

PROSPECT II: A Prospective Natural History Study Using NIRS-IVUS Imaging in Patients with Acute Myocardial Infarction

David Erlinge, MD, PhD

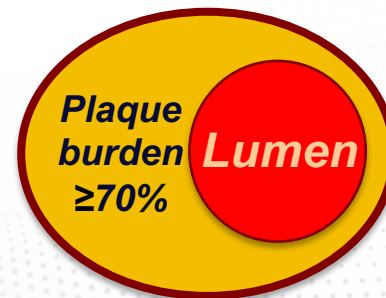
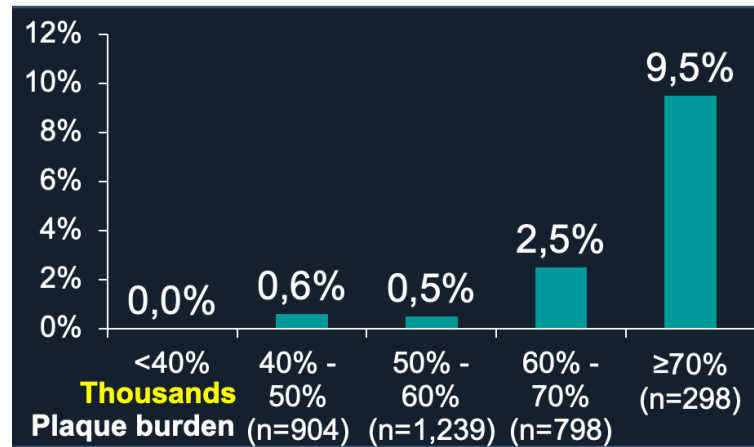
On behalf of Akiko Maehara, Ori Ben-Yehuda, Hans Erik Bøtker, Michael Maeng, Lars Kjøller-Hansen, Thomas Engstrøm, Mitsuaki Matsumura, Aaron Crowley, Ovidiu Dressler, Gary S. Mintz, Ole Frøbert, Jonas Persson, Rune Wiseth, Alf Inge Larsen, Lisette Okkels Jensen, Jan Erik Nordrehaug, Öyvind Bleie, Elmir Omerovic, Claes Held, Stefan K. James, Ziad A. Ali, James. E Muller and Gregg W. Stone for the PROSPECT II Investigators

Disclosures

- **In the past 12 months David Erlinge has received Speakers fees – Amgen, AstraZeneca, Bayer, Chiesi and fees for Advisory boards – Bayer, Boehringer-Ingelheim, Sanofi.**

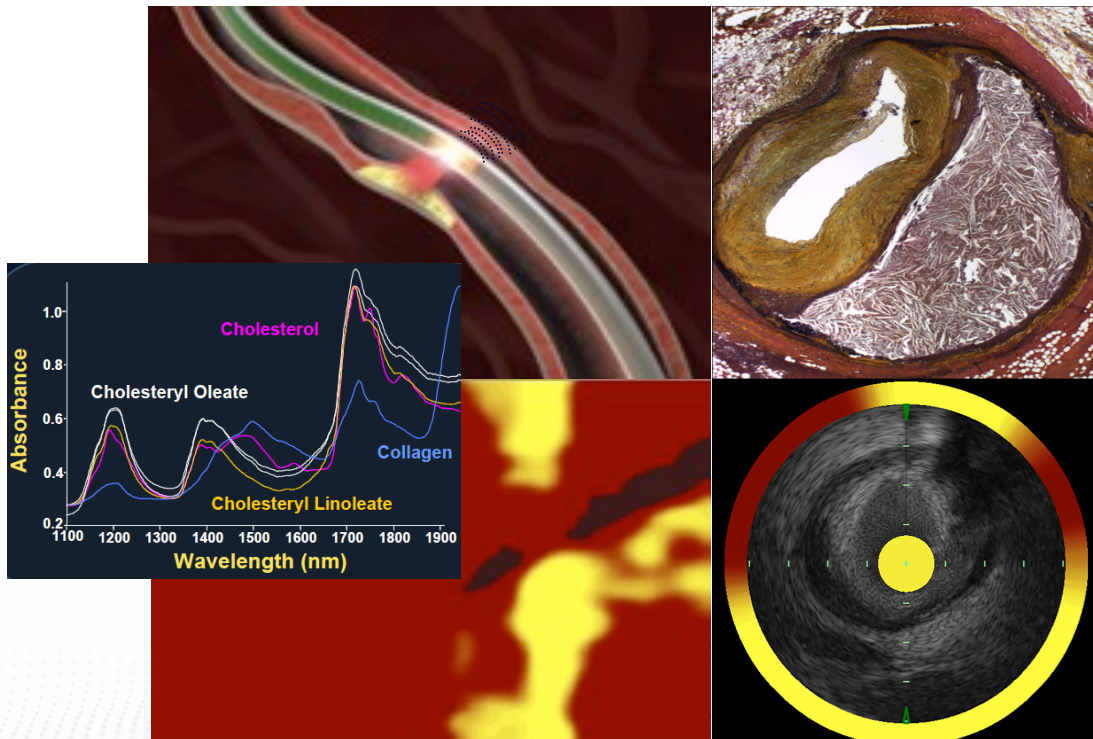
Background

- ACS most often arise from disruption and thrombosis of lipid-rich atherosclerotic plaques
- Identification of such “vulnerable” plaques before they progress may enable pre-emptive pharmacologic or other strategies to stabilize the plaque, prevent atherosclerosis progression and improve outcomes
- In the PROSPECT study, a large plaque burden, small lumen area and VH-TCFA assessed by intravascular ultrasound (IVUS) identified angiographically mild lesions at increased risk to cause future adverse events



Lipid-rich Core and NIRS

- Plaques causing MI and sudden cardiac death commonly contain a lipid-rich core
- Lipid content can be quantified by **near-infrared spectroscopy (NIRS)** in human coronary arteries (FDA approved)
- Retrospective reports and a recent prospective study have suggested that lipid-rich plaques detected by intracoronary NIRS imaging are associated with adverse **outcomes**



¹Virmani R et al. ATVB 2000;20:1262-75

²Madder RD et al. ATVB 2016;36:1010-5

³Waksman R et al. Lancet 2019;394:1629-37

PROSPECT II: Design

- After successful treatment of all flow-limiting lesions in pts with recent MI (STEMI or troponin + NSTEMI), intravascular imaging was performed in the proximal 6-10 cm of all 3 coronary arteries with a combination NIRS-IVUS catheter
- Untreated “non-culprit” lesions (NCLs) were prospectively identified by IVUS and their lipid content was assessed by blinded NIRS
- Based on follow-up angiography, adverse cardiovascular events were classified as attributable to:
 - Originally-treated culprit lesions
 - Scaffold-randomized treated lesions
 - Untreated non-culprit lesions (NCLs)
 - Indeterminate (no follow-up angiography)



PROSPECT II: Design, cont

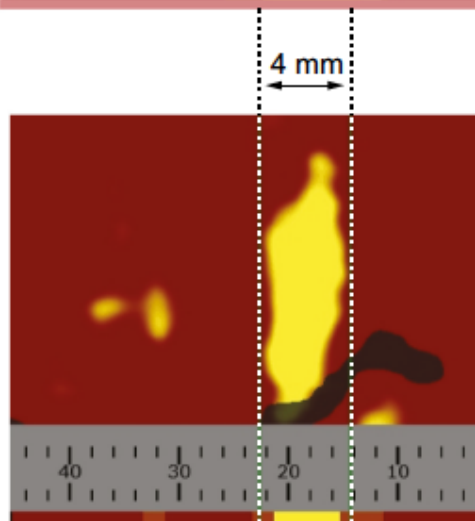
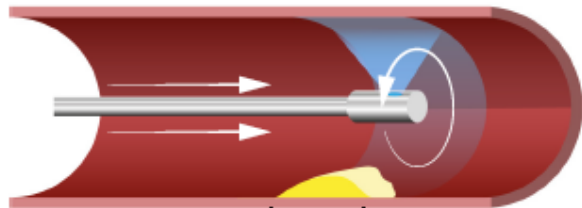
- The primary outcome was MACE during long-term follow-up, the composite of cardiac death, MI, unstable angina or progressive angina either requiring revascularization or with rapid lesion progression, attributed to originally untreated NCLs
- A RCT, PROSPECT ABSORB, was embedded in PROSPECT II
 - Angiographically non-obstructive lesions with IVUS plaque burden $\geq 65\%$ were randomized to treatment with BVS plus guideline-directed medical therapy (GDMT) versus GDMT alone
 - Randomized lesions treated with a scaffold were excluded from the PROSPECT II natural history analysis

Imaging Analysis

Angiography and IVUS

- Angiograms and intravascular images were prospectively analyzed at an independent core laboratory (CRF) without knowledge of patient outcomes
- Angiographic analyses were performed of all lesions with $\geq 30\%$ DS in each epicardial vessel and sidebranch ≥ 1.5 mm in diameter using an automated edge-detection algorithm
- IVUS evaluation of all image cross-sections and quantitative measurements every mm were performed
- Culprit lesions were defined by IVUS as the treated segment including 5 mm proximal and distal stent edges
- NCLs were defined as untreated coronary segments ≥ 2 mm in length with $\geq 40\%$ plaque burden

Imaging Analysis: NIRS



maxLCBI = 625 (62.5%)

- NIRS spectroscopic data generates a chemogram, a color-coded distribution of lipid probability with the x-axis corresponding to the axial vessel position (0.1 mm/pixel) and the y-axis corresponding to the circumferential position (1°/pixel)
- Low probability of lipid is shown as red and high probability of lipid is shown as yellow
- Lipid core burden index (LCBI) = the fraction of pixels with probability of lipid >0.6 divided by all analyzable pixels within the region of interest, multiplied by 1000
- $\text{MaxLCBI}_{4\text{mm}}$ = the maximum LCBI within any 4 mm segment across the entire lesion

Statistical Analysis

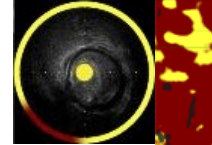
- The principal study objective was to establish the covariate-adjusted relationship between high-risk characteristics of untreated NCLs and subsequent patient-level (1°) and lesion-level (2°) outcomes
- High-risk untreated plaque characteristics were pre-specified as:
 - Lipid-rich plaque (defined as the upper quartile of maxLCBI_{4mm} of all NCLs)
 - Maximum plaque burden (PB) $\geq 70\%$
 - Minimum lumen area (MLA) $\leq 4.0 \text{ mm}^2$
- Each individual high-risk plaque characteristic was introduced in a separate multivariable model in a hierarchical order (LRP followed by PB followed by MLA) to account for multiplicity

PROSPECT II Organization, Leadership, Committees and Core Laboratories

- Coordinating PIs and Study Chairmen: David Erlinge and Gregg W. Stone
- AROs: CRF (Ori-Ben-Yehuda, Executive Director) and UCR (Jonas Oldgren, Executive Director)
- Sponsor, Project and Data Management: UCR, Frida Kåver (Project Manager), Lars Wallentin (sponsor representative)
- Clinical Events Committee: UCR, Claes Held (Chair)
- Angiographic Core Lab: CRF, Ziad A. Ali (Director)
- IVUS-NIRS Core Lab: CRF, Akiko Maehara (Director)
- Programming, Biostatistics and Data Analysis: CRF, Aaron Crowley (Director)
- DSMB: Patrick W. Serruys (Chair)
- Funding support: Abbott Vascular, Infraredx Inc, The Medicines Company

PROSPECT II Natural History Study

PROSPECT ABSORB RCT



902 pts with troponin + ACS after successful PCI enrolled at 16 centers

3 vessel IVUS + NIRS (blinded)

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 $\geq 65\%$ plaque burden?

Yes
(N=182)

No
(n=716)

R
1:1

ABSORB BVS
+ GDMT (N=93)

GDMT
(N=89)

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



PROSPECT II

Hospitals and Principal Investigators

- **Denmark (529 enrolled):** National Coordinating Investigator: Thomas Engstrøm.
Aarhus: Hans Erik Bøtker, Michael Maeng, Roskilde: Lars Kjøller-Hansen,
Copenhagen: Thomas Engstrøm, Odense: Lisette Okkels Jensen
- **Sweden (261 enrolled):** National Coordinating Investigator: David Erlinge.
Lund: David Erlinge, Örebro: Ole Fröbert, Danderyd Hospital, Stockholm: Jonas Persson, Gothenburg: Elmir Omerovic, Uppsala: Stefan James, Södersjukhuset, Stockholm: Ulf Jensen, Falun: Iwar Sjögren, Kalmar: Jörg Carlsson
- **Norway (112 enrolled):** National Coordinating Investigator: Jan Erik Nordrehaug.
Trondheim: Rune Wiseth, Stavanger: Alf Inge Larsen, Bergen: Öyvind Bleie,
Tromsø: Thor Trovik

Baseline Characteristics

- 898 patients* with recent MI -

Baseline feature		Clinical presentation	
Age (years)	63.0 (55.0, 70.0)	STEMI	22.2% (199/898)
Sex, female	17.0% (153/898)	NSTEMI	77.8% (699/898)
Current or recent smoker	31.8% (282/886)	BMI (kg/m ²)	27.1 (24.8, 30.3)
Diabetes mellitus	12.1% (109/898)	Total cholesterol (mg/dL)	201.1 (166.3, 228.2)
- Insulin-treated	4.1% (38/898)	- LDL (mg/dL)	127.6 (100.5, 154.7)
Prior PCI	11.9% (107/898)	- HDL (mg/dL)	42.5 (37.1, 54.1)
Prior MI	9.9% (89/896)	- TGs (mg/dL)	124.0 (84.1, 186.0)
Hypertension requiring medication	37.2% (334/898)	Hemoglobin A1c, %	5.6 (5.4, 6.0)
Hyperlipidemia requiring medication	25.2% (226/898)	Creatinine clearance* (mL/min)	99.2 (80.1, 120.9)
Prior stroke or TIA	5.2% (47/898)	High-sensitivity CRP (µg/mL)	3.4 (1.5, 6.1)

*Per protocol, 4 consented pts were not followed beyond 30 days because NCL imaging data was not acquired

Imaging Findings: NCLs

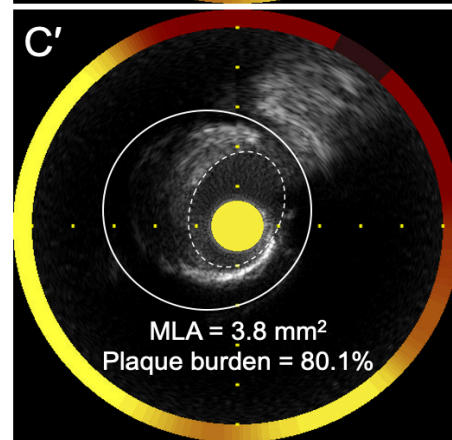
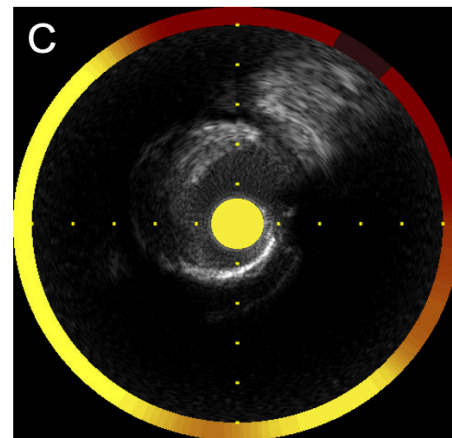
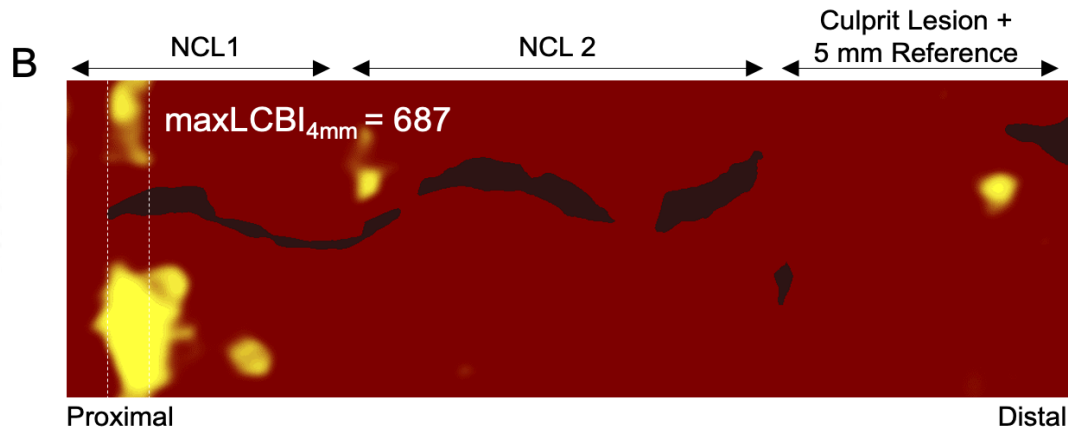
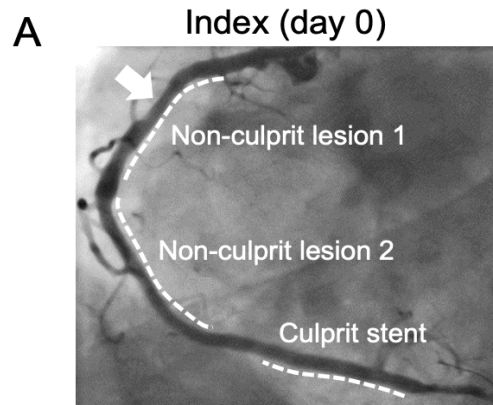
- **Angiography:** 1791 untreated lesions with diameter stenosis $\geq 30\%$ were identified (median 2.0 [1.0, 3.0] per patient)
- **NIRS-IVUS:** Was performed in 2.7 ± 0.6 coronary arteries per pt over a median total length 224 (182, 263) mm per patient
 - A total of 3629 untreated NCLs were prospectively identified by IVUS
 - Median 4.0 [3.0, 5.0] NCLs per patient
 - 24.3% of NCLs had a $\text{maxLCBI}_{4\text{mm}} \geq$ the upper quartile of 324.7 (i.e. 32.5% lipid)
 - 21.7% of NCLs had plaque burden $\geq 70\%$
 - 37.9% of NCLs had $\text{MLA} \leq 4.0 \text{ mm}^2$
- **One or more untreated NCLs:** With a $\text{maxLCBI}_{4\text{mm}} \geq 324.7$, plaque burden $\geq 70\%$ or $\text{MLA} \leq 4.0 \text{ mm}^2$ were present in 58.8%, 59.0% and 75.6% of pts respectively

Imaging-related Adverse Events

- The primary safety outcome of intravascular imaging-related major complications requiring treatment occurred in 2/902 patients (0.2%)
 - 1 new stenosis due to spasm or dissection requiring balloon angioplasty
 - 1 acute occlusion, in retrospect due to air injection for which an additional stent was implanted

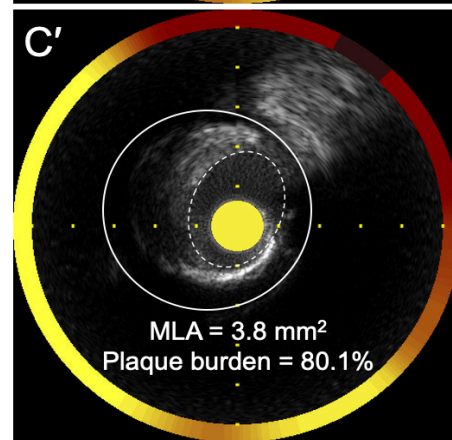
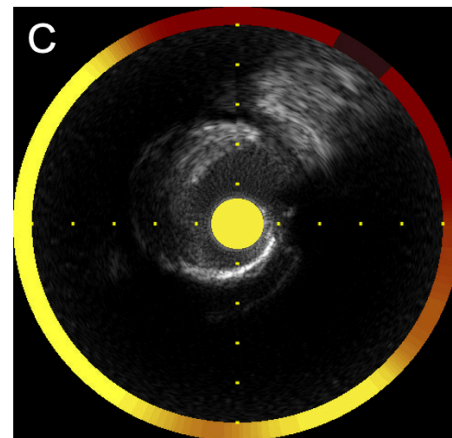
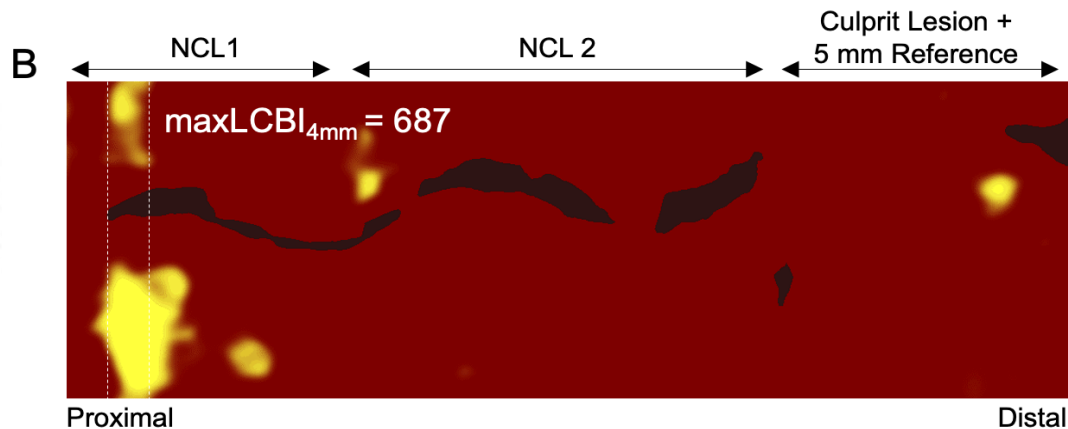
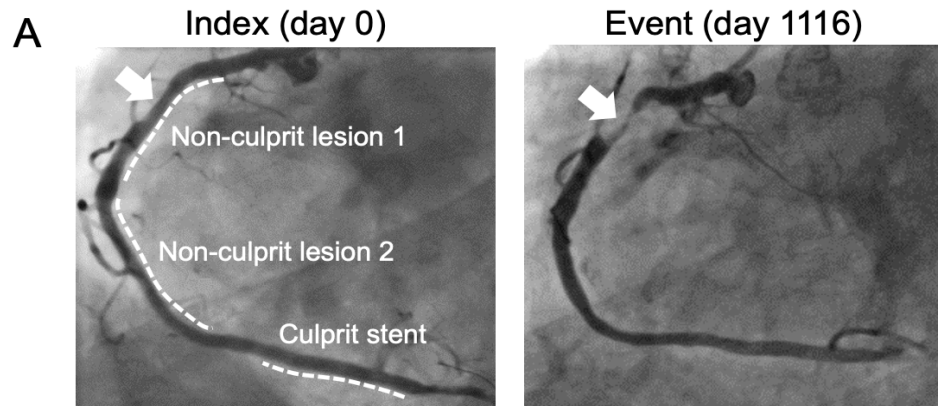
Representative case

An adverse event attributed to an untreated NCL

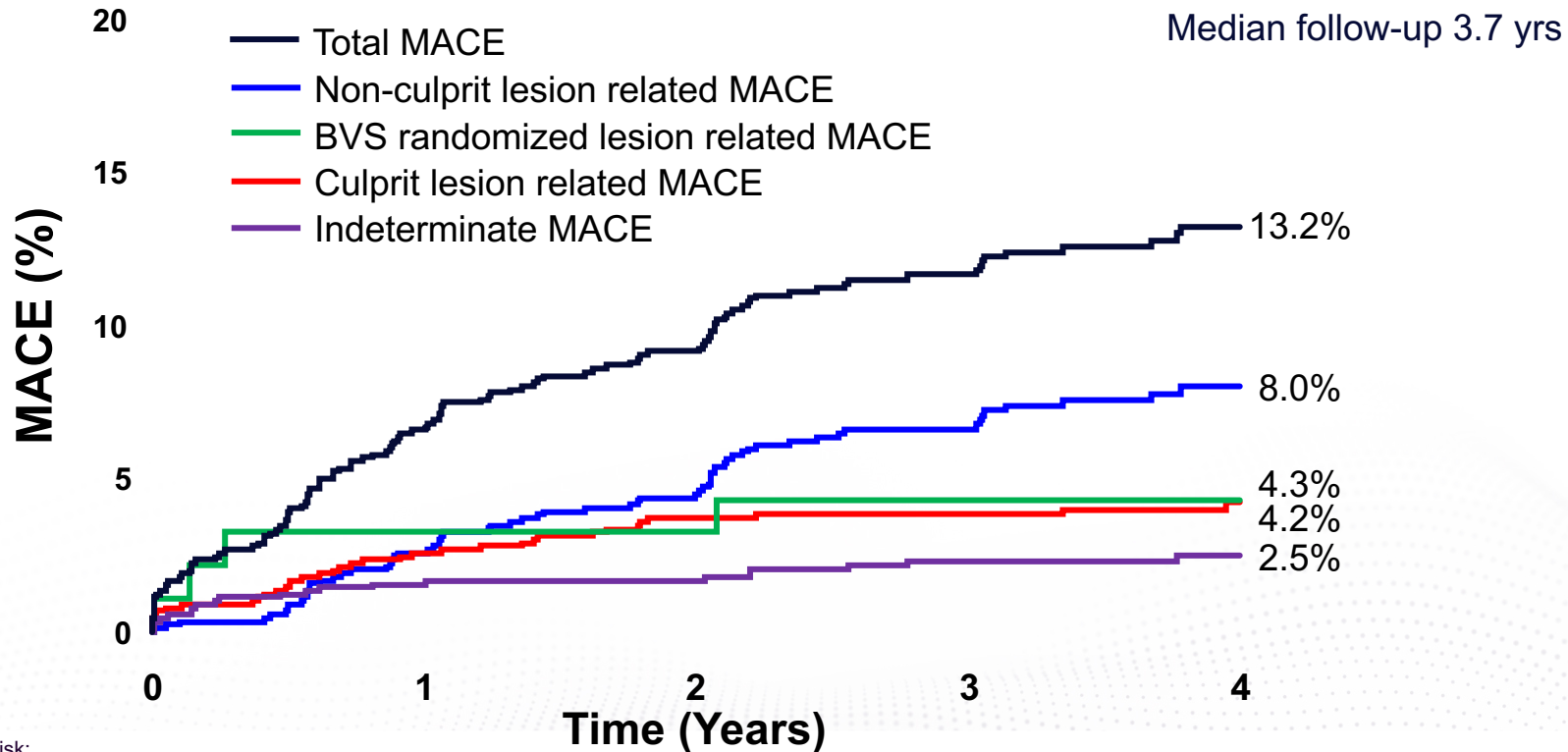


Representative case

An adverse event attributed to an untreated NCL



MACE Through 4-year Follow-up



Number at risk:

Non-culprit	898	869	848	623	331
Culprit	898	869	855	646	351
BVS	93	90	90	78	45
Indeterminate	898	882	877	653	357
Total	898	837	810	593	317

MACE During the Entire Study Duration

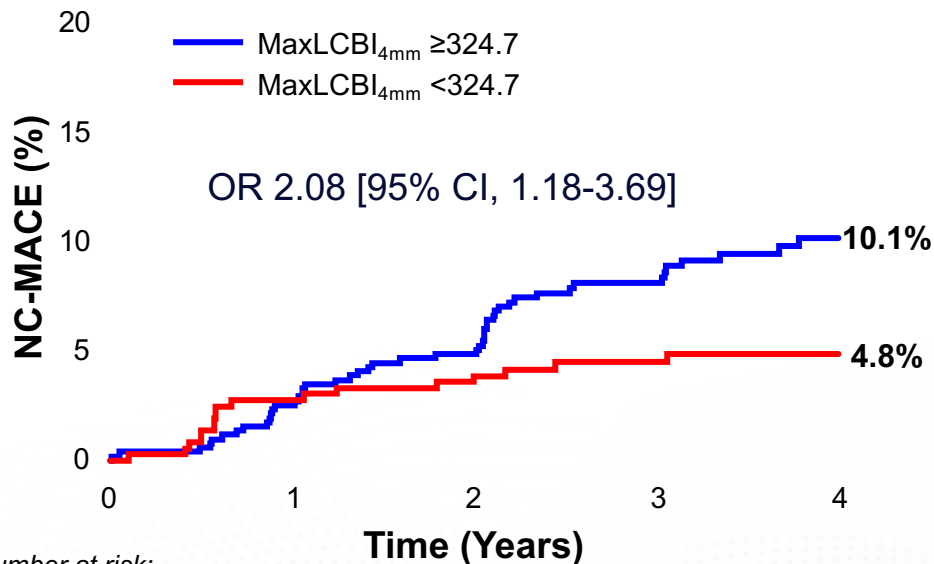
	All	Culprit lesion-related	Non-culprit lesion-related	BVS randomized lesion-related	Indeterminate
Major adverse cardiac events	14.4% (114)	4.6% (37)	8.0% (66)	4.3% (4)	3.3% (22)
- Cardiac death	1.6% (7)	0.0% (0)	0.0% (0)	0.0% (0)	1.6% (7)
- Myocardial infarction	6.9% (54)	2.7% (22)	3.2% (23)	2.2% (2)	1.6% (14)
- Procedure related	0.6% (5)	0.6% (5)	0.0% (0)	0.0% (0)	0.0% (0)
- Non-procedure related	6.3% (49)	2.2% (17)	3.2% (23)	2.2% (2)	1.6% (14)
- Unstable angina	1.3% (12)	0.2% (2)	1.0% (9)	1.1% (1)	0.0% (0)
- Progressive angina	5.7% (48)	1.8% (15)	4.5% (38)	1.1% (1)	0.1% (1)
- Requiring revascularization	4.2% (35)	1.5% (12)	3.1% (27)	1.1% (1)	0.1% (1)
- With rapid lesion progression	1.7% (14)	0.3% (3)	1.4% (12)	0.0% (0)	0.0% (0)

MACE Related to NCLs

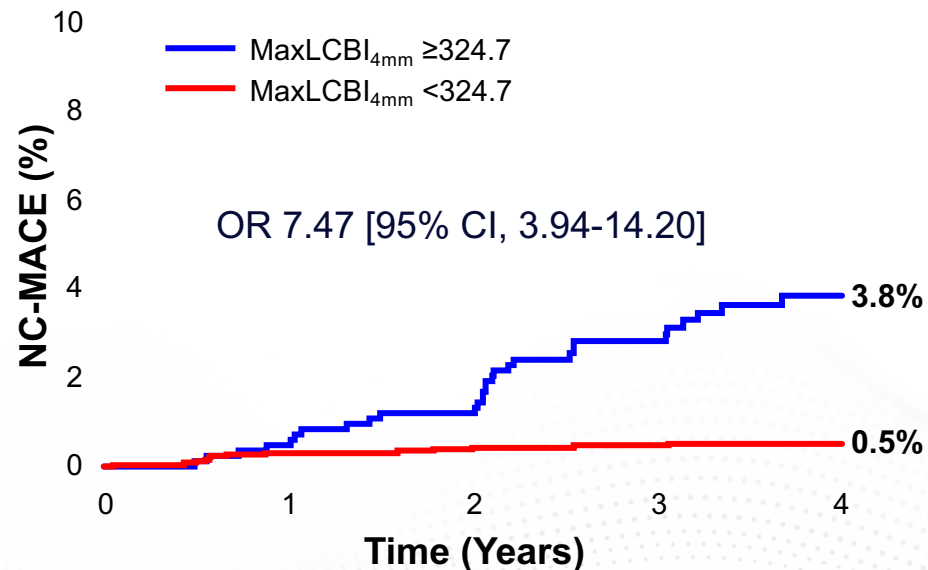
- There were 78 first NCL-MACE events
 - The mean QCA DS of these 78 NCLs was $46.9 \pm 15.9\%$ at baseline and $68.4 \pm 17.7\%$ at the time of the event
- Among these 78 NCLs, 44 (56.4%) were imaged at baseline by NIRS-IVUS
 - All had plaque burden of at least 56.2%
 - Median $\text{maxLCBI}_{4\text{mm}}$ was 473.9; 69.8% were ≥ 324.7

NCL-related MACE According to the Presence of HR Plaque Defined by **Upper Quartile MaxLCBI_{4mm}**

Patient-level events



Lesion-level events

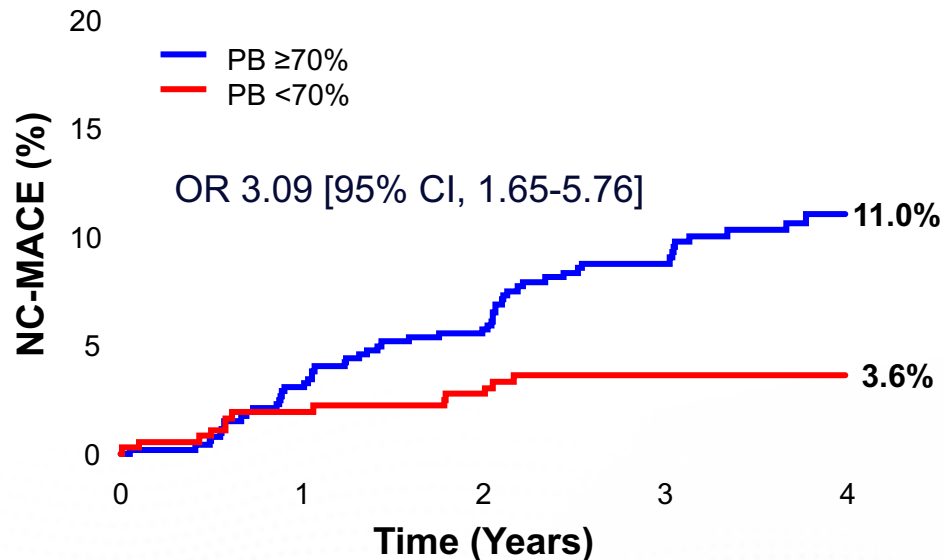


Number at risk:

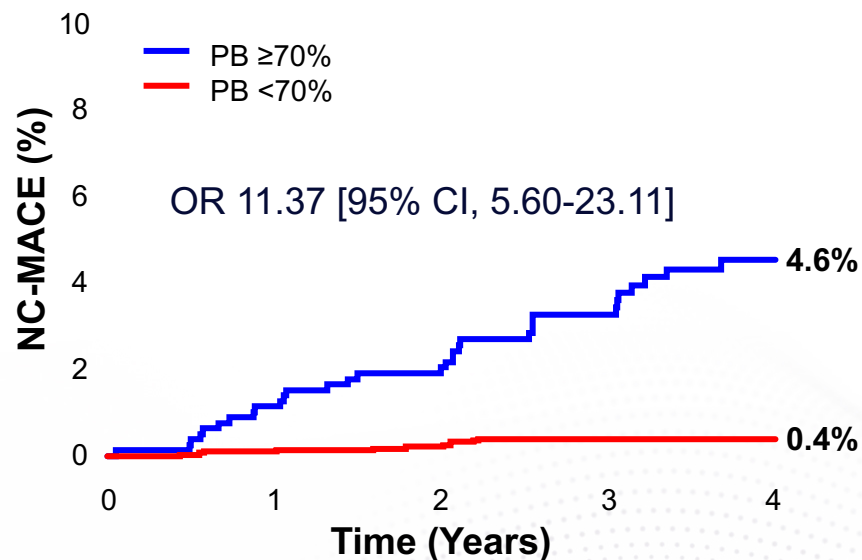
≥324.7	520	503	490	359	202	851	837	830	621	359
<324.7	364	352	345	255	127	2,649	2,623	2,610	1,976	1,092

NCL-related MACE According to the Presence of HR Plaque Defined by **Plaque Burden $\geq 70\%$**

Patient-level events



Lesion-level events



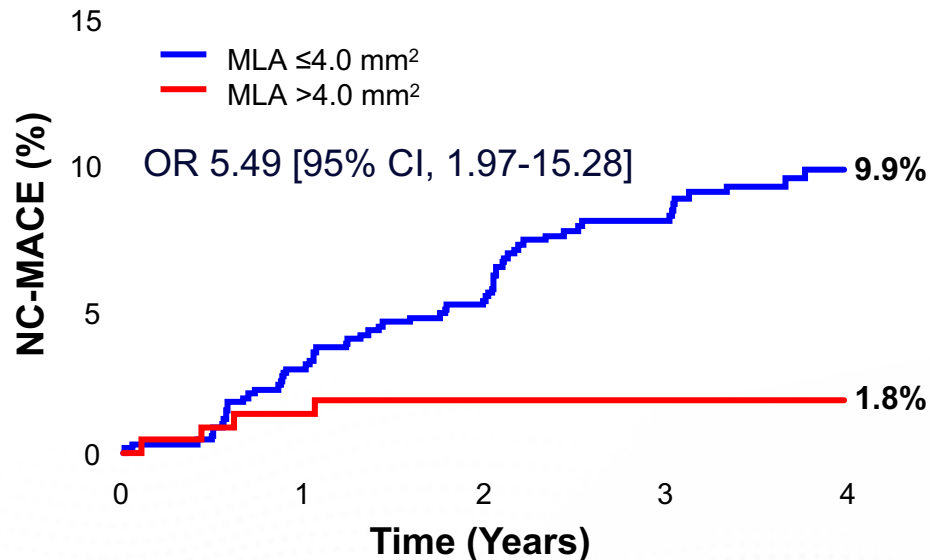
Number at risk:

PB $\geq 70\%$	530	510	494	367	199
PB $< 70\%$	368	359	354	256	132

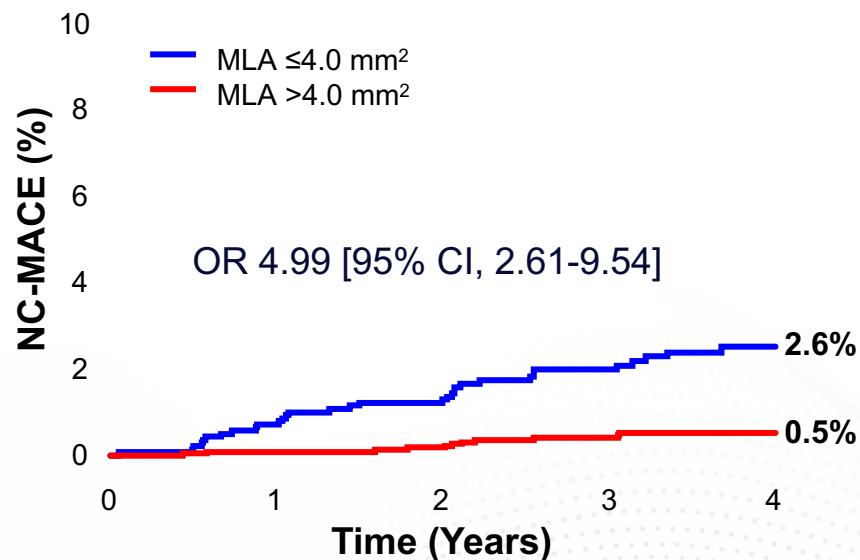
787	773	764	576	338
2,842	2,816	2,804	2,107	1,162

NCL-related MACE According to the Presence of HR Plaque Defined by **MLA ≤ 4.0 mm²**

Patient-level events



Lesion-level events



Number at risk:

≤ 4.0 mm ²	679	654	636	465	259
> 4.0 mm ²	219	215	212	158	72

	1,375	1,354	1,340	1,108	593
	2,254	2,235	2,228	1,665	907

High-risk Plaque Characteristics and Patient-level NCL-MACE

High-risk plaque characteristic	Pts with ≥ 1 NCL with HRP characteristic	Pts without NCLs with HRP characteristic	OR (95% CI) Unadjusted
<u>MaxLCBI_{4mm} ≥ 324.7</u>	N=520 patients	N=364 patients	
Non-culprit MACE	10.1% (48)	4.8% (17)	2.08 (1.18, 3.69)
- Myocardial infarction	4.4% (18)	1.1% (4)	3.20 (1.07, 9.55)
- Unstable angina	0.8% (4)	1.4% (5)	0.54 (0.14, 2.04)
- Progressive angina	6.1% (30)	2.3% (8)	2.73 (1.24, 6.03)
<u>Plaque burden $\geq 70\%$</u>	N=530 patients	N=368 patients	
Non-culprit MACE	11.0% (53)	3.6% (13)	3.09 (1.65, 5.76)
- Myocardial infarction	4.7% (20)	0.8% (3)	4.72 (1.39, 16.01)
- Unstable angina	1.0% (5)	1.1% (4)	0.85 (0.23, 3.17)
- Progressive angina	6.4% (32)	1.7% (6)	3.89 (1.61, 9.42)
<u>MLA ≤ 4.0 mm²</u>	N=679 patients	N=219 patients	
Non-culprit MACE	9.9% (62)	1.8% (4)	5.49 (1.97, 15.28)
- Myocardial infarction	4.0% (22)	0.5% (1)	7.16 (0.96, 53.41)
- Unstable angina	1.0% (7)	0.9% (2)	1.09 (0.23, 5.31)
- Progressive angina	5.8% (37)	0.5% (1)	12.55 (1.71, 92.08)

Multivariable Models of NCL-related MACE

	OR (95% CI)	P-value
Patient-level models*		
Model 1: MaxLCBI _{4mm} ≥324.7	2.27 (1.25-4.13)	0.007
Model 2: Plaque burden ≥70%	3.49 (1.83-6.63)	<0.001
Model 3: MLA ≤4.0 mm ²	6.00 (2.12-17.00)	<0.001
Lesion-level models*		
Model 1: MaxLCBI _{4mm} ≥324.7	7.83 (4.12-14.89)	<0.001
Model 2: Plaque burden ≥70%	12.94 (6.36-26.32)	<0.001
Model 3: MLA ≤4.0 mm ²	4.97 (2.59-9.53)	<0.001

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

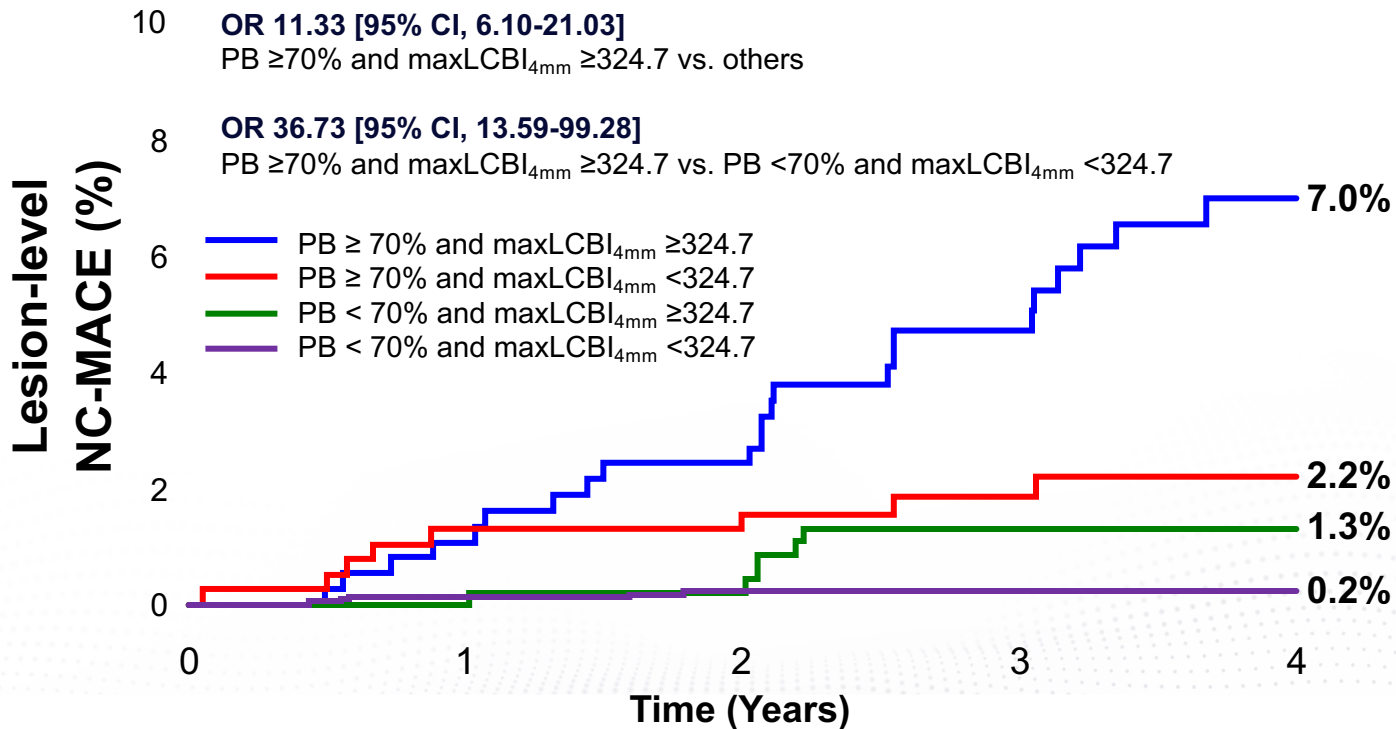
**Younger age and insulin-treated diabetes
were also independent predictors of events**

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

Lesion-level predictors*	OR (95% CI)
MaxLCBI _{4mm} ≥ 324.7	3.80 (1.87-7.70)
Plaque burden $\geq 70\%$	5.37 (2.42-11.89)
Minimum lumen area ≤ 4.0 mm 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

Lesion-level NCL-MACE According to the Presence of HR Plaque Defined by $\text{MaxLCBI}_{4\text{mm}} \geq 324.7$ and $\text{PB} \geq 70\%$



Number at risk:

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

Conclusions

- Following treatment of flow-limiting lesions in AMI with contemporary DES, MACE occurred in 14.4% of pts at median 3.7-year FU
 - 8.0% were caused by unanticipated events arising from untreated non-flow-limiting plaques vs. 4.6% from recurrent events at treated culprit lesions
- 3-vessel intracoronary imaging with NIRS-IVUS was safe
- NIRS identified lipid-rich angiographically mild non-flow-limiting plaques that were responsible for future coronary events
- The combination of lipid-rich plaque and large plaque burden identified vulnerable plaques that placed patients at especially high risk for future MACE
- Whether prophylactic treatment of these high-risk plaques is safe and effective was investigated in the integrated PROSPECT ABSORB trial