Association between high-intensity lipid-lowering therapy and atherosclerotic plaque content changes assessed by iMAP-IVUS and near-infrared spectroscopy in patients with premature atherosclerosis

M. Lapsovs[1], K. Trusinskis[1], B. Kokina[1], E. Knoka[1], M. Karantajere[1], L. Caunite[2], I. Kumsars[1], A. Erglis[1]

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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INTRODUCTION

The Global Cardiovasc

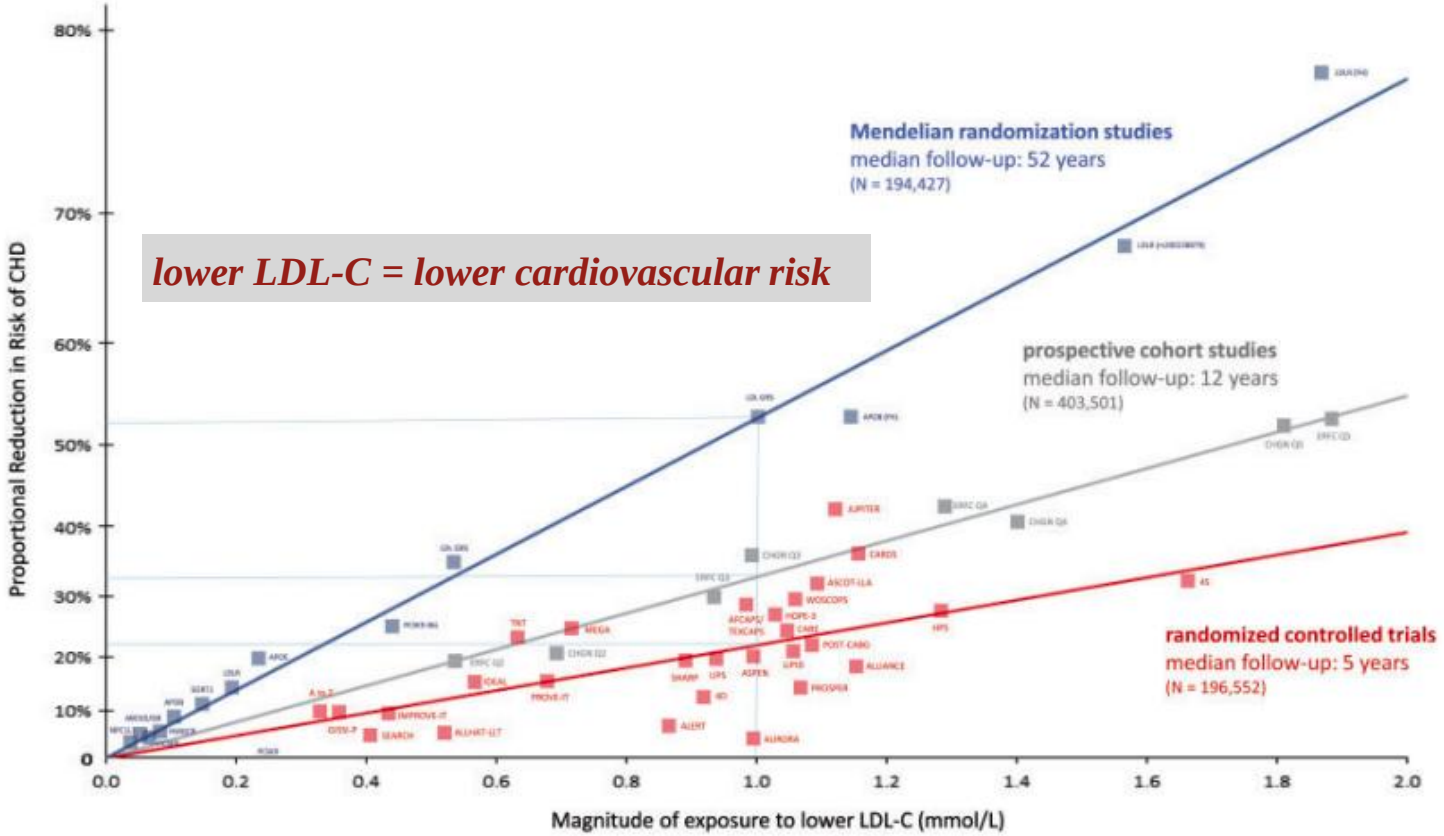
A Compass for I

Muthiah Vaduganathan, MI
Gregory A. Roth, MD, MPH

TABLE 1 Global Ranking of Cardiovascular Deaths by Cause

Rank	Cause of Death	Number of Deaths in 2021 (95% UI)	Number of DALYs (95% UI)
1	Ischemic heart disease	9,440,000 (8,820,000-9,960,000)	185,000,000 (175,000,000-196,000,000)
2	Ischemic stroke	3,870,000 (3,550,000-4,170,000)	70,200,000 (64,500,000-76,800,000)
3	Intracerebral hemorrhage	3,460,000 (3,210,000-3,750,000)	78,600,000 (73,300,000-84,600,000)
4	Hypertensive heart disease	1,410,000 (1,170,000-1,560,000)	24,900,000 (20,900,000-27,200,000)
5	Rheumatic heart disease	391,000 (340,000-454,000)	13,400,000 (11,600,000-15,400,000)
6	Atrial fibrillation and flutter	366,000 (313,000-396,000)	8,200,000 (6,830,000-9,940,000)
7	Subarachnoid hemorrhage	365,000 (329,000-411,000)	10,400,000 (9,370,000-11,800,000)
8	Other cardiomyopathy	320,000 (289,000-348,000)	8,450,000 (7,800,000-9,170,000)
9	Other cardiovascular diseases	232,000 (212,000-252,000)	10,100,000 (8,500,000-11,900,000)
10	Aortic aneurysm	160,000 (144,000-170,000)	3,040,000 (2,820,000-3,210,000)
11	Nonrheumatic calcific aortic valve disease	151,000 (127,000-164,000)	2,140,000 (1,950,000-2,370,000)
12	Endocarditis	81,100 (74,400-90,400)	2,040,000 (1,880,000-2,270,000)
13	Lower extremity peripheral arterial disease	71,200 (61,400-76,300)	1,520,000 (1,230,000-2,010,000)
14	Alcoholic cardiomyopathy	66,000 (55,600-74,200)	2,190,000 (1,850,000-2,460,000)
15	Nonrheumatic degenerative mitral valve disease	38,600 (33,900-43,100)	924,000 (827,000-1,070,000)
16	Myocarditis	33,600 (27,100-38,000)	962,000 (810,000-1,090,000)
17	Pulmonary arterial hypertension	23,300 (20,000-26,000)	640,000 (565,000-726,000)
18	Other nonrheumatic valve diseases	2,120 (1,580-2,690)	51,500 (37,100-66,200)

DALY = disability-adjusted life year; UI = uncertainty interval.



Okuyama, Harumi & Hamazaki, Tomohito & Hama, Rokuro & Ogushi, Yoichi & Kobayashi, Tetsuyuki & Ohara, Naoki & Uchino, Hajime. (2018). A Critical Review of the Consensus Statement from the European Atherosclerosis Society Consensus Panel 2017. Pharmacology. 101. 184-218. 10.1159/000486374.

ESC European Society of Cardiology

European Heart Journal (2020) **41**, 111–188
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

Recommendations	Class[a]	Level[b]
In secondary prevention for patients at very-high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[33–35,119,120]	I	A

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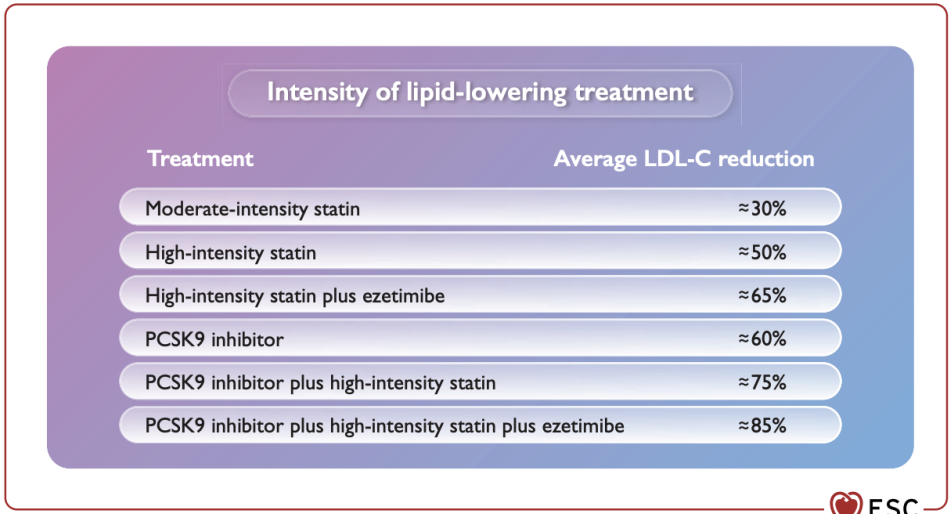
Recommendations	Class[a]	Level[b]
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk.[32,34,38]	I	A
If the goals[c] are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.[33]	I	B
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb	C
For secondary prevention, patients at very-high risk not achieving their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.[119,120]	I	A



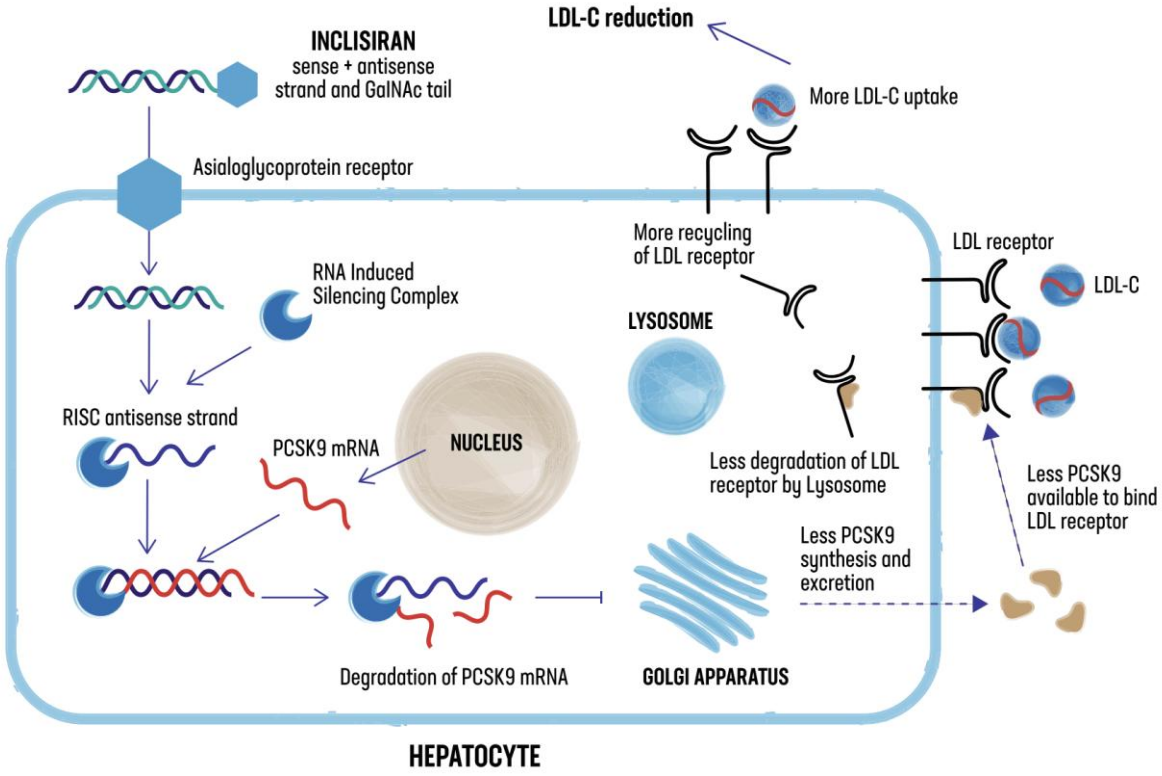
Current Cardiology Reports (2020) 22: 176
https://doi.org/10.1007/s11886-020-01427-6

NEW THERAPIES FOR CARDIOVASCULAR DISEASE (AA BAVRY, SECTION EDITOR)

Low-density Lipoprotein-Cholesterol Lowering Strategies for Prevention of Atherosclerotic Cardiovascular Disease: Focus on siRNA Treatment Targeting PCSK9 (Inclisiran)

David Sinning[1] · Ulf Landmesser[1,2,3]

Accepted: 22 September 2020 / Published online: 21 October 2020



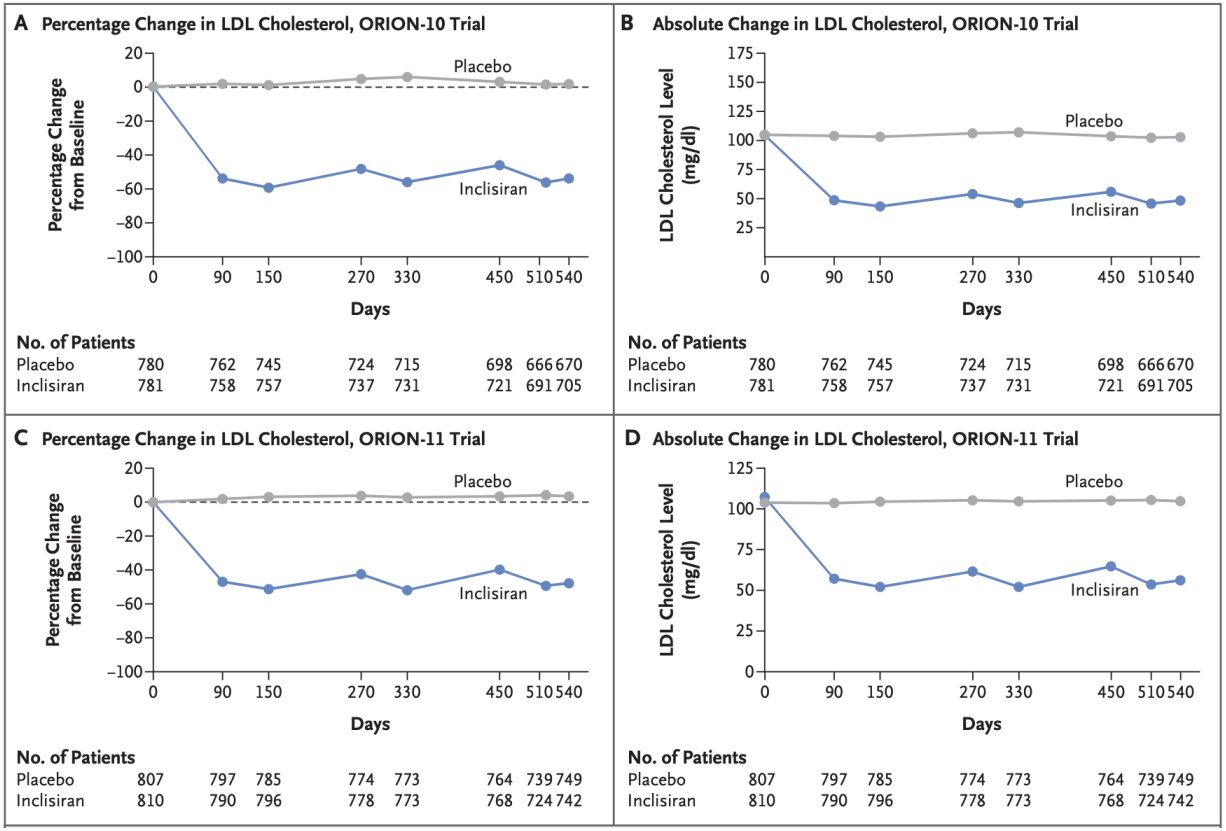
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol

Kausik K. Ray, M.D., M.Phil., R. Scott Wright, M.D., David Kallend, M.D., Wolfgang Koenig, M.D., Lawrence A. Leiter, M.D., Frederick J. Raal, Ph.D., Jenna A. Bisch, B.A., Tara Richardson, B.A., Mark Jaros, Ph.D., Peter L.J. Wijngaard, Ph.D., and John J.P. Kastelein, M.D., Ph.D., for the ORION-10 and ORION-11 Investigators*

- The regimen of inclisiran every 6 months was feasible and significantly reduced LDL cholesterol levels by approximately 50%.

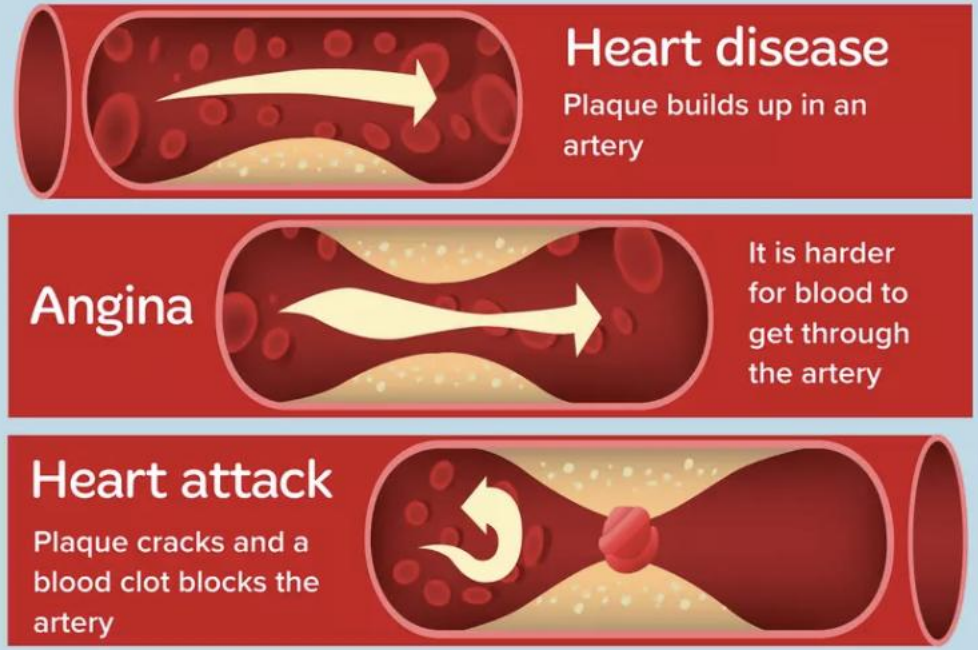


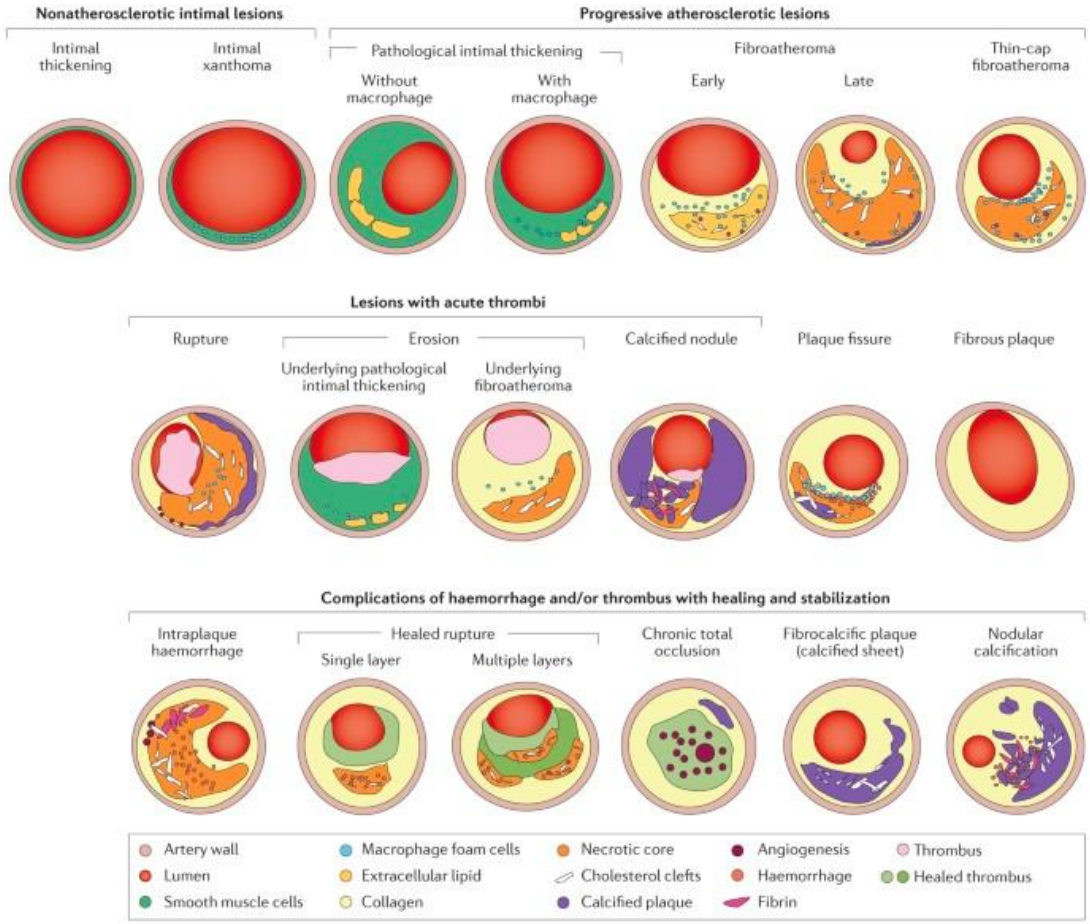
A guide to coronary angiography and angioplasty

Heart Foundation

How the heart works

Your heart pumps blood around your body through arteries and other blood vessels, allowing you to walk, talk and think. Heart disease often begins when the coronary arteries that feed blood to your heart start to narrow.

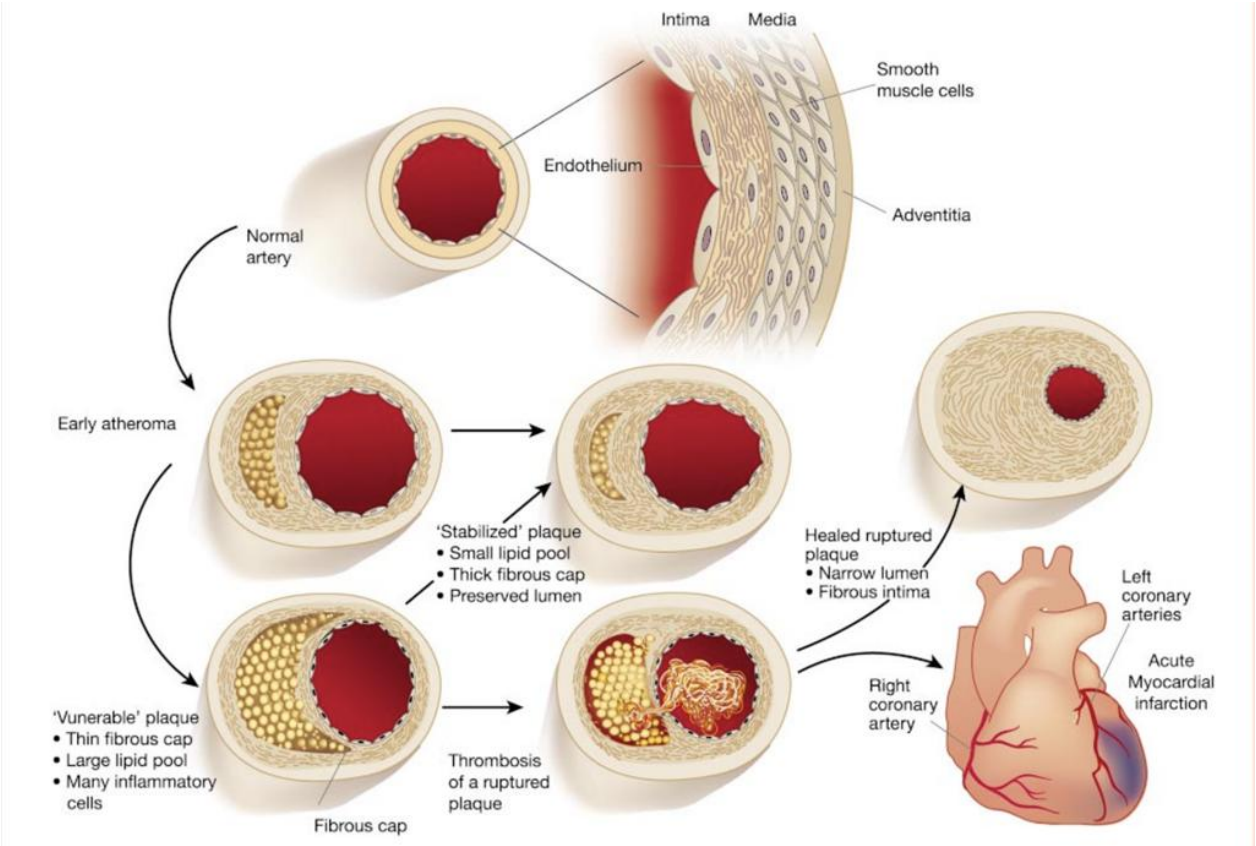




Nature Reviews | Cardiology

Pathophysiology of native coronary, vein graft, and in-stent atherosclerosis

Kazuyuki Yahagi[1], Frank D. Kolodgie[1], Fumiyuki Otsuka[1], Aloke V. Finn[2], Harry R. Davis[1], Michael Joner[1] and Renu Virmani[1]



***Source**: Libby, P. Inflammation in atherosclerosis. Nature 420, 868–874 (2002). https://doi.org/10.1038/nature01323*

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VOL. 74, NO. 12, 2019

JACC FOCUS SEMINAR: HISTORICAL AND CONCEPTUAL CHANGES OF CORONARY ARTERY DISEASE (1980–2020)

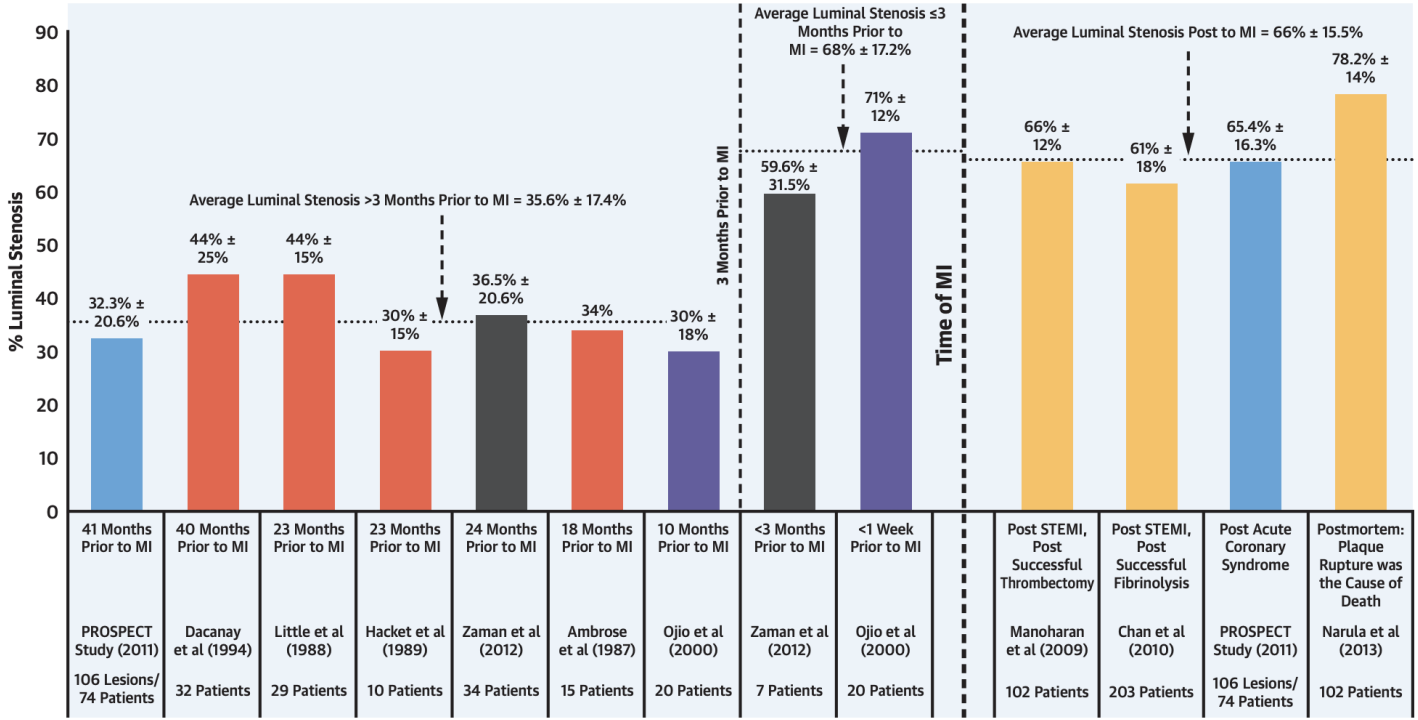
JACC STATE-OF-THE-ART REVIEW

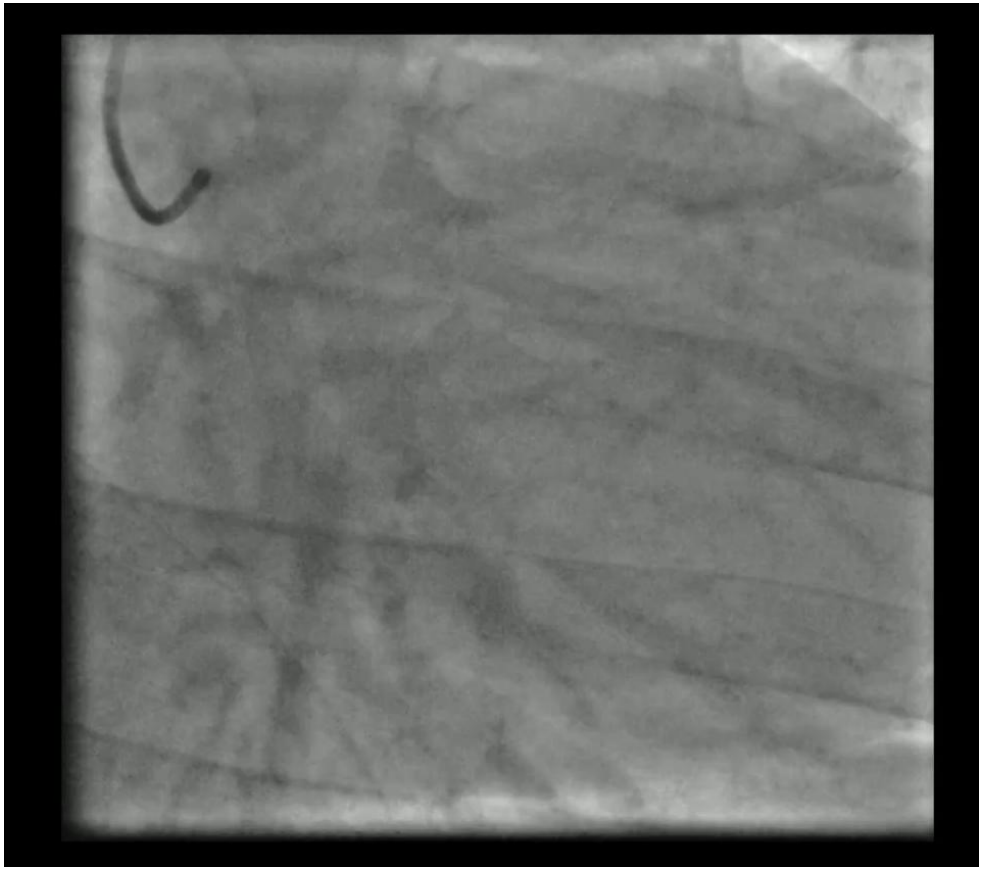
From Subclinical Atherosclerosis to Plaque Progression and Acute Coronary Events

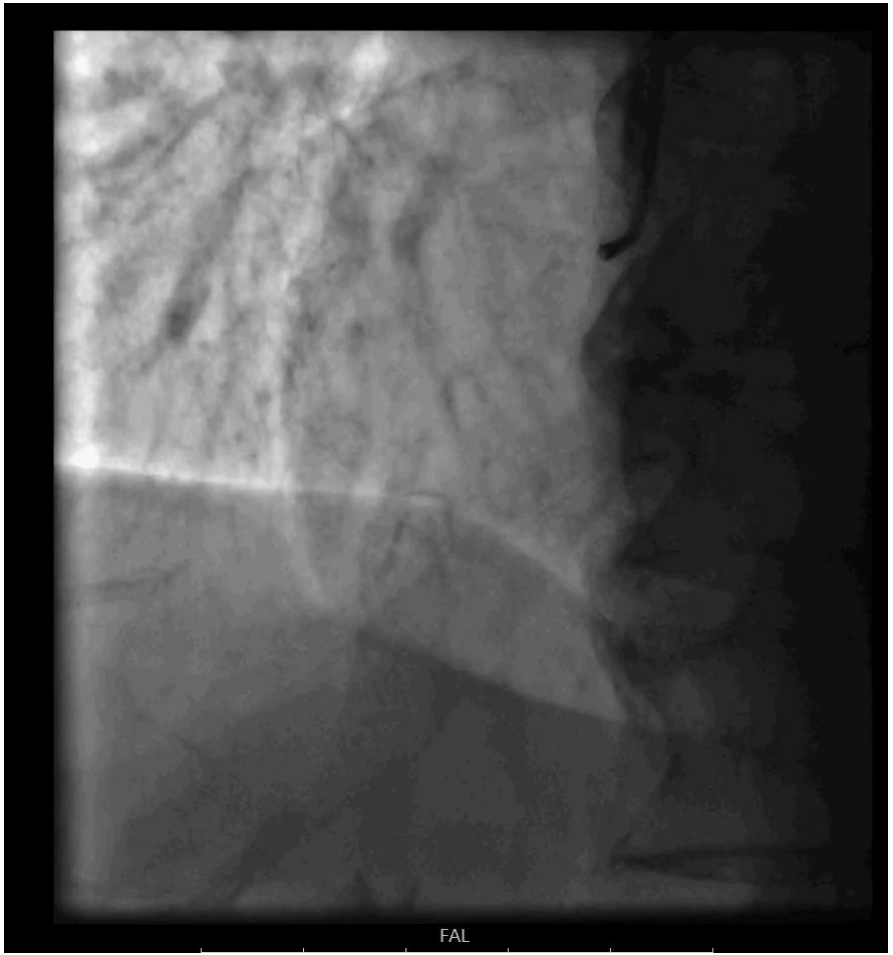
JACC State-of-the-Art Review

Amir Ahmadi, MD,[a,b] Edgar Argulian, MD,[b] Jonathon Leipsic, MD,[b] David E. Newby, MD,[c] Jagat Narula, MD, PhD[a]

FIGURE 1 Is Plaque Progression a Necessary Step Before Plaque Rupture?






FAL

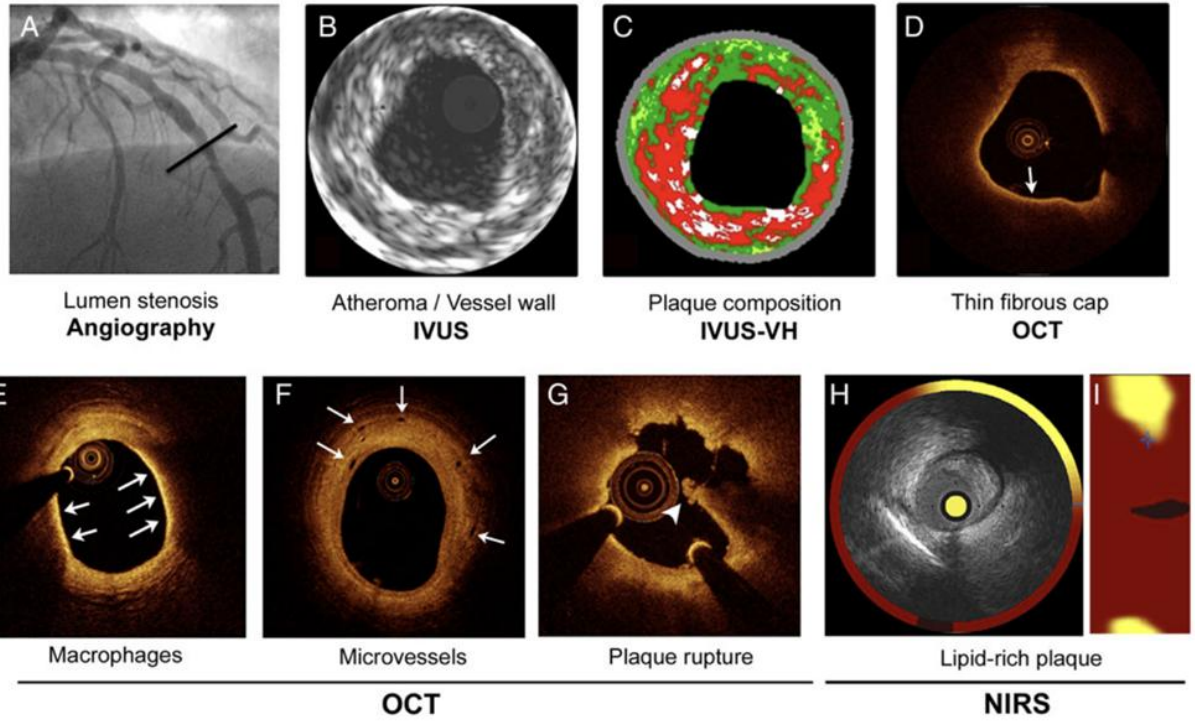
European Heart Journal (2016) **37**, 524–535
doi:10.1093/eurheartj/ehv642

REVIEW

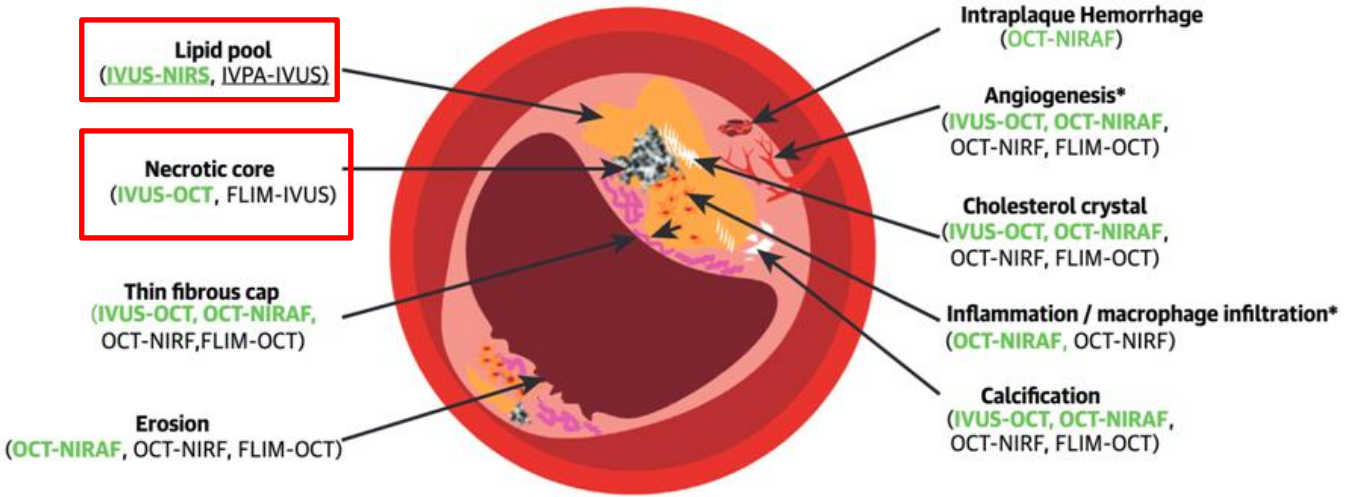
Imaging

Intracoronary imaging of coronary atherosclerosis: validation for diagnosis, prognosis and treatment

Konstantinos C. Koskinas[1], Giovanni J. Ughi[2], Stephan Windecker[1], Guillermo J. Tearney[3,4], and Lorenz Räber[1]*

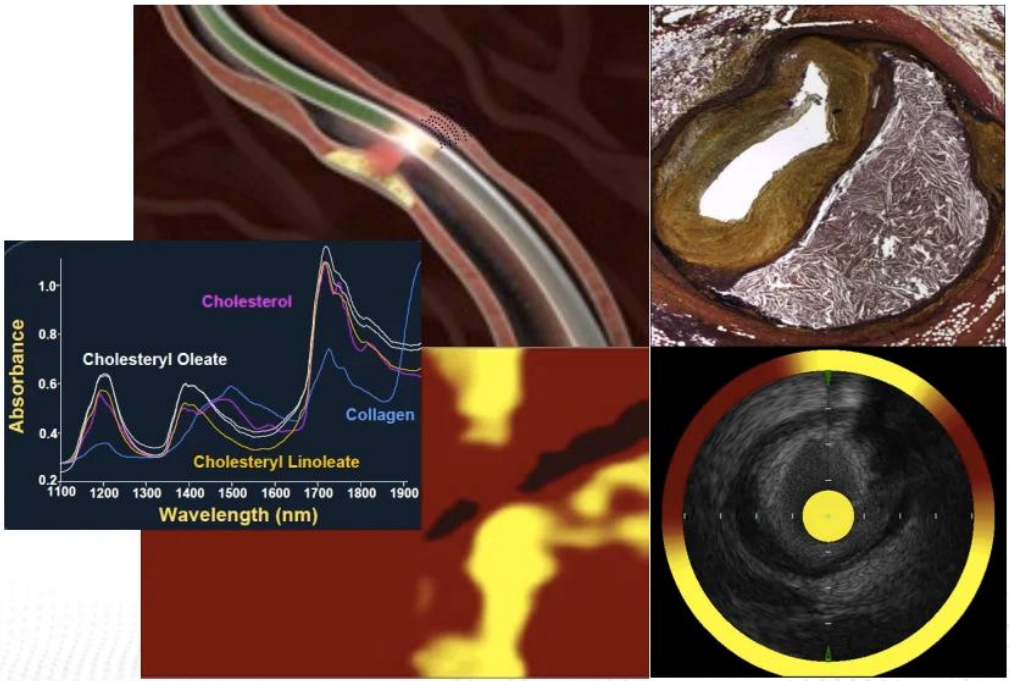


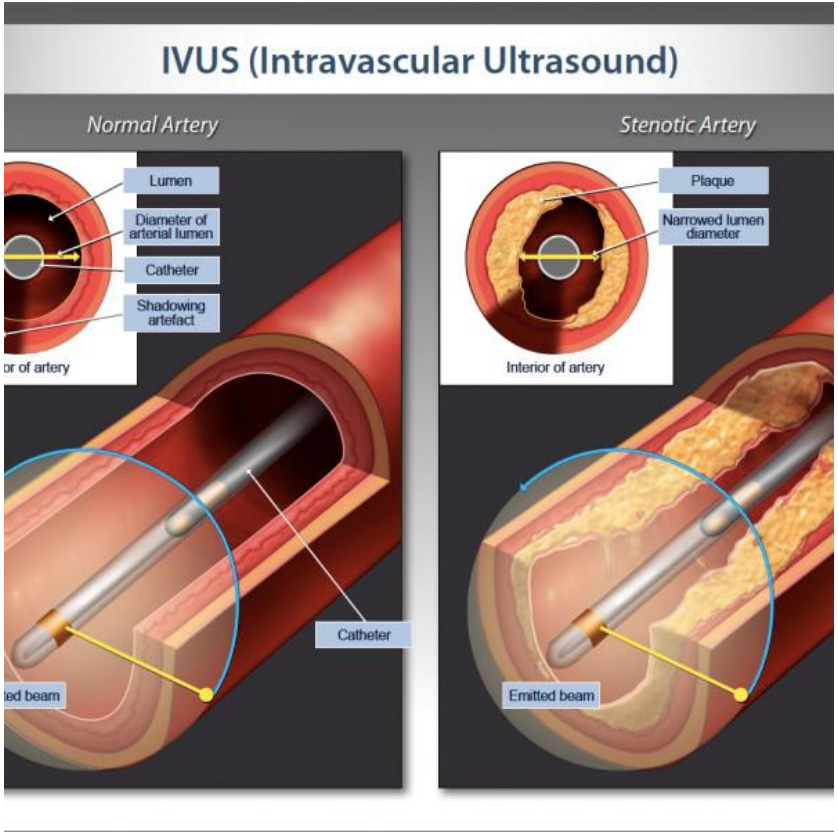
CENTRAL ILLUSTRATION Multimodality Imaging Techniques to Detect Vulnerable Plaque Characteristics



Li, J. et al. J Am Coll Cardiol Img. 2022;15(1):145–159.

Schematic showing a coronary artery plaque and different features associated with increased risk of plaque rupture and atherothrombotic complications. According to Prati et al. (19), including what had been published until December 2020, the types of multimodality imaging technology best suited to detect each high-risk feature are presented in **parentheses**. Techniques labeled in **green** have been successfully used in humans. Techniques labeled with **underlines** can get clear images in vivo without the need for blood clearance. *The ability of clinically available OCT to detect angiogenesis and macrophage infiltration is limited, due to its shallow penetration depth and resolution.


Cholesterol
Cholesteryl Oleate
Collagen
Cholesteryl Linoleate
Absorbance
1.0
0.8
0.6
0.4
0.2
1100 1200 1300 1400 1500 1600 1700 1800 1900
Wavelength (nm)


IVUS (Intravascular Ultrasound)
Normal Artery
Stenotic Artery
Lumen
Diameter of arterial lumen
Catheter
Shadowing artefact
Plaque
Narrowed lumen diameter
Interior of artery
Catheter
Emitted beam

Key messages:

- NIRS can identify plaque composition and features associated with plaque vulnerability in postmortem human aortic specimens.

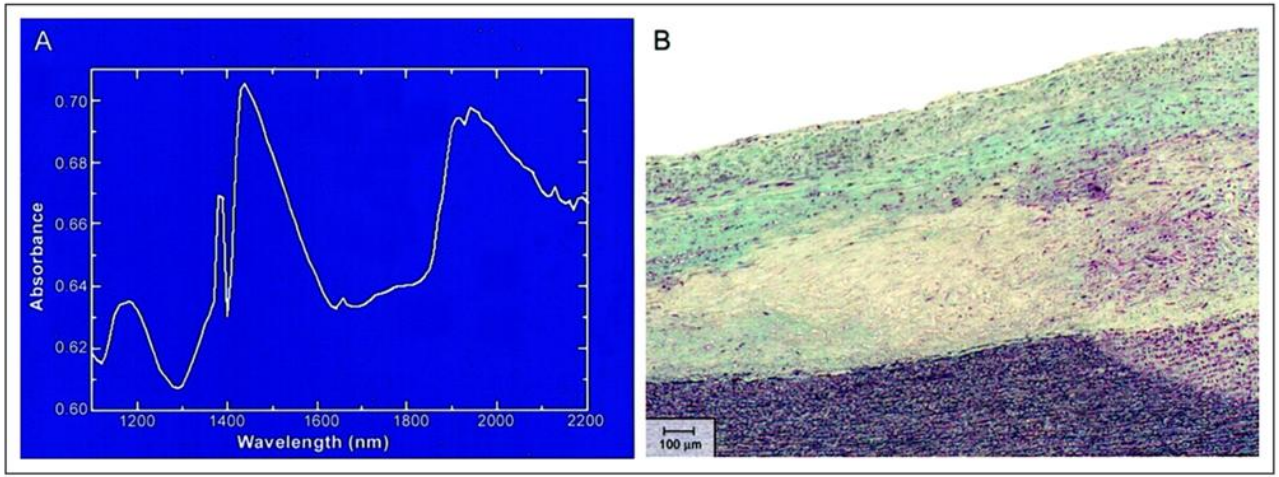
- NIRS sensitivity and specificity for histological features of plaque vulnerability were 90% and **93% for lipid pool**, 77% and 93% for thin cap, and 84% and 89% for inflammatory cells, respectively.

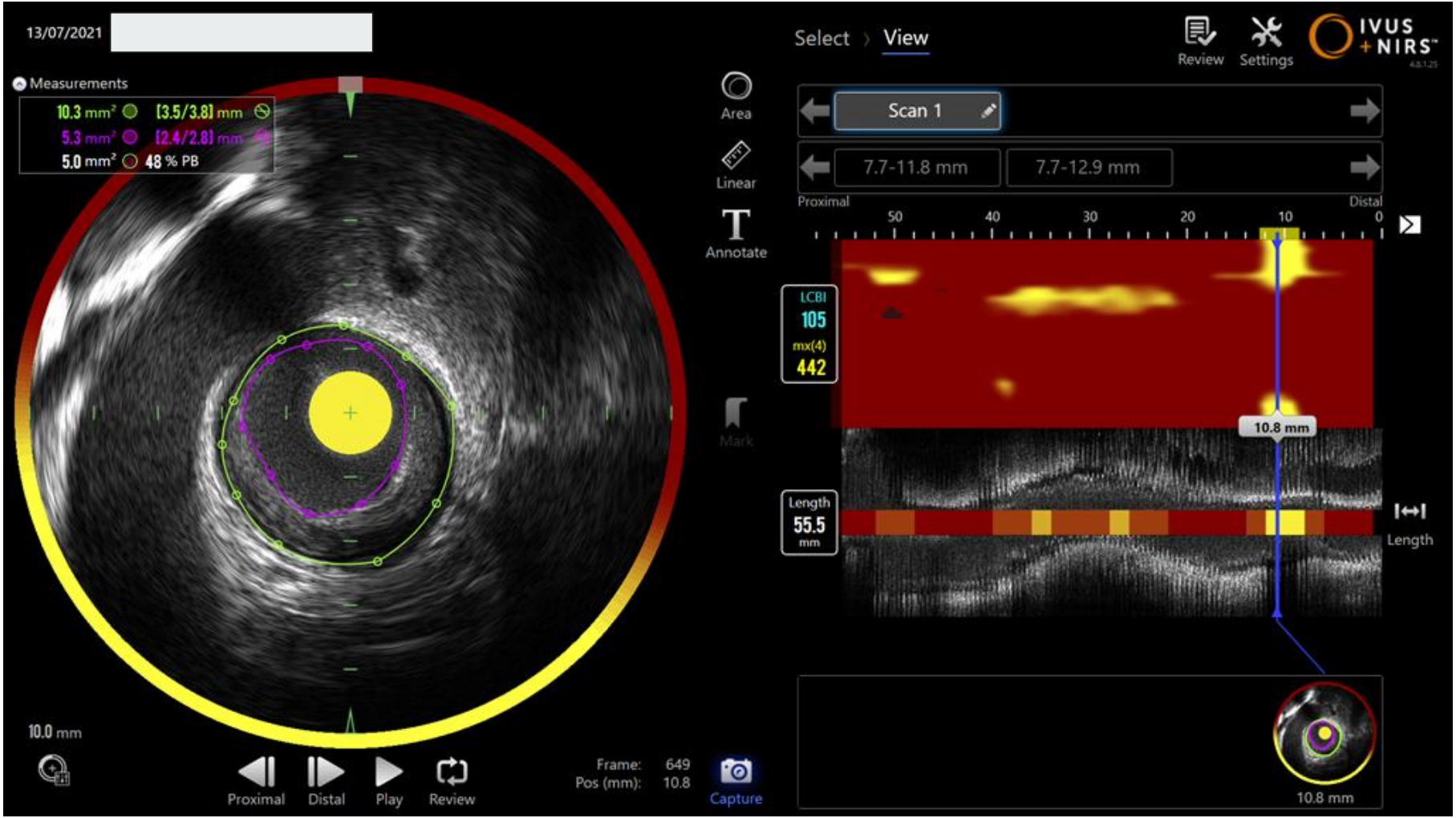
Circulation
Volume 105, Issue 8, 26 February 2002; Pages 923-927
https://doi.org/10.1161/hc0802.104291

CLINICAL INVESTIGATION AND REPORTS

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

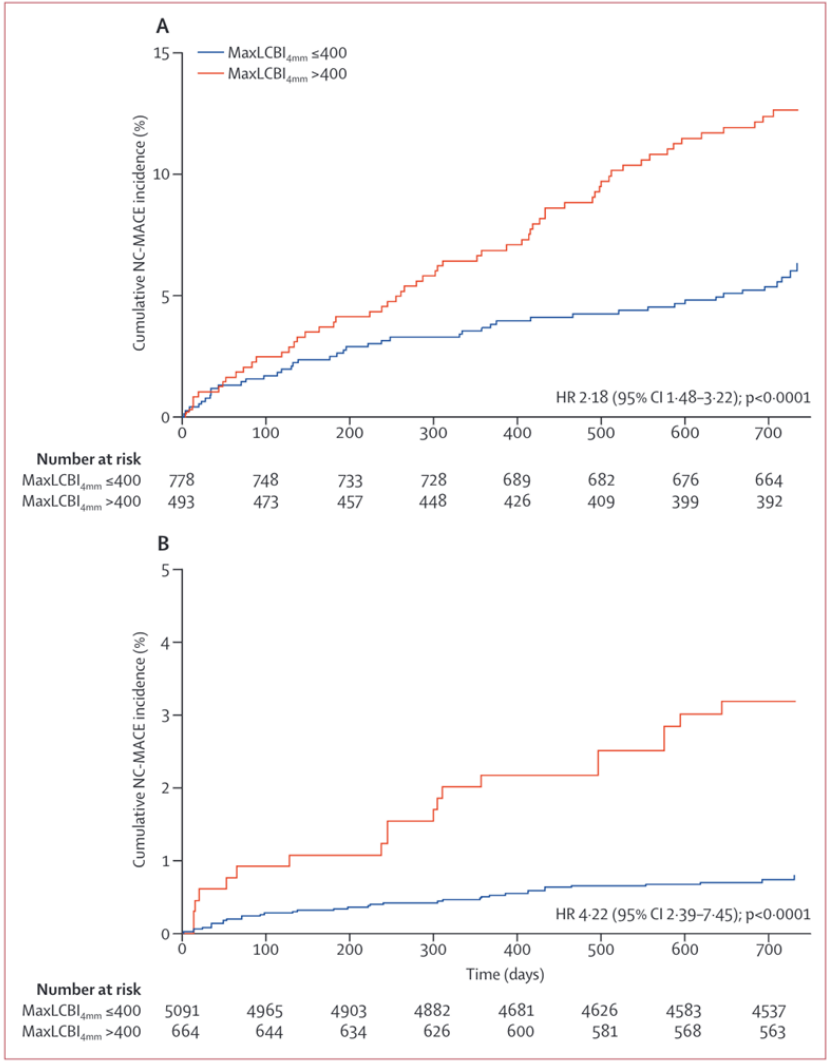
Pedro R. Moreno, MD, Robert A. Lodder, PhD, K. Raman Purushothaman, MD, William E. Charash, MD, PhD, William N. O'Connor, MD, and James E. Muller, MD




13/07/2021
Measurements
10.3 mm² [3.5/3.8] mm
5.3 mm² [2.4/2.8] mm
5.0 mm² 48 % PB
10.0 mm
Proximal
Distal
Play
Review
Frame: 649
Pos (mm): 10.8
Capture
Area
Linear
Annotate
Mark
Select
View
Review
Settings
IVUS + NIRS
Scan 1
7.7-11.8 mm
7.7-12.9 mm
Proximal
Distal
50
40
30
20
10
0
LCBI
105
mx(4)
442
10.8 mm
Length
55.5
mm
Length
10.8 mm

Identification of patients and plaques vulnerable to future coronary events with near-infrared spectroscopy intravascular ultrasound imaging: a prospective, cohort study

*Ron Waksman, Carlo Di Mario, Rebecca Torguson, Ziad A Ali, Varinder Singh, William H Skinner, Andre K Artis, Tim Ten Cate, Eric Powers, Christopher Kim, Evelyn Regar, S Chiu Wong, Stephen Lewis, Joanna Wykrzykowska, Sandeep Dube, Samer Kazziha, Martin van der Ent, Priti Shah, Paige E Craig, Quan Zou, Paul Kolm, H Bryan Brewer, Hector M Garcia-Garcia, on behalf of the LRP Investigators**



ESC European Society of Cardiology
European Heart Journal - Cardiovascular Imaging (2021) **00**, 1–12
doi:10.1093/ehjci/jeab034

Clinical impact of PCSK9 inhibitor on stabilization and regression of lipid-rich coronary plaques: a near-infrared spectroscopy study

Hideaki Ota [1]*, Hiroyuki Omori[1], Masanori Kawasaki[1], Akihiro Hirakawa[2], and Hitoshi Matsuo[1]

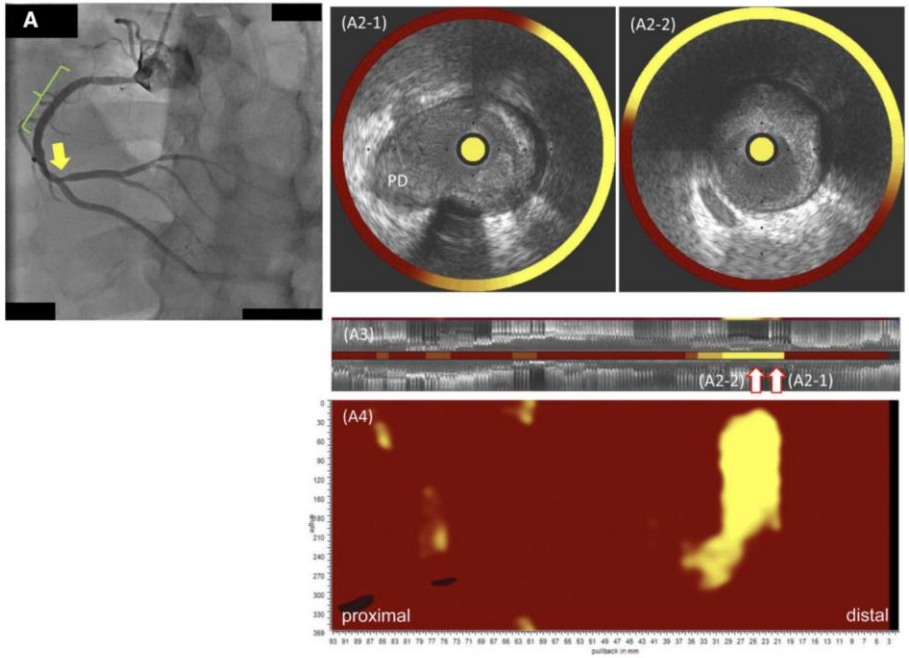
[1]Department of Cardiology, Gifu Heart Center, 4-14-4 Yabuta-minami, Gifu 500-8384, Japan; and [2]Division of Biostatistics and Data Science, Clinical Research Center, Tokyo Medical and Dental University, Tokyo, Japan

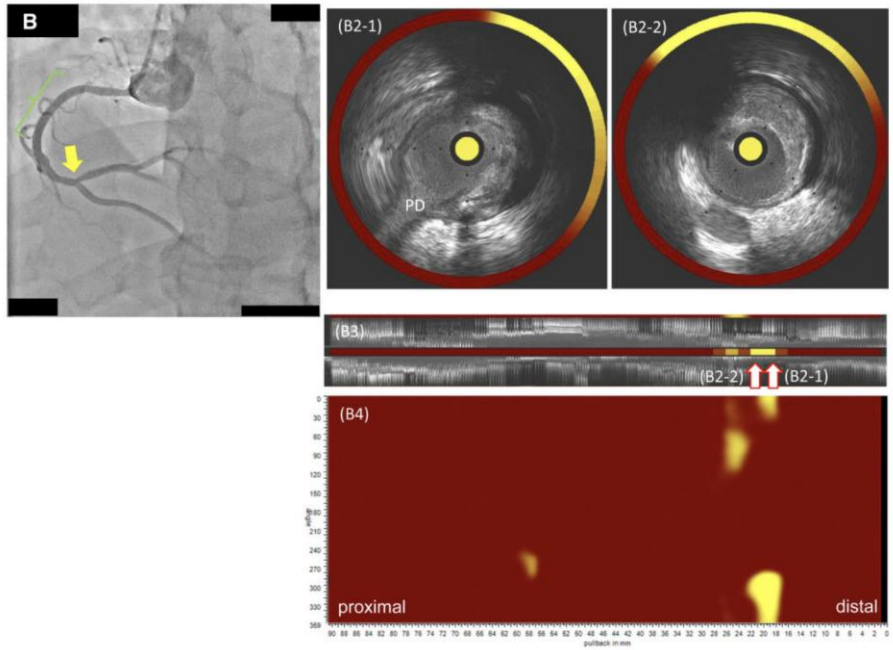
Received 28 October 2020; editorial decision 8 February 2021; accepted 10 February 2021

Table 3 **Grey-scale IVUS and NIRS measurements at baseline and follow-up**

	PCSK9i ($n = 40$)	Control ($n = 50$)	*P*-value
Normalized lumen volume (mm^3)			
Baseline	66.0 (48.9–88.9)	71.5 (60.4–89.2)	0.42
Follow-up	77.1 (52.4–106.9)	72.0 (61.2–84.5)	0.53
P-value (between baseline and follow-up)	<0.001	0.85	
Normalized EEM volume (mm^3)			
Baseline	142.3 (106.3–199.6)	138.3 (114.8–167.8)	0.74
Follow-up	142.4 (106.4–201.8)	135.2 (115.4–163.8)	0.59
P-value (between baseline and follow-up)	0.55	0.64	
Normalized TAV (mm^3)			
Baseline	70.7 (44.9–98.6)	61.1 (41.9–90.3)	0.45
Follow-up	65.3 (39.0–93.2)	63.5 (41.3–88.8)	0.85
P-value (between baseline and follow-up)	<0.001	0.50	
PAV (%)			
Baseline	51.0 (38.9–59.8)	44.2 (36.5–57.3)	0.16
Follow-up	45.2 (35.9–53.7)	45.7 (36.6–54.0)	0.96
P-value (between baseline and follow-up)	<0.001	0.65	
Remodelling index			
Baseline	1.04 (0.98–1.09)	1.00 (0.94–1.08)	0.13
Follow-up	1.01 (0.96–1.10)	1.01 (0.95–1.08)	0.77
P-value (between baseline and follow-up)	0.038	0.12	
maxLCBI4mm			
Baseline	277.5 (44.3–417.3)	155.5 (2.3–361.0)	0.20
Follow-up	83.5 (1.0–237.5)	137.0 (0.0–290.5)	0.74
P-value (between baseline and follow-up)	<0.001	0.026	
Lesion length at baseline (mm)	13.0 (10.2–15.6)	13.0 (8.4–14.3)	0.38

~12 months

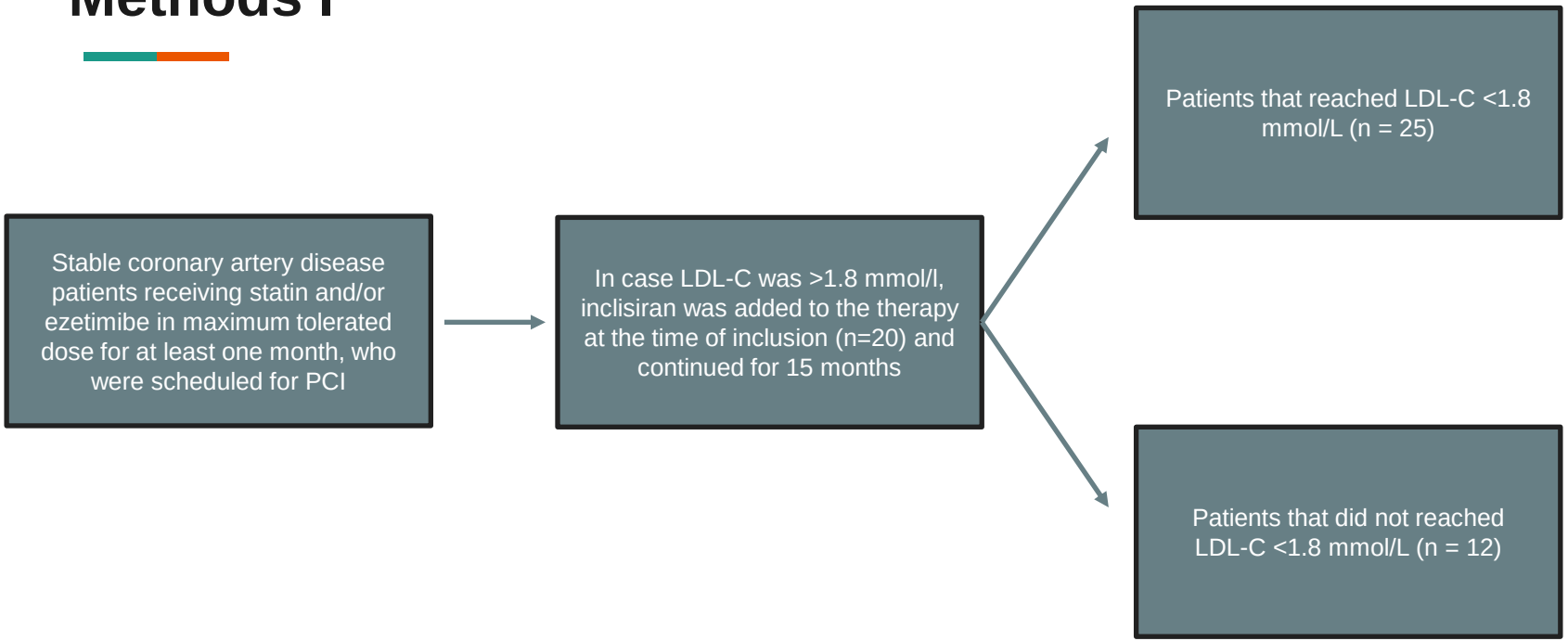

A
(A2-1)
(A2-2)
PD
(A3)
(A2-2)
(A2-1)
(A4)
proximal
distal


B
(B2-1)
(B2-2)
PD
(B3)
(B2-2)
(B2-1)
(B4)
proximal
distal

Aim of the study

- Our study aimed to evaluate atherosclerotic plaque composition in very high cardiovascular-risk patients, who received high-intensity lipid-lowering therapy for 15 months.

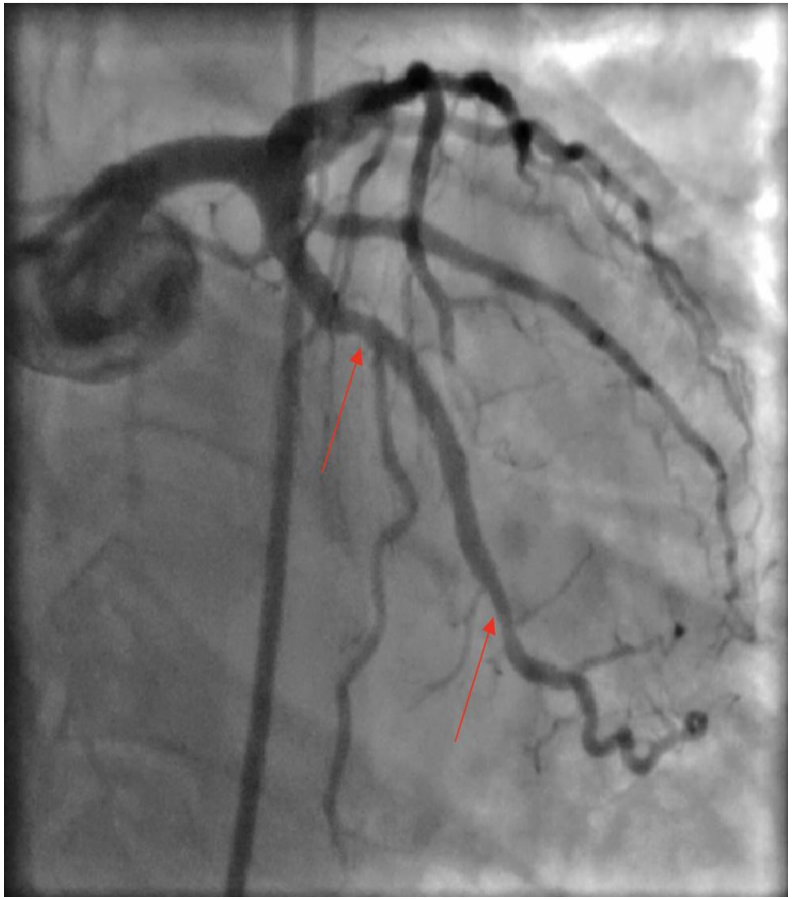
Methods I


Stable coronary artery disease patients receiving statin and/or ezetimibe in maximum tolerated dose for at least one month, who were scheduled for PCI
In case LDL-C was >1.8 mmol/l, inclisiran was added to the therapy at the time of inclusion (n=20) and continued for 15 months
Patients that reached LDL-C <1.8 mmol/L (n = 25)
Patients that did not reached LDL-C <1.8 mmol/L (n = 12)

Methods II

- The region of interest was a proximal or middle segment with angiographic evidence of nonobstructive de novo atherosclerosis >20% and <50%, evaluated by NIRS and iMAP-IVUS at baseline and 15 months later.

- Statistical analysis was carried out with SPSS Statistics software, defining a significance level of 0.05.

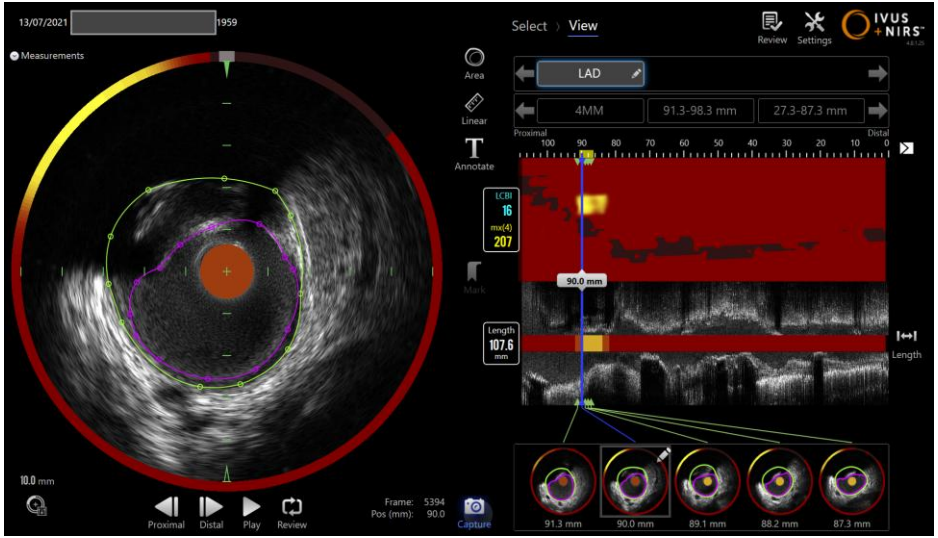


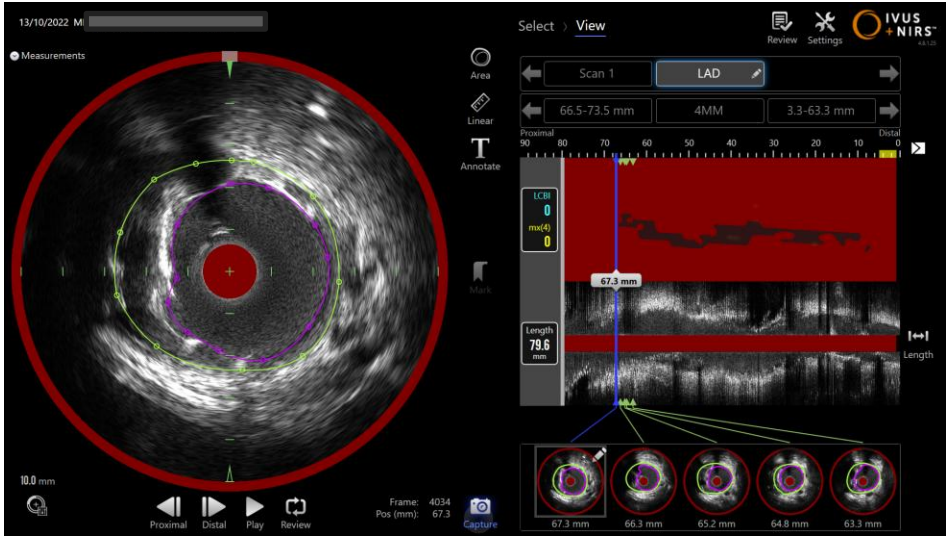
Results

- 37 eligible patients had undergone IVUS/NIRS investigation
- The mean patient age was 53 years
- After 15 months the mean LDL-C level decreased from 2.70 mmol/L to 1.79 mmol/l and 25 patients reached a target of <1.8 mmol/L
- Differences between results in both groups can be observed in 1.table

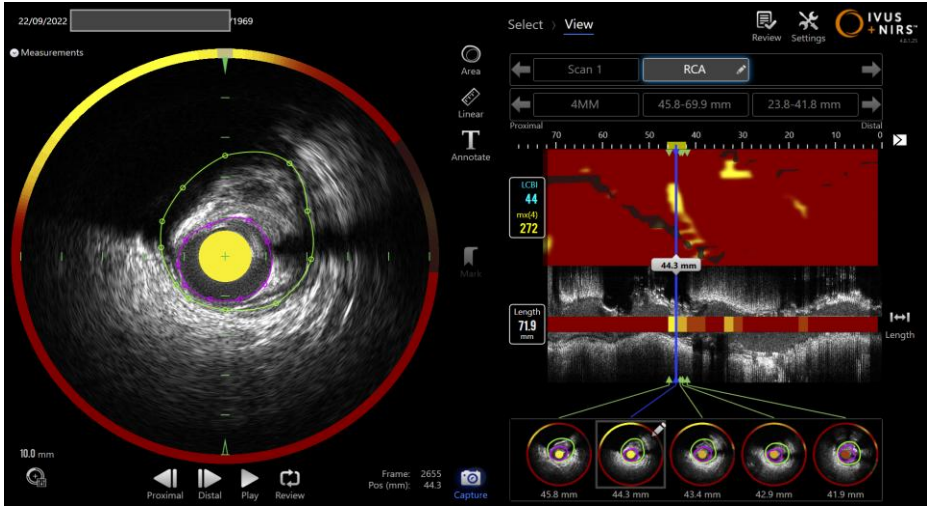
Variables	Study groups according LDL-C level			
	< 1.8 (n = 25)		> 1.8 (n = 12)	
Index LDL-C (mmol/l), mean ± SD	2.48 ± 0.83	**p <0.001**	3.18 ± 1.14	p = 0.99
FU LDL-C (mmol/l), mean ± SD	1.30 ± 0.33		2.56 ± 0.53	
Index maxLCBI4mm	184 ± 160.07	**p = 0.001**	211 ± 167.76	p = 0.074
FU maxLCBI4mm	62.72 ± 142.19		125.04 ± 152.21	
Index total LCBI	37.04 ± 40.80	**p = 0.007**	40.33 ± 43.38	p = 0.086
FU total LCBI	15.60 ± 27.87		22.41 ± 24.97	
Index Fibrotic, mm3	139.50 ± 69.86	**p = 0.002**	149.71 ± 82.79	**p = 0.008**
FU Fibrotic, mm3	147.32 ± 73.56		160.09 ± 89.01	
Index Necrolipidic, mm3	78.50 ± 42.77	p = 0.422	97.43 ± 58.04	p = 0.066
FU Necrolipidic, mm3	84.77 ± 46.03		89.40 ± 49.03	

Case Nr1 – patient who reached LDL-C <1.8 mmo/l





Case Nr2 – patient that failed to reached LDL-C <1.8 mmo/l



Conclusion

- **Our study showed that after 15 months of high-intensity lipid-lowering therapy, patients that reached LDL-C levels <1.8 mmol/L, showed lower LCBImax4mm and total LCBI.**

- **Both groups showed significant changes in iMAP plaque fibrotic tissues.**

Thank you for your attention!

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