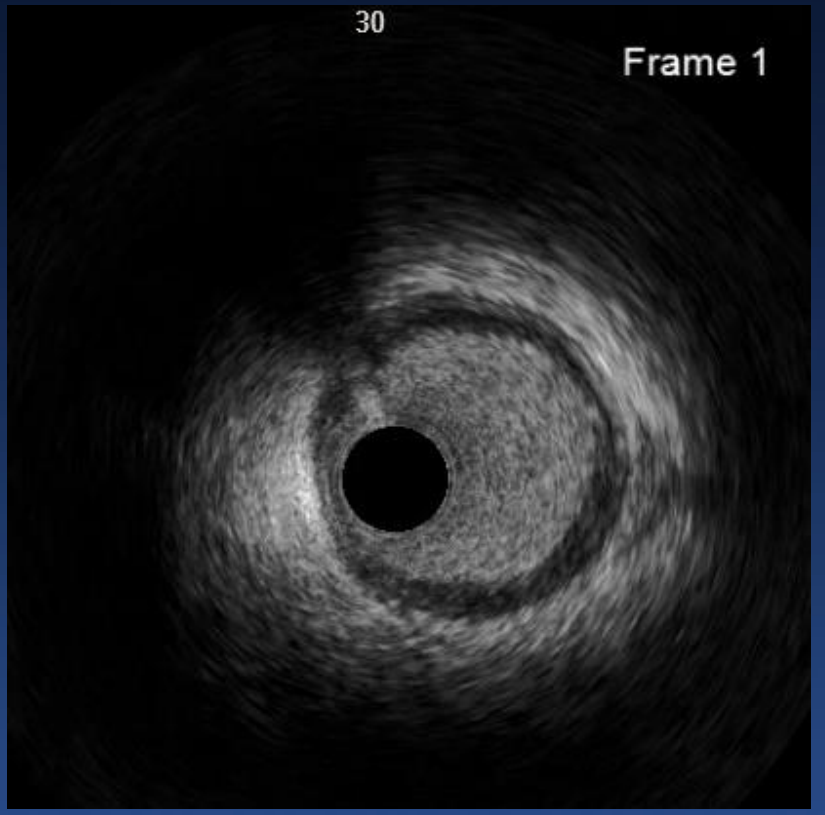


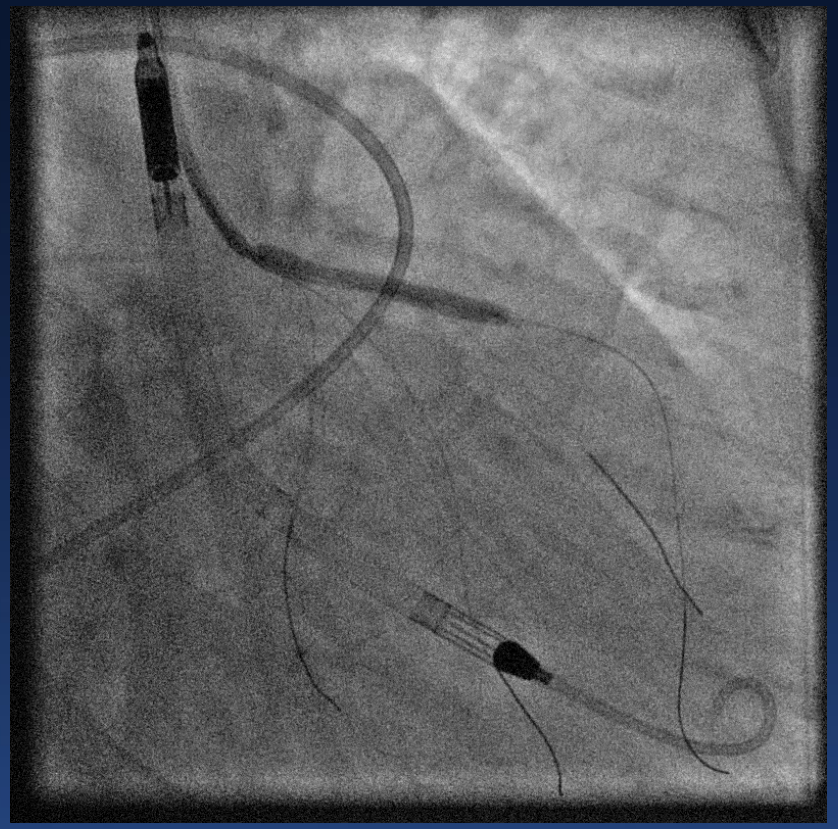
- hsTnT 36 → 41 ng/L
- sCr 0.69, eGFR 68
- Na 135, K 4.6
- Hgb 12.8, Plt 307k, WBC 10.7k
- INR 1.1, aPTT 33.9
- TC 192, HDL 40, LDL 144, TG 42
- COVID positive

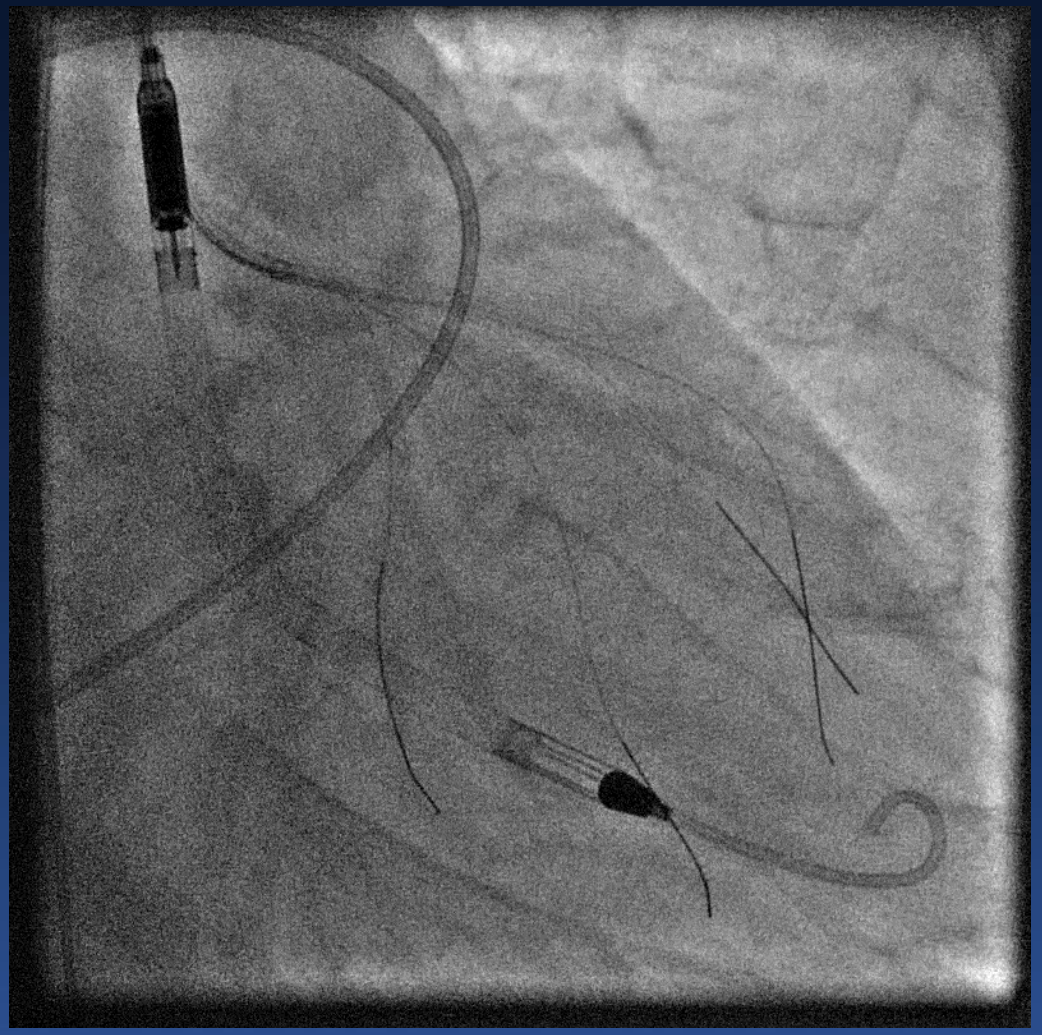
- TTE
  - LV EF 25%, global hypokinesis
  - No LV thrombus noted
  - Normal RV systolic function
  - No significant valvulopathy






30
Frame 1





Predilation with a non-compliant 3.0x20mm balloon at 12 atm
Implantation of a 3.50x34mm ZES at 16 atm

VAMPIRE Trial

VAcuuM asPIration thrombus Removal

200 pts with STEMI/NSTEMI/USA within 2 months and a single native coronary artery lesion and **>180° attenuated plaque by grayscale IVUS >5mm in length**

Randomized

PCI with distal protection (Filtrap, Nipro, Japan)
(n=101)

↓

98 included in analysis of no-reflow

PCI without distal protection
(n=99)

↓

96 included in analysis of no-reflow

Primary endpoint = No-reflow during PCI

Secondary endpoints = Post-PCI TIMI flow, corrected TIMI frame count, CK or CK-MB elevation 6-24h post-PCI, MACE pre-discharge

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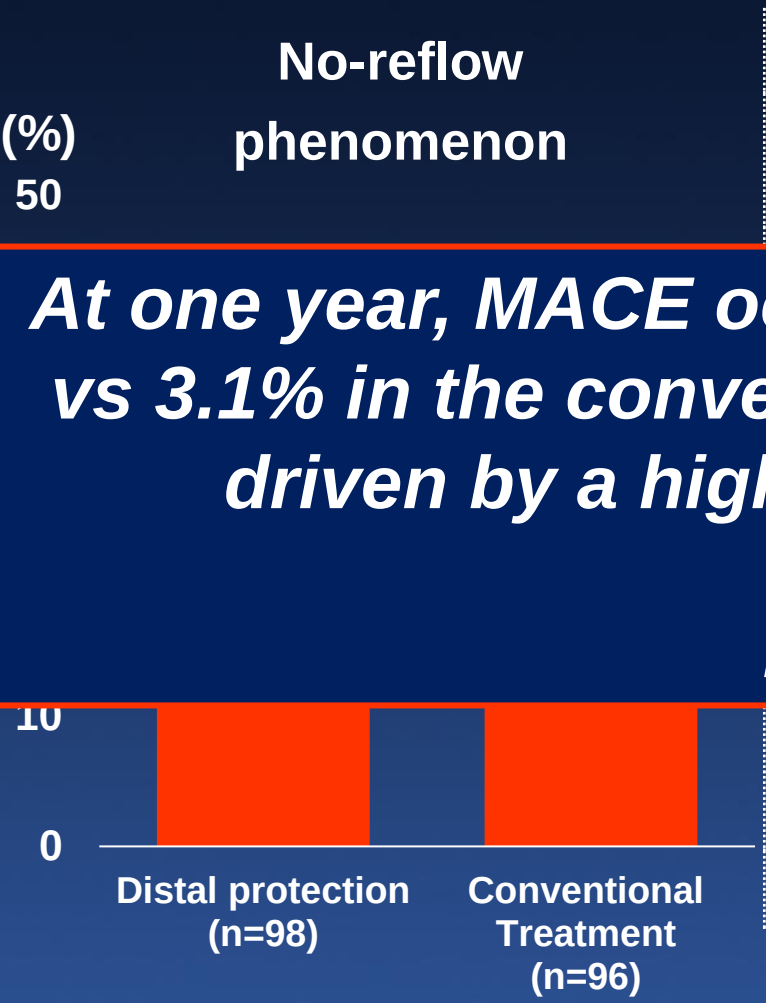
Hibi et al. JACC Cardiovasc Interv. 2018;11:1545-55

Primary endpoint: Incidence of no-reflow phenomenon



At one year, MACE occurred in 12.2% in the distal protection group vs 3.1% in the conventional treatment group (P=0.029), which was driven by a higher risk of TVR (11.2% vs. 2.1%, p=0.018).

Hibi et al. Circ J. 2020;85:44-49.

Secondary Endpoints			
	Distal Protection	Conventional Treatment	P-Value
CK-MB @ 6-24 hours	53	49.5	0.6
In-hospital MACE	1.0%	8.3%	0.0179
Cardiac arrest/shock	0%	5.2%	0.028

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Hibi et al. JACC Cardiovasc Interv. 2018;11:1545-55

"Higher" probability of distal embolization. . . The common denominator was presence of a TCFA

- ***Attenuated plaque – grayscale IVUS***
  - *Lee et al. JACC Cardiovasc Interv. 2009;2:65-72*
  - *Wu et al, Am J Cardiol 2010;105:48-53*
  - *Okura et al, Circ J 2007;71:648-53*
  - *Wu et al. JACC Cardiovasc Interv 2011;4:495-502*
  - *Lee et al JACC Cardiovasc Interv. 2011;4:483-91*
  - *Kubo et al. Cardiol Res Pract. 2011;687515*
  - *Pu et al. Eur Heart J 2012;33:372-83*
  - *Shiono et al, JACC Cardiovasc Interv 2013;6:847-53*
  - *Jang et al. Am J Cardiol 2013;111:968-72*
  - *Amano et al. Int Heart J 2016;57:285-91*
  - *Okutsu et al.* Heart Vessels. 2018;33:1121-1128
- ***VH- or IB-IVUS TCFA or large lipidic or necrotic core***
  - *Claessen et al. JACC Cardiovasc Imaging 2012;5:S111-8*
  - *Amano et al.* J Interv Cardiol. 2013 Jun;26(3):295-301
  - *Ding et al. PLoS One. 2014 Nov 6;9(11):e106583*
  - *Matsu et al. EuroIntervention 2013;9;235-242*
  - *Ozaki et al. Circ J 2015;79:808-17*
  - *Daidoji et al.* Catheter Cardiovasc Interv. 2015;85:43-50
  - *Suda et al.* Heart Vessels. 2016 Dec;31(12):1904-1914
  - *Kitagawa et al. Atherosclerosis 2017;258:72-8*
- ***OCT-TCFA or plaque rupture***
  - *Tanaka et al. Eur Heart J 2009;30:1348-55*
  - *Yonetsu et al. Int J Cardiol 2011;146:80-5*
  - *Lee et al. Circ Cardiovasc Intv 2011;4:378-86*
  - *Lee et al. J Am Coll Cardiol Intv 2011;4:483-91*
  - *Porto et al. Circ Cardiovasc Intv 2012;5:89-96*
  - *Imola et al. Am J Cardiol 2013;111:526-31*
  - *Ueda et al. Coron Artery Dis 2014;25:384-91*
  - *Higuma et al. JACC Cardiovasc Imaging 2015;17:1166-76*
  - *Lee et al. Circ Cardiovasc Intv 2015, doi: 10.1161/CIRCINTERVENTIONS.114.001727.*
  - *Kini et al. JACC Cardiovasc Interv 2015;8:937-45*
  - *Ikenaga, et al. Eur Heart J Cardiovasc Imaging. 2017;0:1-9*
  - *Hu et al. J Am Heart Assoc. 2017 Feb 24;6(3). pii: e004730*
  - *Soeda et al.* Eur Heart J Cardiovasc Imaging. 2017;18:103-110
  - *Uzu et al. J Cardiol 2017;70:545-52*
  - *Otsuka et al. Heart Vessels. 2020:35:451-62*
  - *Gui et al.* Heart Surg Forum. 2023;26:E051-E055
  - *Katayama et al.* Int J Cardiol Heart Vasc. 2022 Jan 11;38:100953. doi: 10.1016/j.ijcha.2022.100953
- ***Large lipid core plaque - NIRS***
  - ***Goldstein et al. Circ Cardiovasc Interv 2011;4:429-437***
  - *Stone et al. JACC Cardiovasc Interv 2015;8:927-36*
  - *Kini et al. JACC Cardiovasc Interv 2015;8:937-45*
  - *Sato et al. J Thromb Thrombolysis. 2018 Aug;46(2):203-210*
  - *Matsuoka et al. Cathet Cardiovasc Interv 2021;98:E695-E704*
  - *Terada et al. EuroIntervention. 2021;17:e999-e1006.*
  - *Lim et al. J Clin Medlin Med 2022;11:5401. doi: 10.3390/jcm11185401.*

Low probability of distal embolization predictable by *absence of*

- Attenuated plaque – grayscale IVUS
- VH-TCFA or large necrotic core
- OCT-TCFA or plaque rupture
- Large lipid core plaque - NIRS