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Plaque modificatie: inzichten door intracoronaire beeldvorming

Pentalfa Lipidenaanpak in de cardiologie 08-02-2024

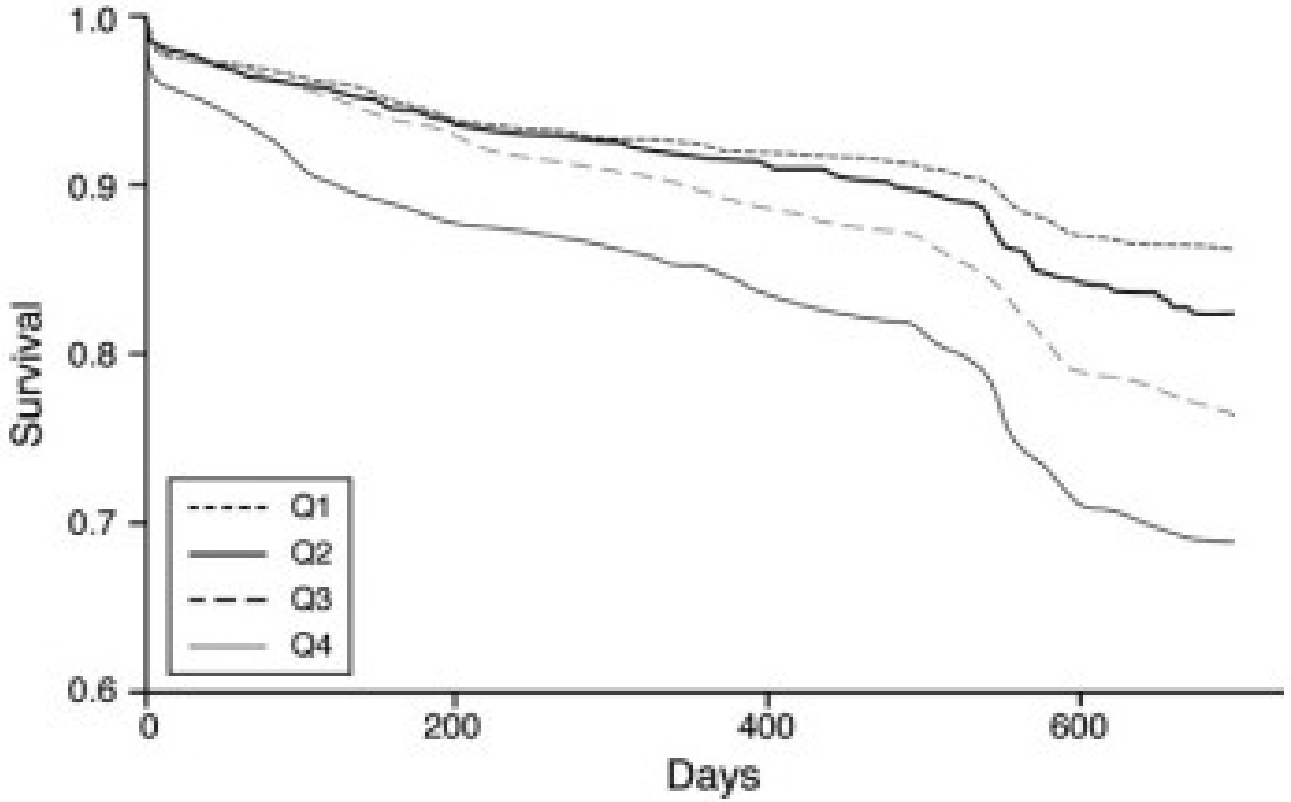
Prof. T. Adriaenssens
Dienst Hart- en Vaatziekten UZ Leuven

Plaque modificatie: inzichten door IC beeldvorming

- **Relevantie van seriële IC beeldvorming**
- **Initiële IC beeldvormingsstudies (IVUS): statines-ezetimibe**
  - **REVERSAL**
  - **ASTEROID**
  - **SATURN**
  - **PRECISE-IVUS**
- **Een nieuw tijdperk: PCSK9 inhibitoren en beeldvorming met OCT**
  - **GLAGOV**
  - **EASY-FIT**
  - **HUYGENS**
  - **PACMAN-AMI**
- **OCT beeldvorming kort na ACS**
- **Niet-invasieve beeldvorming van de kransslagaders**
- **Conclusie**

Relevantie van seriële intracoronaire beeldvorming

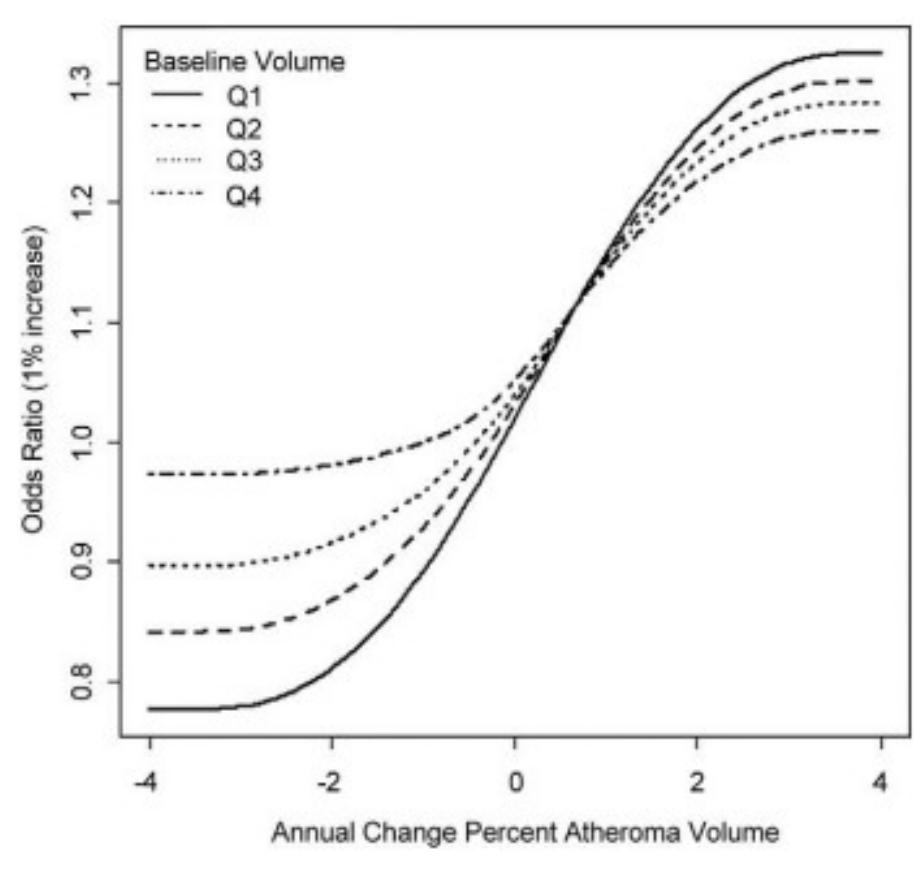
Baseline Plaque Burden en Cardiovasculaire events



Quartielen van PAV (Percentage Atheroma Volume), beoordeeld met IVUS (intravascular ultrasound)

Nicholls et al. J Am Coll Cardiol 2010; 55:2399-2407.

Plaque Progressie en Cardiovasculaire events



Relatie tussen verandering in PAV en OR voor cardiovasculaire events
PAV= Percentage Atheroma Volume

Nicholls et al. J Am Coll Cardiol 2010; 55:2399-2407.

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Table 8 Multivariate Model With Risk Factors Associated With Major Adverse Cardiovascular Events, Controlling for Study

Variable	OR (95% CI)	p Value
Baseline PAV per SD	1.45 (1.32 to 1.59)	<0.0001
Change PAV per SD	1.15 (1.05 to 1.26)	0.002
History of hypertension	1.34 (1.06 to 1.68)	0.01
Current smoker	1.49 (1.21 to 1.84)	0.0002

Nicholls et al. J Am Coll Cardiol 2010; 55:2399-2407.

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Relevantie van seriële IC beeldvorming met IVUS

- Zowel de ***burden*** als de ***snelheid van progressie*** van coronaire atherosclerose (met IVUS gemeten) is direct geässocieerd met het risico op cardiovasculaire events
- Elke ***1%*** nominale verlaging in ***PAV (percentage atheroma volume)*** is geässocieerd met een ***18% reductie*** in het risico op majeure cardiovasculaire events ***(MACE)***

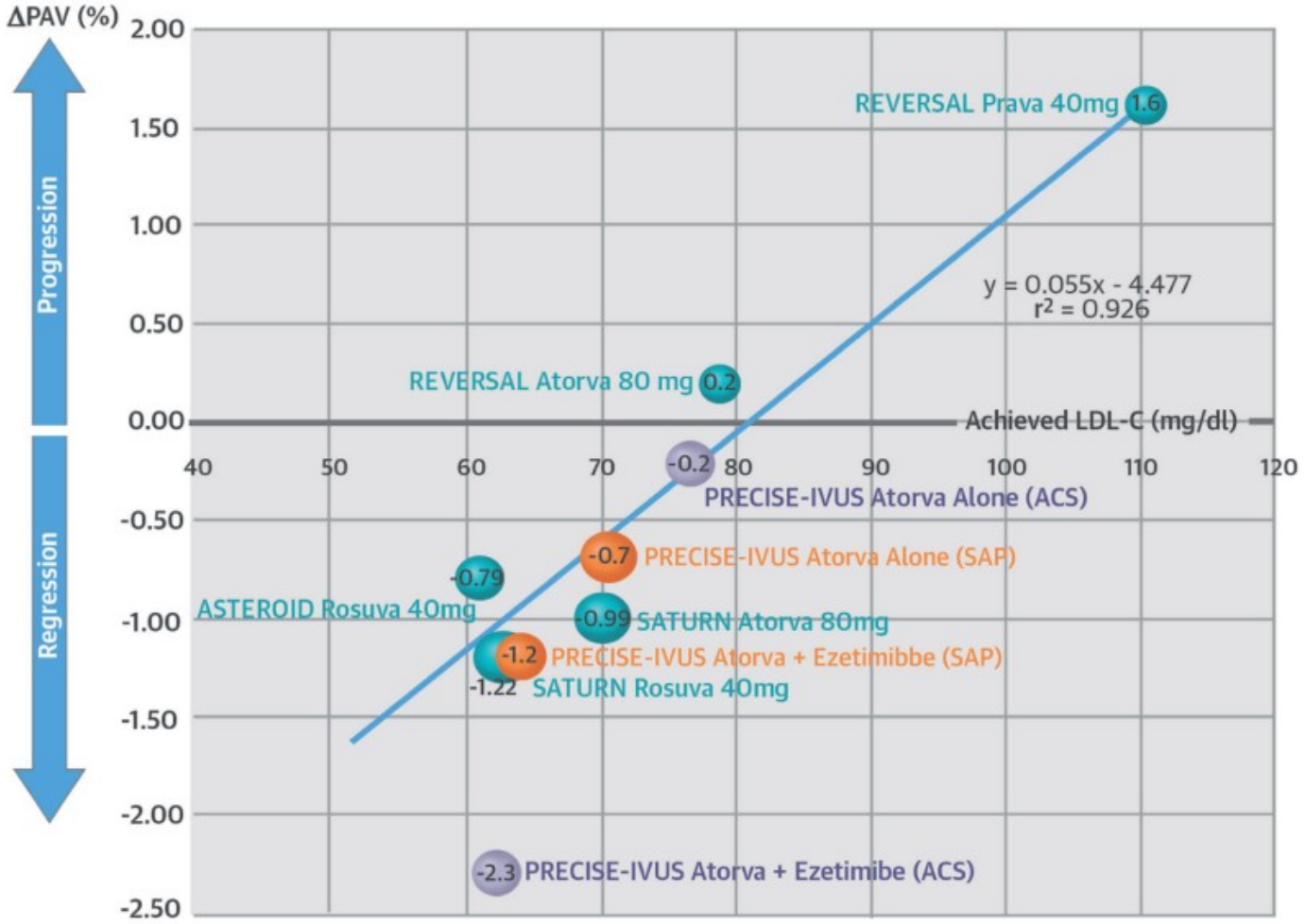
PAV (Percent atheroma volume): proportie van de gehele vaatwand die ingenomen wordt door atherosclerotische plaque

Nicholls et al. J Am Coll Cardiol 2010; 55:2399-2407.

Initiële IC beeldvormingsstudies (IVUS): statines-ezetimibe



Relatie bereikte LDL-C verlaging en Δ PAV (IVUS)



Tsujita et al. J Am Coll Cardiol 2015; 66:495-507.

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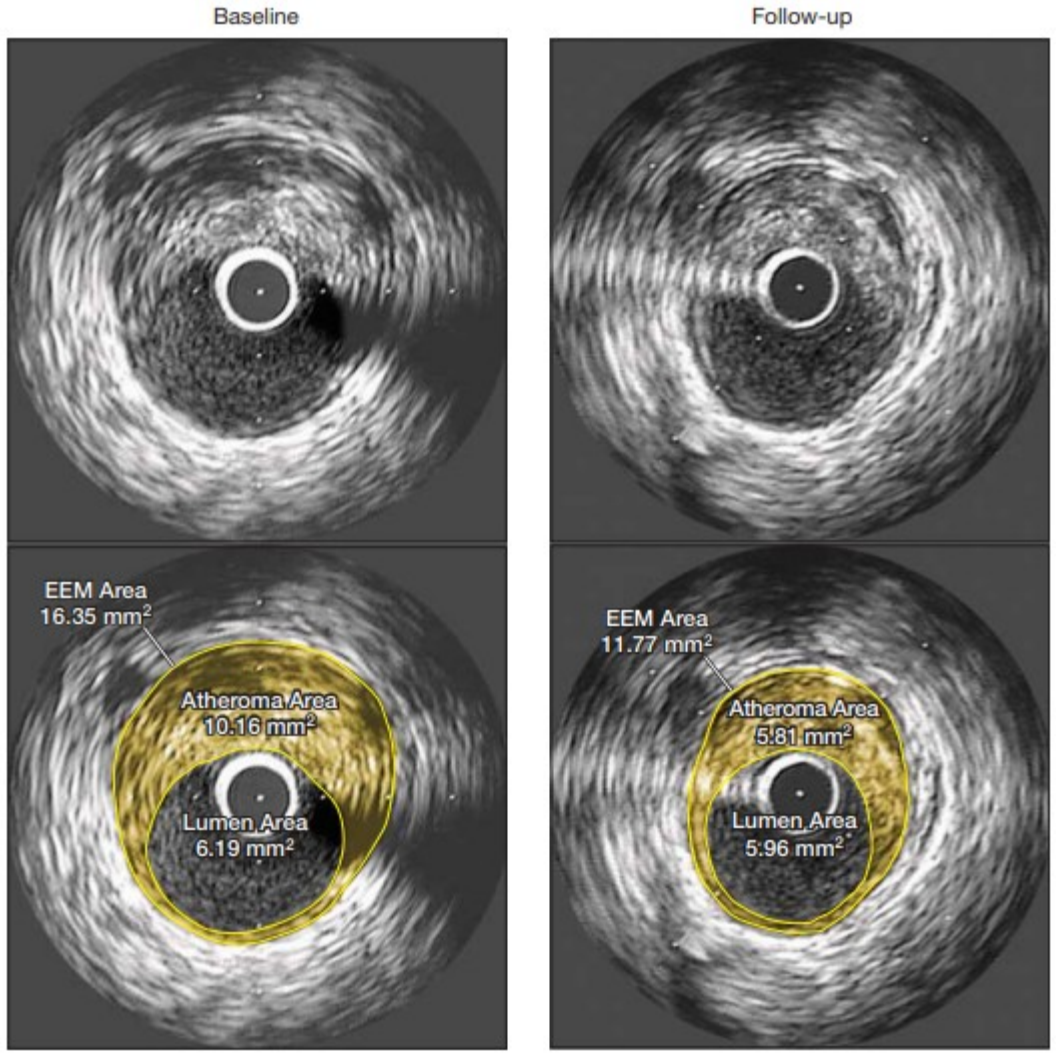
ASTEROID: plaque regressie met rosuvastatine 40 mg



Nissen et al. JAMA 2006; 295: 1556-65.

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Een nieuw tijdperk: PCSK9 inhibitoren en beeldvorming met IC optical coherence tomography (OCT)

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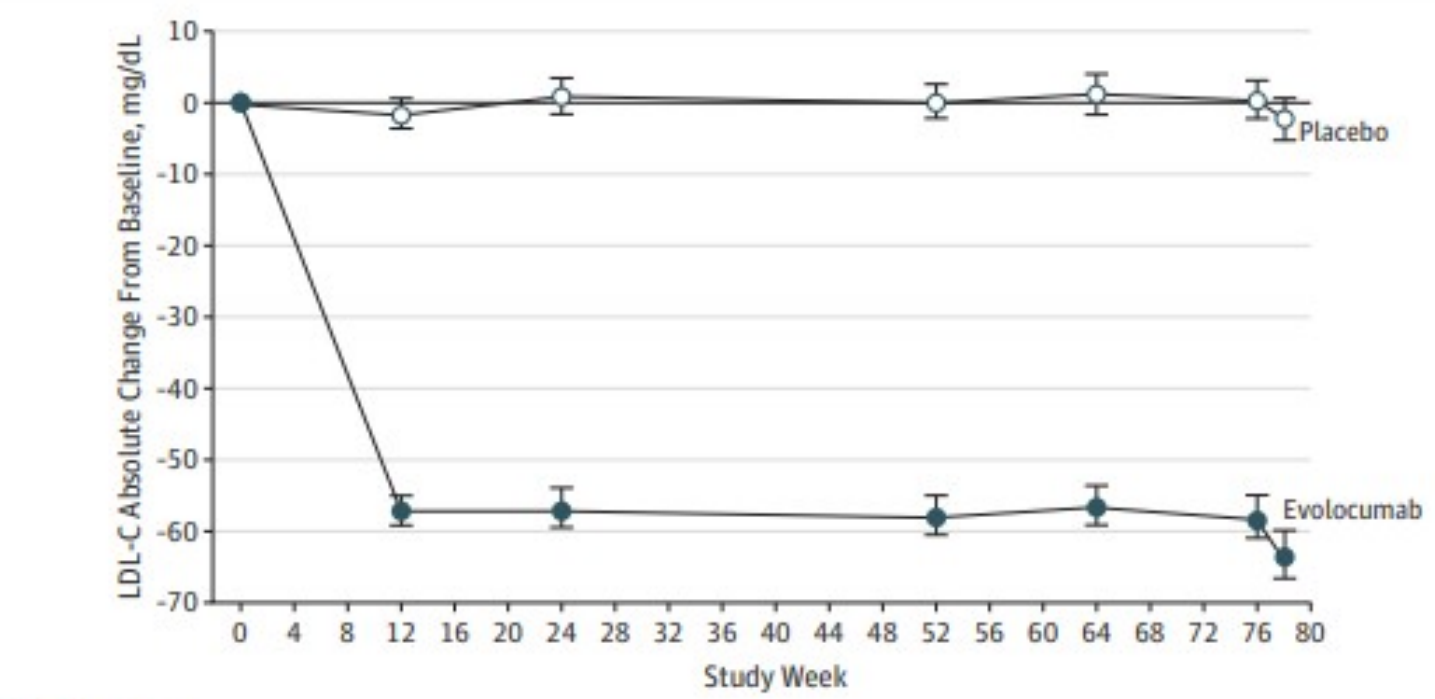
GLAGOV trial: effect van evolocumab op progressie van CAD in patiënten onder behandeling met statines



Nicholls et al. JAMA 2016; 316:2373-2384.

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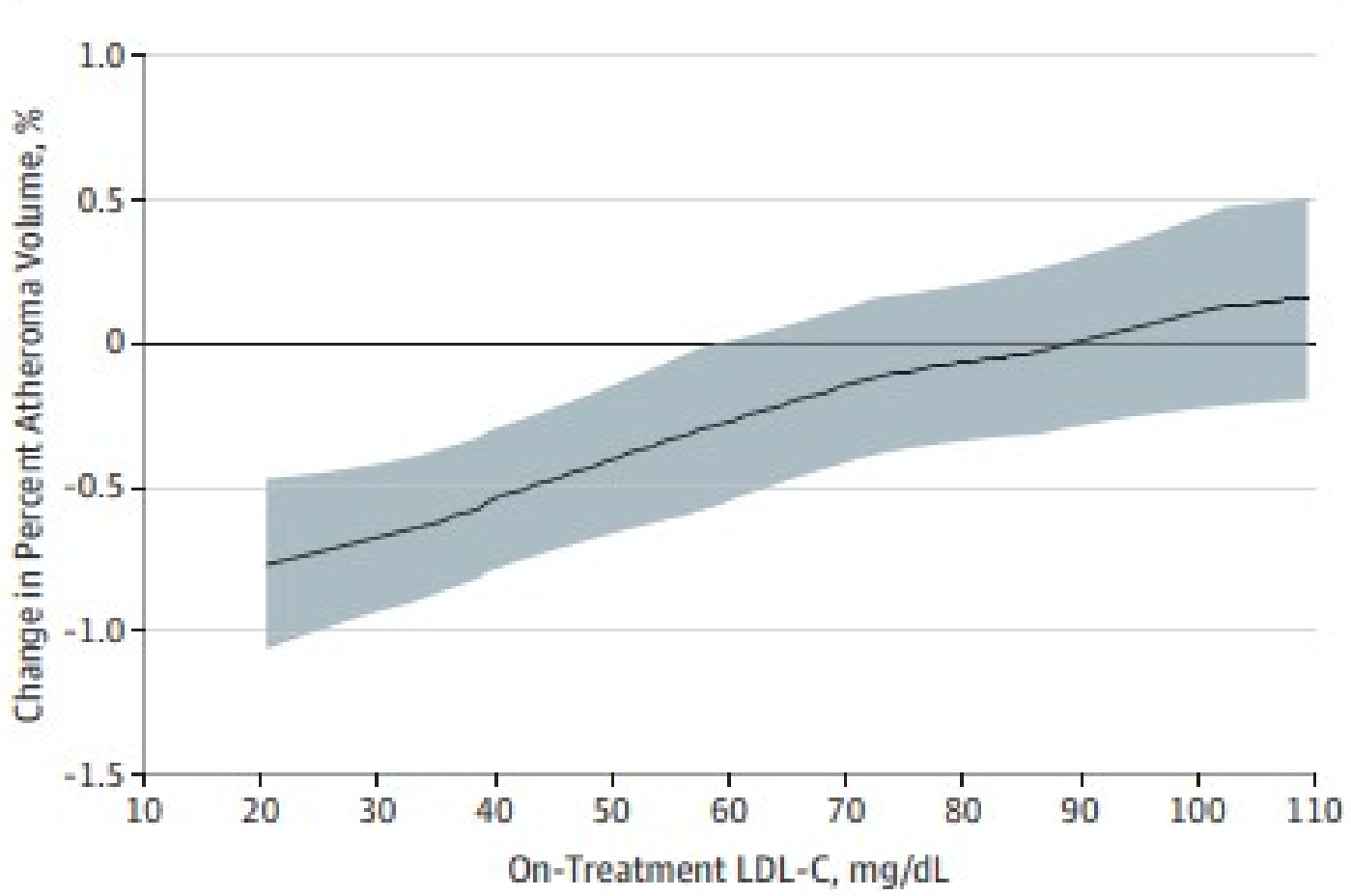
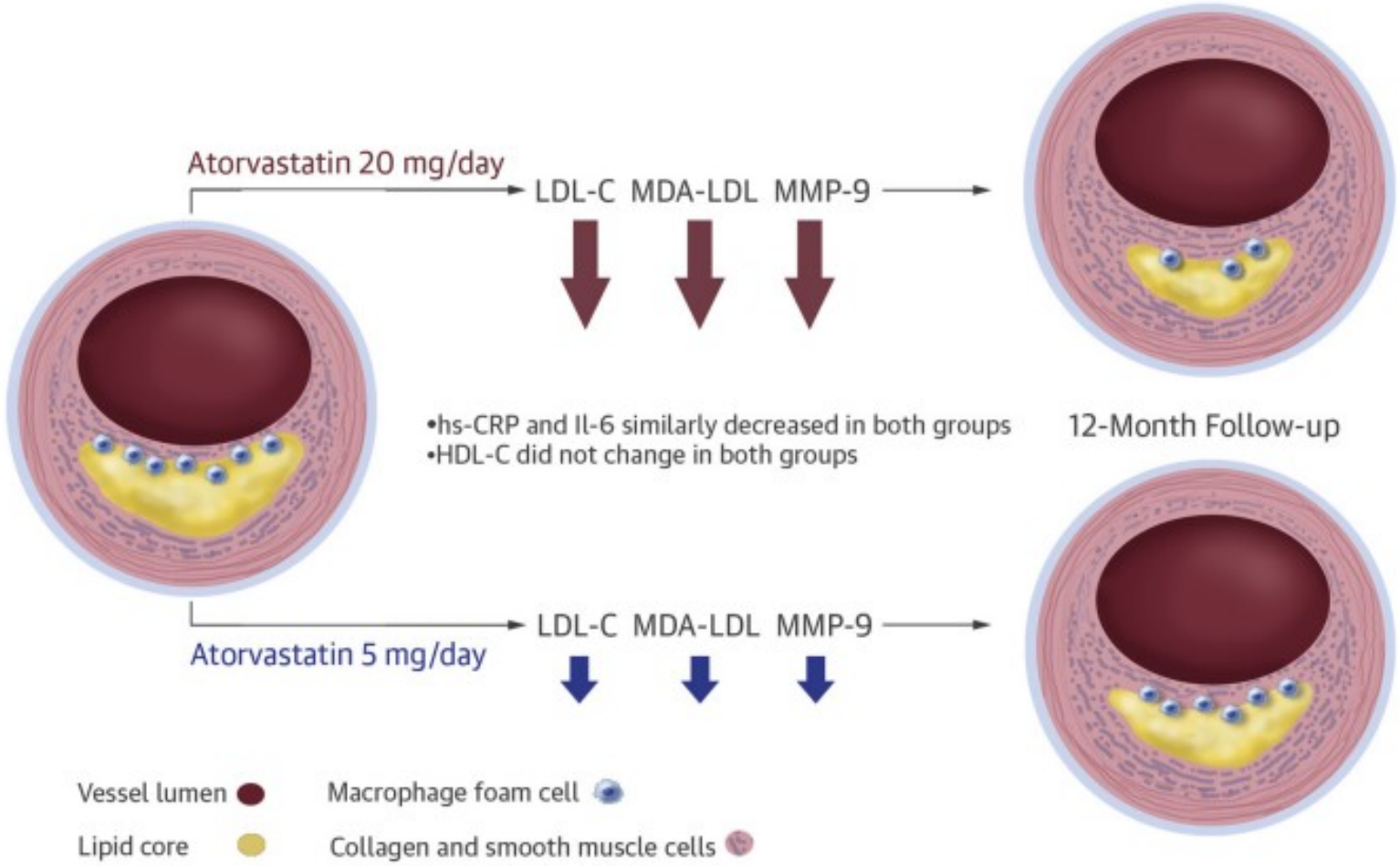
Relatie bereikt LDL-C verlaging en Δ PAV (IVUS)



Nicholls et al. JAMA 2016; 316:2373-2384.

EASY-FIT: effect van atorvastatine op fibrous cap thickness (FCT) en macrofaag intensiteit



Komukai et al. J Am Coll Cardiol 2014; 64: 2207-17

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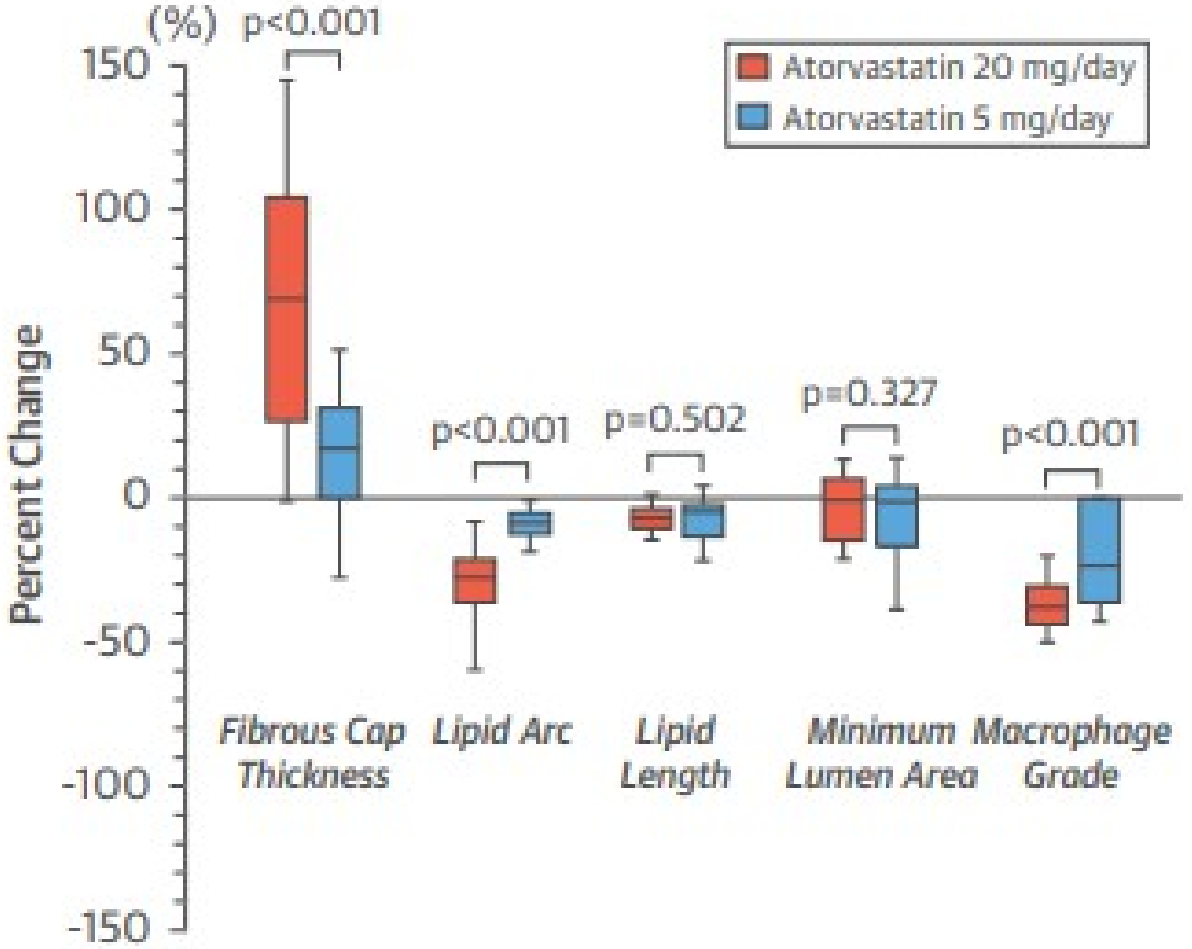
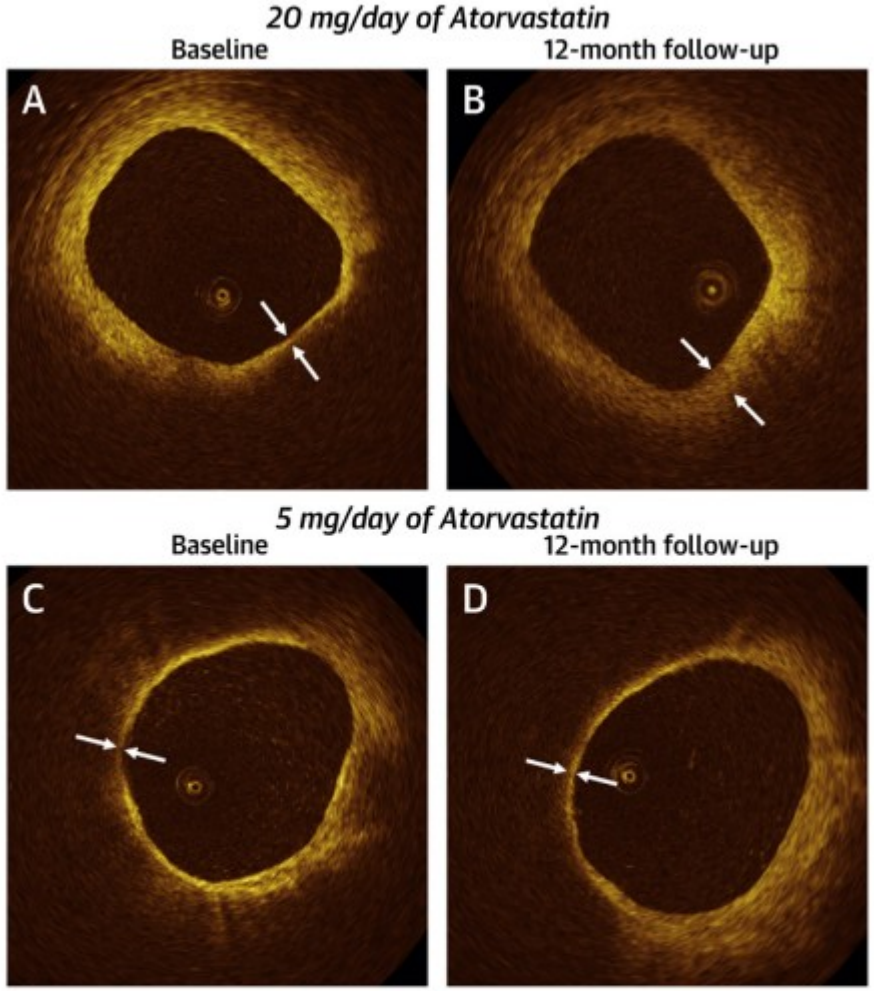
OCT baseline & follow-up



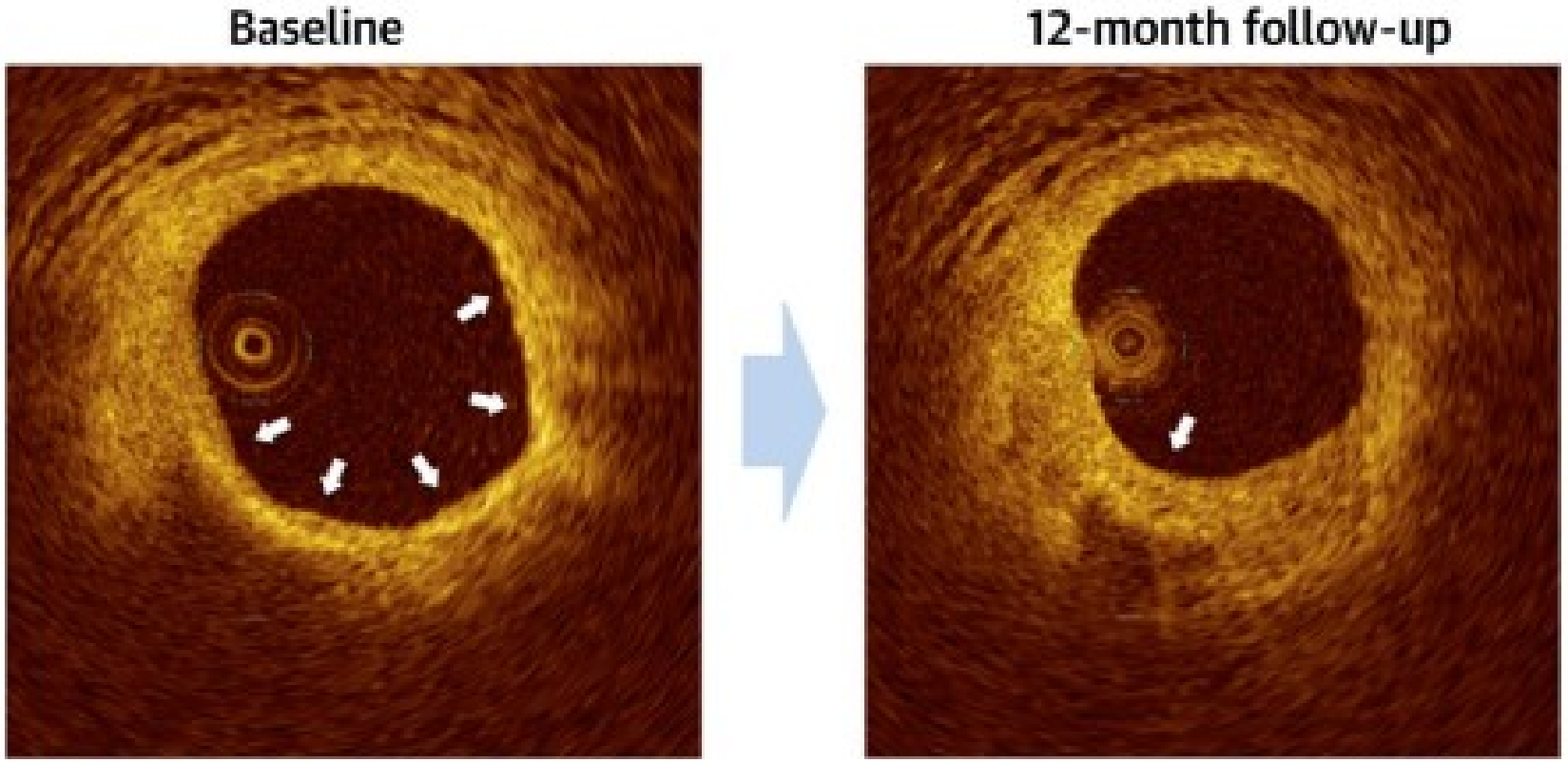
Komukai et al. J Am Coll Cardiol 2014; 64: 2207-17

Toename Fibrous cap thickness



Komukai et al. J Am Coll Cardiol 2014; 64: 2207-17

Vermindering in macrofaag signaal intensiteit



Komukai et al. J Am Coll Cardiol 2014;64: 2207-17

Effect of Evolocumab on Coronary Plaque Phenotype and Burden in Statin-Treated Patients Following Myocardial Infarction

Stephen J. Nicholls, MBBS, PhD,[a,*] Yu Kataoka, MD, PhD,[b,*] Steven E. Nissen, MD,[c] Francesco Prati, MD,[d] Stephan Windecker, MD,[e] Rishi Puri, MBBS, PhD,[c] Thomas Hucko, MD,[f] Daniel Aradi, MD, PhD,[g,h,i] Jean-Paul R. Herrman, MD, PhD,[j] Renicus S. Hermanides, MD, PhD,[k] Bei Wang, PhD,[f] Huei Wang, PhD,[f] Julie Butters, BHSc, MBA,[a] Giuseppe Di Giovanni, BSc (Hons),[l] Stephen Jones, BAppSc, BHSc (Hons),[l] Gianluca Pompili, BSc, BA,[l] Peter J. Psaltis, MBBS, PhD[l,m]

HUYGENS trial

Nicholls et al. JACC CV Img 2022; 15:1308-1321.

TABLE 2 Baseline and On-Treatment Biochemical Measures and Blood Pressure in the Randomized Population Who Received Study Drug

	Baseline		On-Treatment (Week 50)		Absolute Change (Week 50)		
	Placebo (n = 81)	Evolocumab (n = 80)	Placebo (n = 81)	Evolocumab (n = 80)	Placebo (n = 81)	Evolocumab (n = 80)	*P* Value[a]
Total cholesterol, mg/dL	175.2 ± 40.3	174.7 ± 37.3	159.7 ± 43.6	98.9 ± 30.9	−14.8 ± 47.4	−78.9 ± 44.6	<0.001
LDL cholesterol, mg/dL[b]	142.1 ± 32.3	140.4 ± 34.0	87.2 ± 36.5	28.1 ± 25.4	−55.3 ± 47.1	−114.2 ± 41.7	<0.001
HDL cholesterol, mg/dL	41.7 ± 11.5	43.8 ± 10.4	47.1 ± 12.4	51.2 ± 13.2	6.1 ± 9.3	7.6 ± 9.4	0.26
Triglycerides, mg/dL	158.9 ± 72.8	148.4 ± 75.5	133.5 ± 57.5	114.8 ± 84.9	−23.1 ± 69.2	−38.5 ± 88.4	0.13
Non-HDL cholesterol, mg/dL	133.4 ± 38.7	130.9 ± 36.6	112.6 ± 39.2	47.7 ± 34.3	−20.8 ± 47.1	−86.5 ± 45.6	<0.001
Total/HDL cholesterol	4.4 ± 1.2	4.2 ± 1.3	3.5 ± 0.9	2.1 ± 1.4	−0.9 ± 1.2	−2.1 ± 1.4	<0.001
ApoB, mg/dL	92.9 ± 21.9	91.0 ± 22.9	79.6 ± 23.1	38.8 ± 22.0	−13.5 ± 27.2	−53.3 ± 30.3	<0.001
ApoA-I, mg/dL	131.0 ± 22.4	135.0 ± 21.0	142.9 ± 26.6	149.6 ± 22.3	10.6 ± 21.8	15.4 ± 20.0	0.09
ApoB/A-I	0.72 ± 0.19	0.69 ± 0.19	0.57 ± 0.17	0.27 ± 0.17	−0.15 ± 0.21	−0.42 ± 0.22	<0.001
Lp(a), nmol/L[c]	96.2 ± 100.0	107.7 ± 111.0	95.1 ± 106.5	84.5 ± 91.2	−4.1 ± 36.7	−24.0 ± 42.4	0.003

Nicholls et al. JACC CV Img2022; 15:1308-1321.

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TABLE 7 Intravascular Ultrasound Assessment of Plaque Burden

	Placebo (n = 39)[a]	Evolocumab (n = 40)[a]	*P* Value
Percent atheroma volume, %			
Baseline	45.1 ± 0.9	45.8 ± 0.9	0.56
Follow-up	43.9 ± 0.9	43.1 ± 1.1	0.009
LS mean change	−0.61 ± 0.46	−2.29 ± 0.47	0.009
Percent regressors	56.4	77.5	0.04
Total atheroma volume, mm^3			
Baseline	244.7 ± 10.6	244.3 ± 12.1	0.97
Follow-up	240.0 ± 11.4	204.1 ± 13.1	0.04
LS mean change	−8.9 ± 3.5	−19.0 ± 3.7	0.04
Percent regressors	66.7	80.0	0.18

Values are mean ± SE. Measures of plaque burden measured by intravascular ultrasound. [a]Number of subjects with observed data at both baseline and follow-up.

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TABLE 3 Coronary Artery Segment Based Measurements as Evaluated on OCT

	Placebo (n = 81)	Evolocumab (n = 80)	Between-Group Difference	Adjusted *P* Value[a]
Primary endpoint: minimum fibrous cap thickness, μm				
Baseline (n = 161)	54.6 ± 15.1	56.6 ± 17.8		0.44
Follow-up at week 50[b] (n = 119)	81.7 ± 35.4 (n = 63)	100.6 ± 40.6 (n = 56)		0.02
Absolute change from baseline[b] (n = 119)	22.0 (8.0 to 36.0) (n = 63)	39.0 (20.5 to 71.0) (n = 56)		0.015
Imputed change from baseline[a] (n = 161)	21.5 (10.9 to 32.1)	42.7 (32.4 to 53.1)	21.2 (4.7 to 37.7)	0.015
Coronary artery segment-based secondary endpoints				
Minimum fibrous cap thickness				
Percent change from baseline[b] (n = 119)	44.9 (14.3 to 72.0) (n = 63)	80.5 (40.2 to 120.3) (n = 56)		0.04
Imputed change from baseline[a] (n = 161)	44.3 (20.3 to 68.3)	81.8 (59.9 to 103.6)	37.5 (1.6 to 73.3)	0.04
Average minimum fibrous cap thickness (μm) for all images				
Baseline (n = 161)	133.6 ± 45.0	142.3 ± 37.4		0.18
Follow-up at week 50[b] (n = 119)	172.8 ± 49.5 (n = 63)	210.5 ± 55.1 (n = 56)		0.005
Absolute change from baseline[b] (n = 119)	37.1 (3.5 to 70.0) (n = 63)	60.8 (23.0 to 90.1) (n = 56)		0.02
Imputed change from baseline[a] (n = 161)	29.8 (15.7 to 43.9)	62.3 (50.5 to 74.1)	32.5 (12.7 to 52.4)	0.02
Maximum lipid arc, °				
Baseline (n = 161)	224.8 ± 75.8	230.2 ± 74.1		0.65
Follow-up at week 50[b] (n = 119)	193.6 ± 80.5 (n = 63)	171.9 ± 73.1 (n = 56)		0.07
Absolute change from baseline[b] (n = 119)	−25.0 (−72.0 to 4.0) (n = 63)	−51.0 (−99.0 to −20.5) (n = 56)		0.04
Imputed change from baseline[a] (n = 161)	−31.4 (−50.2 to −12.7)	−57.5 (−72.2 to −42.7)	−26.0 (−49.6 to −2.4)	0.04

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Nicholls et al. JACC CV Img 2022; 15:1308-1321.

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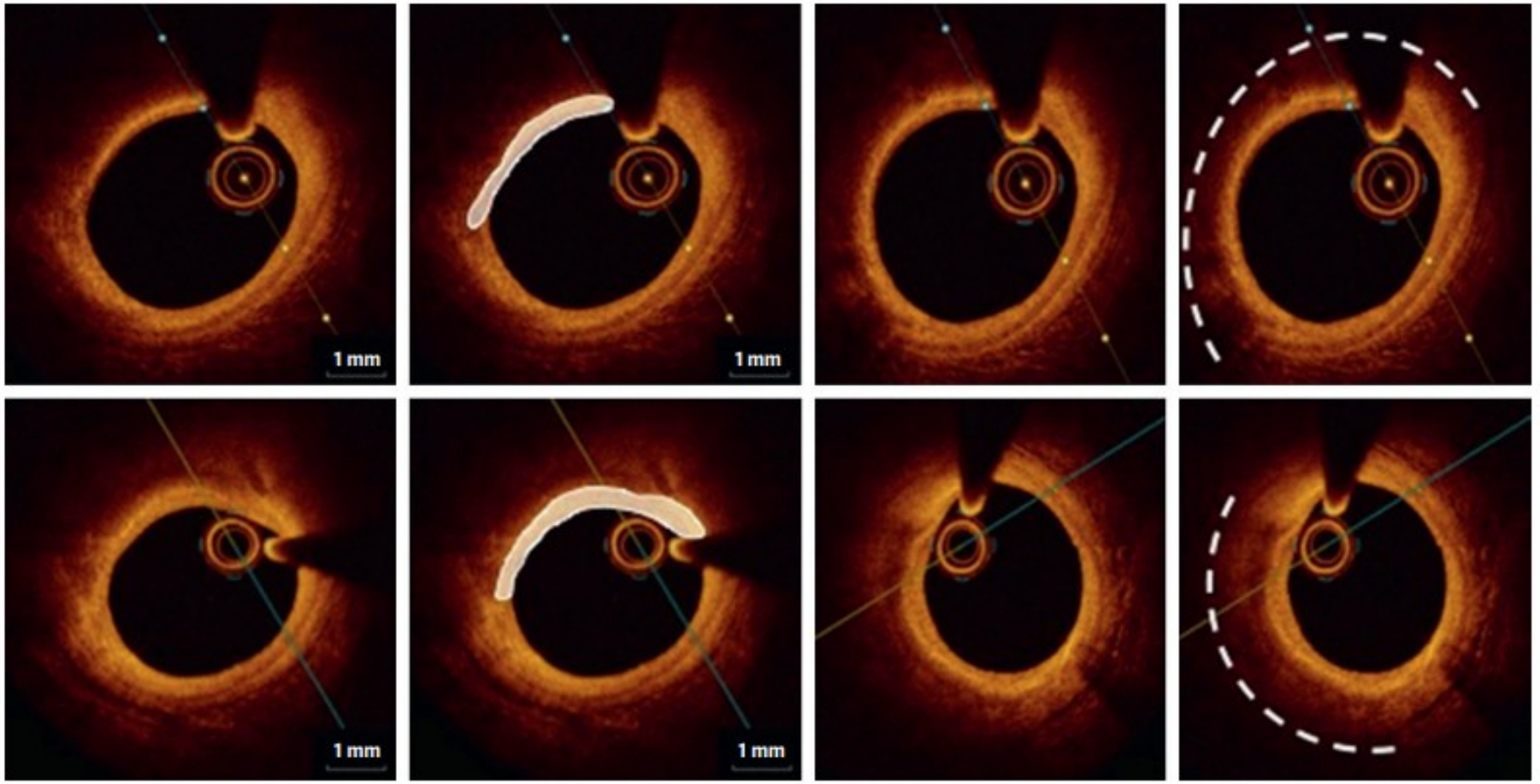
HUYGENS: Minimum fibrous cap thickness en lipid arc



Nicholls et al. JACC CV Img 2022; 15:1308-1321.

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JAMA | Original Investigation

Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction
The PACMAN-AMI Randomized Clinical Trial

Lorenz Räber, MD, PhD; Yasushi Ueki, MD, PhD; Tatsuhiko Otsuka, MD; Sylvain Losdat, PhD; Jonas D. Häner, MD; Jacob Lonborg, MD; Gregor Fahrni, MD; Juan F. Iglesias, MD; Robert-Jan van Geuns, MD, PhD; Anna S. Ondracek, MSc; Maria D. Radu Juul Jensen, MD, PhD; Christian Zanchin, MD, PhD; Stefan Stortecky, MD; David Spirk, MD; George C. M. Siontis, MD, PhD; Lanja Saleh, PhD; Christian M. Matter, MD; Joost Daemen, MD, PhD; François Mach, MD; Dik Heg, PhD; Stephan Windecker, MD; Thomas Engstrøm, MD, PhD; Irene M. Lang, MD; Konstantinos C. Koskinas, MD, MSc; for the PACMAN-AMI collaborators

Räber et al JAMA ;2022; 327:1771-1781.

Table 3. Primary and Secondary Imaging Outcomes Assessed by Intravascular Ultrasonography, Near-Infrared Spectroscopy, and Optical Coherence Tomography[a]

Outcome	Baseline, mean (SD)		Week 52, mean (SD)		Change from baseline to week 52, mean (95% CI)		Difference in change (95% CI)	*P* value[b]
	Alirocumab	Placebo	Alirocumab	Placebo	Alirocumab	Placebo		
Primary								
No. of vessels imaged with intravascular ultrasonography (No. of patients)	263 (130)	274 (135)	263 (130)	274 (135)				
Percent atheroma volume, %	40.91 (8.61)	43.01 (9.84)	38.78 (8.20)	42.09 (9.94)	−2.13 (−2.53 to −1.73)	−0.92 (−1.28 to −0.56)	−1.21 (−1.78 to −0.65)	<.001
Secondary								
Normalized total atheroma volume, mm^3[c]	261.37 (121.42)	250.41 (112.69)	235.25 (107.89)	235.44 (107.72)	−26.12 (−30.07 to −22.17)	−14.97 (−18.14 to −11.80)	−11.55 (−17.44 to −5.66)	<.001
Patients with percent atheroma volume regression, No. (%)[d]			110 (84.6)	89 (65.9)			18.7% (7.8 to 29.6); odds ratio, 2.8 (95% CI, 1.6 to 5.2)	
No. of vessels imaged with near-infrared spectroscopy (No. of patients)	252 (129)	260 (134)	252 (129)	260 (134)				
Maximum lipid core burden index at 4 mm[e]	260.60 (184.49)	276.23 (195.65)	181.17 (171.93)	238.63 (194.51)	−79.42 (−100.39 to −58.46)	−37.60 (−57.40 to −17.80)	−41.24 (−70.71 to −11.77)	.006
Total lipid core burden index	73.16 (76.39)	82.11 (84.19)	43.86 (57.03)	69.73 (82.35)	−29.30 (−37.52 to −21.08)	−12.38 (−20.66 to −4.10)	−17.29 (−28.98 to −5.60)	.004
No. of vessels imaged with optical coherence tomography (No. of patients)	245 (122)	270 (133)	245 (122)	270 (133)				
Minimal fibrous cap thickness, μm[e]	106.97 (70.19) [173 vessels (105 patients)][f]	110.53 (84.98) [197 vessels (116 patients)][f]	169.64 (97.78) [173 vessels (105 patients)][f]	143.72 (84.03) [197 vessels (116 patients)][f]	62.67 (48.84 to 76.50)	33.19 (22.22 to 44.16)	29.65 (11.75 to 47.55)	.001
Mean fibrous cap thickness, μm	328.74 (97.25) [173 vessels (105 patients)][f]	328.91 (112.58) [197 vessels (116 patients)][f]	419.69 (108.79) [173 vessels (105 patients)][f]	391.27 (100.29) [197 vessels (116 patients)][f]	90.95 (72.96 to 108.94) [173 vessels (105 patients)]	62.36 (46.23 to 78.50) [197 vessels (116 patients)]	28.22 (3.21 to 53.23)	.03
Mean angular extension of macrophages, °	58.54 (20.81) [232 vessels (121 patients)][g]	57.57 (22.51) [251 vessels (131 patients)][g]	32.57 (21.01) [232 vessels (121 patients)][g]	41.62 (22.25) [251 vessels (131 patients)][g]	−25.98 (−29.35 to −22.61) [232 vessels (121 patients)]	−15.95 (−19.02 to −12.87) [251 vessels (131 patients)]	−10.08 (−14.72 to −5.43)	<.001

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Patients with percent atheroma volume regression, No. (%)[d]			110 (84.6)	89 (65.9)			18.7% (7.8 to 29.6); odds ratio, 2.8 (95% CI, 1.6 to 5.2)	
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Minimal fibrous cap thickness, μm[e]	106.97 (70.19) [173 vessels (105 patients)][f]	110.53 (84.98) [197 vessels (116 patients)][f]	169.64 (97.78) [173 vessels (105 patients)][f]	143.72 (84.03) [197 vessels (116 patients)][f]	62.67 (48.84 to 76.50)	33.19 (22.22 to 44.16)	29.65 (11.75 to 47.55)	.001
Mean fibrous cap thickness, μm	328.74 (97.25) [173 vessels (105 patients)][f]	328.91 (112.58) [197 vessels (116 patients)][f]	419.69 (108.79) [173 vessels (105 patients)][f]	391.27 (100.29) [197 vessels (116 patients)][f]	90.95 (72.96 to 108.94) [173 vessels (105 patients)]	62.36 (46.23 to 78.50) [197 vessels (116 patients)]	28.22 (3.21 to 53.23)	.03
Mean angular extension of macrophages, °	58.54 (20.81) [232 vessels (121 patients)][g]	57.57 (22.51) [251 vessels (131 patients)][g]	32.57 (21.01) [232 vessels (121 patients)][g]	41.62 (22.25) [251 vessels (131 patients)][g]	−25.98 (−29.35 to −22.61) [232 vessels (121 patients)]	−15.95 (−19.02 to −12.87) [251 vessels (131 patients)]	−10.08 (−14.72 to −5.43)	<.001

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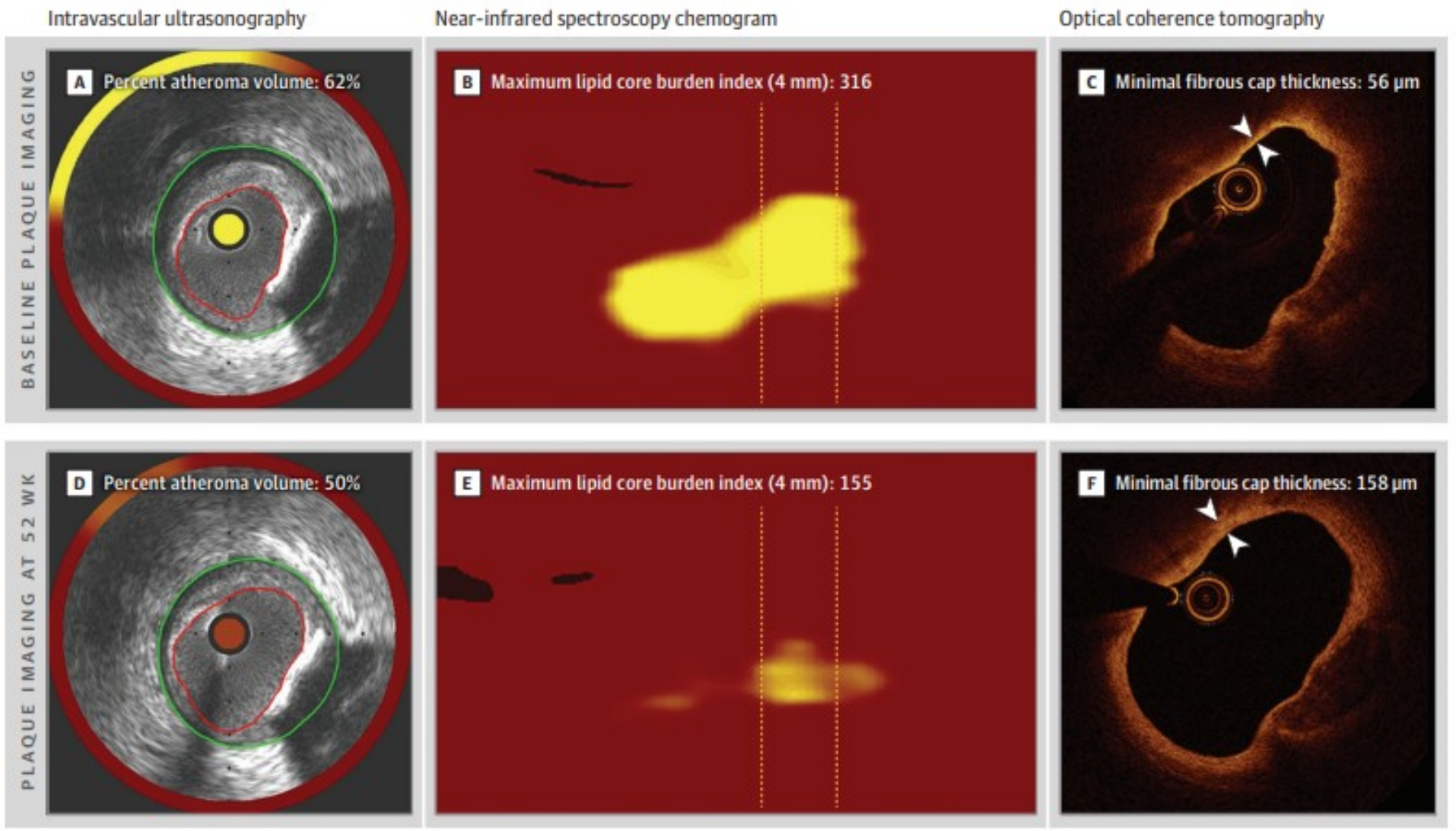
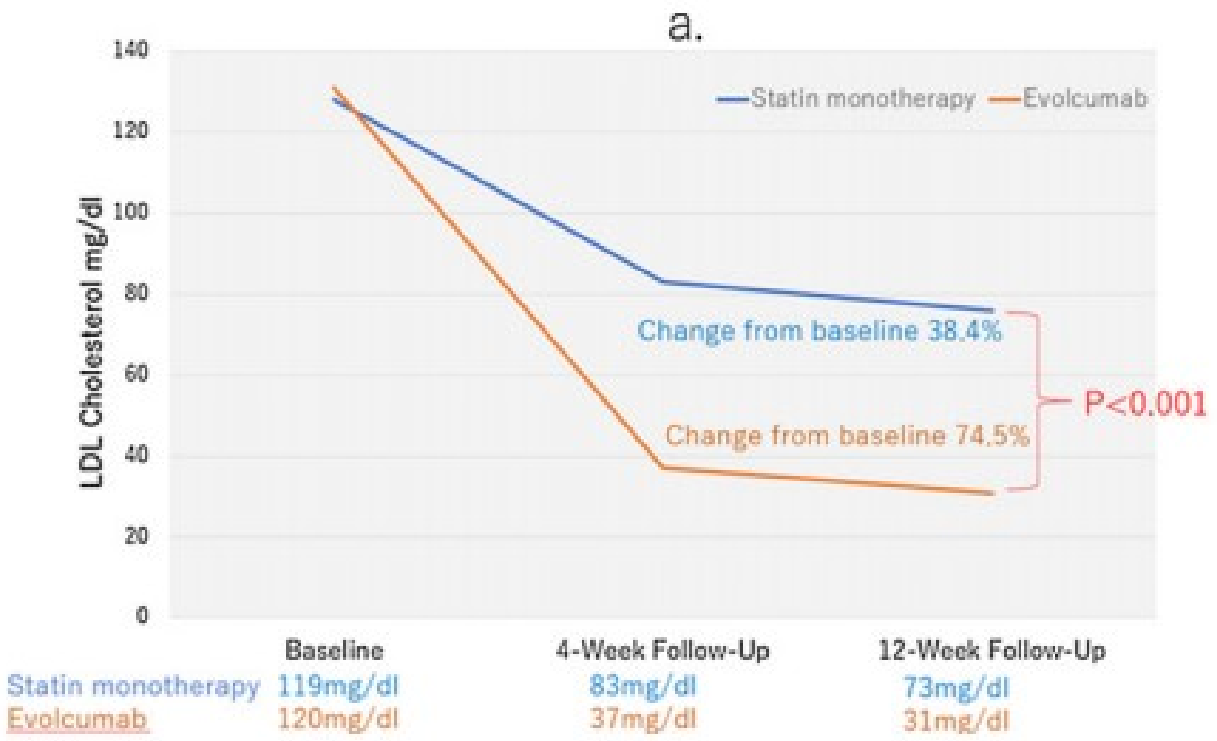
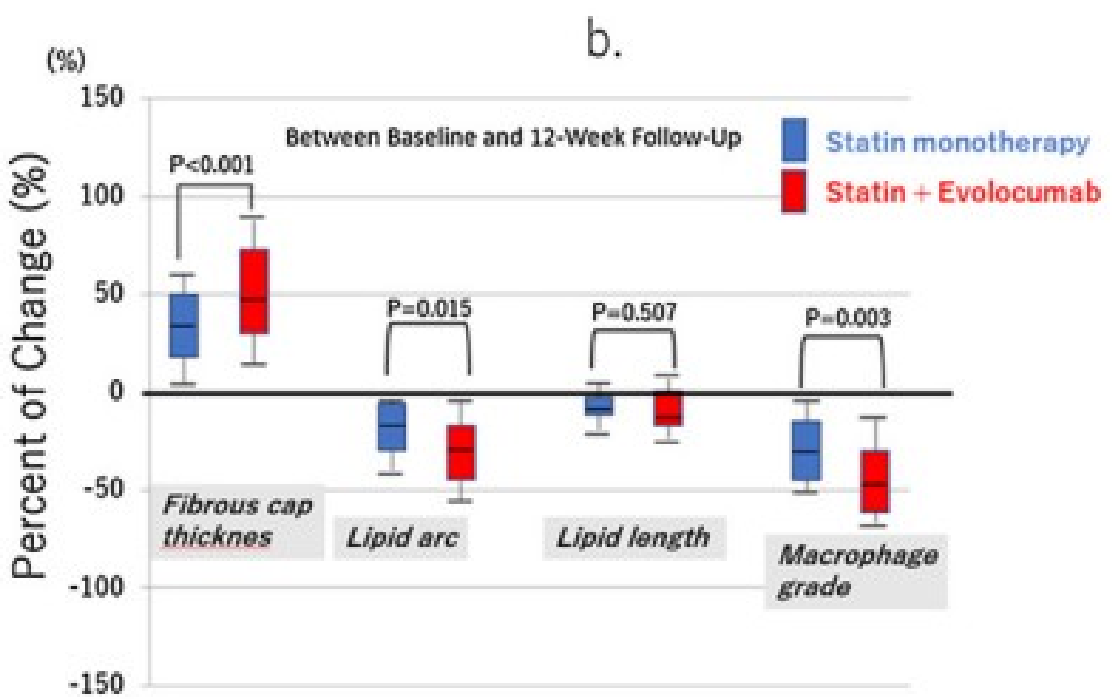
Figure 3. Example of Plaque Regression, Lipid Regression, and Fibrous Cap Thickening in a Trial Patient



Räber et al JAMA ;2022; 327:1771-1781.

OCT beeldvorming kort na ACS (acuut coronair syndroom)





Yano et al.J Cardiol 2020;75:289-295.

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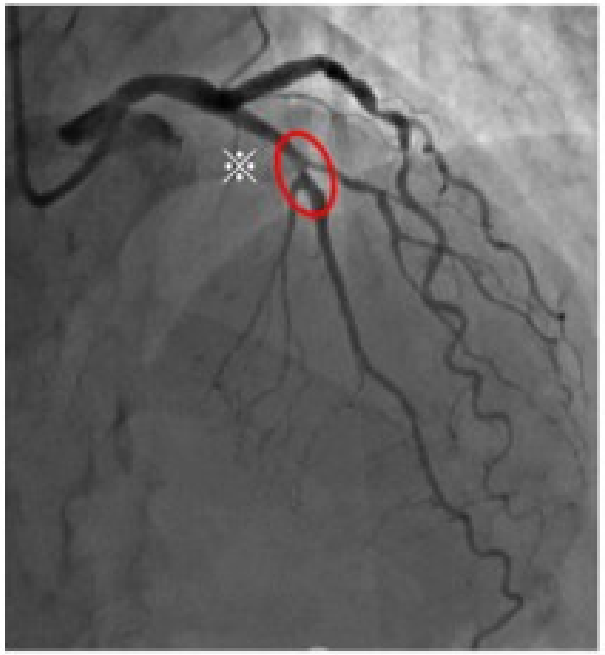
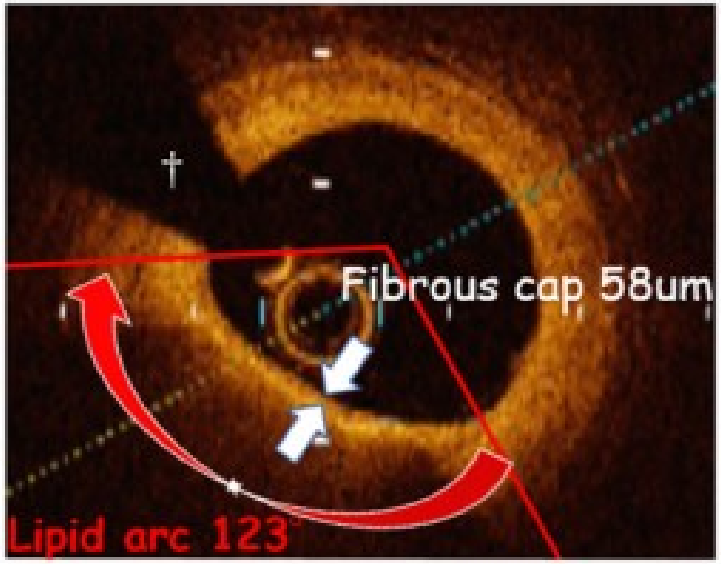
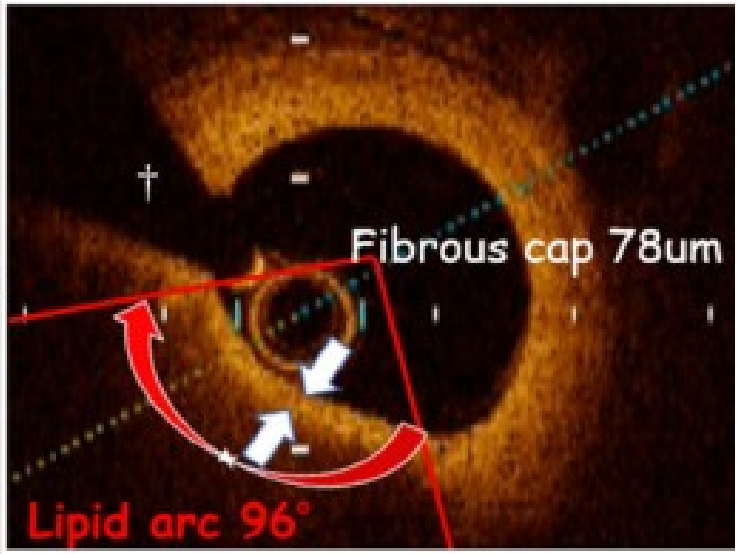


Intermediate stenosis
LAD mid portion

Baseline



12-week follow-up



Yano et al.J Cardiol 2020;75:289-295.

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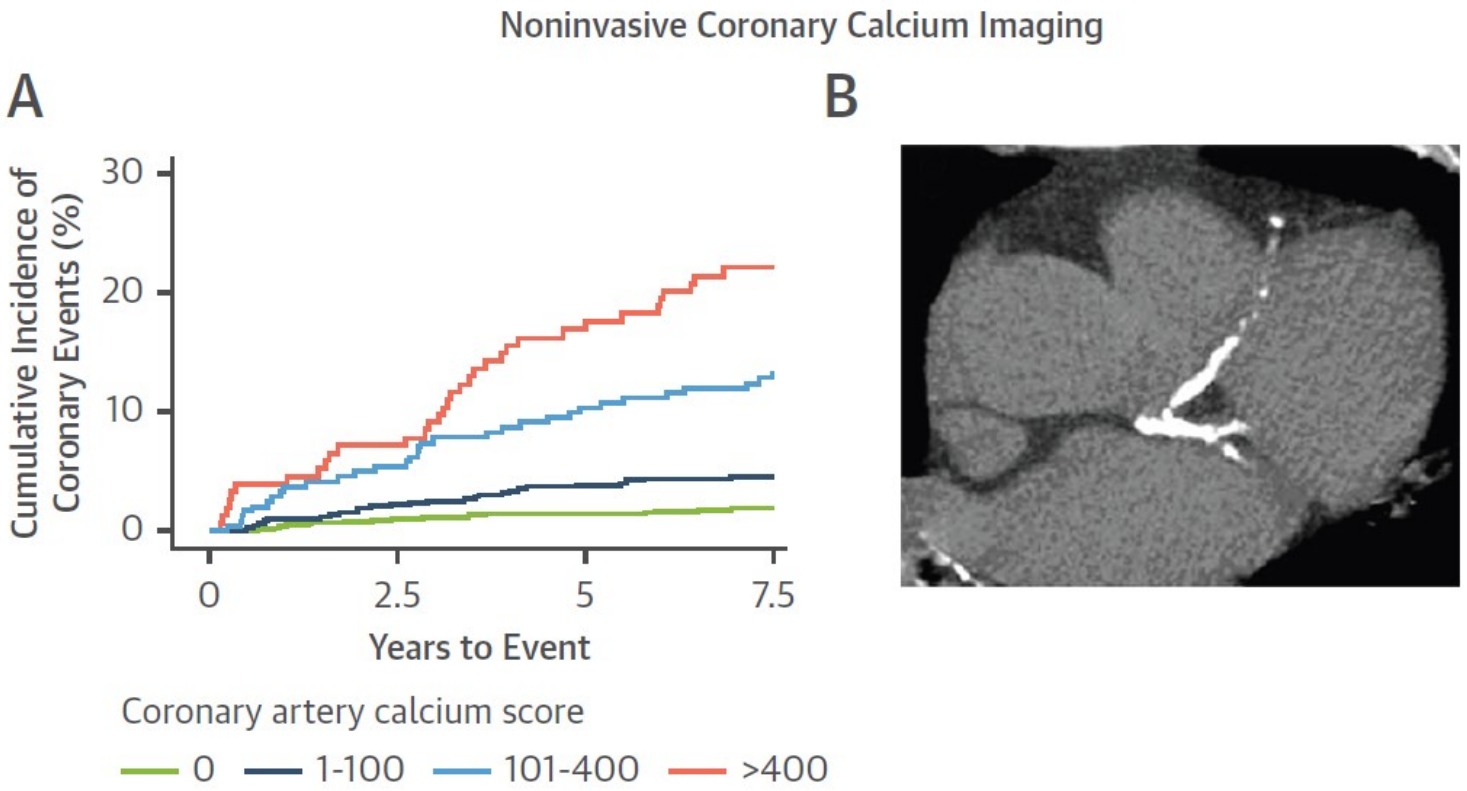
Niet-invasieve beeldvorming van de kransslagaders

Coronary artery Calcium score



Kwiecinski et al. JACC CV Img 2023; 16: 1608-22.

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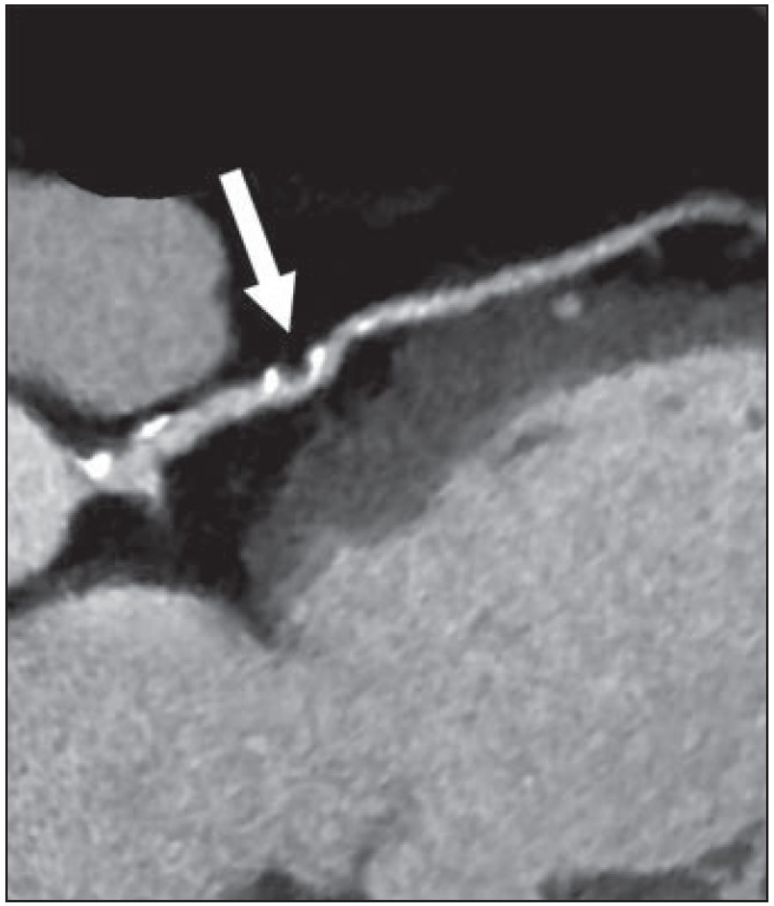
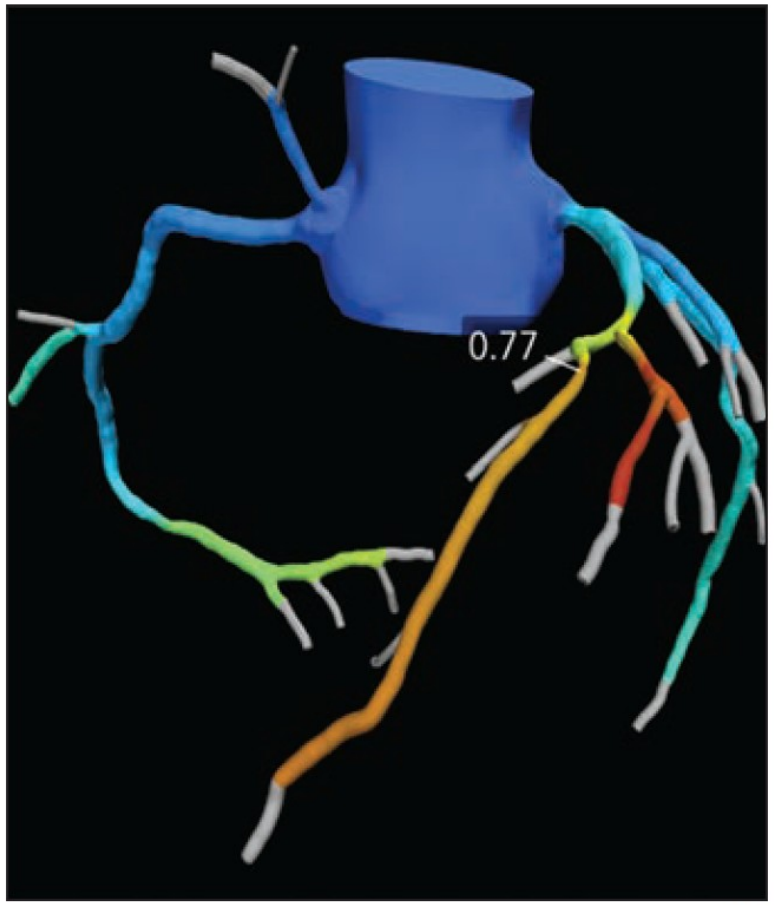
FFR_{CT}



A



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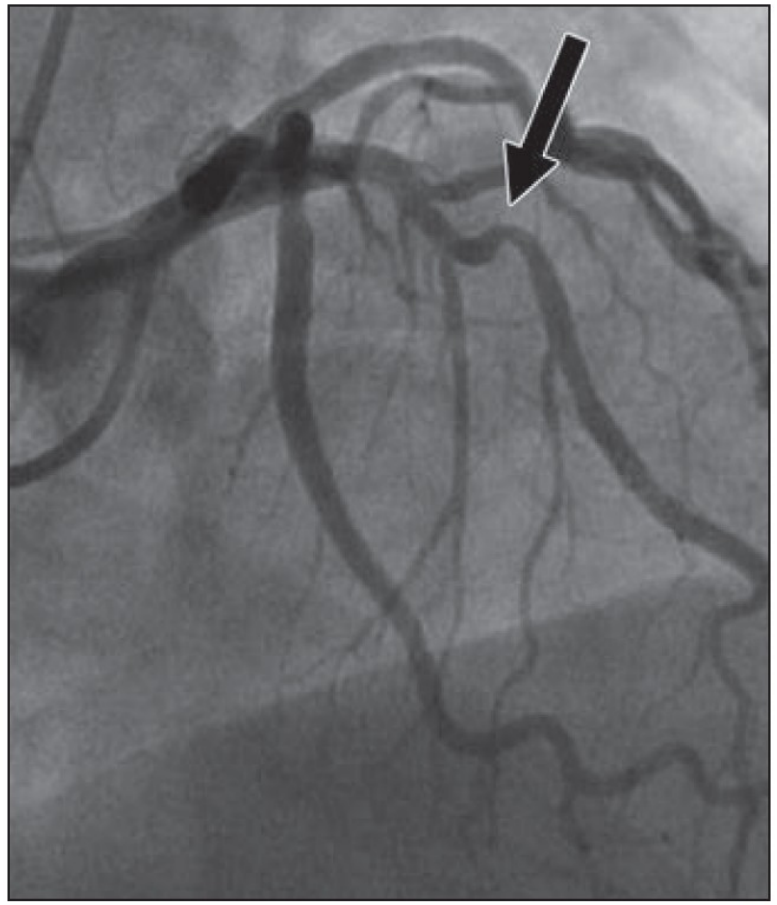

C

Chen et al. AJR 2021; 216: 640-48.

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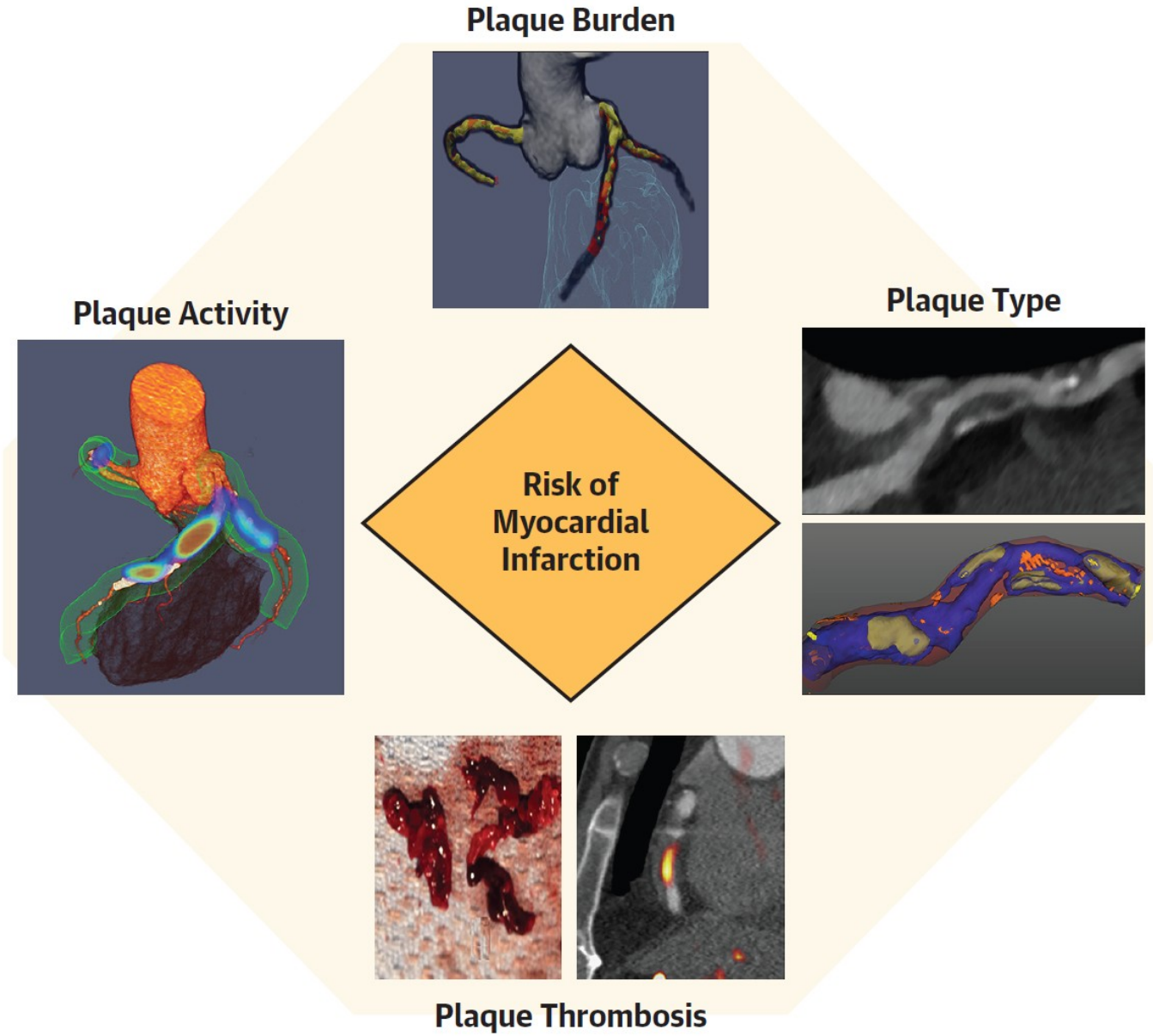

Kwiecinski et al. J Am Coll Cardiol Img 2023; 16: 1608-1622.

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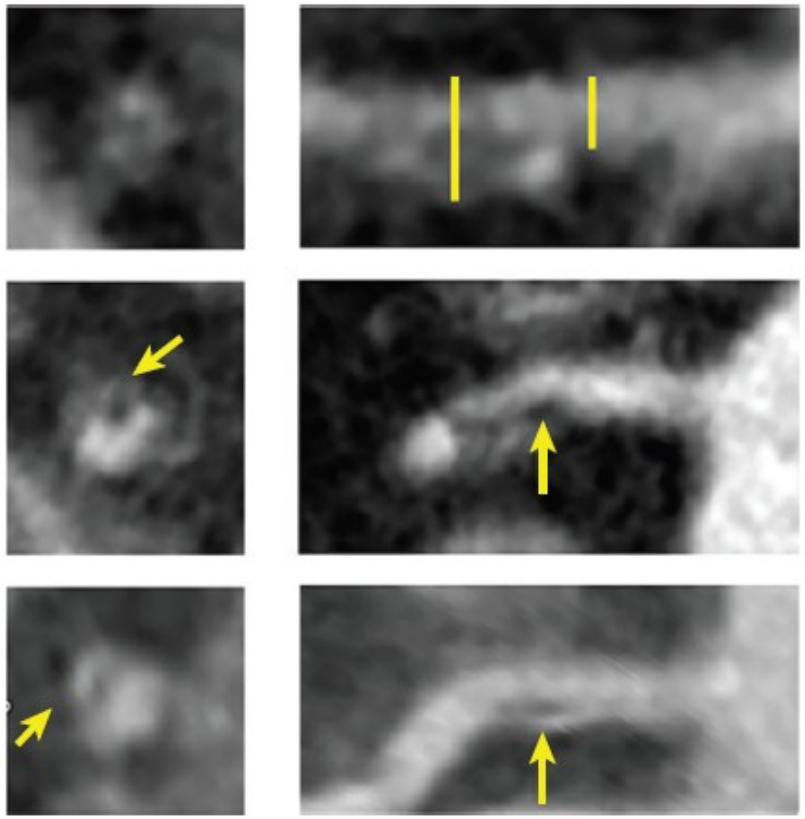
A



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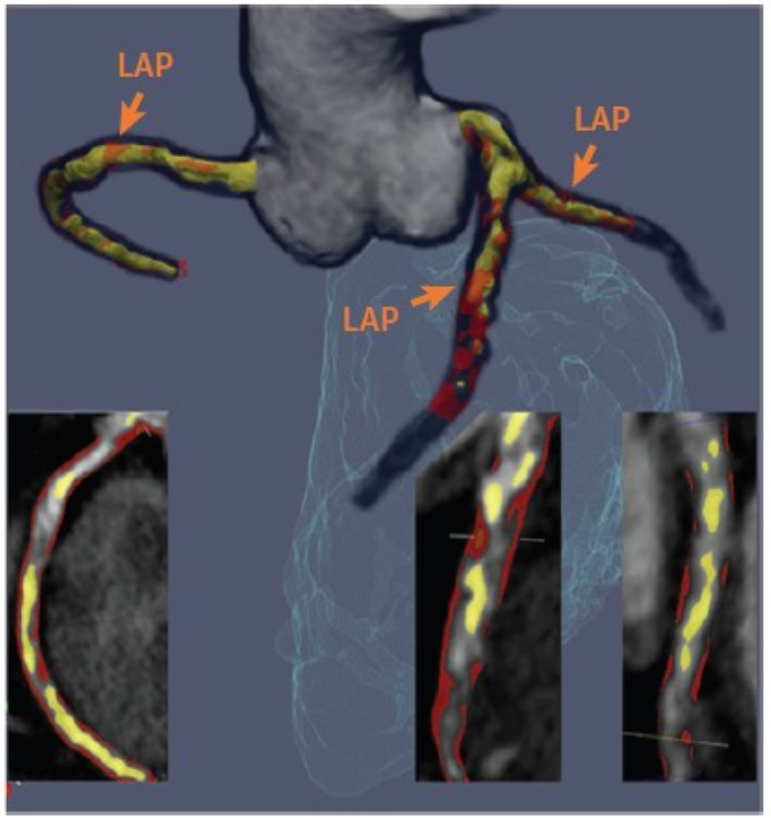
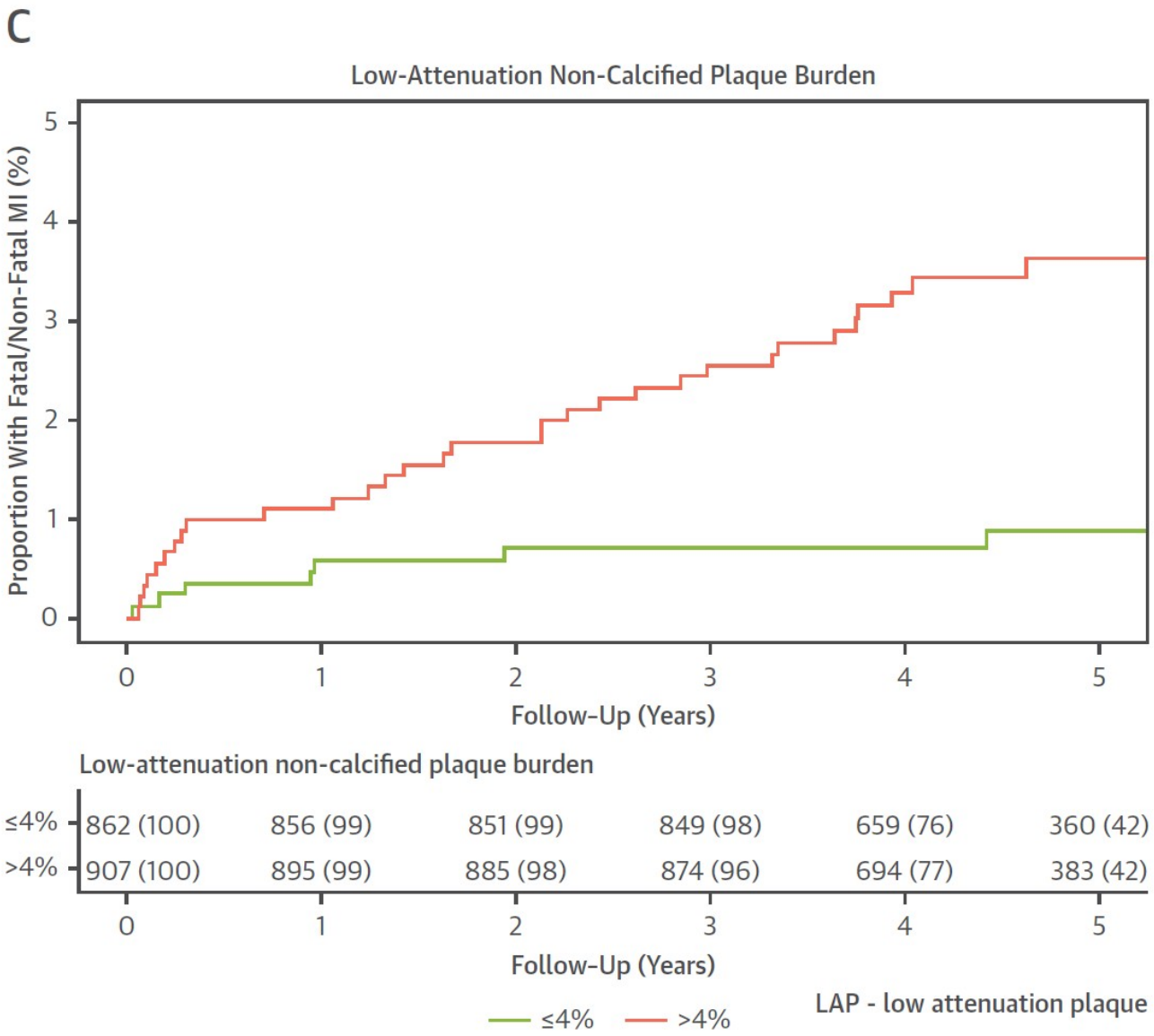


Williams et al. Circulation 2020; 141: 1452-62.



Williams et al. Circulation 2020; 141: 1452-62.

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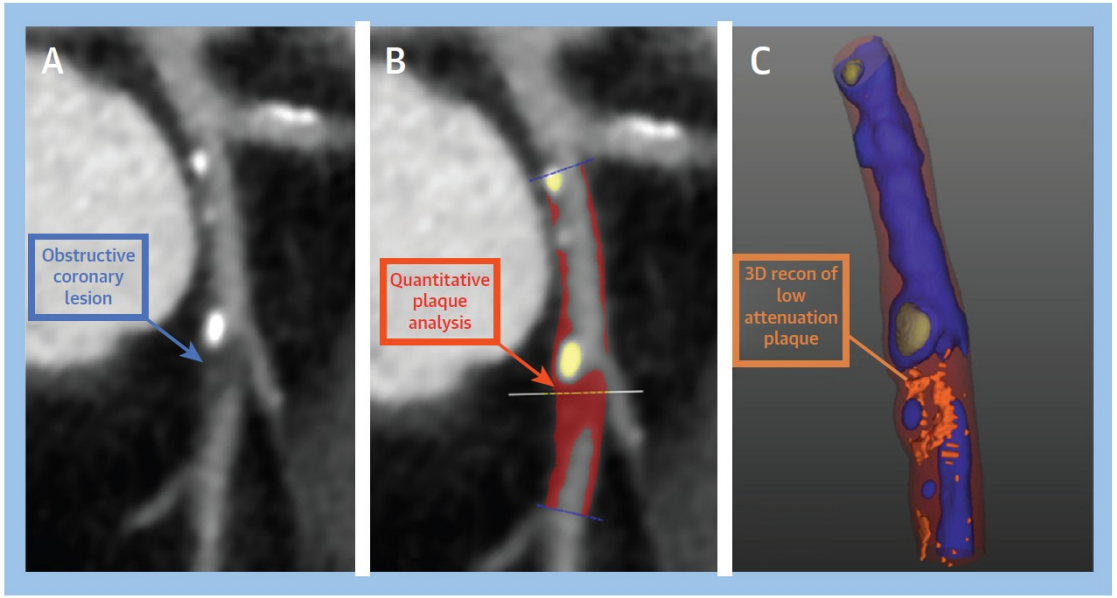
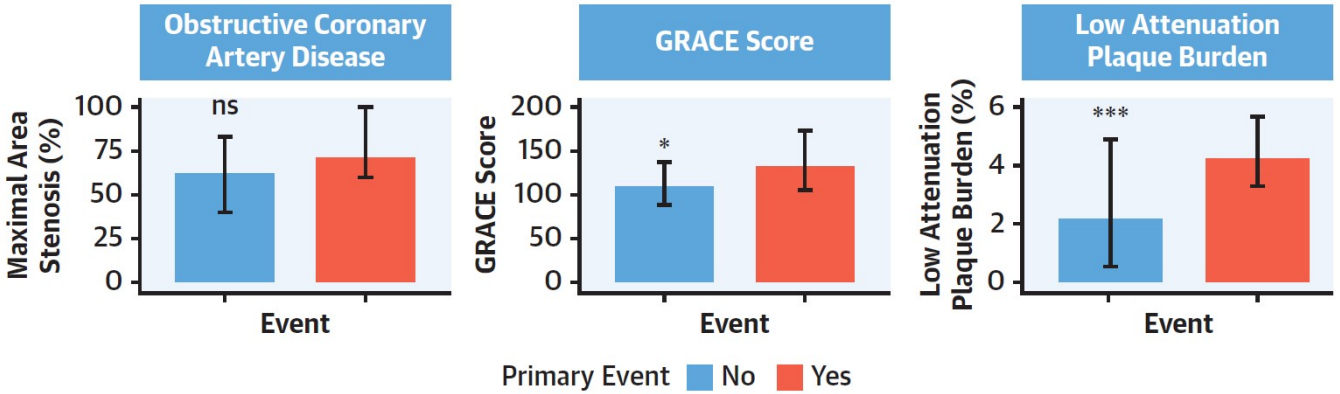
404 Patients With Suspected Acute Coronary Syndrome Underwent Quantitative Plaque Analysis



Higher Burdens of Low-Attenuation Plaque Were Associated With 1-Year All-Cause Death or Myocardial Infarction



Meah et al. J Am Coll Cardiol Img 2022; 15: 1916-1925

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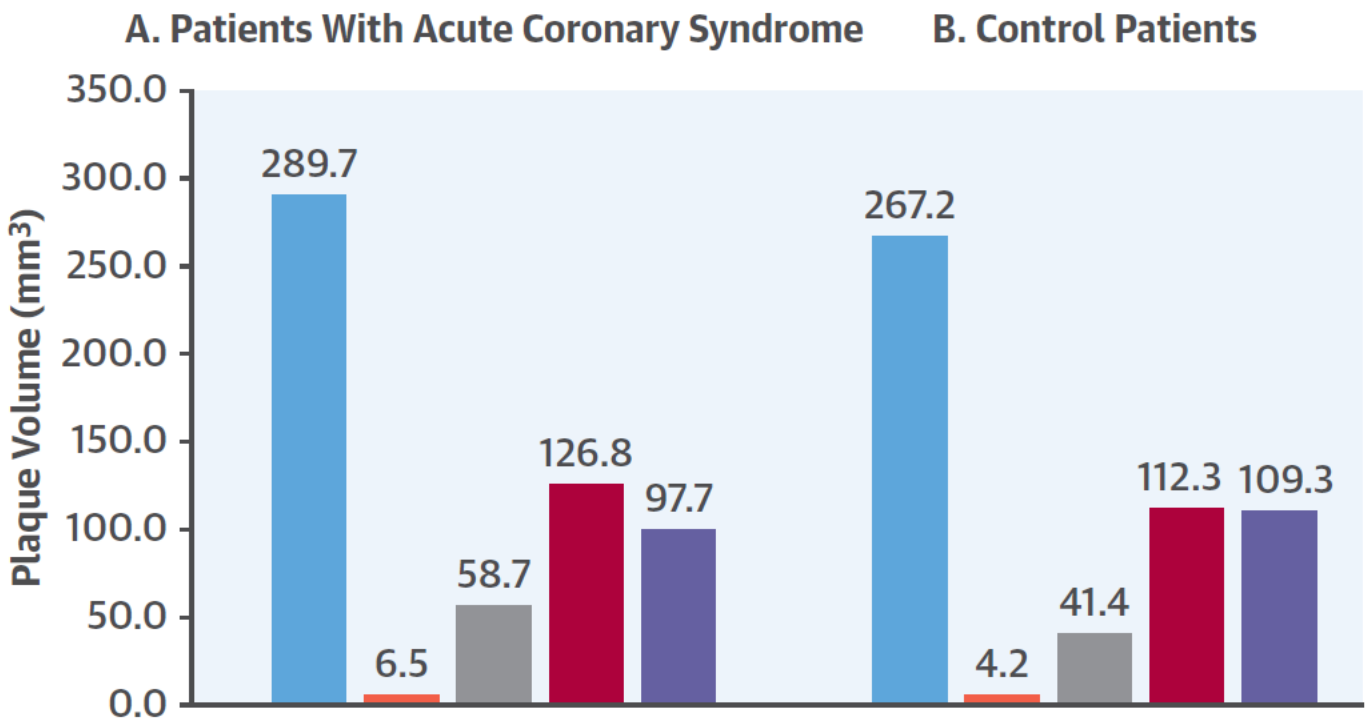
PER PATIENT PRECURSORS OF ACUTE CORONARY SYNDROME



Chang et al. J Am Coll Cardiol 2018; 71: 2511-22

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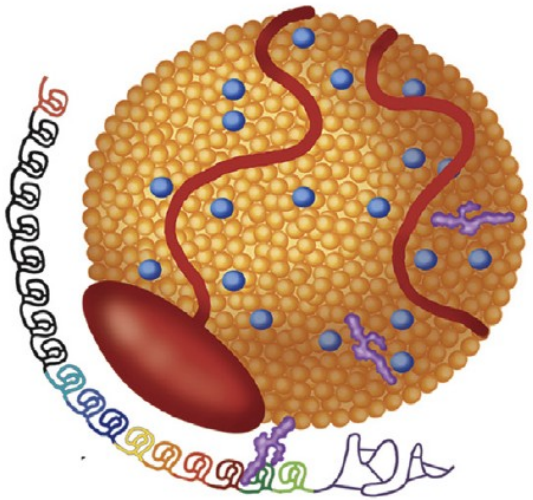
191 Patients With Advanced Multivessel Coronary Artery Disease on Long-Term Guideline-Directed Preventive Therapies

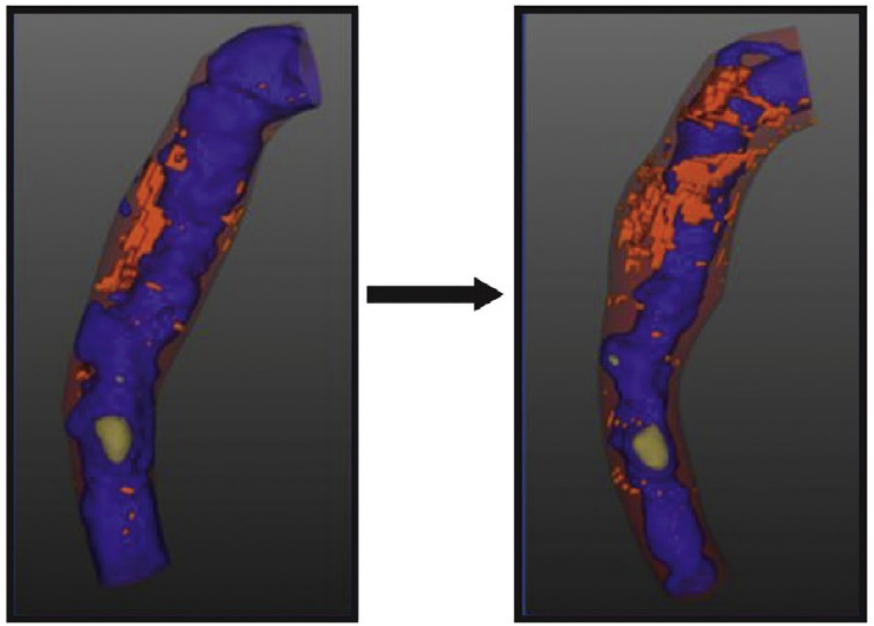
Lp(a) Measurement

Example patient Lp(a) concentration: 82.2 mg/dL



Repeat CCTA to Assess Plaque Progression

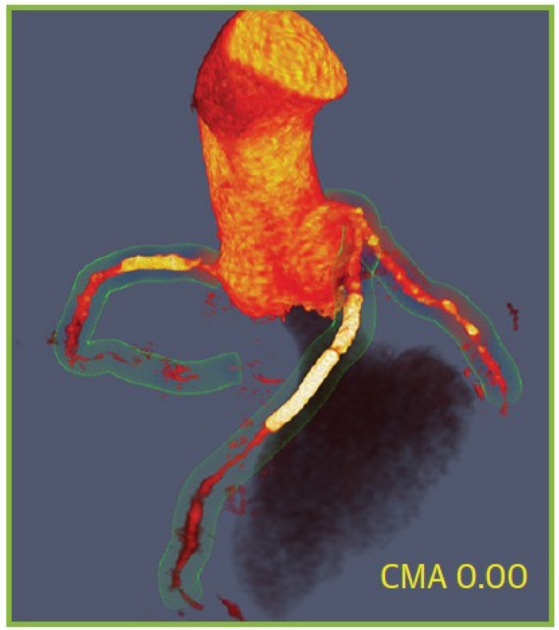
Low-attenuation plaque volume (orange regions) increased from 81.4 mm³ to 132.9 mm³



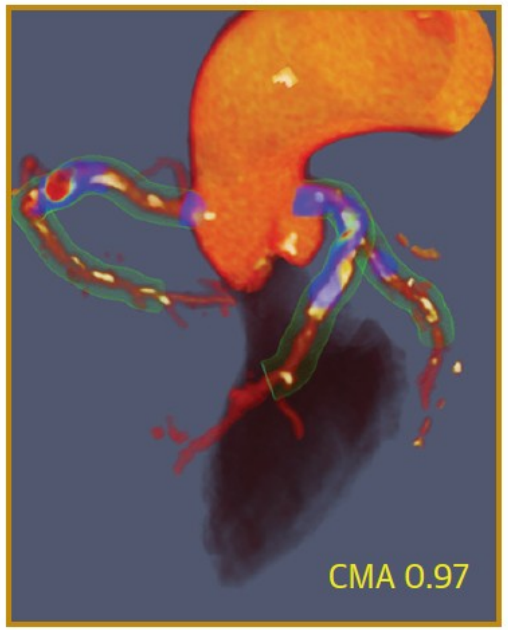
Elevated lipoprotein(a) is associated with accelerated progression of low-attenuation plaque, independent of traditional cardiovascular risk factors

Kaiser et al. J Am Coll Cardiol 2022; 79:223-233.

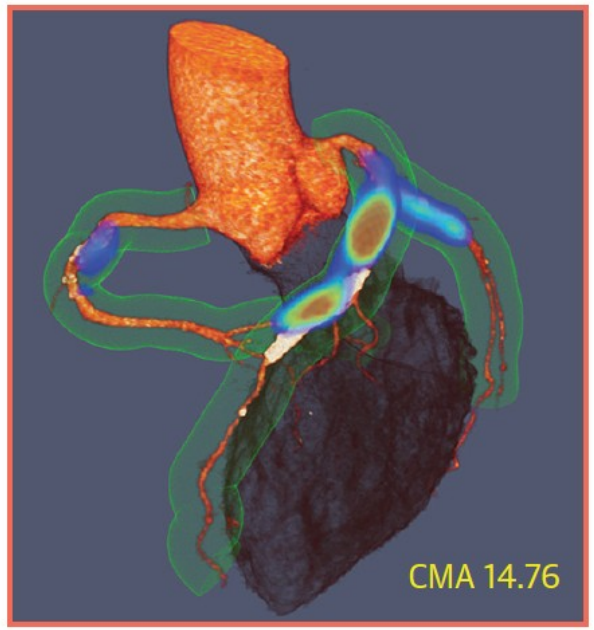
^{18}F-Sodium fluoride PET predicts fatal or non-fatal myocardial infarction
(independent of calcium score, coronary artery lumen stenosis,
risk scores & comorbidities)



No Activity
(CMA = 0)
No myocardial infarction on follow up
Continue medical therapy
n = 90



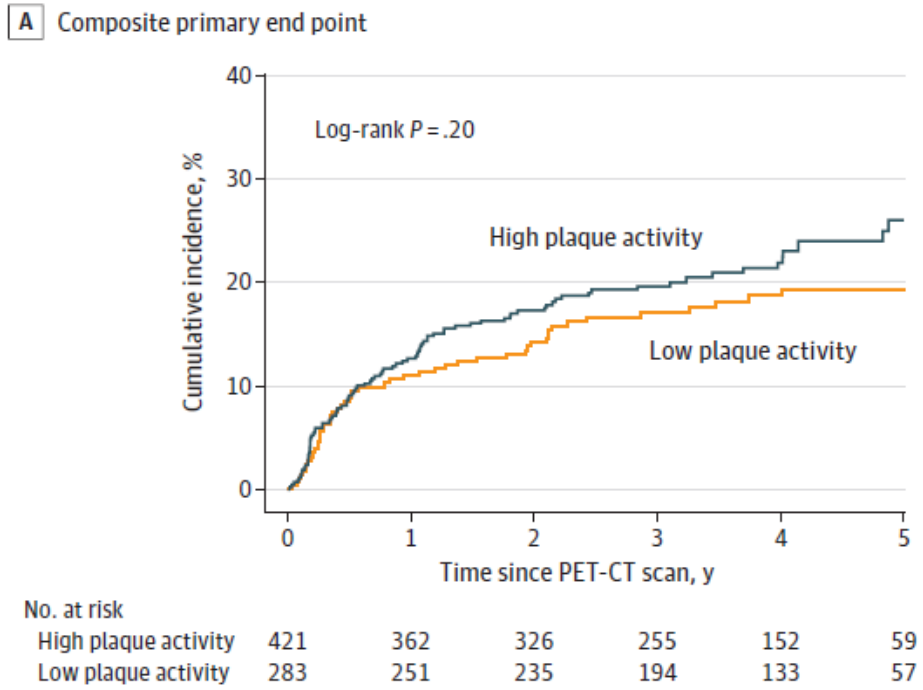
Low Activity
(CMA 0.01 to 1.56)
Intermediate risk
Close Observation
n = 94

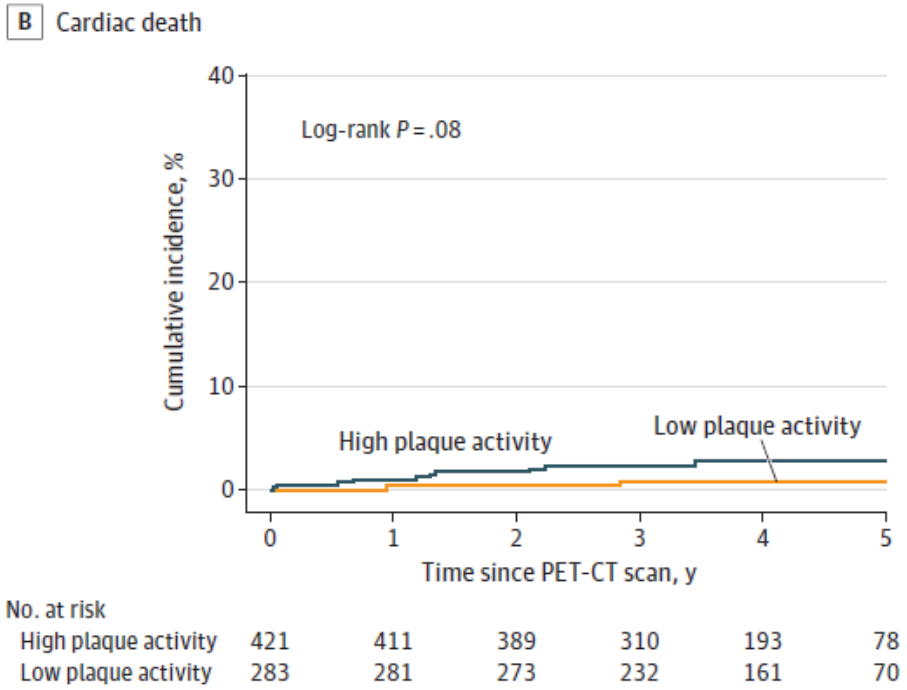


High Activity
(CMA >1.56)
7-fold risk of future myocardial infarction
Intensify Therapy
n = 109

Kwiecinski et al. J Am Coll Cardiol 2020; 75: 3061-74.

PREFFIR trial (Coronary ^{18}F-sodium fluoride PET and CCTA)





Moss et al.JAMA Cardiol 2023; 8: 755-64

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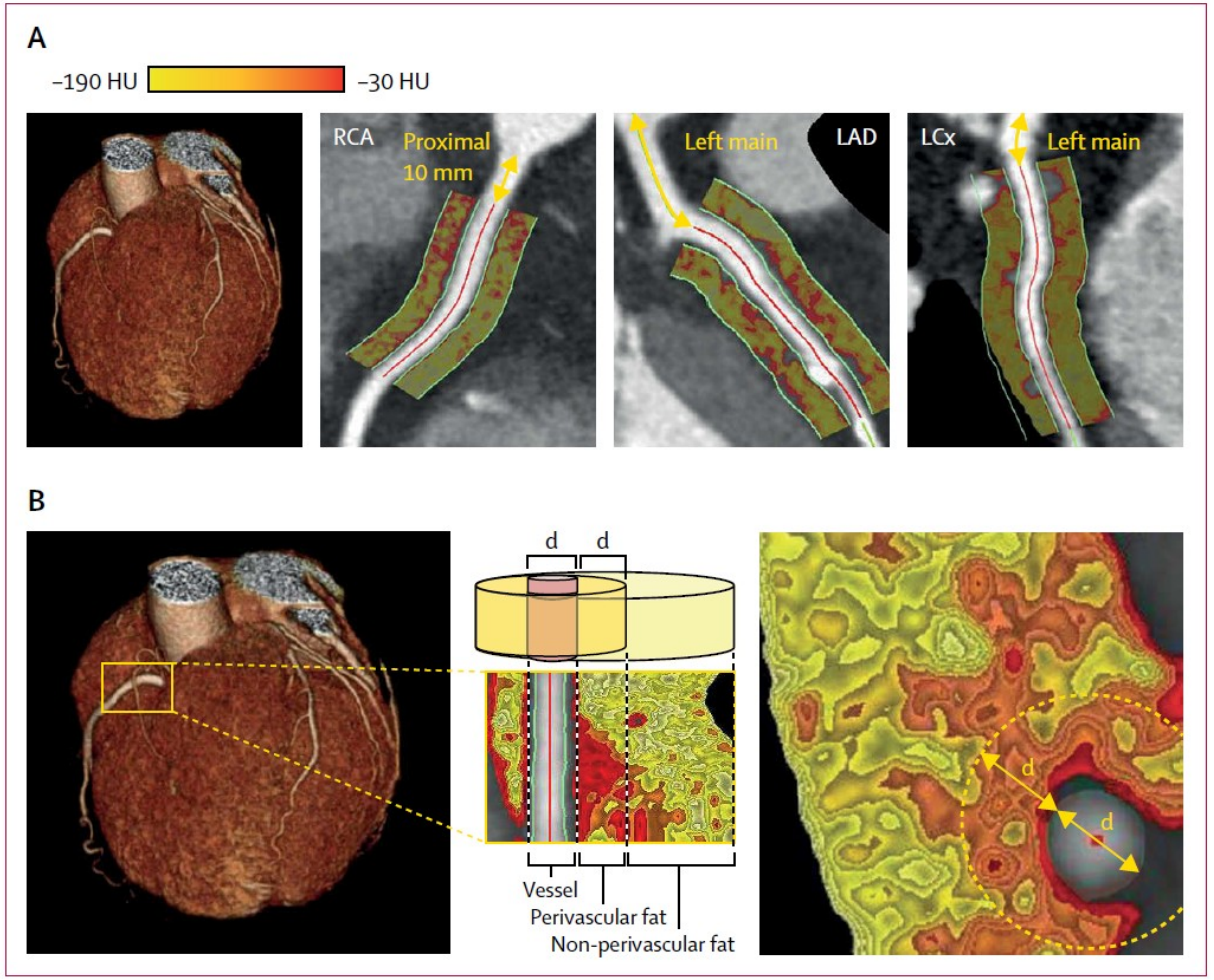
Pericoronary adipose tissue (PCAT) density



Oikonomou et al. Lancet 2018; 392: 929-939.

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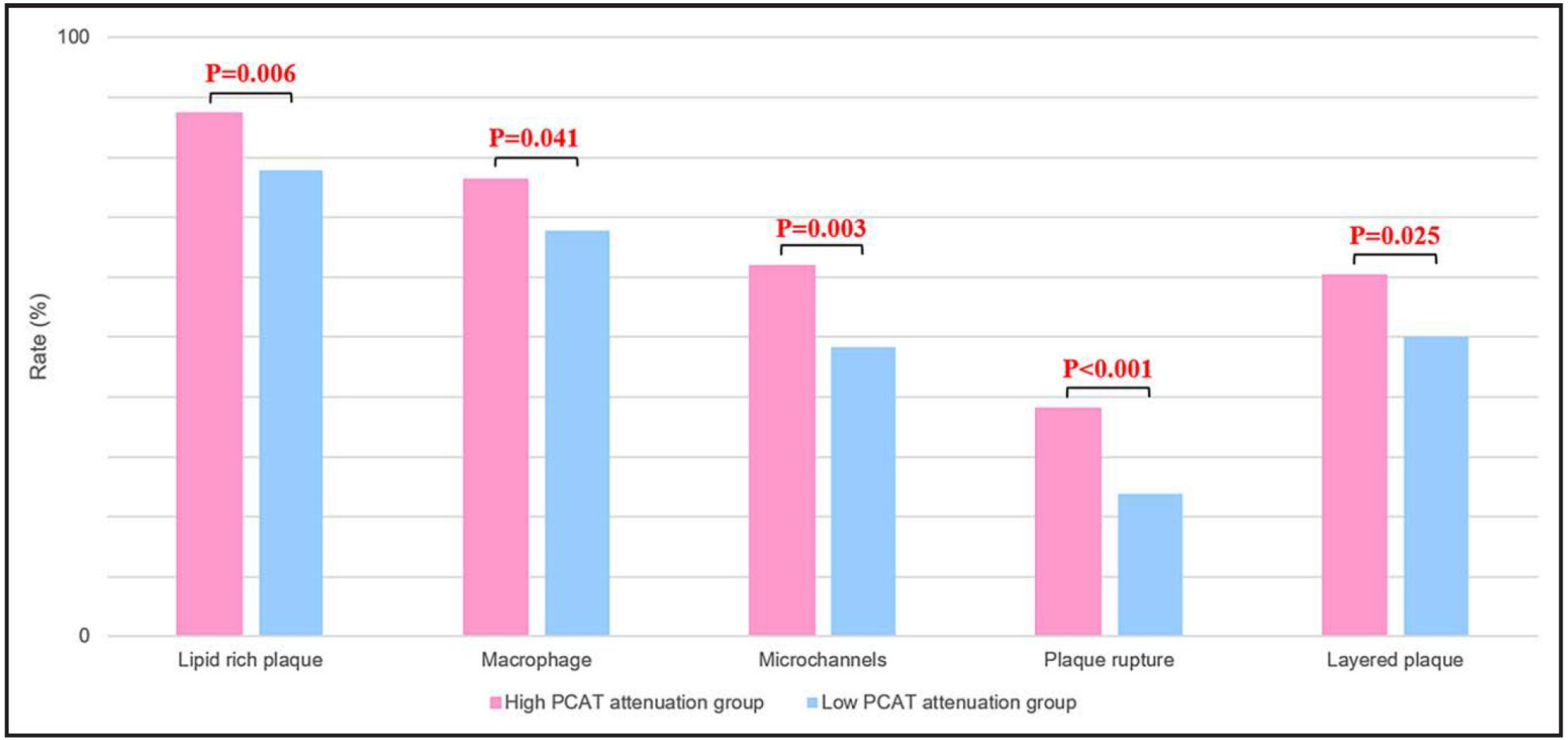

Figure 2. Prevalence of optical coherence tomography (OCT) features of plaque vulnerability in high versus low peri-coronary adipose tissue (PCAT) attenuation at the culprit vessel level.

Lipid-rich plaque, macrophage, microchannels, plaque rupture, and layered plaque were more frequently observed in the high PCAT attenuation group than in the low group.

Yuki et al. Circ Cardiovasc Imaging 2023; 16e014959

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Conclusie

- Karakterisatie van de ***impact van lipidenverlagende therapie*** op coronaire atherosclerose.
- ***Plaque regressie en plaque stabilisatie*** met toenemende intensiteit van lipidenverlagende therapie.
- Rationale voor de impact van een combinatie van statines en PCSK9 inhibitoren op cardiovasculaire events. Belang van het bereiken van ***zeer lage LDL-C waarden*** bij patiënten met hoog cardiovasculaire risico.
- Plaque stabiliserende effecten van PCSK9 inhibitoren kunnen op ***korte termijn*** waargenomen worden
- Niet-invasieve beeldvorming: ***low attenuation plaque (LAP)*** burden en plaque activiteit