The Next Chapter of Vulnerable Plaque Diagnosis and Treatment

Gary S Mintz, MD

Cardiovascular Research Foundation

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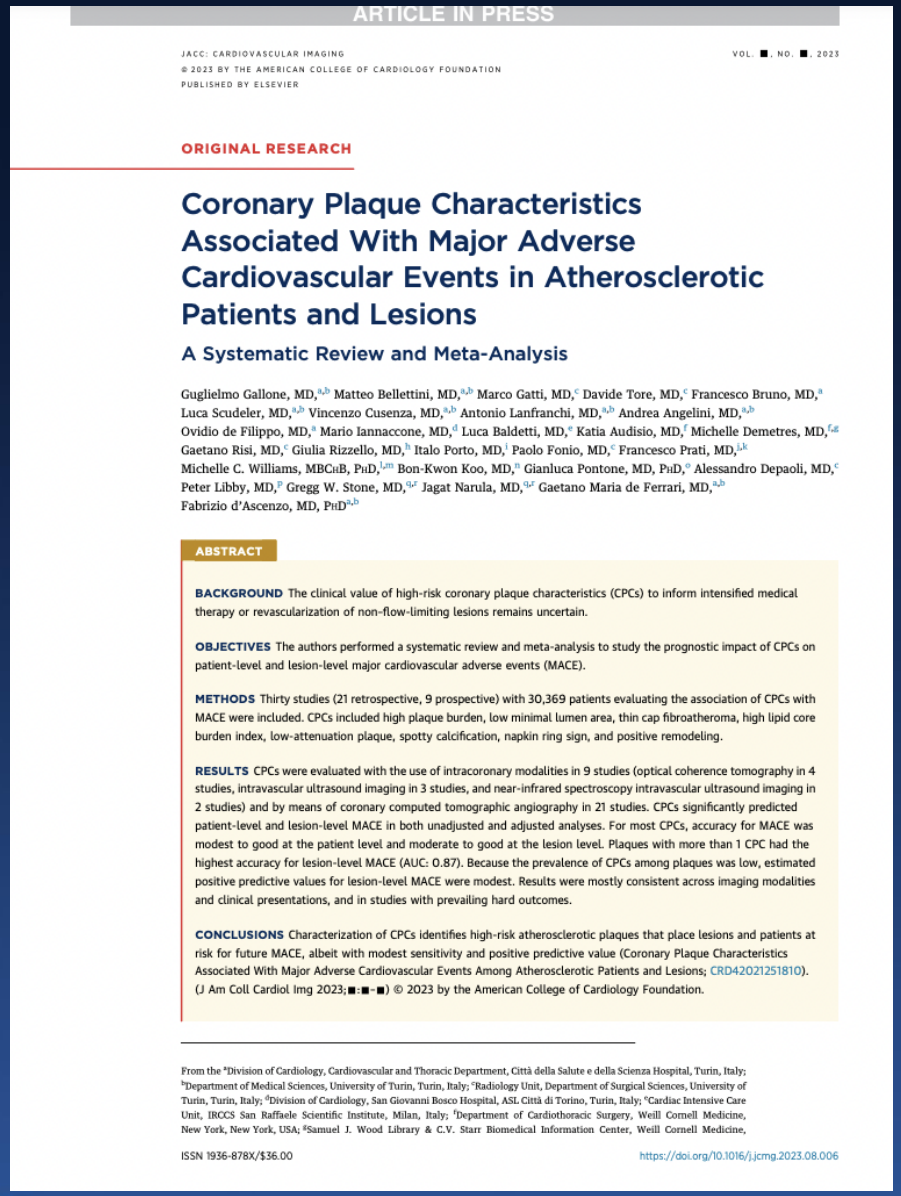
- **What are the best criteria and the best ways to diagnose vulnerable plaque?**
- What are the events and event rates associated with vulnerable plaque? What events are prevented by treating vulnerable plaque with PCI?
- What is optimal medical therapy – guideline directed or otherwise? And what % of patients in the OMT group in PREVENT actually took optimal medical therapy?
- What is optimal PCI in 2024?
- What clinical pathways make sense? Who should undergo IVI to assess and treat vulnerable plaque?



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JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2023
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ORIGINAL RESEARCH

Coronary Plaque Characteristics Associated With Major Adverse Cardiovascular Events in Atherosclerotic Patients and Lesions

A Systematic Review and Meta-Analysis

Guglielmo Gallone, MD,[a,b] Matteo Bellettini, MD,[a,b] Marco Gatti, MD,[c] Davide Tore, MD,[c] Francesco Bruno, MD,[a] Luca Scudeler, MD,[a,b] Vincenzo Cusenza, MD,[a,b] Antonio Lanfranchi, MD,[a,b] Andrea Angelini, MD,[a,b] Ovidio de Filippo, MD,[a] Mario Iannaccone, MD,[d] Luca Baldetti, MD,[e] Katia Audisio, MD,[f] Michelle Demetres, MD,[f,g] Gaetano Risi, MD,[c] Giulia Rizzello, MD,[h] Italo Porto, MD,[i] Paolo Fonio, MD,[c] Francesco Prati, MD,[j,k] Michelle C. Williams, MBChB, PhD,[l,m] Bon-Kwon Koo, MD,[n] Gianluca Pontone, MD, PhD,[o] Alessandro Depaoli, MD,[c] Peter Libby, MD,[p] Gregg W. Stone, MD,[q,r] Jagat Narula, MD,[q,r] Gaetano Maria de Ferrari, MD,[a,b] Fabrizio d'Ascenzo, MD, PhD[a,b]

ABSTRACT

BACKGROUND The clinical value of high-risk coronary plaque characteristics (CPCs) to inform intensified medical therapy or revascularization of non-flow-limiting lesions remains uncertain.

OBJECTIVES The authors performed a systematic review and meta-analysis to study the prognostic impact of CPCs on patient-level and lesion-level major cardiovascular adverse events (MACE).

METHODS Thirty studies (21 retrospective, 9 prospective) with 30,369 patients evaluating the association of CPCs with MACE were included. CPCs included high plaque burden, low minimal lumen area, thin cap fibroatheroma, high lipid core burden index, low-attenuation plaque, spotty calcification, napkin ring sign, and positive remodeling.

RESULTS CPCs were evaluated with the use of intracoronary modalities in 9 studies (optical coherence tomography in 4 studies, intravascular ultrasound imaging in 3 studies, and near-infrared spectroscopy intravascular ultrasound imaging in 2 studies) and by means of coronary computed tomographic angiography in 21 studies. CPCs significantly predicted patient-level and lesion-level MACE in both unadjusted and adjusted analyses. For most CPCs, accuracy for MACE was modest to good at the patient level and moderate to good at the lesion level. Plaques with more than 1 CPC had the highest accuracy for lesion-level MACE (AUC: 0.87). Because the prevalence of CPCs among plaques was low, estimated positive predictive values for lesion-level MACE were modest. Results were mostly consistent across imaging modalities and clinical presentations, and in studies with prevailing hard outcomes.

CONCLUSIONS Characterization of CPCs identifies high-risk atherosclerotic plaques that place lesions and patients at risk for future MACE, albeit with modest sensitivity and positive predictive value (Coronary Plaque Characteristics Associated With Major Adverse Cardiovascular Events Among Atherosclerotic Patients and Lesions; CRD42021251810). (J Am Coll Cardiol Img 2023;■:■-■) © 2023 by the American College of Cardiology Foundation.

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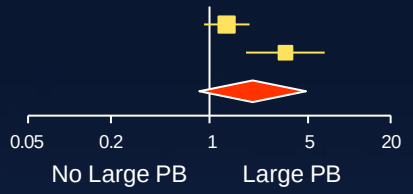
ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2023.08.006

IVI Predictors of patient-level events

Large Plaque Burden

	Log [Hazard Ratio]	SE	Weight	Hazard Ratio [95% CI]
Schuurman, 2018	0.2852	0.188	53.9%	1.33 [0.92, 1.92]
Erlinge, 2021	1.2499	0.3294	46.1%	3.49 [1.83, 6.66]
Total (95% CI)			100.0%	2.07 [0.81, 5.32]

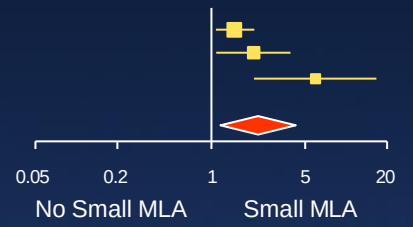
Heterogeneity: $Tau^2 = 0.39$; $Chi^2 = 6.47$, df = 1 ($P = 0.01$); $I^2 = 85\%$
Test for overall effect: Z = 1.52 ($P = 0.13$)



Small Minimal Lumen Area

	Log [Hazard Ratio]	SE	Weight	Hazard Ratio [95% CI}
Schuurman, 2018	0.3988	0.1689	44.1%	1.49 [1.07, 2.07]
Prati, 2019	0.7275	0.3226	33.9%	2.07 [1.10, 3.90]
Erlinge, 2021	1.7918	0.5308	22.0%	6.00 [2.12, 16.98]
Total (95% CI)			100.0%	2.26 [1.18, 4.34]

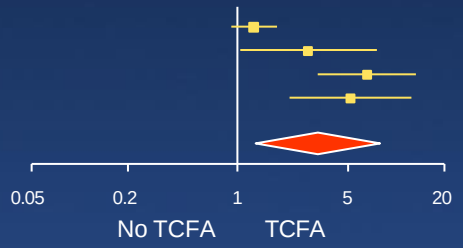
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 6.56$, df = 2 ($P = 0.04$); $I^2 = 70\%$
Test for overall effect: Z = 2.45 ($P = 0.01$)



Thin Cap Fibroatheroma (VH-IVUS/OCT)

	Log [Hazard Ratio]	SE	Weight	Hazard Ratio [95% CI}
Schuurman, 2018	0.239	0.1701	28.7%	1.27 [0.91, 1.77]
Vergallo, 2019	1.0296	0.5053	22.3%	2.80 [1.04, 7.54]
Prati, 2019	1.8764	0.3639	25.4%	6.53 [3.20, 13.32]
Kedhi, 2021	1.6332	0.4499	23.6%	5.12 [2.12, 12.37]
Total (95% CI)			100.0%	3.19 [1.25, 8.11]

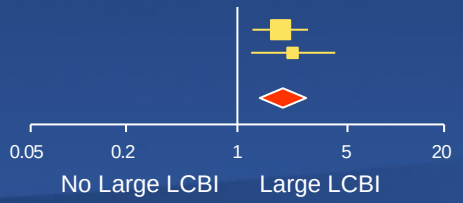
Heterogeneity: $Tau^2 = 0.76$; $Chi^2 = 22.50$, df = 3 ($P < 0.0001$); $I^2 = 87\%$
Test for overall effect: Z = 2.44 ($P = 0.01$)



Large Lipid Core Burden Index

	Log [Hazard Ratio]	SE	Weight	Hazard Ratio [95% CI}
Waksman, 2019	0.6366	0.2069	68.4%	1.89 [1.26, 2.84]
Erlinge, 2021	0.8198	0.3044	31.6%	2.27 [1.25, 4.12]
Total (95% CI)			100.0%	2.00 [1.43, 2.80]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.25$, df = 1 ($P = 0.62$); $I^2 = 0\%$
Test for overall effect: Z = 4.06 ($P < 0.0001$)



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Gallone et al. JACC Cardiovasc Imaging. 2023:S1936-878X(23)00389-3. doi: 10.1016/j.jcmg.2023.08.006

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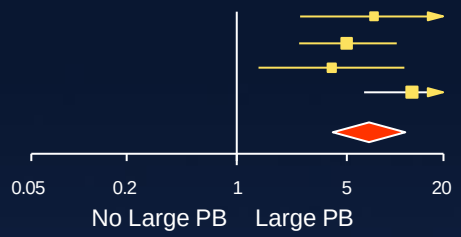
ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2023.08.006

IVI Predictors of lesion-level events

Large Plaque Burden

	Log [Hazard Ratio]	SE	Weight	Hazard Ratio [95% CI]
Calvert, 2011	2.0122	0.5592	18.0%	7.48 [2.50, 22.38]
Stone, 2011	1.6154	0.3547	31.9%	5.03 [2.51, 10.08]
Waksman, 2019	1.3838	0.5417	18.9%	3.99 [1.38, 11.54]
Erlinge, 2021	2.5603	0.3624	31.2%	12.94 [6.36, 26.33]
Total (95% CI)			100.0%	6.95 [4.03, 11.98]

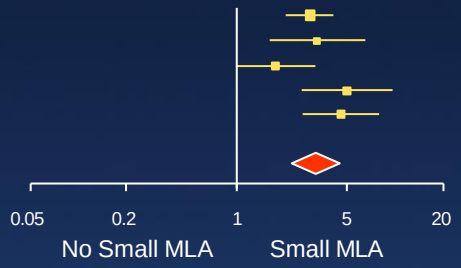
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 4.83$, df = 3 ($P = 0.18$); $I^2 = 38\%$
Test for overall effect: $Z = 6.97$ ($P < 0.00001$)



Small Minimal Lumen Area

	Log [Hazard Ratio]	SE	Weight	Hazard Ratio [95% CI]
Calvert, 2011	1.0682	0.1738	29.5%	2.91 [2.07, 4.09]
Stone, 2011	1.1663	0.3521	15.1%	3.21 [1.61, 6.40]
Waksman, 2019	0.5822	0.287	19.3%	1.79 [1.02, 3.14]
Erlinge, 2021	1.6034	0.3325	16.3%	4.97 [2.59, 9.54]
Kubo, 2021	1.5173	0.2808	19.8%	4.56 [2.63, 7.91]
Total (95% CI)			100.0%	3.21 [2.30, 4.48]

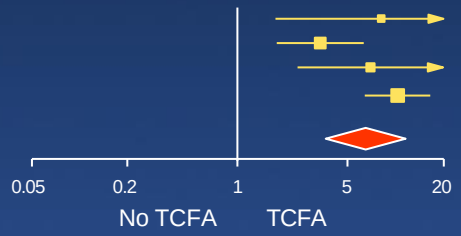
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 7.70$, df = 4 ($P = 0.10$); $I^2 = 48\%$
Test for overall effect: $Z = 6.84$ ($P < 0.00001$)



Thin Cap Fibroatheroma (VH-IVUS/OCT)

	Log [Hazard Ratio]	SE	Weight	Hazard Ratio [95% CI]
Calvert, 2011	2.0992	0.7769	13.0%	8.16 [1.78, 37.41]
Stone, 2011	1.209	0.3255	30.9%	3.35 [1.77, 6.34]
Kedhi, 2021	1.9459	0.5398	20.4%	7.00 [2.43, 20.16]
Kubo, 2021	2.3428	0.2419	35.6%	10.41 [6.48, 16.73]
Total (95% CI)			100.0%	6.55 [3.40, 12.60]

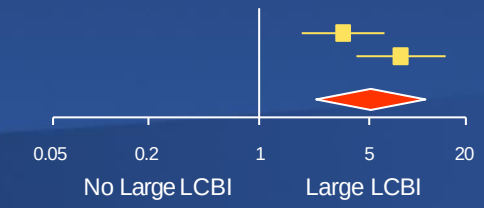
Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 7.86$, df = 3 ($P = 0.05$); $I^2 = 62\%$
Test for overall effect: $Z = 5.63$ ($P < 0.00001$)



Large Lipid Core Burden Index

Study or Subgroup	Log [Hazard Ratio]	SE	Weight	Hazard Ratio [95% CI]
Waksman, 2019	1.2208	0.309	50.8%	3.39 [1.85, 6.21]
Erlinge, 2021	2.058	0.3276	49.2%	7.83 [4.12, 14.88]
Total (95% CI)			100.0%	5.12 [2.25, 11.62]

Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 3.46$, df = 1 ($P = 0.06$); $I^2 = 71\%$
Test for overall effect: $Z = 3.90$ ($P < 0.0001$)



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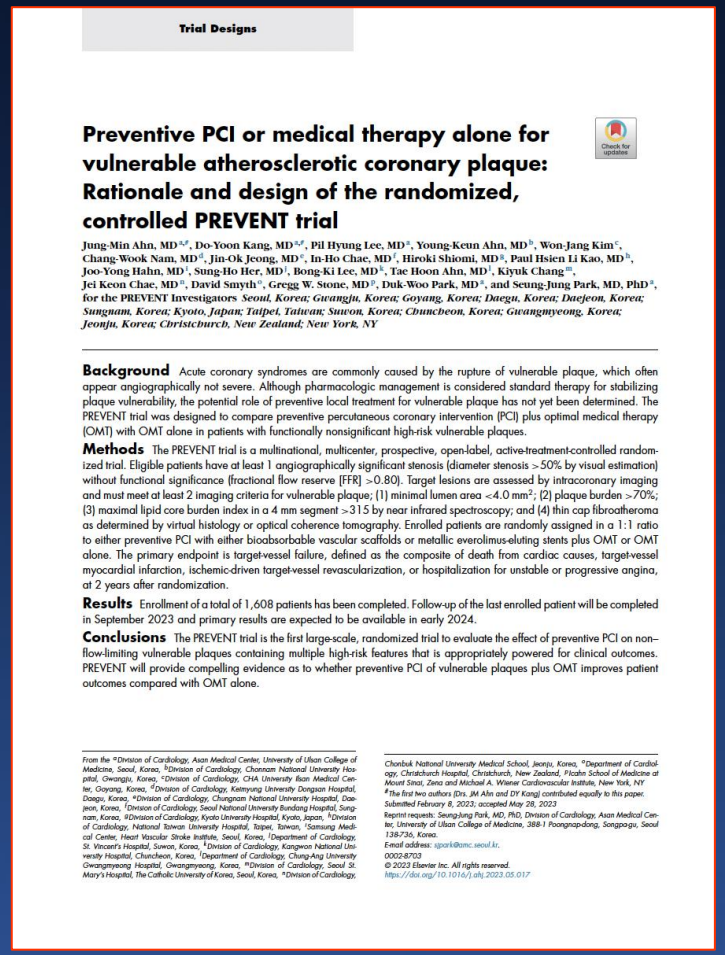
PREVENT



Trial Designs

Preventive PCI or medical therapy alone for vulnerable atherosclerotic coronary plaque: Rationale and design of the randomized, controlled PREVENT trial

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Background Acute coronary syndromes are commonly caused by the rupture of vulnerable plaque, which often appear angiographically not severe. Although pharmacologic management is considered standard therapy for stabilizing plaque vulnerability, the potential role of preventive local treatment for vulnerable plaque has not yet been determined. The PREVENT trial was designed to compare preventive percutaneous coronary intervention (PCI) plus optimal medical therapy (OMT) with OMT alone in patients with functionally nonsignificant high-risk vulnerable plaques.

Methods The PREVENT trial is a multinational, multicenter, prospective, open-label, active-treatment-controlled randomized trial. Eligible patients have at least 1 angiographically significant stenosis (diameter stenosis >50% by visual estimation) without functional significance (fractional flow reserve [FFR] >0.80). Target lesions are assessed by intracoronary imaging and must meet at least 2 imaging criteria for vulnerable plaque; (1) minimal lumen area <4.0 mm^2; (2) plaque burden >70%; (3) maximal lipid core burden index in a 4 mm segment >315 by near infrared spectroscopy; and (4) thin cap fibroatheroma as determined by virtual histology or optical coherence tomography. Enrolled patients are randomly assigned in a 1:1 ratio to either preventive PCI with either bioabsorbable vascular scaffolds or metallic everolimus-eluting stents plus OMT or OMT alone. The primary endpoint is target-vessel failure, defined as the composite of death from cardiac causes, target-vessel myocardial infarction, ischemic-driven target-vessel revascularization, or hospitalization for unstable or progressive angina, at 2 years after randomization.

Results Enrollment of a total of 1,608 patients has been completed. Follow-up of the last enrolled patient will be completed in September 2023 and primary results are expected to be available in early 2024.

Conclusions The PREVENT trial is the first large-scale, randomized trial to evaluate the effect of preventive PCI on non–flow-limiting vulnerable plaques containing multiple high-risk features that is appropriately powered for clinical outcomes. PREVENT will provide compelling evidence as to whether preventive PCI of vulnerable plaques plus OMT improves patient outcomes compared with OMT alone.

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[e]The first two authors (Drs. JM Ahn and DY Kang) contributed equally to this paper.

Submitted February 8, 2023; accepted May 28, 2023

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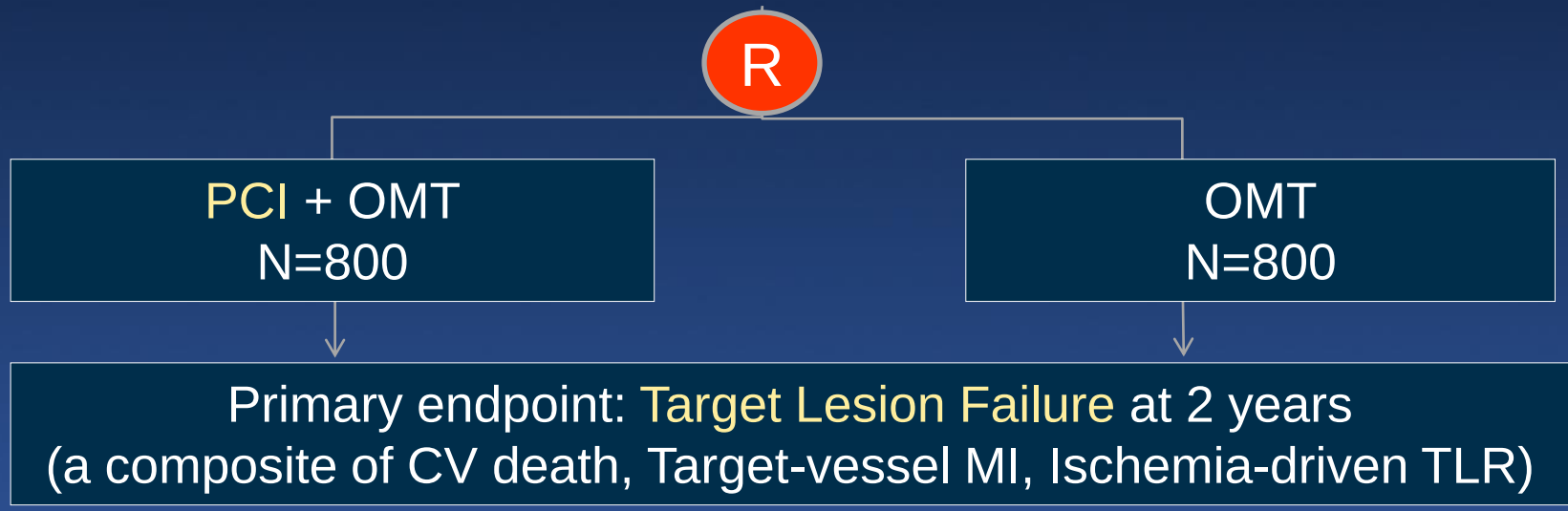
0002-8703

https://doi.org/10.1016/j.ahj.2023.05.017

Any Significant Epicardial Coronary Stenosis >50% with FFR >0.80 and with TWO of the following

1. IVUS MLA <4.0mm^2
2. IVUS Plaque Burden >70%
3. Lipid-Rich Plaque on NIRS ($_{max}LCBI_{4mm}$>315)
4. TCFA by OCT or VH-IVUS
   - OCT: fibrous cap thickness <65μm and arc >90°
   - VH-IVUS : ≥10% confluent NC with >30° abutting to the lumen in 3 consecutive slices



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Ahn et al. Am Heart J. 2023;264:83-96

IVI Tools used in PREVENT

	Preventive PCI (n=803)	OMT (n=803)
Greyscale IVUS only	306	261
VH-IVUS	506	635
NIRS-IVUS	333	346
OCT	67	20

Cardiac death, TV-MI, ischemia-driven TVR, or hospitalization for unstable or progressive angina

	Two Years			Maximum Follow-up		
	Preventive PCI	OMT	HR (95% CI)	Preventive PCI	OMT	HR (95% CI)
Greyscale IVUS only	**1.0%**	**2.4%**	**0.41 (0.10–1.66)**	**3.3%**	**5.4%**	**0.50 (0.22-1.12)**
VH-IVUS	**0%**	**2.9%**	**NC**	**3.0%**	**4.9%**	**0.55 (0.29-1.01)**
NIRS-IVUS	**0.3%**	**3.5%**	**0.09 (0.01–0.66)**	**4.5%**	**6.9%**	**0.63 (0.33-1.20)**
OCT	**1.5%**	**5.0%**	**0.30 (0.02–4.76)**	**7.5%**	**15.0%**	**0.41 (0.10-1.71)**

Park et al. Lancet 2024, in press

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OCT	**1.5%**	**5.0%**	**0.30 (0.02–4.76)**	**7.5%**	**15.0%**	**0.41 (0.10-1.71)**

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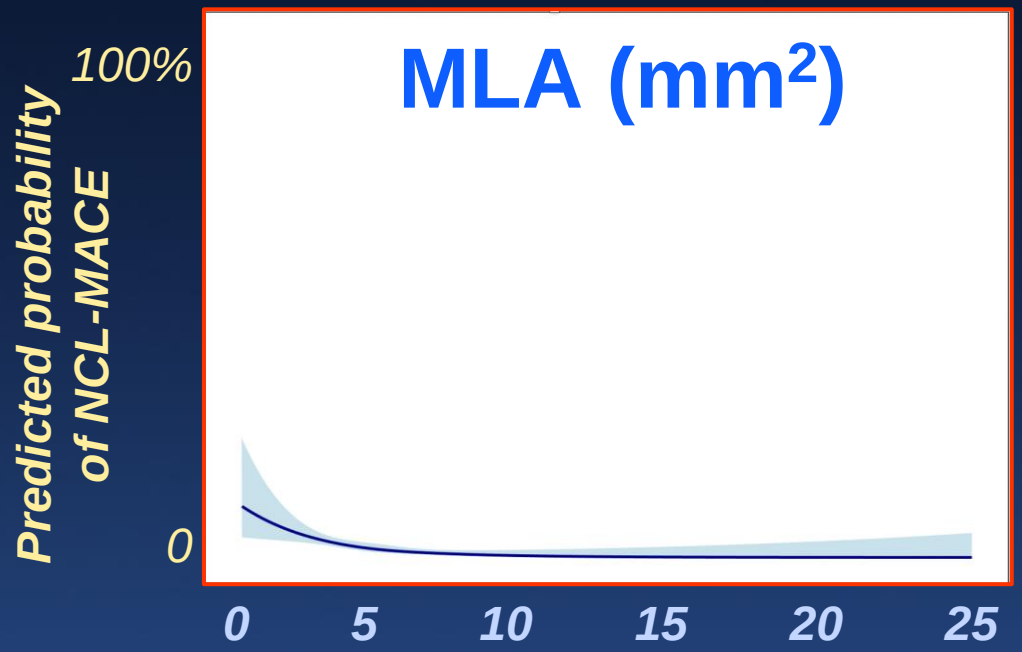
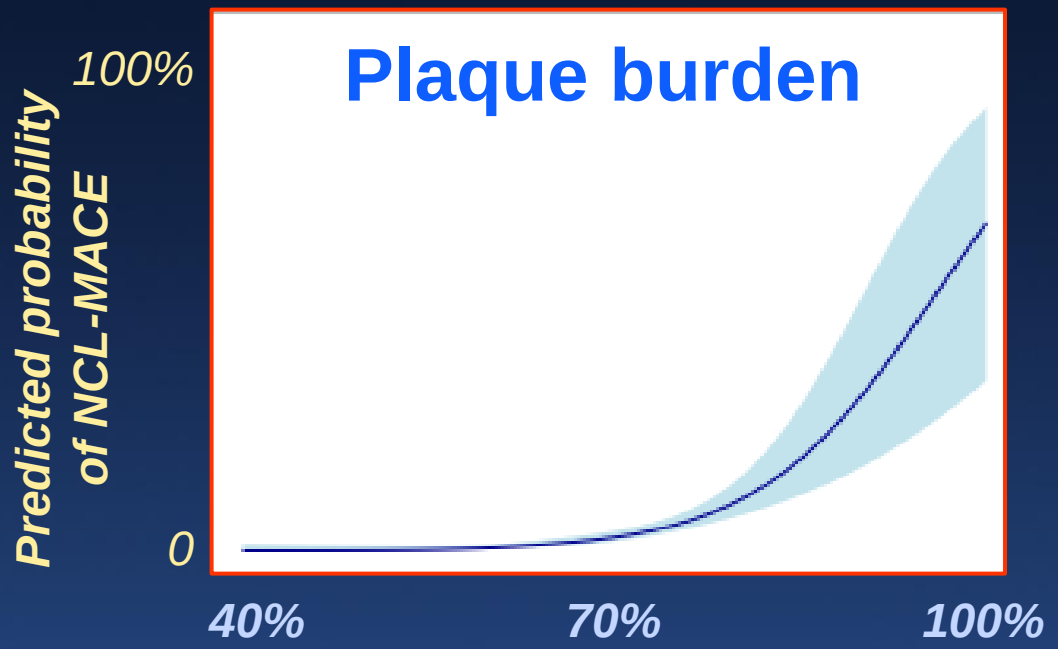
Park et al. Lancet 2024, in press

PROSPECT II: Spline & ROC analyses of continuous relationship between lesion-level plaque burden and MLA vs probability of 4 yr NCL-MACE



AUC (95% CI)	0.72 (0.65, 0.78)
Optimal cutoff (95% CI)	**4.25mm² (3.15, 5.22)**
Sensitivity	0.80
Specificity	0.59
Accuracy	0.59



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

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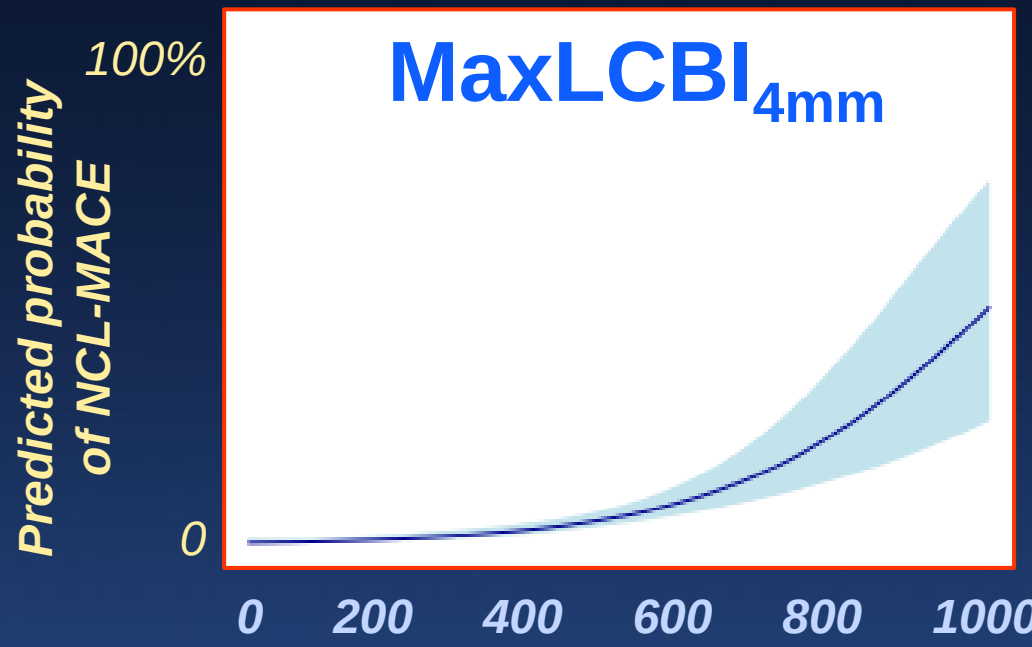
Erlinge et al. Lancet. 2021;397:985-95

PROSPECT II: Spline & ROC analyses of continuous relationship between lesion-level $MaxLCBI_{4mm}$ vs probability of 4 yr NCL-MACE



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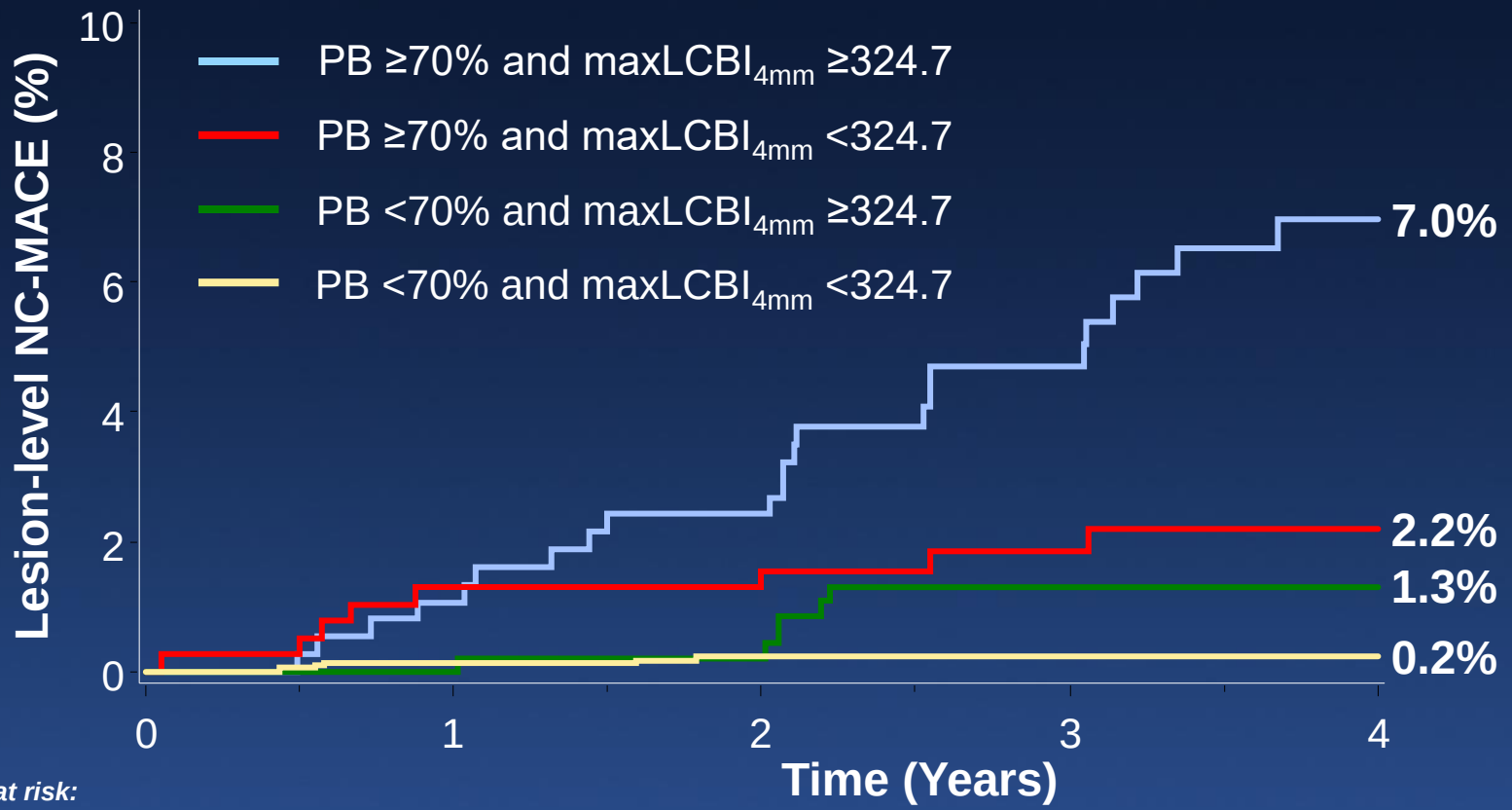
Erlinge et al. Lancet. 2021;397:985-95

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

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2021) 22, 824–834
doi:10.1093/ehjci/jez318

In vivo relationship between near-infrared spectroscopy-detected lipid-rich plaques and morphological plaque characteristics by optical coherence tomography and intravascular ultrasound: a multimodality intravascular imaging study

Christian Zanchin [1], Yasushi Ueki[1], Sylvain Losdat[2], Gregor Fahrni[3], Joost Daemen [4], Anna S. Ondracek[5], Jonas D. Häner[1], Stefan Stortecky[1], Tatsuhiko Otsuka[1], George C.M. Siontis[1], Fabio Rigamonti[6], Maria Radu [7], David Spirk[8], Christoph Kaiser[3], Thomas Engstrom[7], Irene Lang[5], Konstantinos C. Koskinas[1], and Lorenz Räber[1]*

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Received 28 October 2019; editorial decision 16 December 2019; accepted 9 January 2020; online publish-ahead-of-print 28 January 2020

Aims We assessed morphological features of near-infrared spectroscopy (NIRS)-detected lipid-rich plaques (LRPs) by using optical coherence tomography (OCT) and intravascular ultrasound (IVUS).

Methods and results IVUS-NIRS and OCT were performed in the two non-infarct-related arteries (non-IRAs) in patients undergoing percutaneous coronary intervention for treatment of an acute coronary syndrome. A lesion was defined as the 4 mm segment with the maximum amount of lipid core burden index ($maxLCBI_{4mm}$) of each LRP detected by NIRS. We divided the lesions into three groups based on the $maxLCBI_{4mm}$ value: <250, 250–399, and ≥400. OCT analysis and IVUS analysis were performed blinded for NIRS. We measured fibrous cap thickness (FCT) by using a semi-automated method. A total of 104 patients underwent multimodality imaging of 209 non-IRAs. NIRS detected 299 LRPs. Of those, 41% showed a $maxLCBI_{4mm}$ <250, 39% a $maxLCBI_{4mm}$ 251–399, and 19% a $maxLCBI_{4mm}$ ≥400. LRPs with a $maxLCBI_{4mm}$ ≥400, as compared with LRPs with a $maxLCBI_{4mm}$ 250–399 and <250, were more frequently thin-cap fibroatheroma (TCFA) (42.1% vs. 5.1% and 0.8%; $P < 0.001$) with a smaller minimum FCT (80 µm vs. 110 µm and 120 µm; $P < 0.001$); a higher IVUS-derived percent atheroma volume (53% vs. 53% and 44%; $P < 0.001$) and a higher remodelling index (1.08 vs. 1.02 and 1.01; $P < 0.001$). $MaxLCBI_{4mm}$ correlated with OCT-derived FCT ($r = 0.404$; $P < 0.001$) and was the best predictor for TCFA with an optimal cut-off value of 401 (area under the curve = 0.882; $P < 0.001$).

Conclusion LRPs with increasing $maxLCBI_{4mm}$ exhibit OCT and IVUS features of presumed plaque vulnerability including TCFA morphology, increased plaque burden, and positive remodelling.

Keywords Coronary artery disease • Intravascular imaging • $maxLCBI_{4mm}$ • Plaque vulnerability • Lipid-rich plaque

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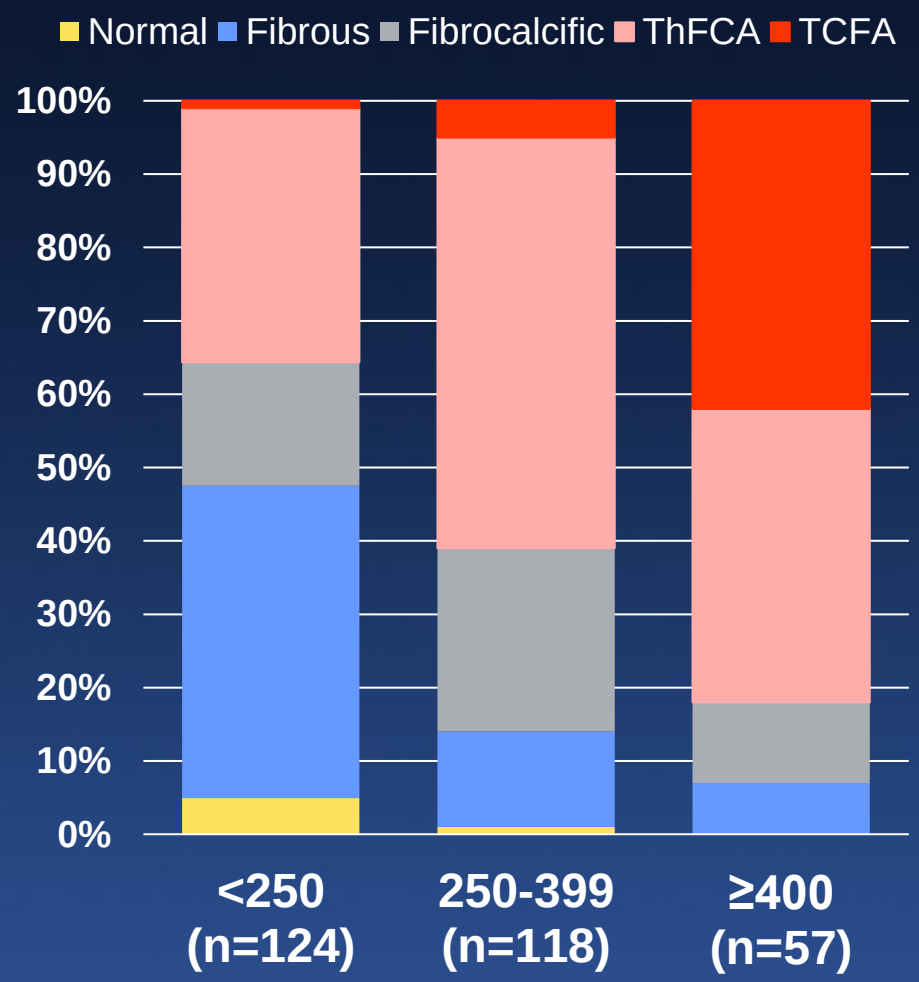
OCT Plaque Phenotype



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Zanchin et al. Eur Heart J Cardiovasc Imaging 2021;22:824-34

nature reviews cardiology

https://doi.org/10.1038/s41569-023-00900-3

Roadmap

Check for updates

Roadmap on the use of artificial intelligence for imaging of vulnerable atherosclerotic plaque in coronary arteries

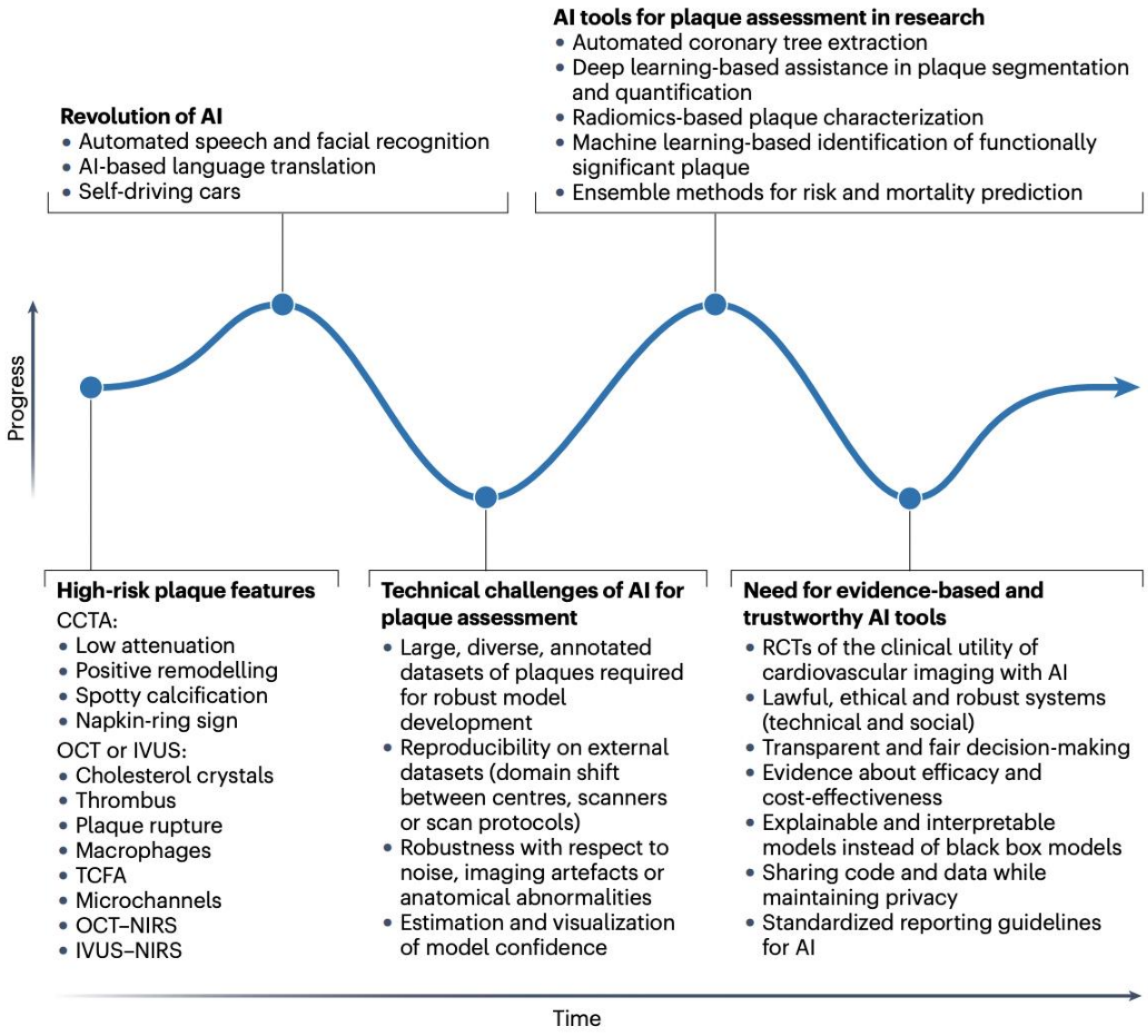
Bernhard Föllmer[1,21], Michelle C. Williams[2,21], Damini Dey[3], Armin Arbab-Zadeh[4], Pál Maurovich-Horvat[5], Rick H. J. A. Volleberg[6], Daniel Rueckert[7,8], Julia A. Schnabel[9,10,11], David E. Newby[2], Marc R. Dweck[2], Giulio Guagliumi[12], Volkmar Falk[13,14,15], Aldo J. Vázquez Mézquita[1], Federico Biavati[1], Ivana Išgum[16,17,18,22] & Marc Dewey[1,19,20,22]

Abstract

Artificial intelligence (AI) is likely to revolutionize the way medical images are analysed and has the potential to improve the identification and analysis of vulnerable or high-risk atherosclerotic plaques in coronary arteries, leading to advances in the treatment of coronary artery disease. However, coronary plaque analysis is challenging owing to cardiac and respiratory motion, as well as the small size of cardiovascular structures. Moreover, the analysis of coronary imaging data is time-consuming, can be performed only by clinicians with dedicated cardiovascular imaging training, and is subject to considerable interreader and intrareader variability. AI has the potential to improve the assessment of images of vulnerable plaque in coronary arteries, but requires robust development, testing and validation. Combining human expertise with AI might facilitate the reliable and valid interpretation of images obtained using CT, MRI, PET, intravascular ultrasonography and optical coherence tomography. In this Roadmap, we review existing evidence on the application of AI to the imaging of vulnerable plaque in coronary arteries and provide consensus recommendations developed by an interdisciplinary group of experts on AI and non-invasive and invasive coronary imaging. We also outline future requirements of AI technology to address bias, uncertainty, explainability and generalizability, which are all essential for the acceptance of AI and its clinical utility in handling the anticipated growing volume of coronary imaging procedures.

Sections

A full list of affiliations appears at the end of the paper. e-mail: bernhard.foellmer@charite.de; dewey@charite.de



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Föllmer et al. Nat Rev Cardiol. 2024;21:51-64

Artificial Intelligence and OCT Lesion Morphology

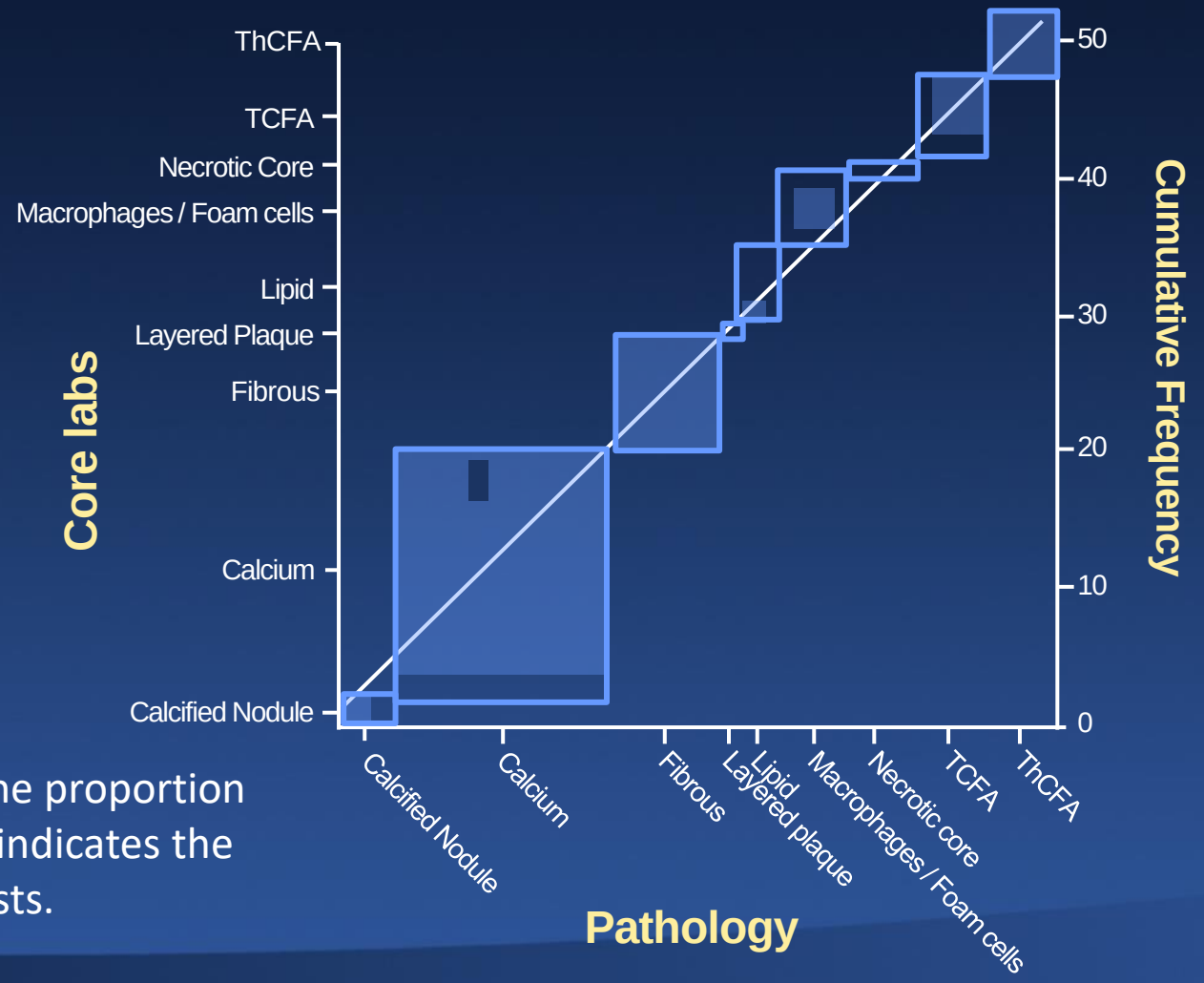
	# of samples	Tissue type	Ground truth	Findings
Shibutani. Atherosclerosis 2021; 328: 100-105	1103 slices in 45 autopsy	Fibroatheroma, PIT, fibrous, healed plaque	Pathology	AUC for fibroatheroma: 0.86 PCI: 0.85
Holmberg. Frontiers in CM 2021;8:779807	62slices in 7 autopsy, 222 slices 51 pts	TCFA, fibroatheroma, PIT, fibrous, calcium	Pathology & **Expert analysis**	Overall accuracy in clinical pts: 85.8%
Min. Eurointervention 2020;16:404-12	602 lesions in 602 pts	TCFA	**Expert analysis**	Accuracy for TCFA: 91.3%
Lee. Nature Research OPEN 2020;10:2596	6556 slices in 49 pts	Fibrolipidic, fibrocalcific	**Expert analysis**	Sensitivity/specificity for lipid:84.8%/97.8%
Chu. Eurointervention 2021;17:41-50	11673 slices in 509 pullbacks, 300 slices (ext)	Lipid pool, cholesterol crystal, macrophage fibrous, calcium	**Expert analysis**	Accuracy for lipid 90.5%
Niioka. Nature Research OPEN 2022;12:14067	44947 slices in 1791 pts	TCFA	**Expert analysis**	AI TCFA predicts clinical outcome

Accuracy of OCT Core Labs in Compared to Pathology

7 OCT Core Labs (Vengrenyuk/Kini, Akasaka, Garcia-Garcia, Jang, Räber, Maehara, Feldman) vs 2 Pathology Sites

Plaque Type	Median Kappa
Fibrous	0.93
Calcium	0.83
Thick-cap fibroatheroma	0.63
Calcified nodule	0.50
Macrophage/foam cells	0.39
Lipid pools	0.35
Necrotic core	0.22
Thin-cap fibroatheroma	0.22

Agreement of Core Labs vs Pathology



For each plaque component, the size of the box indicates the proportion of images assigned to the plaque type. The light blue area indicates the agreement between the panel and the pathologists.

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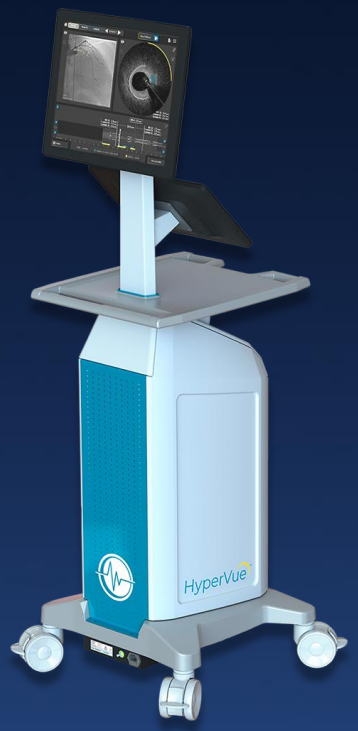
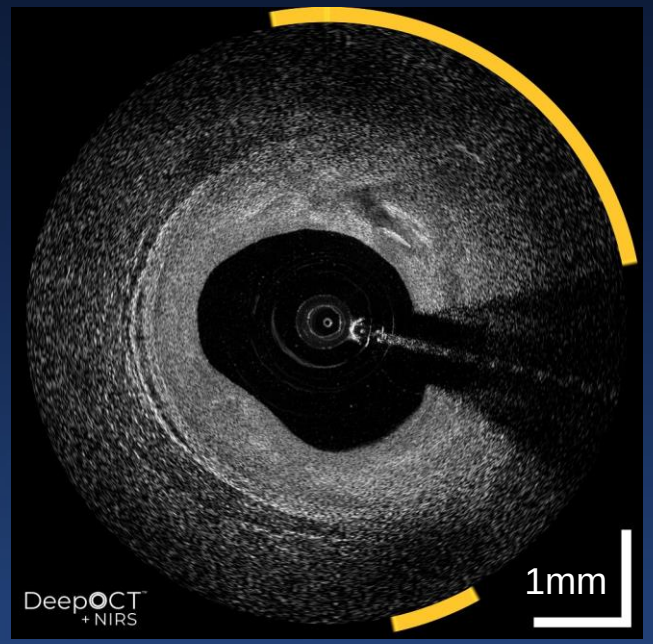
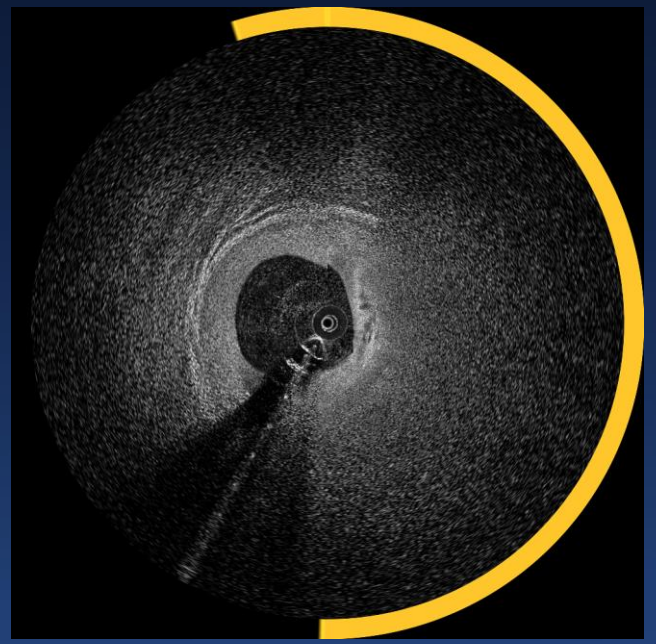
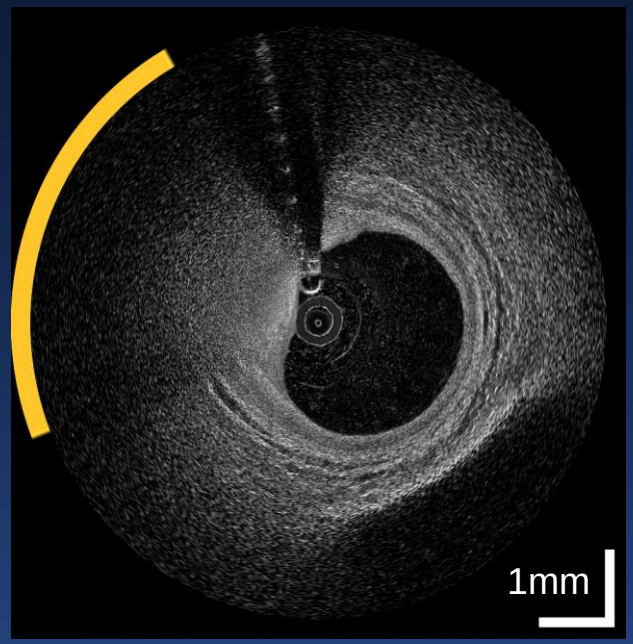
Gruslova et al. JACC Cardiovasc Imaging 2024;17:448-50

HyperVue™
Imaging System









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Research Foundation

EuroIntervention 2023;19:e318-e320 published online ahead of print April 2023 ■ published online e-edition July 2023

CORONARY INTERVENTIONS
RESEARCH CORRESPONDENCE

Clinical performance of a novel hybrid IVUS-OCT system: a multicentre, randomised, non-inferiority trial (PANOVISION)

Haibo Jia[1,2], MD, PhD; Chen Zhao[1,2], MD; Huai Yu[1,2], MD; Zhao Wang[3], PhD; Huimin Liu [1,2], MD, PhD; Maoen Xu[1,2], MD, PhD; Sining Hu[1,2], MD, PhD; Lulu Li[1,2], PhD; Luping He[1,2], MD; Ziqian Weng[1,2], MD; Yuhan Qin[1,2], MD; Yishuo Xu[1,2], MD; Ming Zeng[1,2], MD; Xi Su[4], MD, PhD; Bin Liu[5], MD, PhD; Jingbo Hou[1,2]*, MD, PhD; Bo Yu[1,2], MD, PhD

1. Department of Cardiology, The 2nd Affiliated Hospital of Hari
2. The Key Laboratory of Myocardial Ischemia, Chinese Ministry
of Electronic Science and Engineering, University of Electronic S
China; 4. Department of Cardiology, Wuhan Asia Heart Hospita
Cardiology, The Second Hospital of Jilin University, Changchun,

H. Jia and C. Zhao contributed equally to this study.

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have been established as important diagnostic and guidance tools for percutaneous coronary intervention (PCI) procedures[1]. Sequential use of the two modalities might overcome the inherent limitations of each technology; however, the potential risks of complications and cost are hard to ignore. Hybrid IVUS-OCT systems can overcome the limitations associated with each technology and integrate the advantages of both modalities. In 2018, a hybrid IVUS-OCT system for clinical application was reported for the first time[3]. Recently, a novel hybrid imaging system was approved for clinical use (PANOVISON; Panovision Co., Ltd), allowing synchronous acquisition of the two imaging modalities and an immediate, coregistered image review. We conducted this first-in-human study to test each modality of the hybrid imaging system, representing this novel device's first large-scale human application.

The study was a prospective, multicentre, randomised, open-label, self-controlled, non-inferiority trial. The protocol was approved by the institutional review boards and ethics committees in all participating centres. All patients provided written informed consent. Specific inclusion and exclusion criteria are described at ClinicalTrials.gov: NCT05596279. We used a web-based randomisation service (sealed envelope; Sealed Envelope Ltd) to randomly assign participants (1:1) to receive either control IVUS (IVUS arm) or control OCT (OCT arm) and all the participants underwent hybrid imaging before or after the control imaging. This

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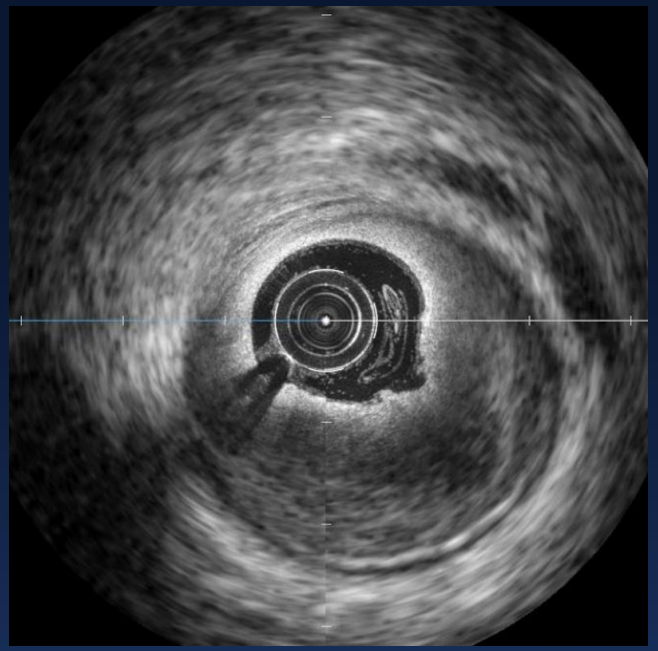
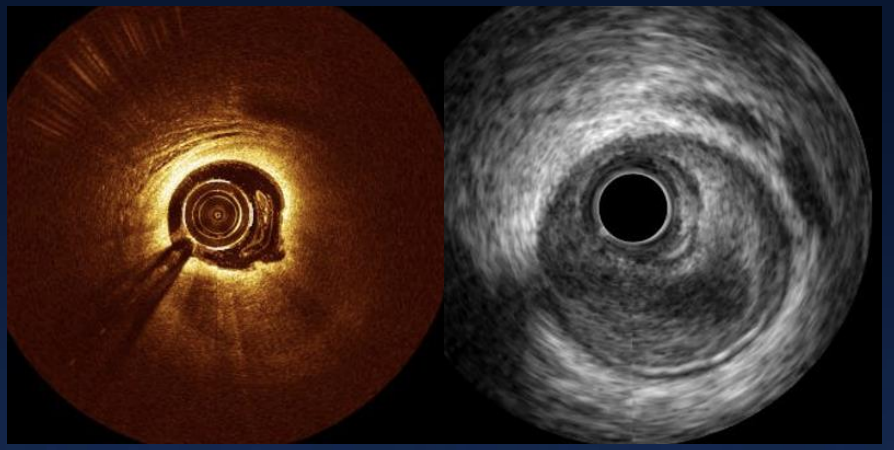
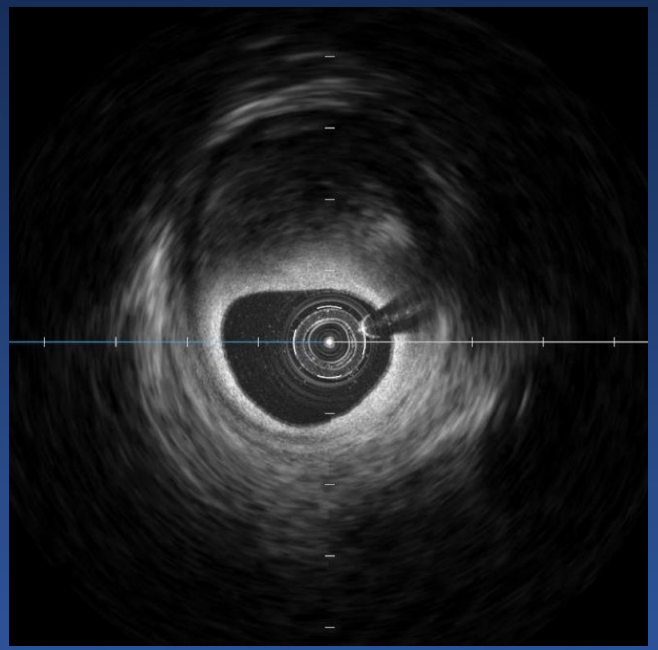
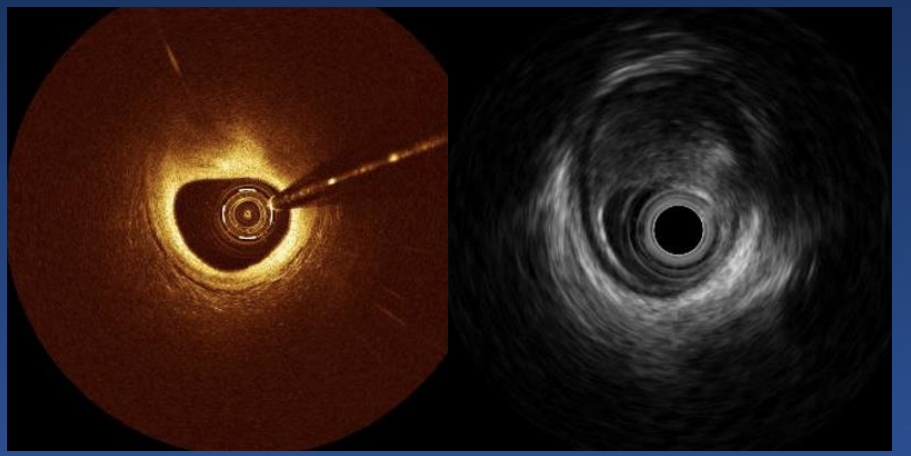
DOI: 10.4244/EIJ-D-22-01058









Jia et al. EuroIntervention 2023;19:e318-e320.

c/o Shaosong Zhang.

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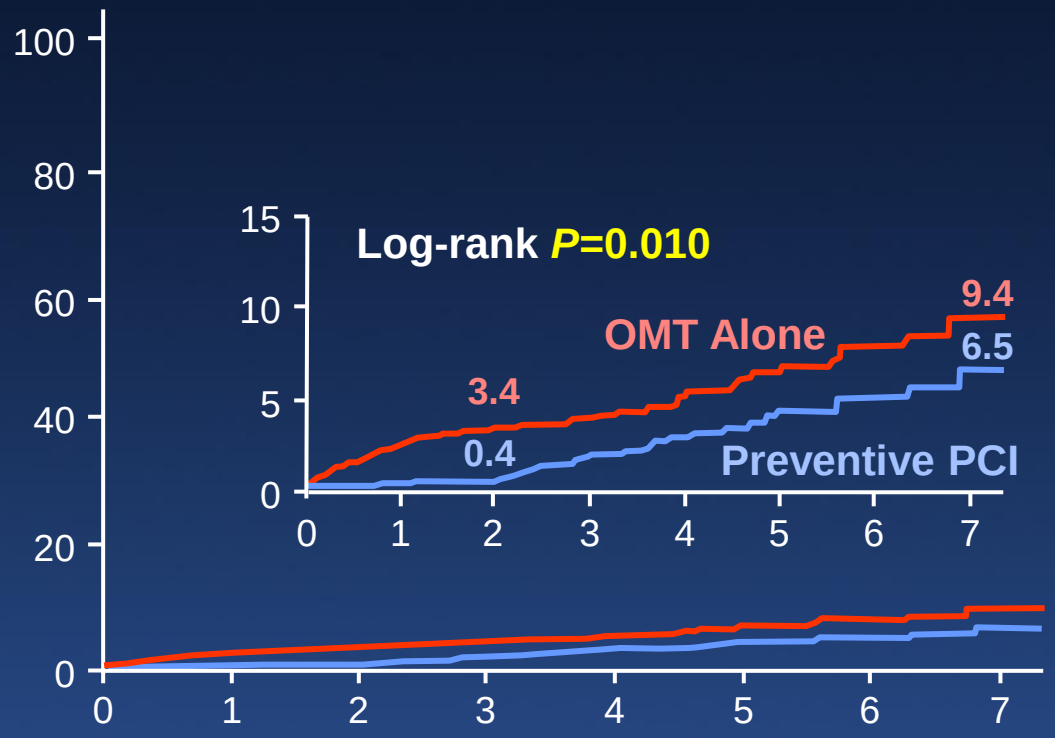
- What are the best criteria and the best ways to diagnose vulnerable plaque?
- **What are the events and event rates associated with vulnerable plaque? What events are prevented by treating vulnerable plaque with PCI?**
- What is optimal medical therapy – guideline directed or otherwise? And what % of patients in the OMT group in PREVENT actually took optimal medical therapy?
- What is optimal PCI in 2024?
- What clinical pathways make sense? Who should undergo IVI to assess and treat vulnerable plaque?

PREVENT: Cardiac death, TV-MI, ischemia-driven TVR, or hospitalization for unstable or progressive angina (%)



No. at Risk

OMT Alone	803	765	710	544	432	308	198	61
Preventive PCI	803	792	745	570	450	320	198	77

	Preventive PCI	OMT	Δ (95% CI)	HR (95% CI)
Cardiac death				
2 yrs	0.1%	0.8%	–0·6 (–1·3 to 0·02)	0·87 (0·31 to 2·39)
4 yrs	0.8%	0.9%	–0·1 (–1·1 to 0·9)	
TV-MI				
2 yrs	0.1%	0.8%	–0·6 (–1·3 to 0·02)	0·62 (0·20 to 1·90)
4 yrs	0.6%	1.0%	–0·3 (–1·6 to 1·6)	

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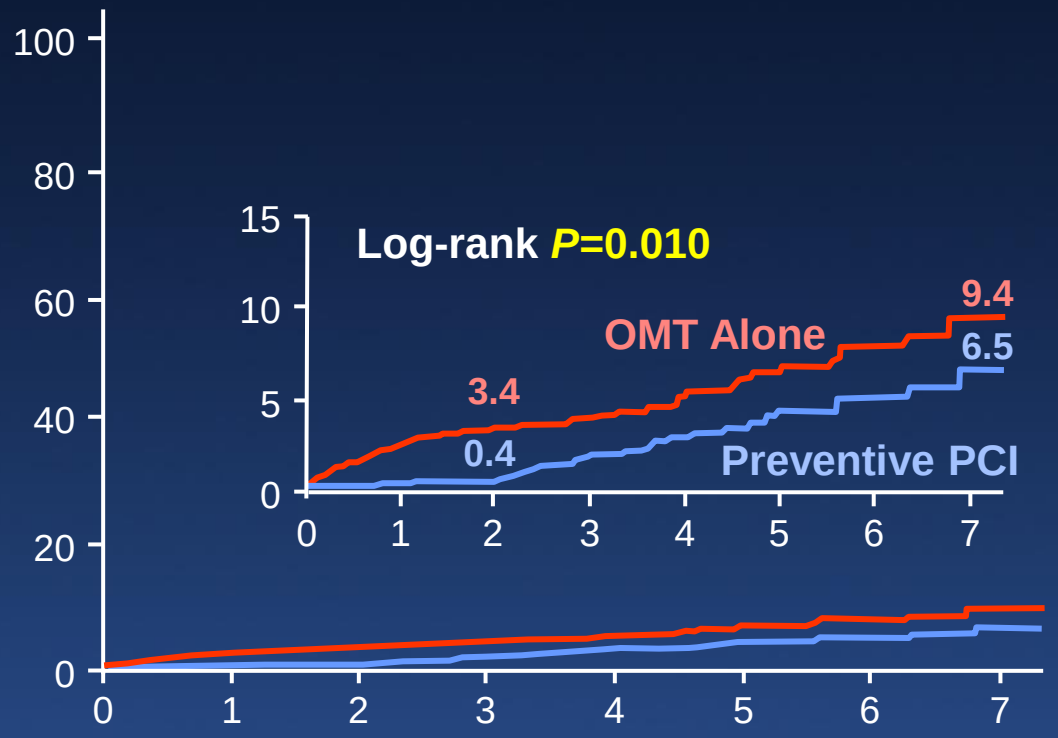
Park et al. Lancet 2024, in press

PREVENT: Cardiac death, TV-MI, ischemia-driven TVR, or hospitalization for unstable or progressive angina (%)



No. at Risk								
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	Preventive PCI	OMT	Δ (95% CI)	HR (95% CI)
Cardiac death				0·87 (0·31 to 2·39)
2 yrs	0.1%	0.8%	–0·6 (–1·3 to 0·02)	
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TV-MI				0·62 (0·20 to 1·90)
2 yrs	0.1%	0.8%	–0·6 (–1·3 to 0·02)	
4 yrs	0.6%	1.0%	–0·3 (–1·6 to 1·6)	
ID-TVR				0·44 (0·25 to 0·77)
2 yrs	0.1%	2.4%	–2·3 (–3·4 to –1·2)	
4 yrs	1.7%	4.4%	–2·7 (–4·6 to 0·8)	
Rehospitalization for unstable/progressive angina				0·19 (0·06 to 0·54)
2 yrs	0.1%	1.5%	–1·4 (–2·3 to –0·5)	
4 yrs	0.7%	2.4%	–1·7 (–3·0 to –0·4)	

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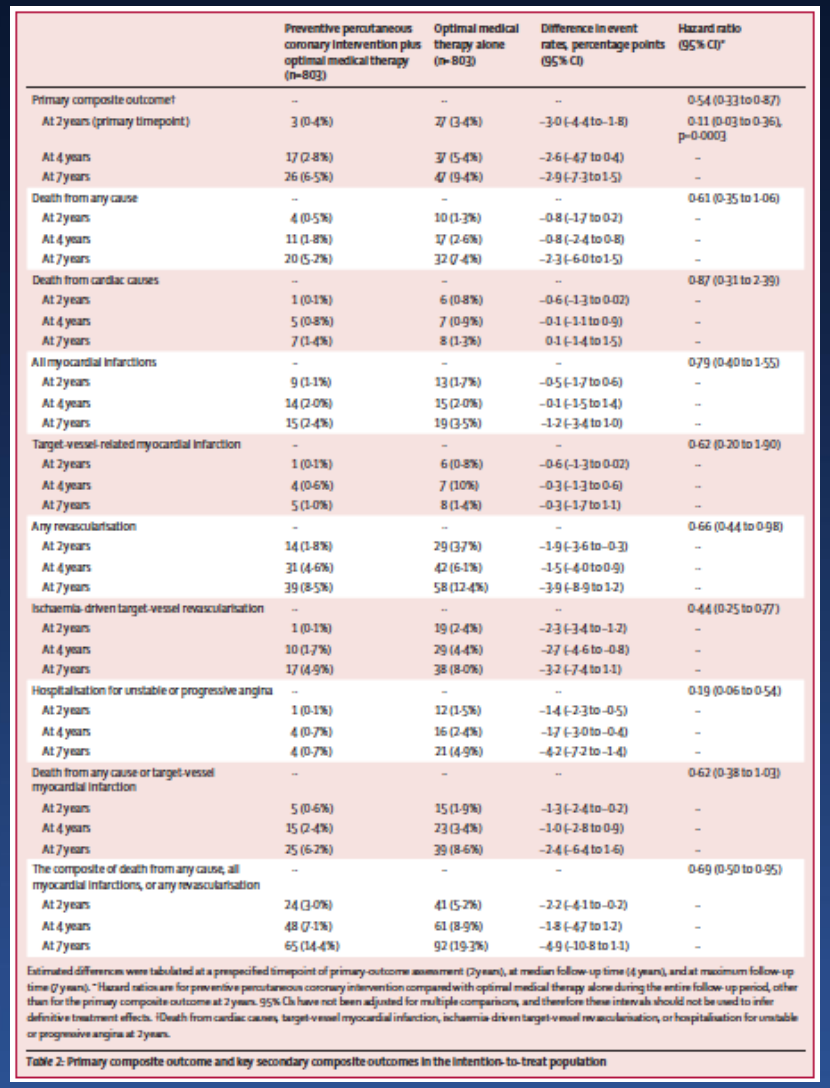
Park et al. Lancet 2024, in press

Hard Events -- Death, Cardiac Arrest, Spontaneous MI – Are Uncommon

	PROSPECT (3.4 yrs)		CLIMA (1 yr)	LRP (2 yrs)	CLIMA (1.5 yrs)	PROSPECT-II (4 yrs)		Harbin (3.3 yrs)	PREVENT (OMT) (2 yrs) [4 yrs]
	Non-culprit lesion	Indeterminant	Non-culprit lesion	Non-culprit lesion	Non-culprit lesion	Non-culprit lesion	Indeterminant	Non-culprit lesion	
Death from cardiac causes	**0**	**1.8%**	**2.5%**	**2.0%**	**0.2%**	**0**	**1.6%**	**1.9%**	**0.8% [0.8%]**
Cardiac arrest	**0**	**0.2%**		**0.3%**					
MI	**1.0%**	**0.3%**	**1.3%**	**3.0%**	**3.8%**	**3.2%**	**1.6%**	**1.0%**	**1.7% [2.0%]**

Stone et al. N Engl J Med 2011;361:226-35
Prati et al. Eur Heart J 2020;41:383-91
Waksman et al. Lancet. 2019;394:1629-37
Kedhi et al. Eur Heart J. 2021;42:4671-4679
Erlinge et al. Lancet. 2021;397:985-95
Jiang et al. J Am Coll Cardiol 2023;81:1217-30
Park et al. Lancet 2024, in press

Preventive PCI: Doing PCI to Prevent PCI



	Preventive percutaneous coronary intervention plus optimal medical therapy (n=803)	Optimal medical therapy alone (n=803)	Difference in event rates, percentage points (95% CI)	Hazard ratio (95% CI)*
Primary composite outcome†	..	..	..	0·54 (0·33 to 0·87)
At 2 years (primary timepoint)	3 (0·4%)	27 (3·4%)	−3·0 (−4·4 to −1·8)	0·11 (0·03 to 0·36), p<0·0001
At 4 years	17 (2·8%)	37 (5·4%)	−2·6 (−4·7 to 0·4)	..
At 7 years	26 (6·5%)	47 (9·4%)	−2·9 (−7·3 to 1·5)	..
Death from any cause	..	..	..	0·61 (0·35 to 1·06)
At 2 years	4 (0·5%)	10 (1·3%)	−0·8 (−1·7 to 0·2)	..
At 4 years	11 (1·8%)	17 (2·6%)	−0·8 (−2·4 to 0·8)	..
At 7 years	20 (5·2%)	32 (7·4%)	−2·3 (−6·0 to 1·5)	..
Death from cardiac causes	..	..	..	0·87 (0·31 to 2·39)
At 2 years	1 (0·1%)	6 (0·8%)	−0·6 (−1·3 to 0·02)	..
At 4 years	5 (0·8%)	7 (0·9%)	−0·1 (−1·1 to 0·9)	..
At 7 years	7 (1·4%)	8 (1·3%)	0·1 (−1·4 to 1·5)	..
All myocardial infarctions	..	..	..	0·79 (0·40 to 1·55)
At 2 years	9 (1·1%)	13 (1·7%)	−0·5 (−1·7 to 0·6)	..
At 4 years	14 (2·0%)	15 (2·0%)	−0·1 (−1·5 to 1·4)	..
At 7 years	15 (2·4%)	19 (3·5%)	−1·2 (−3·4 to 1·0)	..
Target-vessel-related myocardial infarction	..	..	..	0·62 (0·20 to 1·90)
At 2 years	1 (0·1%)	6 (0·8%)	−0·6 (−1·3 to 0·02)	..
At 4 years	4 (0·6%)	7 (10%)	−0·3 (−1·3 to 0·6)	..
At 7 years	5 (1·0%)	8 (1·4%)	−0·3 (−1·7 to 1·1)	..
Any revascularisation	..	..	..	0·66 (0·44 to 0·98)
At 2 years	14 (1·8%)	29 (3·7%)	−1·9 (−3·6 to −0·3)	..
At 4 years	31 (4·6%)	42 (6·1%)	−1·5 (−4·0 to 0·9)	..
At 7 years	39 (8·5%)	58 (12·4%)	−3·9 (−8·9 to 1·2)	..
Ischaemia-driven target-vessel revascularisation	..	..	..	0·44 (0·25 to 0·77)
At 2 years	1 (0·1%)	19 (2·4%)	−2·3 (−3·4 to −1·2)	..
At 4 years	10 (1·7%)	29 (4·4%)	−2·7 (−4·6 to −0·8)	..
At 7 years	17 (4·9%)	38 (8·0%)	−3·2 (−7·4 to 1·1)	..
Hospitalisation for unstable or progressive angina	..	..	..	0·19 (0·06 to 0·54)
At 2 years	1 (0·1%)	12 (1·5%)	−1·4 (−2·3 to −0·5)	..
At 4 years	4 (0·7%)	16 (2·4%)	−1·7 (−3·0 to −0·4)	..
At 7 years	4 (0·7%)	21 (4·9%)	−4·2 (−7·2 to −1·4)	..
Death from any cause or target-vessel myocardial infarction	..	..	..	0·62 (0·38 to 1·03)
At 2 years	5 (0·6%)	15 (1·9%)	−1·3 (−2·4 to −0·2)	..
At 4 years	15 (2·4%)	23 (3·4%)	−1·0 (−2·8 to 0·9)	..
At 7 years	25 (6·2%)	39 (8·6%)	−2·4 (−6·4 to 1·6)	..
The composite of death from any cause, all myocardial infarctions, or any revascularisation	..	..	..	0·69 (0·50 to 0·95)
At 2 years	24 (3·0%)	41 (5·2%)	−2·2 (−4·1 to −0·2)	..
At 4 years	48 (7·1%)	61 (8·9%)	−1·8 (−4·7 to 1·2)	..
At 7 years	65 (14·4%)	92 (19·3%)	−4·9 (−10·8 to 1·1)	..

Estimated differences were tabulated at a prespecified timepoint of primary-outcome assessment (2 years), at median follow-up time (4 years), and at maximum follow-up time (7 years). *Hazard ratios are for preventive percutaneous coronary intervention compared with optimal medical therapy alone during the entire follow-up period, other than for the primary composite outcome at 2 years. 95% CIs have not been adjusted for multiple comparisons, and therefore these intervals should not be used to infer definitive treatment effects. †Death from cardiac causes, target-vessel myocardial infarction, ischaemia-driven target-vessel revascularisation, or hospitalisation for unstable or progressive angina at 2 years.

Table 2: Primary composite outcome and key secondary composite outcomes in the intention-to-treat population

Does it make sense to do 803 PCIs to prevent 13 cardiac events at 4 years of which 2 were cardiac deaths and 3 were TV-MI and the rest were ischemia-driven TVR or hospitalization for unstable or progressive angina?

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The majority of TCFAs either heal, develop a thicker fibrous cap, remain stable, or rupture silently leading to disease progression and a larger plaque burden rather than to death/MI/cardiac arrest.

Meanwhile, new TCFAs can develop.

Therefore, it is not surprising that in PREVENT, the advantage of preventive PCI was limited to the first 18 months

Serial Intravascular Imaging Studies

		Lesions	Pts	Dx	Time	TCFA				
						Baseline	Healed	Persistent	New	Follow up
Kubo et al. J Am Coll Cardiol 2010;55:1590-7	VH	201	106	Stable	8 mos	20	15	5	12	
Zhao et al. JACC Cardiovasc Imaging 2013;6:86-95	VH	100	100	STEMI	13 mos	33	10	23	22	
Zhang et al. EuroIntervention 2018;13:e2190-200	OCT	257	72	Mixed	6.5 mos	33	26	7	17	
Raber et al. JACC Cardiovasc Imaging 2019;12:1518-28	OCT	191	103	STEMI	13 mos	13	9	4	2	
Total						**99**	**60**	**39**		
								39	**53**	**92**

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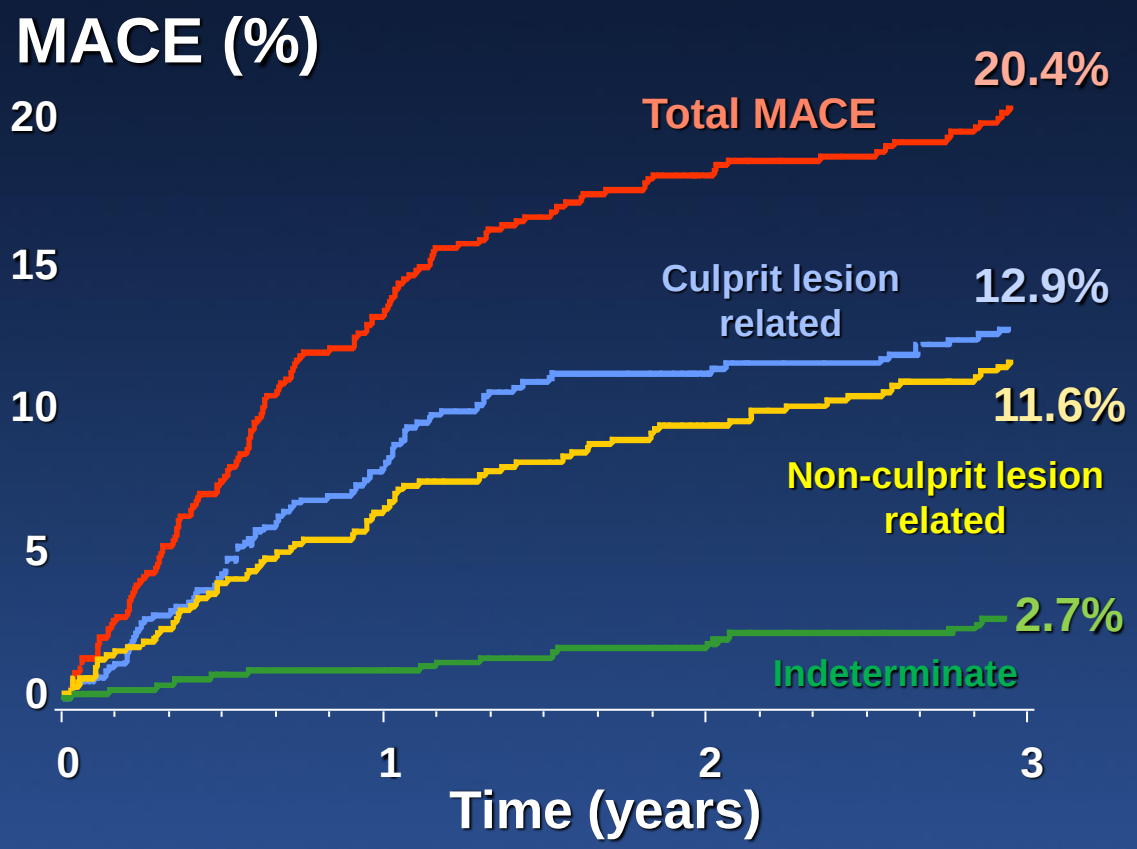
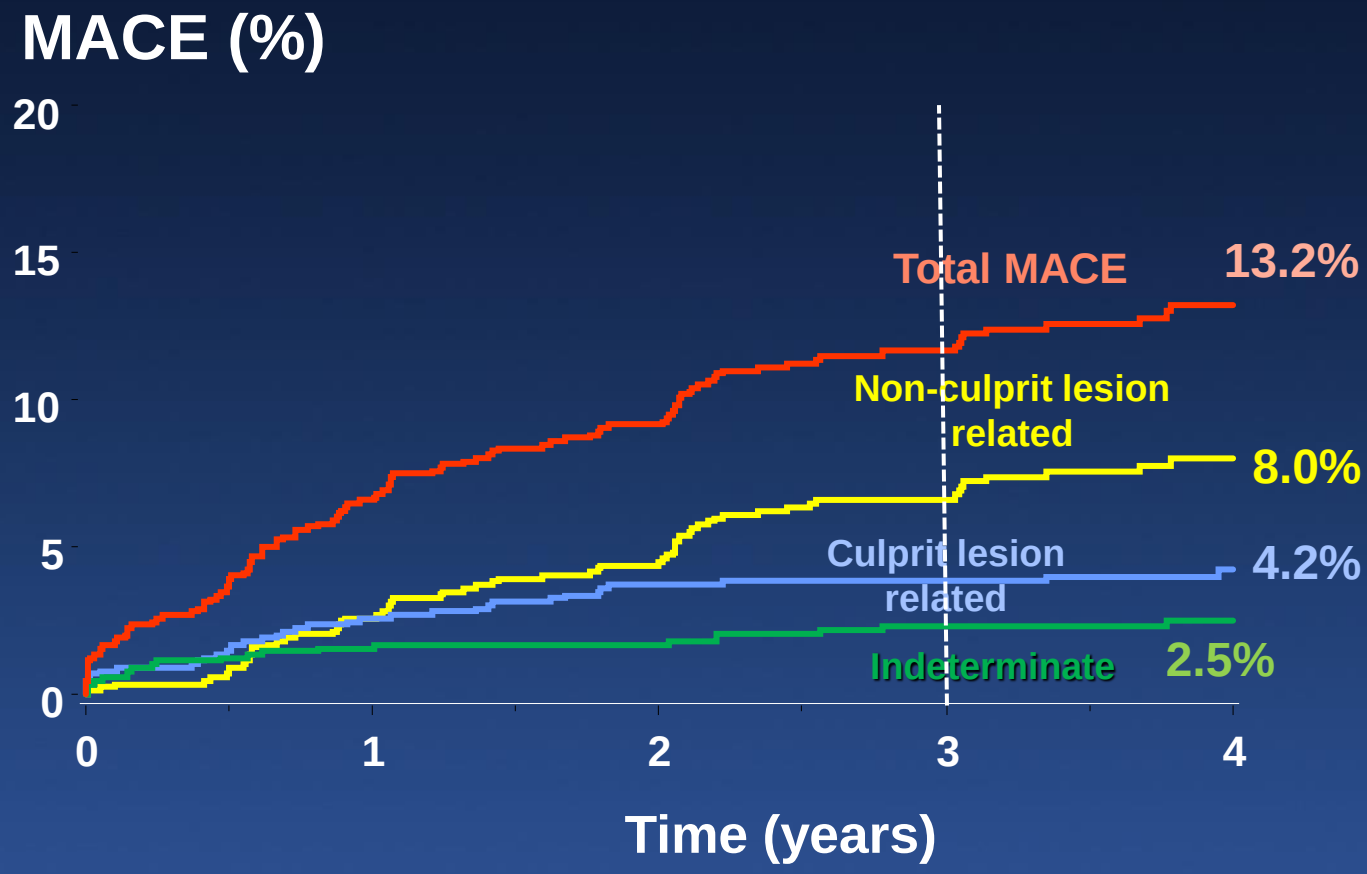
- What are the best criteria and the best ways to diagnose vulnerable plaque?
- What are the events and event rates associated with vulnerable plaque? What events are prevented by treating vulnerable plaque with PCI?
- **What is optimal medical therapy – guideline directed or otherwise? And what % of patients in the OMT group in PREVENT actually took optimal medical therapy?**
- What is optimal PCI in 2024?
- What clinical pathways make sense? Who should undergo IVI to assess and treat vulnerable plaque?

Culprit vs Non-Culprit Events in PROSPECT

10 years

Culprit vs Non-Culprit Events in PROSPECT II





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Stone et al. N Engl J Med 2011;361:226-35
Erlinge et al. Lancet. 2021;397:985-95

NEJM

When planning PREVENT, the cumulative incidence rates of the primary endpoint at 2 years were estimated to be 8.4% in the preventive PCI group and 12.0% in the medical therapy alone group.

Yet, the actual event rates were 0.4% in the preventive PCI group and 3.4% in the medical therapy alone group.

- *Dr. Karol E. Watson*: In this trial, at 2 years of follow-up, serious adverse cardiovascular events did not differ between the “preventive PCI” group and the medical therapy group. The differences in the primary outcome were largely driven by fewer subsequent PCIs in the “preventive PCI” group, and the authors estimate that 45 “preventive PCI” procedures would need to be done to prevent one primary end point. But this study also showed the benefits of optimal guideline-directed medical therapy (GDMT). In this patient population with known coronary artery disease and vulnerable plaques, the primary event rates in both arms were relatively low — a testament to the remarkable efficacy of GDMT.

In PREVENT less than 2% of patients were on a PCSK9 inhibitor -- senior investigator Duk-Woo Park, MD, PhD (Asan Medical Center/University of Ulsan College of Medicine) told TCTMD.

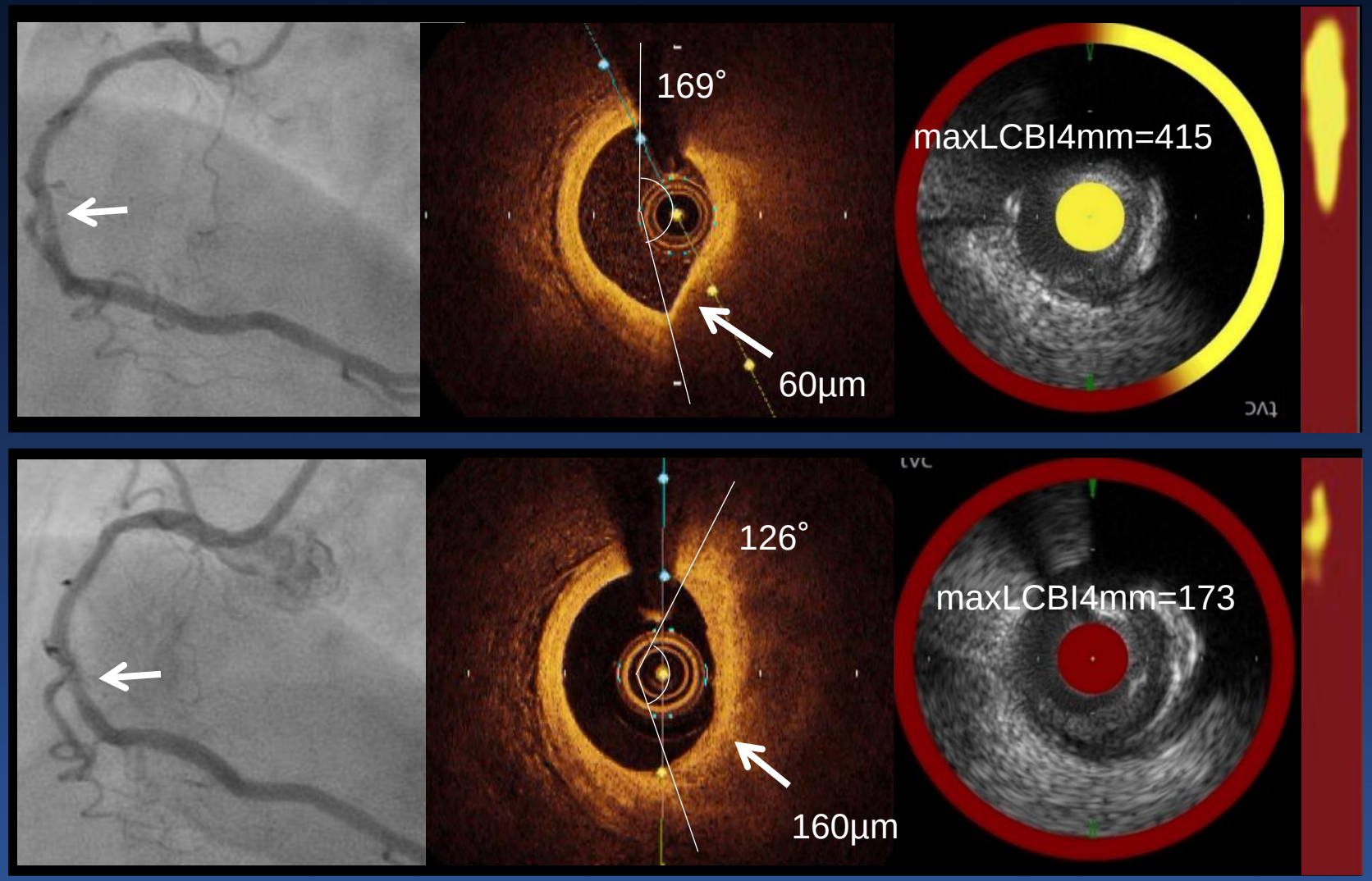
High dose statins or moderate dose statins + ezetimibe were prescribed in 59.8% of OMT at 2 years and 63.1% at 7 years.

Increase in FCT and decrease in LCBI by PCSK9i

Baseline

Rosuvastatin
(10 mg/day)
+
Evolocumab
(140 mg every 2 weeks)

8M follow-up



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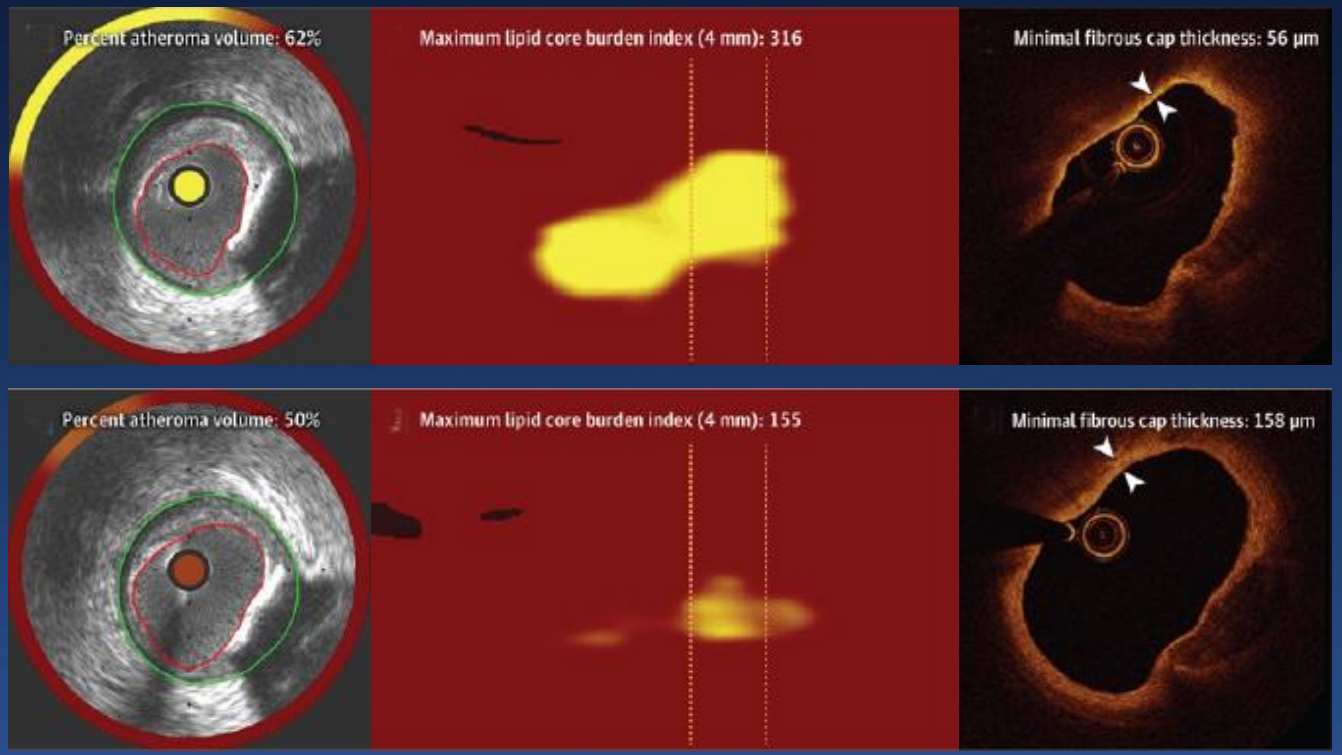
Ino et al. Circ J 2019;83:1765

Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Pts With AMI: The PACMAN-AMI Randomized Clinical Trial



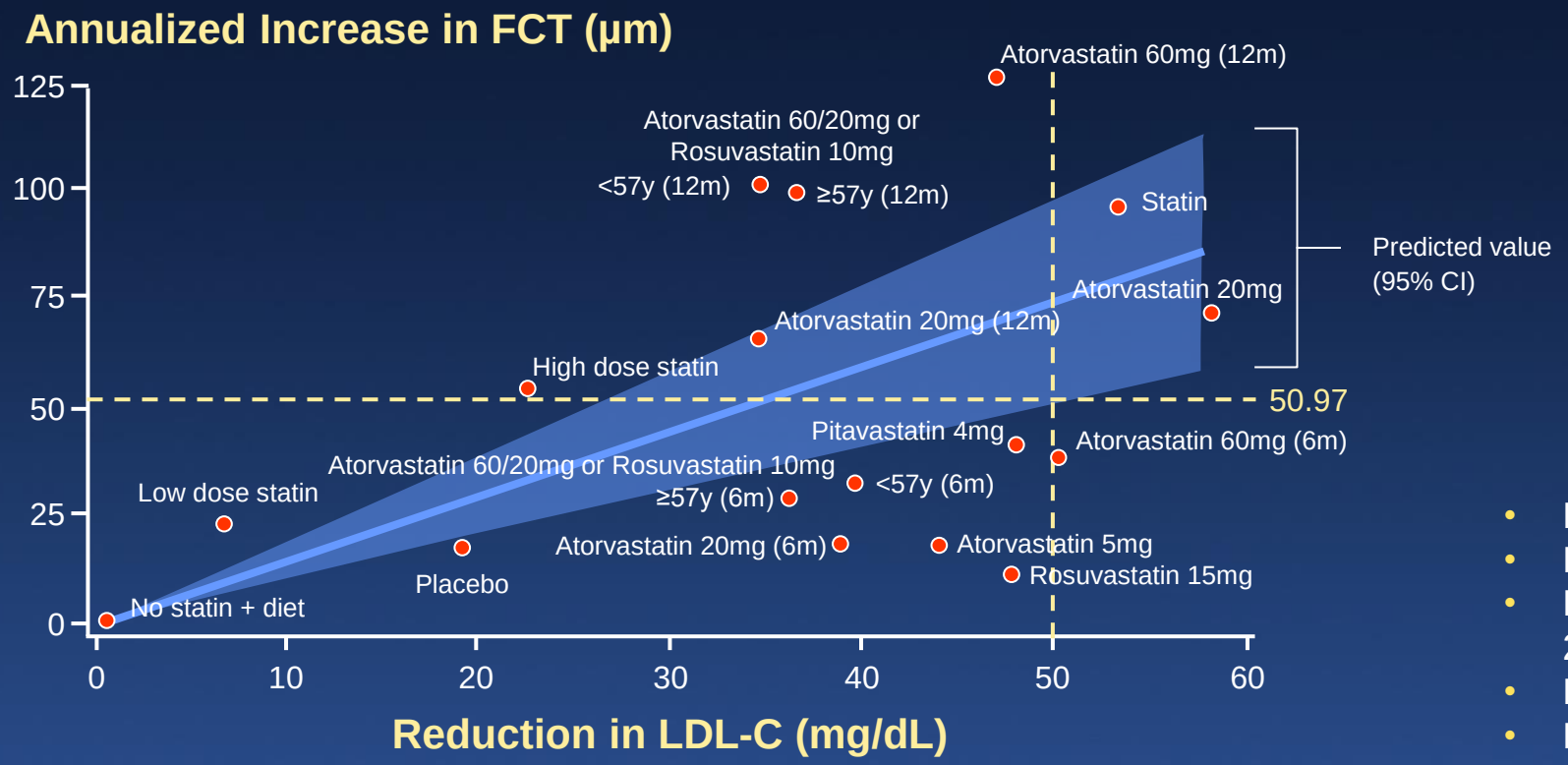
Baseline and 52 week follow-up NIRS-IVUS/OCT in both non-infarct related arteries

	Alirocumab + high intensity statins	High intensity statins	Δ	P-value
n	150	150		
Δ atheroma volume	-2.1%	-0.9%	-1.2%	<0.001
Δ$MaxLCBI_{4mm}$	-79.4	-37.6	-41.2	0.006
ΔFCT	62.7µm	33.2µm	29.7µm	0.001

Cardiovascular Research Foundation

Raber et al. JAMA 2022;327:1771-81

Linear regression meta-analysis of 7 serial OCT studies evaluating the effects of statin therapy



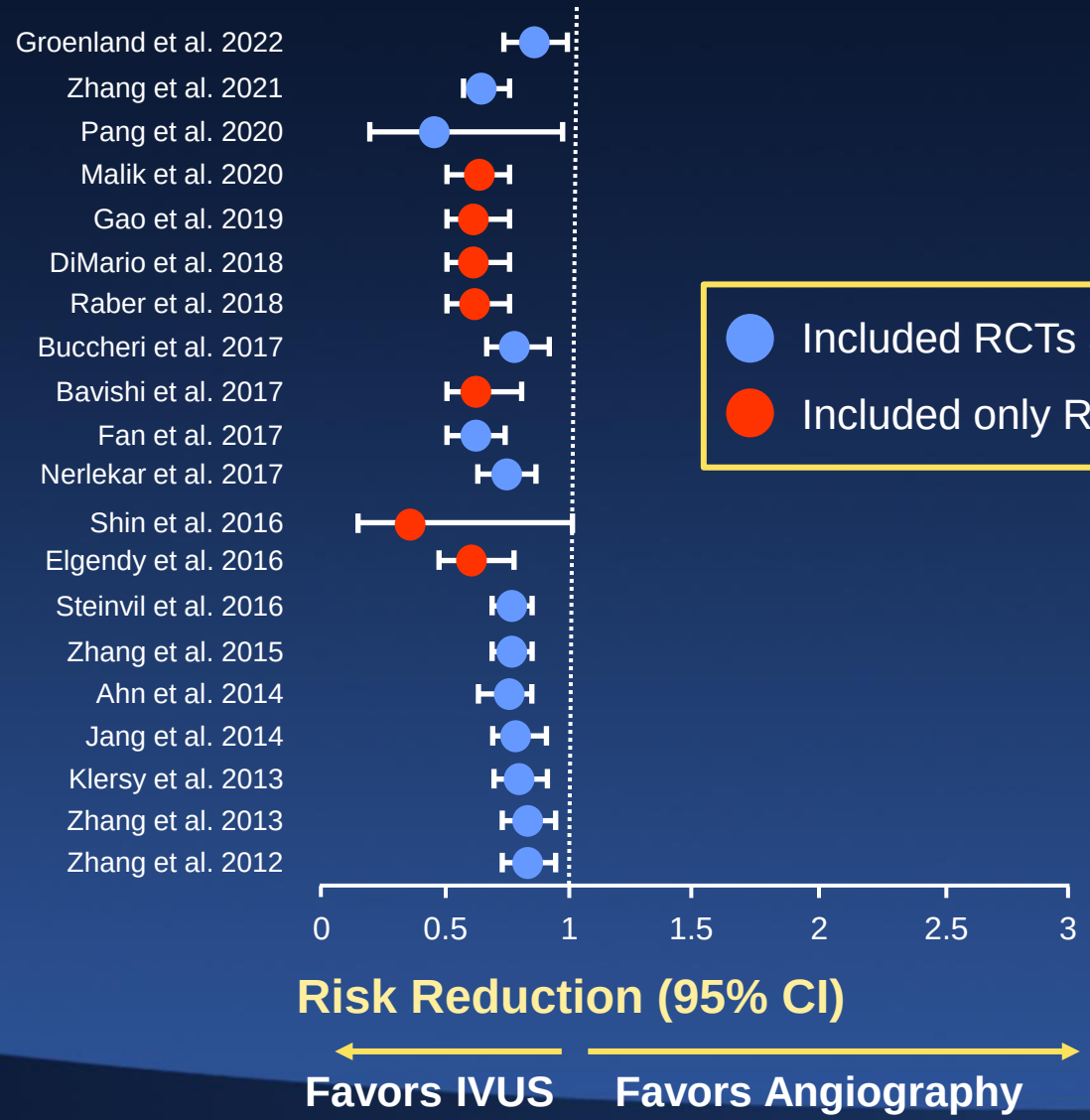
- Kataoka et al. Am J Cardiol 2014;114:549-54.
- Dai et al. Coron Artery Dis 2017;28:209-17
- Hattori et al. JACC Cardiovasc Imaging 2012;5:169-77
- Hou et al. Am J Cardiol 2016;117:800-6.
- Komukai et al. J Am Coll Cardiol 2014;64:2207-17
- Nishio et al. Atherosclerosis 2014;234:114-9
- Tarada et al. Atherosclerosis 2009;202:491-7

Nicholls et al. Cardiovasc Diagn Ther 2021;11:120-9

- What are the best criteria and the best ways to diagnose vulnerable plaque?
- What are the events and event rates associated with vulnerable plaque? What events are prevented by treating vulnerable plaque with PCI?
- What is optimal medical therapy – guideline directed or otherwise? And what % of patients in the OMT group in PREVENT actually took optimal medical therapy?
- **What is optimal PCI in 2024?**
- What clinical pathways make sense? Who should undergo IVI to assess and treat vulnerable plaque?

Meta-analyses of MACE After IVI-guided DES Implantation

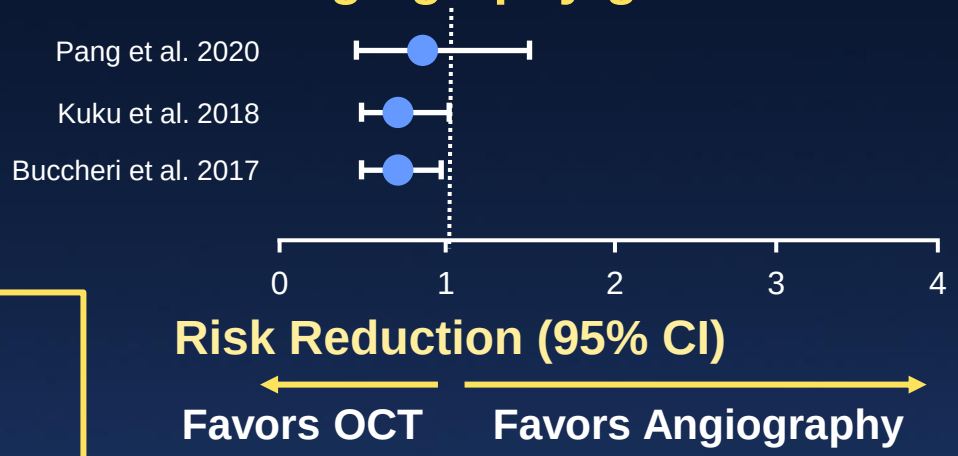
IVUS vs Angiography-guidance



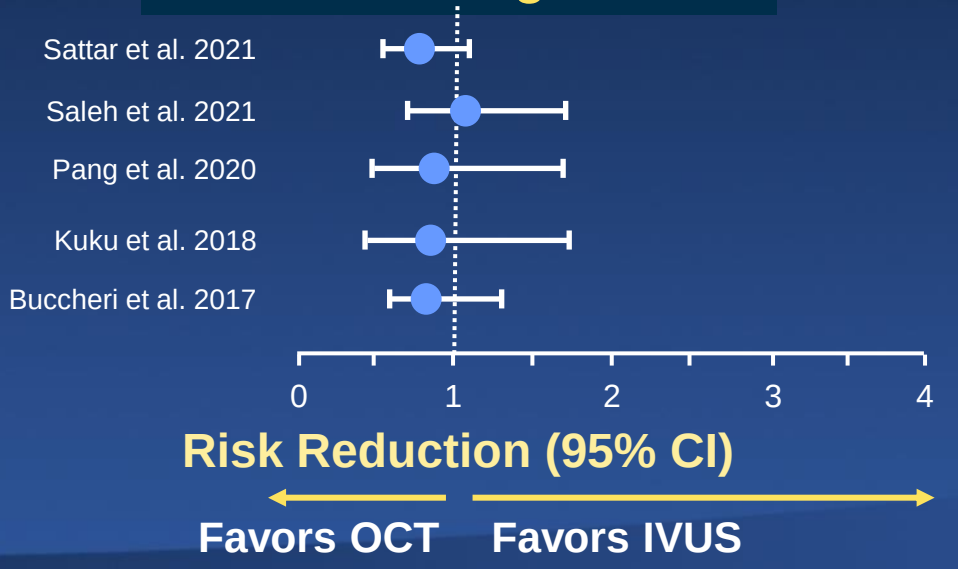
Included RCTs and Registries

Included only RCTs

OCT vs Angiography-guidance



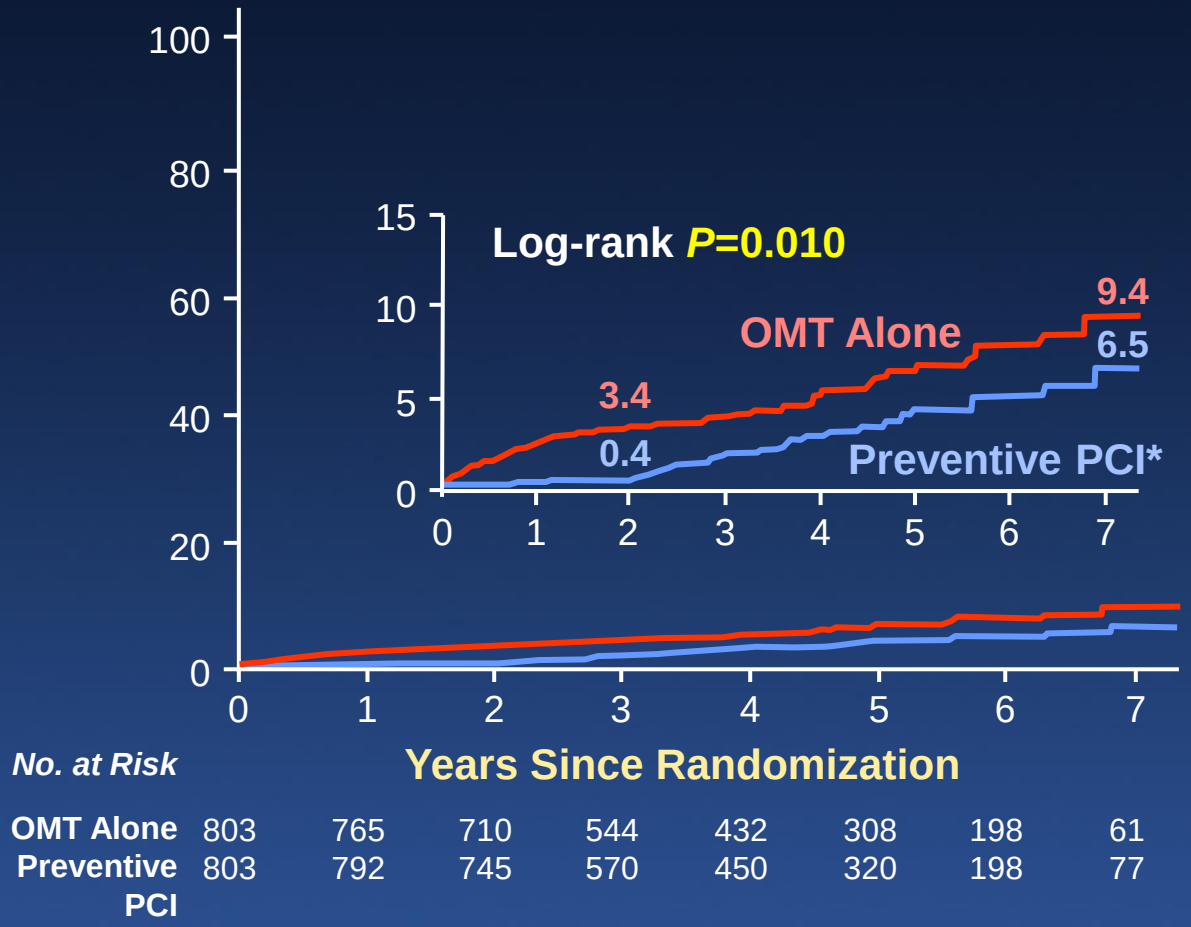
OCT vs IVUS-guidance



Cardiovascular Research Foundation

Mintz et al. JSCAI 2022;1:100413

PREVENT: All PCIs were IVI-guided and optimized



BVS vs OMT			
	Preventive PCI*	OMT	HR (95% CI)
BVS			
2 yrs	1/265 (0.4%)	12/281 (4.3%)	0·09 (0·01–0·67)
7 yrs	12/265 (7.2%)	22/281 (7.9%)	0·89 (0·48 to 1·65)

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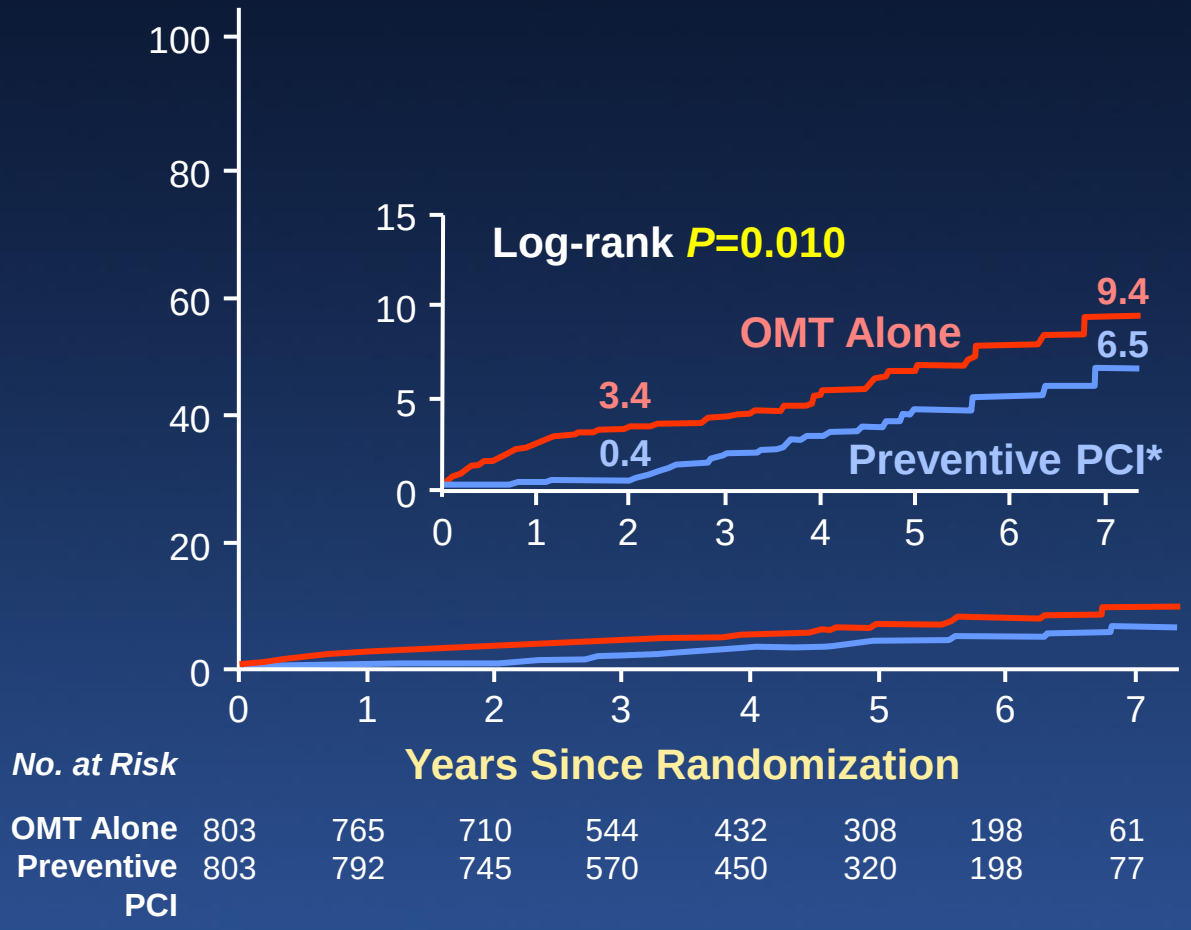
Park et al. Lancet 2024, in press

PREVENT: All PCIs were IVI-guided and optimized



BVS or EES vs OMT			
	Preventive PCI*	OMT	HR (95% CI)
BVS			
2 yrs	1/265 (0.4%)	12/281 (4.3%)	0·09 (0·01–0·67)
7 yrs	12/265 (7.2%)	22/281 (7.9%)	0·89 (0·48 to 1·65)
EES			
2 yrs	2/538 (0.4%)	15/522 (2.9%)	0·13 (0·03–0·55)
7 yrs	7/538 (1.3%)	25/522 (4.8%)	0·25 (0·11 to 0·59)

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Park et al. Lancet 2024, in press

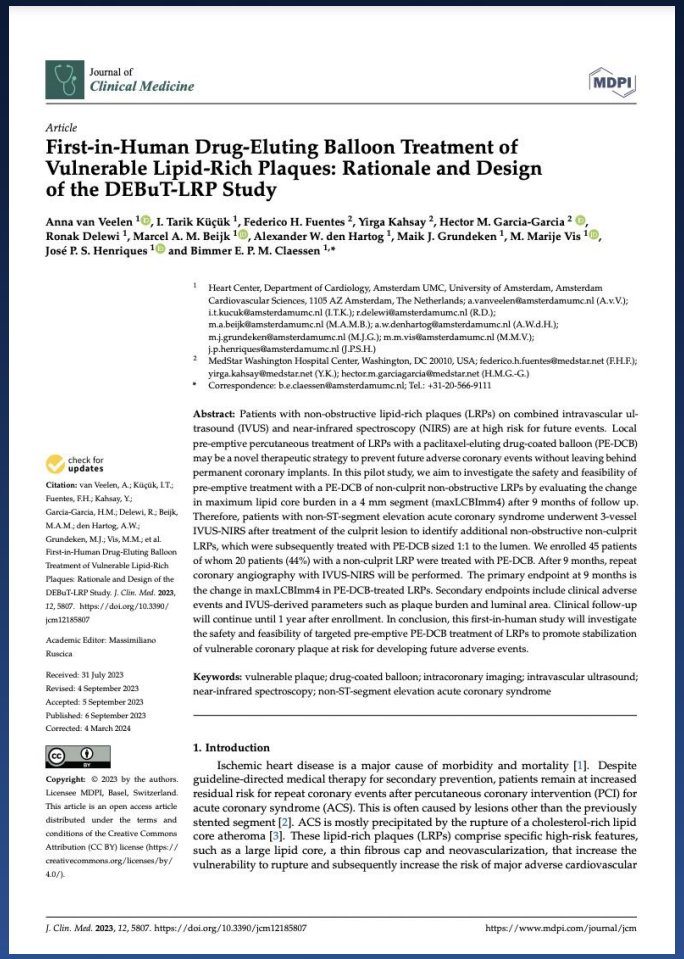
FLAVOUR: Randomized FFR vs IVUS in 1682 patients with intermediate lesions (angiographic DS 40-70%)

	FFR	IVUS
Stent implantation criteria	<0.80	MLA <3mm^2 (or 3-4mm^2 plus plaque burden >70%)
%PCI	44.4%	65.3%
Stents per patient	0.6±0.9	0.9±1.0
Stent optimization criteria	≥0.88 or a difference <0.05 across the stent	MLA ≥5.5mm^2 and plaque burden at stent edge ≤55% or in-stent MLA ≥ distal reference lumen
% optimized	50.1%	54.8%
24-month MACE	**8.1%**	**8.6%**
PCI-treated and optimized	**12.3%**	**8.5%**
Suboptimal PCI	11.8%	9.8%
Medical therapy	5.0%	5.9%

Cardiovascular Research Foundation

Koo et al. N Engl J Med. 2022;387:779-789

Preliminary studies looking at DCB to treat vulnerable plaques



Journal of Clinical Medicine

MDPI

Article

First-in-Human Drug-Eluting Balloon Treatment of Vulnerable Lipid-Rich Plaques: Rationale and Design of the DEBuT-LRP Study

Anna van Veelen [1], I. Tarik Küçük [1], Federico H. Fuentes [2], Yirga Kahsay [2], Hector M. Garcia-Garcia [2], Ronak Delewi [1], Marcel A. M. Beijk [1], Alexander W. den Hartog [1], Maik J. Grundeken [1], M. Marije Vis [1], José P. S. Henriques [1] and Bimmer E. P. M. Claessen [1,*]

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Abstract: Patients with non-obstructive lipid-rich plaques (LRPs) on combined intravascular ultrasound (IVUS) and near-infrared spectroscopy (NIRS) are at high risk for future events. Local pre-emptive percutaneous treatment of LRPs with a paclitaxel-eluting drug-coated balloon (PE-DCB) may be a novel therapeutic strategy to prevent future adverse coronary events without leaving behind permanent coronary implants. In this pilot study, we aim to investigate the safety and feasibility of pre-emptive treatment with a PE-DCB of non-culprit non-obstructive LRPs by evaluating the change in maximum lipid core burden in a 4 mm segment (maxLCBImm4) after 9 months of follow up. Therefore, patients with non-ST-segment elevation acute coronary syndrome underwent 3-vessel IVUS-NIRS after treatment of the culprit lesion to identify additional non-obstructive non-culprit LRPs, which were subsequently treated with PE-DCB sized 1:1 to the lumen. We enrolled 45 patients of whom 20 patients (44%) with a non-culprit LRP were treated with PE-DCB. After 9 months, repeat coronary angiography with IVUS-NIRS will be performed. The primary endpoint at 9 months is the change in maxLCBImm4 in PE-DCB-treated LRPs. Secondary endpoints include clinical adverse events and IVUS-derived parameters such as plaque burden and luminal area. Clinical follow-up will continue until 1 year after enrollment. In conclusion, this first-in-human study will investigate the safety and feasibility of targeted pre-emptive PE-DCB treatment of LRPs to promote stabilization of vulnerable coronary plaque at risk for developing future adverse events.

Keywords: vulnerable plaque; drug-coated balloon; intracoronary imaging; intravascular ultrasound; near-infrared spectroscopy; non-ST-segment elevation acute coronary syndrome

check for updates

Citation: van Veelen, A.; Küçük, I.T.; Fuentes, F.H.; Kahsay, Y.; Garcia-Garcia, H.M.; Delewi, R.; Beijk, M.A.M.; den Hartog, A.W.; Grundeken, M.J.; Vis, M.M.; et al. First-in-Human Drug-Eluting Balloon Treatment of Vulnerable Lipid-Rich Plaques: Rationale and Design of the DEBuT-LRP Study. *J. Clin. Med.* **2023**, *12*, 5807. https://doi.org/10.3390/jcm12185807

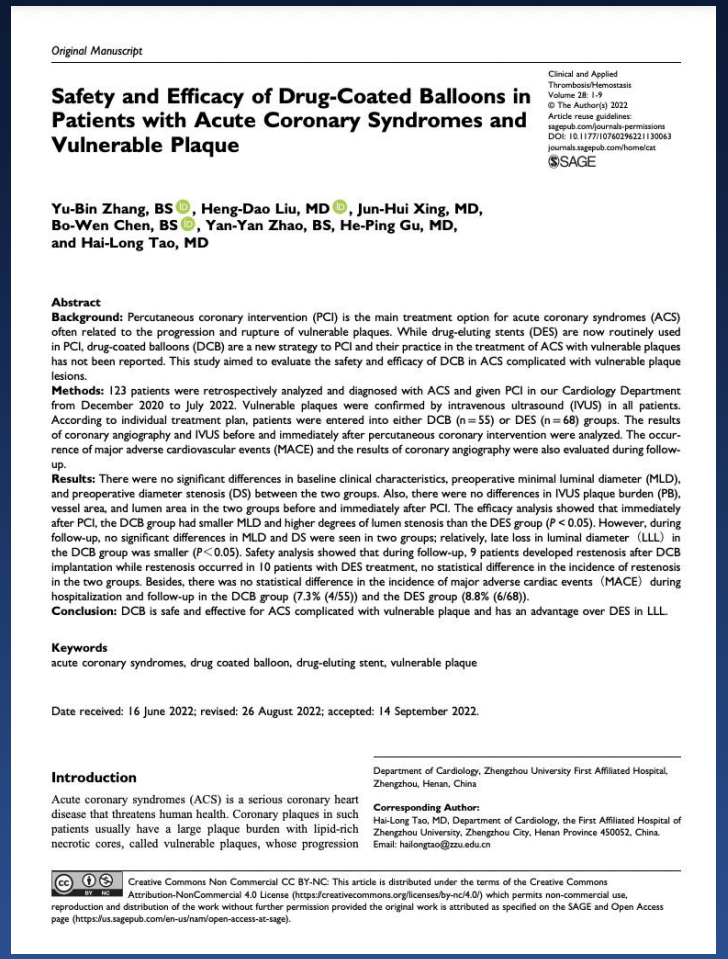
Academic Editor: Massimiliano Ruscica

Received: 31 July 2023
Revised: 4 September 2023
Accepted: 5 September 2023
Published: 6 September 2023
Corrected: 4 March 2024

1. Introduction

Ischemic heart disease is a major cause of morbidity and mortality [1]. Despite guideline-directed medical therapy for secondary prevention, patients remain at increased residual risk for repeat coronary events after percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS). This is often caused by lesions other than the previously stented segment [2]. ACS is mostly precipitated by the rupture of a cholesterol-rich lipid core atheroma [3]. These lipid-rich plaques (LRPs) comprise specific high-risk features, such as a large lipid core, a thin fibrous cap and neovascularization, that increase the vulnerability to rupture and subsequently increase the risk of major adverse cardiovascular

van Veelen et al. J Clin Med 2023;12:5807. doi: 10.3390/jcm12185807



Original Manuscript

Clinical and Applied Thrombosis/Hemostasis
Volume 28: 1-9

DOI: 10.1177/10760296221130063
journals.sagepub.com/home/cat
SAGE

Safety and Efficacy of Drug-Coated Balloons in Patients with Acute Coronary Syndromes and Vulnerable Plaque

Yu-Bin Zhang, BS, Heng-Dao Liu, MD, Jun-Hui Xing, MD, Bo-Wen Chen, BS, Yan-Yan Zhao, BS, He-Ping Gu, MD, and Hai-Long Tao, MD

Abstract

Background: Percutaneous coronary intervention (PCI) is the main treatment option for acute coronary syndromes (ACS) often related to the progression and rupture of vulnerable plaques. While drug-eluting stents (DES) are now routinely used in PCI, drug-coated balloons (DCB) are a new strategy to PCI and their practice in the treatment of ACS with vulnerable plaques has not been reported. This study aimed to evaluate the safety and efficacy of DCB in ACS complicated with vulnerable plaque lesions.

Methods: 123 patients were retrospectively analyzed and diagnosed with ACS and given PCI in our Cardiology Department from December 2020 to July 2022. Vulnerable plaques were confirmed by intravenous ultrasound (IVUS) in all patients. According to individual treatment plan, patients were entered into either DCB (n = 55) or DES (n = 68) groups. The results of coronary angiography and IVUS before and immediately after percutaneous coronary intervention were analyzed. The occurrence of major adverse cardiovascular events (MACE) and the results of coronary angiography were also evaluated during follow-up.

Results: There were no significant differences in baseline clinical characteristics, preoperative minimal luminal diameter (MLD), and preoperative diameter stenosis (DS) between the two groups. Also, there were no differences in IVUS plaque burden (PB), vessel area, and lumen area in the two groups before and immediately after PCI. The efficacy analysis showed that immediately after PCI, the DCB group had smaller MLD and higher degrees of lumen stenosis than the DES group ($P < 0.05$). However, during follow-up, no significant differences in MLD and DS were seen in two groups; relatively, late loss in luminal diameter (LLL) in the DCB group was smaller ($P < 0.05$). Safety analysis showed that during follow-up, 9 patients developed restenosis after DCB implantation while restenosis occurred in 10 patients with DES treatment, no statistical difference in the incidence of restenosis in the two groups. Besides, there was no statistical difference in the incidence of major adverse cardiac events (MACE) during hospitalization and follow-up in the DCB group (7.3% (4/55)) and the DES group (8.8% (6/68)).

Conclusion: DCB is safe and effective for ACS complicated with vulnerable plaque and has an advantage over DES in LLL.

Keywords
acute coronary syndromes, drug coated balloon, drug-eluting stent, vulnerable plaque

Date received: 16 June 2022; revised: 26 August 2022; accepted: 14 September 2022.

Introduction

Acute coronary syndromes (ACS) is a serious coronary heart disease that threatens human health. Coronary plaques in such patients usually have a large plaque burden with lipid-rich necrotic cores, called vulnerable plaques, whose progression

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Email: hailongtao@zzu.edu.cn

Zhang et al. Clin Appl Thromb Hemost 2022 Jan-Dec:28:10760296221130063

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- What are the best criteria and the best ways to diagnose vulnerable plaque?
- What are the events and event rates associated with vulnerable plaque? What events are prevented by treating vulnerable plaque with PCI?
- What is optimal medical therapy – guideline directed or otherwise? And what % of patients in the OMT group in PREVENT actually took optimal medical therapy?
- What is optimal PCI?
- **What clinical pathways make sense? Who should undergo IVI to assess and treat vulnerable plaque?**

CAC Screening

PREVENT

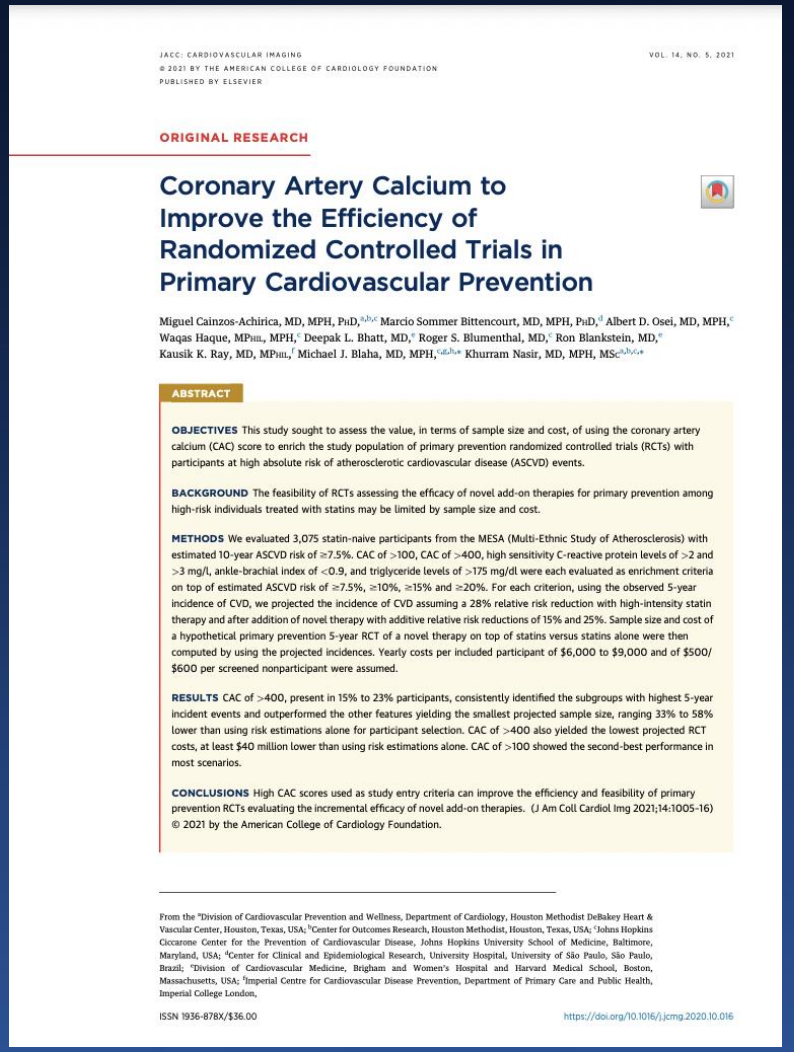
5627 patients with intermediate stenosis

↓

3562 patients with angiographic DS >50% and FFR >0.8

↓

1608 patients met imaging criteria



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VOL. 14, NO. 5, 2021

ORIGINAL RESEARCH

Coronary Artery Calcium to Improve the Efficiency of Randomized Controlled Trials in Primary Cardiovascular Prevention

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ABSTRACT

OBJECTIVES This study sought to assess the value, in terms of sample size and cost, of using the coronary artery calcium (CAC) score to enrich the study population of primary prevention randomized controlled trials (RCTs) with participants at high absolute risk of atherosclerotic cardiovascular disease (ASCVD) events.

BACKGROUND The feasibility of RCTs assessing the efficacy of novel add-on therapies for primary prevention among high-risk individuals treated with statins may be limited by sample size and cost.

METHODS We evaluated 3,075 statin-naive participants from the MESA (Multi-Ethnic Study of Atherosclerosis) with estimated 10-year ASCVD risk of ≥7.5%. CAC of >100, CAC of >400, high sensitivity C-reactive protein levels of >2 and >3 mg/l, ankle-brachial index of <0.9, and triglyceride levels of >175 mg/dl were each evaluated as enrichment criteria on top of estimated ASCVD risk of ≥7.5%, ≥10%, ≥15% and ≥20%. For each criterion, using the observed 5-year incidence of CVD, we projected the incidence of CVD assuming a 28% relative risk reduction with high-intensity statin therapy and after addition of novel therapy with additive relative risk reductions of 15% and 25%. Sample size and cost of a hypothetical primary prevention 5-year RCT of a novel therapy on top of statins versus statins alone were then computed by using the projected incidences. Yearly costs per included participant of $6,000 to $9,000 and of $500/$600 per screened nonparticipant were assumed.

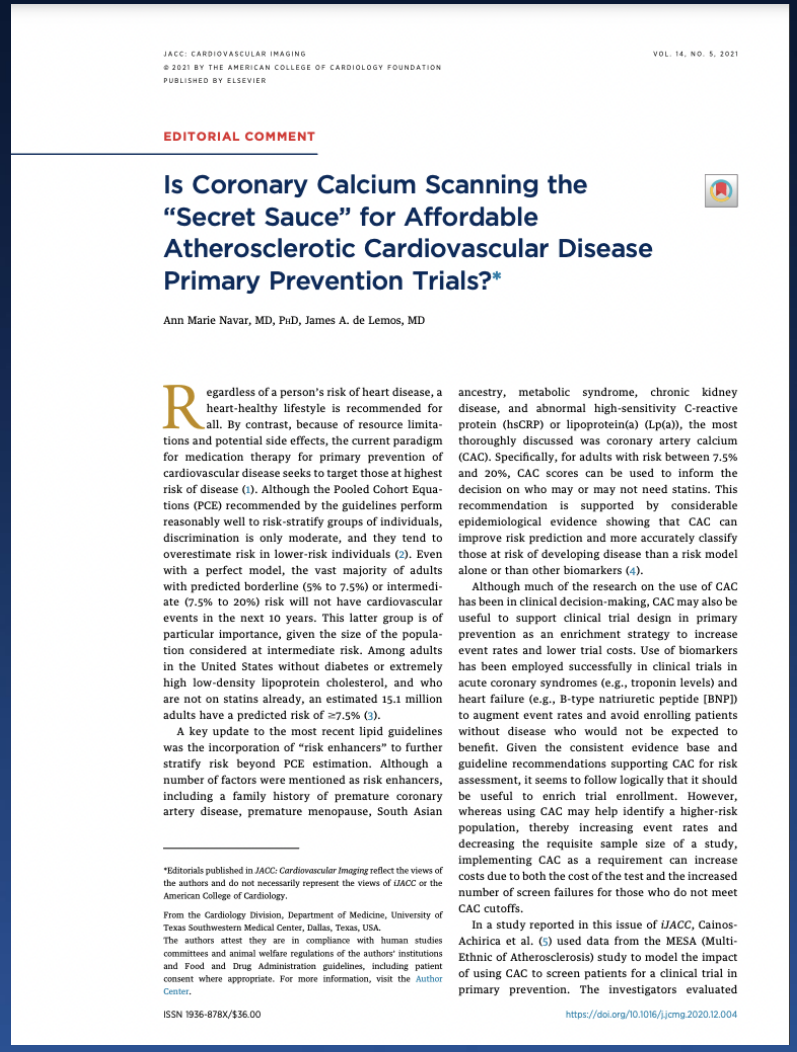
RESULTS CAC of >400, present in 15% to 23% participants, consistently identified the subgroups with highest 5-year incident events and outperformed the other features yielding the smallest projected sample size, ranging 33% to 58% lower than using risk estimations alone for participant selection. CAC of >400 also yielded the lowest projected RCT costs, at least $40 million lower than using risk estimations alone. CAC of >100 showed the second-best performance in most scenarios.

CONCLUSIONS High CAC scores used as study entry criteria can improve the efficiency and feasibility of primary prevention RCTs evaluating the incremental efficacy of novel add-on therapies. (J Am Coll Cardiol Img 2021;14:1005-16)

From the [a]Division of Cardiovascular Prevention and Wellness, Department of Cardiology, Houston Methodist DeBakey Heart & Vascular Center, Houston, Texas, USA; [b]Center for Outcomes Research, Houston Methodist, Houston, Texas, USA; [c]Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [d]Center for Clinical and Epidemiological Research, University Hospital, University of São Paulo, São Paulo, Brazil; [e]Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [f]Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Imperial College London,

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2020.10.016

Cainzos-Achirica. JACC Cardiovasc Imaging 2021;14:1005-16



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VOL. 14, NO. 5, 2021

EDITORIAL COMMENT

Is Coronary Calcium Scanning the "Secret Sauce" for Affordable Atherosclerotic Cardiovascular Disease Primary Prevention Trials?*

Ann Marie Navar, MD, PhD, James A. de Lemos, MD

Regardless of a person's risk of heart disease, a heart-healthy lifestyle is recommended for all. By contrast, because of resource limitations and potential side effects, the current paradigm for medication therapy for primary prevention of cardiovascular disease seeks to target those at highest risk of disease (1). Although the Pooled Cohort Equations (PCE) recommended by the guidelines perform reasonably well to risk-stratify groups of individuals, discrimination is only moderate, and they tend to overestimate risk in lower-risk individuals (2). Even with a perfect model, the vast majority of adults with predicted borderline (5% to 7.5%) or intermediate (7.5% to 20%) risk will not have cardiovascular events in the next 10 years. This latter group is of particular importance, given the size of the population considered at intermediate risk. Among adults in the United States without diabetes or extremely high low-density lipoprotein cholesterol, and who are not on statins already, an estimated 15.1 million adults have a predicted risk of ≥7.5% (3).

A key update to the most recent lipid guidelines was the incorporation of "risk enhancers" to further stratify risk beyond PCE estimation. Although a number of factors were mentioned as risk enhancers, including a family history of premature coronary artery disease, premature menopause, South Asian ancestry, metabolic syndrome, chronic kidney disease, and abnormal high-sensitivity C-reactive protein (hsCRP) or lipoprotein(a) (Lp(a)), the most thoroughly discussed was coronary artery calcium (CAC). Specifically, for adults with risk between 7.5% and 20%, CAC scores can be used to inform the decision on who may or may not need statins. This recommendation is supported by considerable epidemiological evidence showing that CAC can improve risk prediction and more accurately classify those at risk of developing disease than a risk model alone or than other biomarkers (4).

Although much of the research on the use of CAC has been in clinical decision-making, CAC may also be useful to support clinical trial design in primary prevention as an enrichment strategy to increase event rates and lower trial costs. Use of biomarkers has been employed successfully in clinical trials in acute coronary syndromes (e.g., troponin levels) and heart failure (e.g., B-type natriuretic peptide [BNP]) to augment event rates and avoid enrolling patients without disease who would not be expected to benefit. Given the consistent evidence base and guideline recommendations supporting CAC for risk assessment, it seems to follow logically that it should be useful to enrich trial enrollment. However, whereas using CAC may help identify a higher-risk population, thereby increasing event rates and decreasing the requisite sample size of a study, implementing CAC as a requirement can increase costs due to both the cost of the test and the increased number of screen failures for those who do not meet CAC cutoffs.

In a study reported in this issue of *iJACC*, Cainos-Achirica et al. (5) used data from the MESA (Multi-Ethnic of Atherosclerosis) study to model the impact of using CAC to screen patients for a clinical trial in primary prevention. The investigators evaluated

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *iJACC* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2020.12.004

Navar and Lemos. JACC Cardiovasc Imaging 2021;14:1017-19

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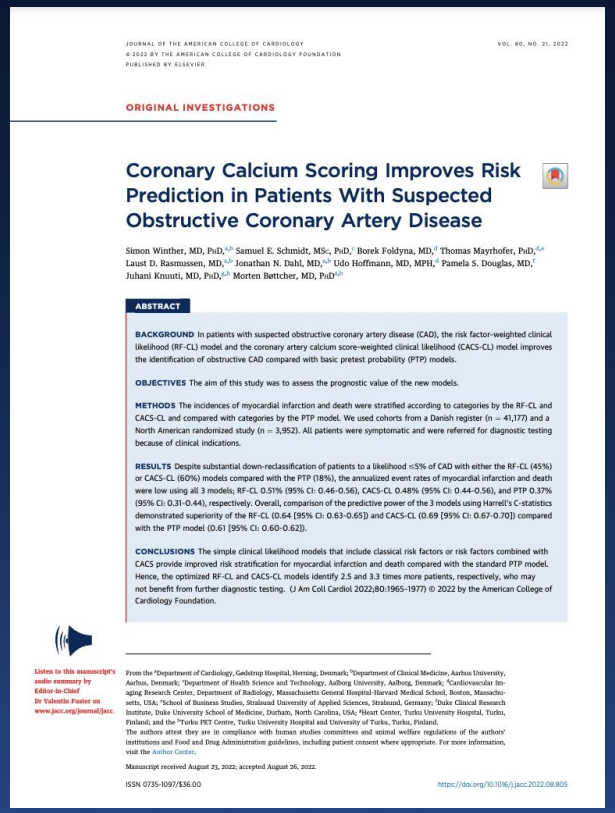
Power of Coronary Artery Calcium Score of Zero



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER
VOL. 80, NO. 21, 2022

ORIGINAL INVESTIGATIONS

Coronary Calcium Scoring Improves Risk Prediction in Patients With Suspected Obstructive Coronary Artery Disease

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ABSTRACT

BACKGROUND In patients with suspected obstructive coronary artery disease (CAD), the risk factor-weighted clinical likelihood (RF-CL) model and the coronary artery calcium score-weighted clinical likelihood (CACS-CL) model improves the identification of obstructive CAD compared with basic pretest probability (PTP) models.

OBJECTIVES The aim of this study was to assess the prognostic value of the new models.

METHODS The incidences of myocardial infarction and death were stratified according to categories by the RF-CL and CACS-CL and compared with categories by the PTP model. We used cohorts from a Danish register (n = 41,177) and a North American randomized study (n = 3,952). All patients were symptomatic and were referred for diagnostic testing because of clinical indications.

RESULTS Despite substantial down-reclassification of patients to a likelihood ≤5% of CAD with either the RF-CL (45%) or CACS-CL (60%) models compared with the PTP (18%), the annualized event rates of myocardial infarction and death were low using all 3 models; RF-CL 0.51% (95% CI: 0.46-0.56), CACS-CL 0.48% (95% CI: 0.44-0.56), and PTP 0.37% (95% CI: 0.31-0.44), respectively. Overall, comparison of the predictive power of the 3 models using Harrell's C-statistics demonstrated superiority of the RF-CL (0.64 [95% CI: 0.63-0.65]) and CACS-CL (0.69 [95% CI: 0.67-0.70]) compared with the PTP model (0.61 [95% CI: 0.60-0.62]).

CONCLUSIONS The simple clinical likelihood models that include classical risk factors or risk factors combined with CACS provide improved risk stratification for myocardial infarction and death compared with the standard PTP model. Hence, the optimized RF-CL and CACS-CL models identify 2.5 and 3.3 times more patients, respectively, who may not benefit from further diagnostic testing. (J Am Coll Cardiol 2022;80:1965-1977) © 2022 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on www.jacc.org/journal/jacc.

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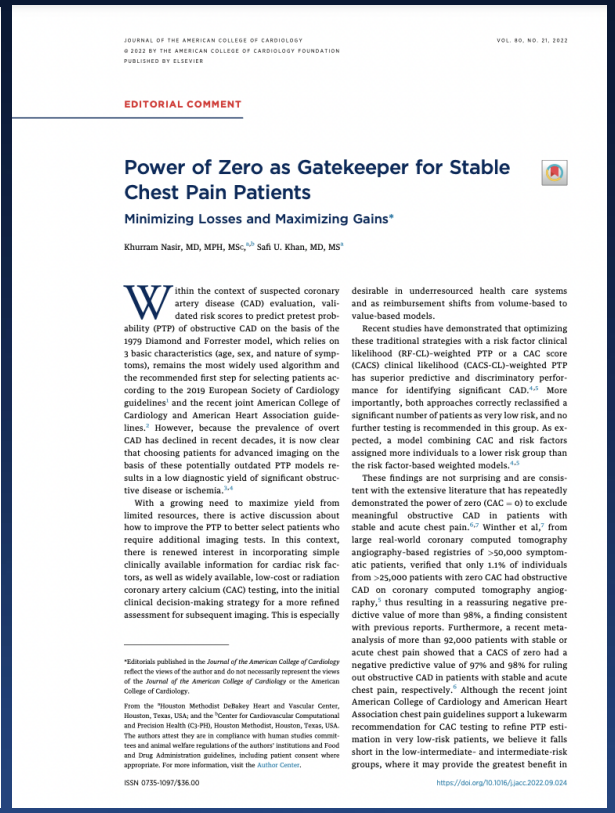
Manuscript received August 23, 2022; accepted August 26, 2022.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2022.08.805

Winther et al. J Am Coll Cardiol 2022;80:1965-77



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VOL. 80, NO. 21, 2022

EDITORIAL COMMENT

Power of Zero as Gatekeeper for Stable Chest Pain Patients

Minimizing Losses and Maximizing Gains*

Khurram Nasir, MD, MPH, MSc,[a,b] Safi U. Khan, MD, MS[a]

Within the context of suspected coronary artery disease (CAD) evaluation, validated risk scores to predict pretest probability (PTP) of obstructive CAD on the basis of the 1979 Diamond and Forrester model, which relies on 3 basic characteristics (age, sex, and nature of symptoms), remains the most widely used algorithm and the recommended first step for selecting patients according to the 2019 European Society of Cardiology guidelines[1] and the recent joint American College of Cardiology and American Heart Association guidelines.[2] However, because the prevalence of overt CAD has declined in recent decades, it is now clear that choosing patients for advanced imaging on the basis of these potentially outdated PTP models results in a low diagnostic yield of significant obstructive disease or ischemia.[3,4]

With a growing need to maximize yield from limited resources, there is active discussion about how to improve the PTP to better select patients who require additional imaging tests. In this context, there is renewed interest in incorporating simple clinically available information for cardiac risk factors, as well as widely available, low-cost or radiation coronary artery calcium (CAC) testing, into the initial clinical decision-making strategy for a more refined assessment for subsequent imaging. This is especially desirable in underresourced health care systems and as reimbursement shifts from volume-based to value-based models.

Recent studies have demonstrated that optimizing these traditional strategies with a risk factor clinical likelihood (RF-CL)–weighted PTP or a CAC score (CACS) clinical likelihood (CACS-CL)–weighted PTP has superior predictive and discriminatory performance for identifying significant CAD.[4,5] More importantly, both approaches correctly reclassified a significant number of patients as very low risk, and no further testing is recommended in this group. As expected, a model combining CAC and risk factors assigned more individuals to a lower risk group than the risk factor-based weighted models.[4,5]

These findings are not surprising and are consistent with the extensive literature that has repeatedly demonstrated the power of zero (CAC = 0) to exclude meaningful obstructive CAD in patients with stable and acute chest pain.[6,7] Winther et al,[7] from large real-world coronary computed tomography angiography-based registries of >50,000 symptomatic patients, verified that only 1.1% of individuals from >25,000 patients with zero CAC had obstructive CAD on coronary computed tomography angiography,[7] thus resulting in a reassuring negative predictive value of more than 98%, a finding consistent with previous reports. Furthermore, a recent meta-analysis of more than 92,000 patients with stable or acute chest pain showed that a CACS of zero had a negative predictive value of 97% and 98% for ruling out obstructive CAD in patients with stable and acute chest pain, respectively.[6] Although the recent joint American College of Cardiology and American Heart Association chest pain guidelines support a lukewarm recommendation for CAC testing to refine PTP estimation in very low-risk patients, we believe it falls short in the low-intermediate- and intermediate-risk groups, where it may provide the greatest benefit in

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the author and do not necessarily represent the views of the *Journal of the American College of Cardiology* or the American College of Cardiology.

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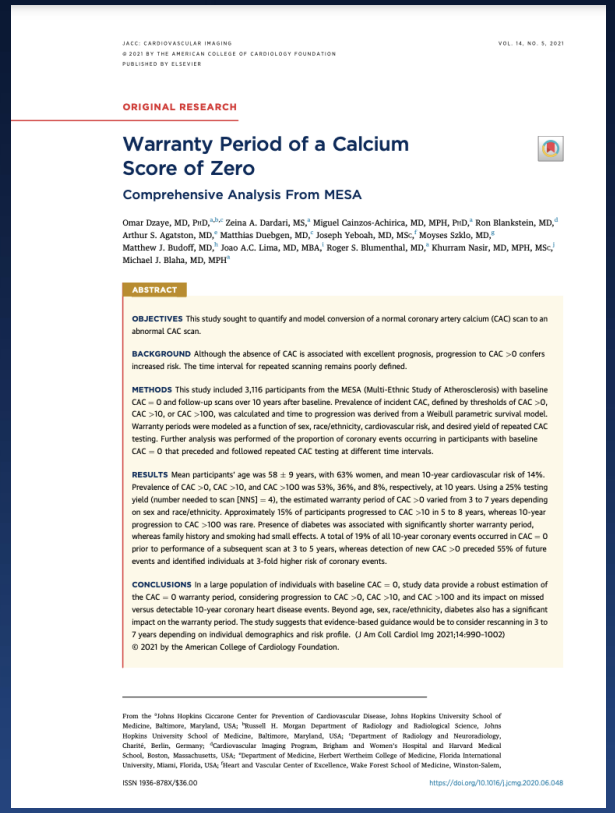
ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2022.09.024

Nasir and Khan. J Am Coll Cardiol 2022;80:1978-80



JACC: CARDIOVASCULAR IMAGING
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VOL. 14, NO. 5, 2021

ORIGINAL RESEARCH

Warranty Period of a Calcium Score of Zero

Comprehensive Analysis From MESA

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ABSTRACT

OBJECTIVES This study sought to quantify and model conversion of a normal coronary artery calcium (CAC) scan to an abnormal CAC scan.

BACKGROUND Although the absence of CAC is associated with excellent prognosis, progression to CAC >0 confers increased risk. The time interval for repeated scanning remains poorly defined.

METHODS This study included 3,116 participants from the MESA (Multi-Ethnic Study of Atherosclerosis) with baseline CAC = 0 and follow-up scans over 10 years after baseline. Prevalence of incident CAC, defined by thresholds of CAC >0, CAC >10, or CAC >100, was calculated and time to progression was derived from a Weibull parametric survival model. Warranty periods were modeled as a function of sex, race/ethnicity, cardiovascular risk, and desired yield of repeated CAC testing. Further analysis was performed of the proportion of coronary events occurring in participants with baseline CAC = 0 that preceded and followed repeated CAC testing at different time intervals.

RESULTS Mean participants' age was 58 ± 9 years, with 63% women, and mean 10-year cardiovascular risk of 14%. Prevalence of CAC >0, CAC >10, and CAC >100 was 53%, 36%, and 8%, respectively, at 10 years. Using a 25% testing yield (number needed to scan [NNS] = 4), the estimated warranty period of CAC >0 varied from 3 to 7 years depending on sex and race/ethnicity. Approximately 15% of participants progressed to CAC >10 in 5 to 8 years, whereas 10-year progression to CAC >100 was rare. Presence of diabetes was associated with significantly shorter warranty period, whereas family history and smoking had small effects. A total of 19% of all 10-year coronary events occurred in CAC = 0 prior to performance of a subsequent scan at 3 to 5 years, whereas detection of new CAC >0 preceded 55% of future events and identified individuals at 3-fold higher risk of coronary events.

CONCLUSIONS In a large population of individuals with baseline CAC = 0, study data provide a robust estimation of the CAC = 0 warranty period, considering progression to CAC >0, CAC >10, and CAC >100 and its impact on missed versus detectable 10-year coronary heart disease events. Beyond age, sex, race/ethnicity, diabetes also has a significant impact on the warranty period. The study suggests that evidence-based guidance would be to consider rescanning in 3 to 7 years depending on individual demographics and risk profile. (J Am Coll Cardiol Img 2021;14:990–1002)
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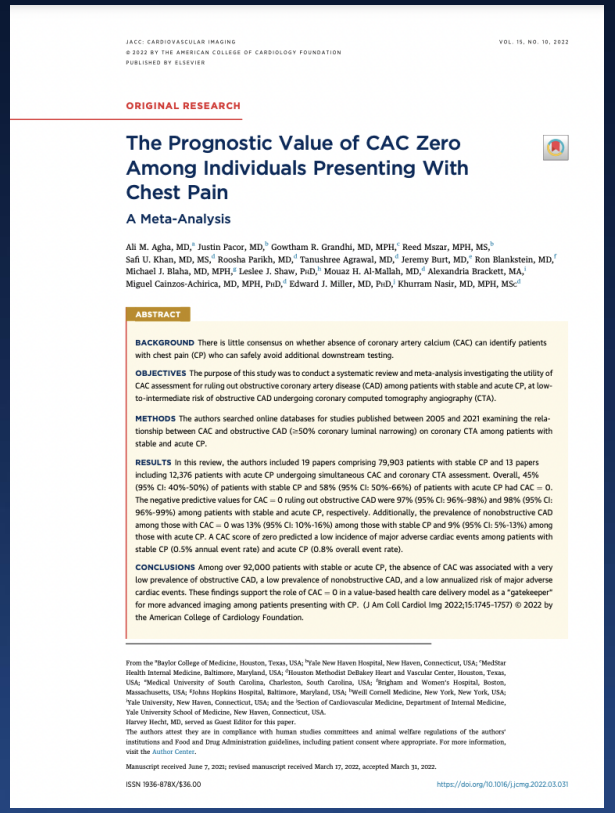
ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2020.06.048

Dzaye et al. JACC Cardiovasc Imaging 2021;14:990-1002



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VOL. 15, NO. 10, 2022

ORIGINAL RESEARCH

The Prognostic Value of CAC Zero Among Individuals Presenting With Chest Pain

A Meta-Analysis

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ABSTRACT

BACKGROUND There is little consensus on whether absence of coronary artery calcium (CAC) can identify patients with chest pain (CP) who can safely avoid additional downstream testing.

OBJECTIVES The purpose of this study was to conduct a systematic review and meta-analysis investigating the utility of CAC assessment for ruling out obstructive coronary artery disease (CAD) among patients with stable and acute CP, at low-to-intermediate risk of obstructive CAD undergoing coronary computed tomography angiography (CTA).

METHODS The authors searched online databases for studies published between 2005 and 2021 examining the relationship between CAC and obstructive CAD (≥50% coronary luminal narrowing) on coronary CTA among patients with stable and acute CP.

RESULTS In this review, the authors included 19 papers comprising 79,903 patients with stable CP and 13 papers including 12,376 patients with acute CP undergoing simultaneous CAC and coronary CTA assessment. Overall, 45% (95% CI: 40%-50%) of patients with stable CP and 58% (95% CI: 50%-66%) of patients with acute CP had CAC = 0. The negative predictive values for CAC = 0 ruling out obstructive CAD were 97% (95% CI: 96%-98%) and 98% (95% CI: 96%-99%) among patients with stable and acute CP, respectively. Additionally, the prevalence of nonobstructive CAD among those with CAC = 0 was 13% (95% CI: 10%-16%) among those with stable CP and 9% (95% CI: 5%-13%) among those with acute CP. A CAC score of zero predicted a low incidence of major adverse cardiac events among patients with stable CP (0.5% annual event rate) and acute CP (0.8% overall event rate).

CONCLUSIONS Among over 92,000 patients with stable or acute CP, the absence of CAC was associated with a very low prevalence of obstructive CAD, a low prevalence of nonobstructive CAD, and a low annualized risk of major adverse cardiac events. These findings support the role of CAC = 0 in a value-based health care delivery model as a "gatekeeper" for more advanced imaging among patients presenting with CP. (J Am Coll Cardiol Img 2022;15:1745-1757) © 2022 by the American College of Cardiology Foundation.

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Harvey Hecht, MD, served as Guest Editor for this paper.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 7, 2021; revised manuscript received March 17, 2022, accepted March 31, 2022.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2022.03.031

Agha et al. JACC Cardiovasc Imaging 2022;15:1745-57

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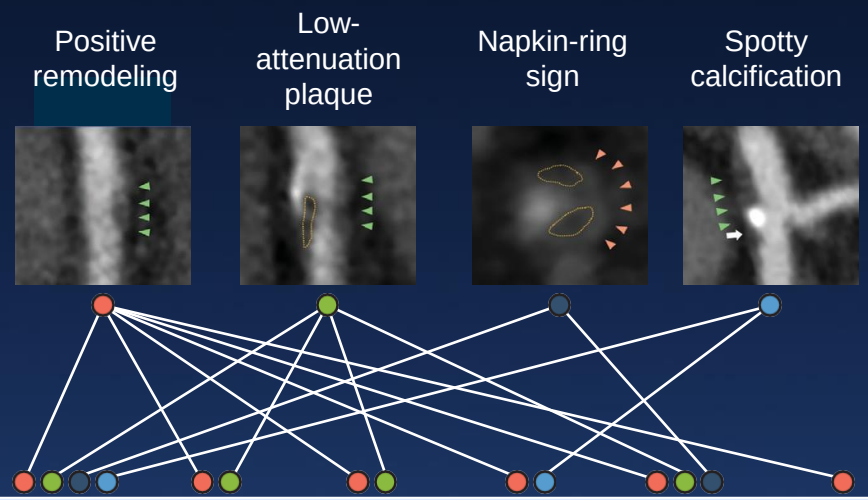
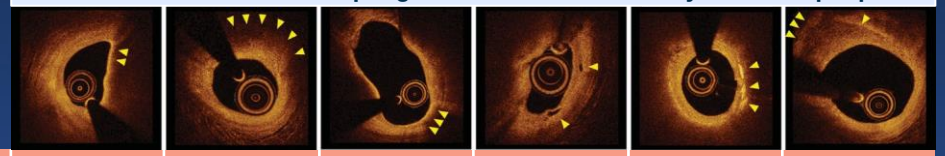
Completeness of Intravascular Imaging Detection of Vulnerable Plaques

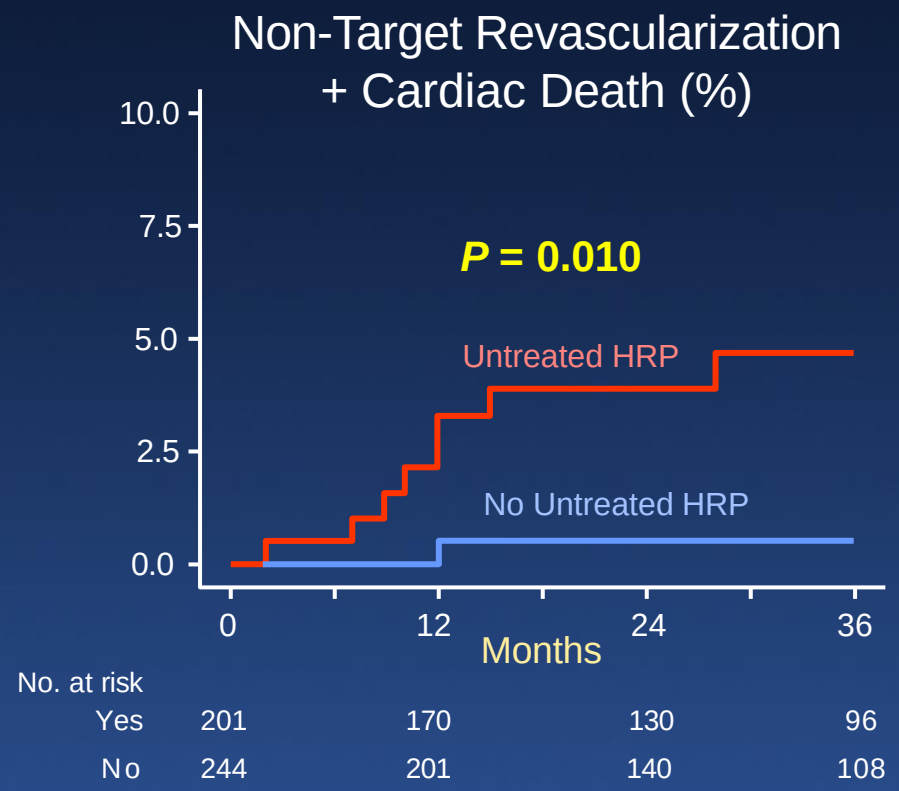
	# of Pts	Length of artery imaged	# of NC events	Did baseline intravascular imaging identify lesions responsible for NC events	
				Yes	No
PROSPECT	698	193mm	106	55 (53%)	61 (47%)
LRP	1271	96mm	73	41 (56%)	32 (44%)
PROSPECT II	898	224mm	78	44 (56%)	34 (44%)

Stone et al. N Engl J Med 2011;361:226-35
Waksman et al. Lancet. 2019;394:1629-37
Erlinge et al. Lancet. 2021;397:985-95
Case et al. Cardiovasc Revasc Med. 2022;39:1-5

Correlation of CTA High-risk Plaques with OCT



	TCFA	Lipid-rich	Macro-phages	Micro-vessels	Cholesterol crystals	Layered plaque
						
Positive remodeling	+	+++	+++	++	+	++
Low-attenuation plaque	+	+++	+++	++	+	++
Napkin-ring sign	+	+++	+++	++	+	++
Spotty calcification	+	+++	++	++	+	++
Non-HRP	–	++	++	+	–	++



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Kinoshita et al. J Am Coll Cardiol Img. 2024;17:382–91.

Causes of ACS (STEMI/NSTEMI) In Vivo OCT Imaging

	#		Ruptured plaques	Plaque erosions	Calcified nodules	SCAD	Other or Indeterminate
Guagliumi et al. JACC Cardiovasc Interv. 2014;7:958-68	140	STEMI	69	35*		2	34
Nishiguchi, et al. Eur Heart J Acute Cardiovasc Care. 2016;5:263-70	326	ACS	160	153*		13	
Wang et al. Eur Heart J Cardiovasc Imaging. 2015;16:1381-9	72	STEMI	37	25*	2		8
Jia, et al. J Am Coll Cardiol 2013;62:1748-58	132	ACS	55	39	10	3	22**
Higuma et al. JACC Cardiovasc Interv 2015;8:1166-76	112	STEMI	72	30	9	1	
Kajander et al. Eurointervention 2016;12:716-23	70	STEMI	34	31*	5		
Kwon et al, Korean Circulation J 2016;46:499-506	133	ACS	90	43			
Hansen et al. Coron Artery Dis 2020;31:671-7	75	STEMI	52	23			
Ino et al. Circ J 2022;86:1388-96	141	STEMI/NSTEMI	85	45	11		
Fang. JACC Cardiovasc Imaging 2022;15:672-81	464	STEMI/NSTEMI	271	117	11		
Kondo et al. J Am Heart Assoc. 2023;12:e030412. doi: 10.1161/JAHA.123.030412	695	STEMI/NSEMI/ACS	411	178	28	1	77
Total	**1896**		**57%**	**38%**	**5%**		

*included all plaques with intact fibrous caps

** included tight stenosis, coronary spasm, fissure, Takotsubos, and lesions without any specific characteristics

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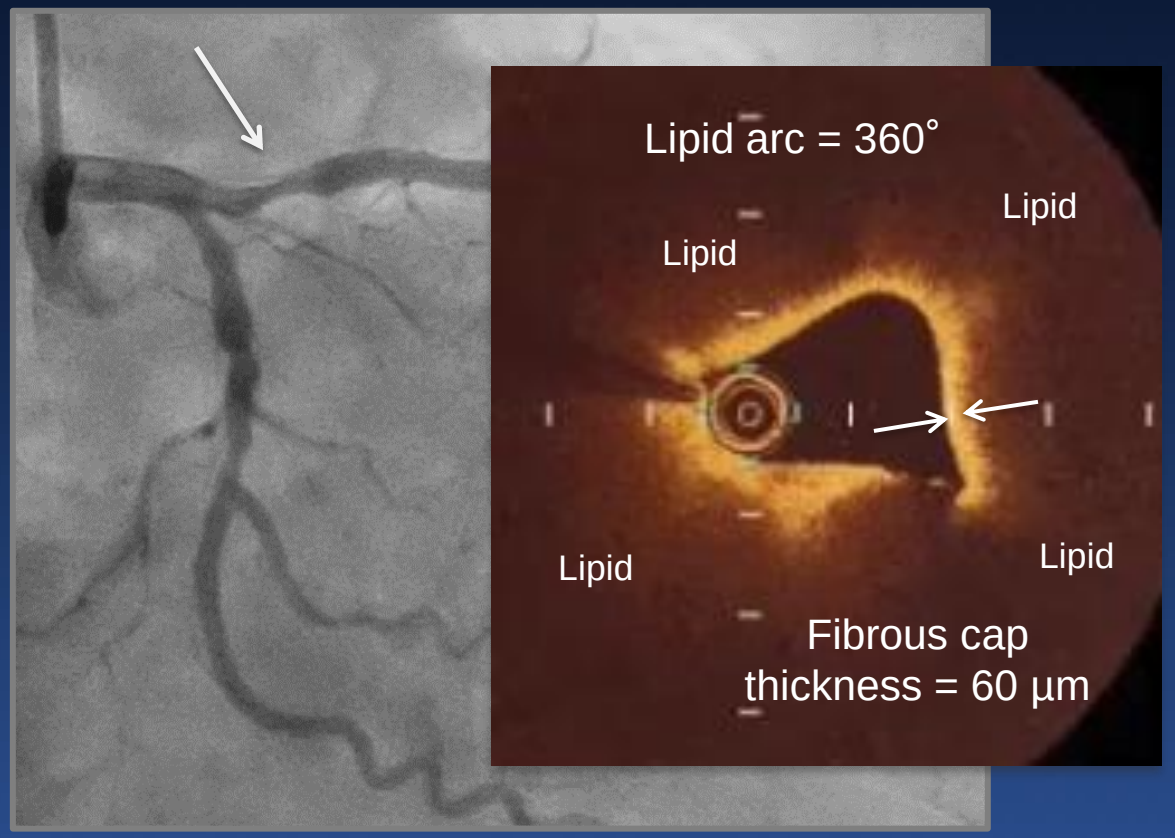
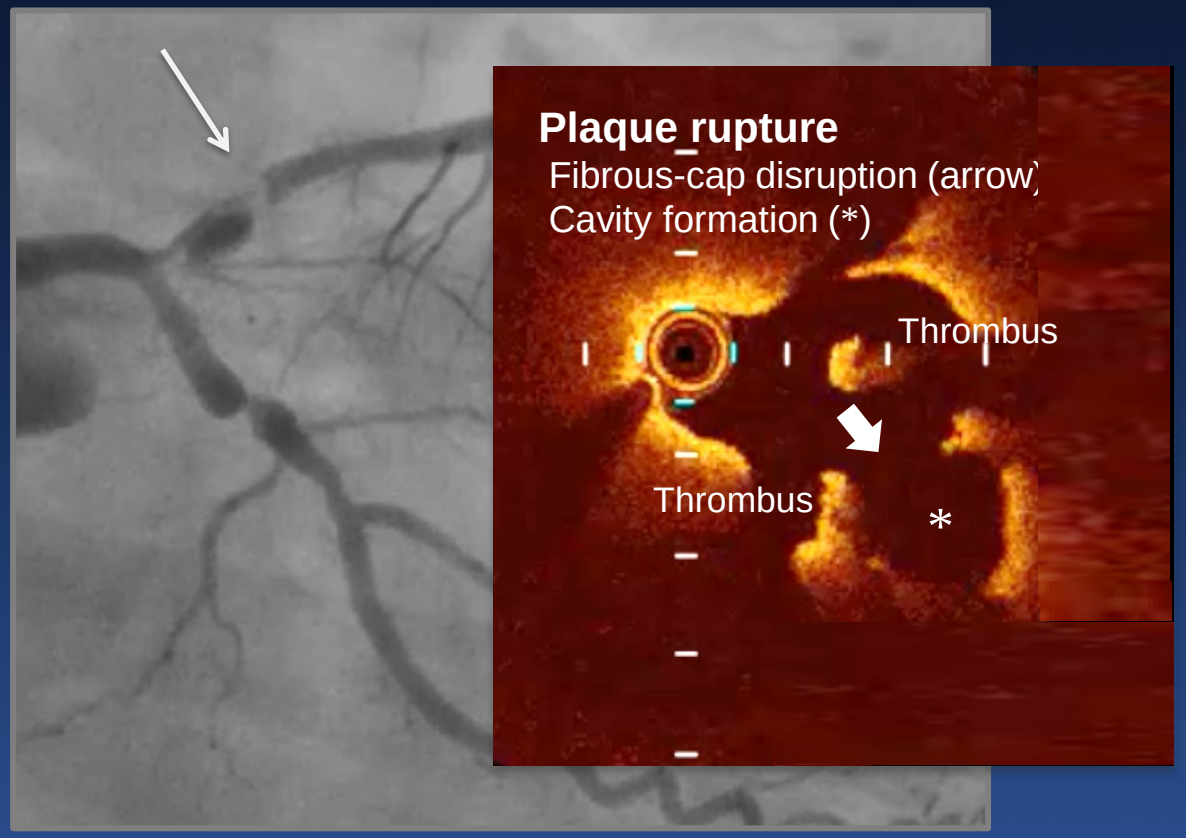
Baseline



7 months follow-up



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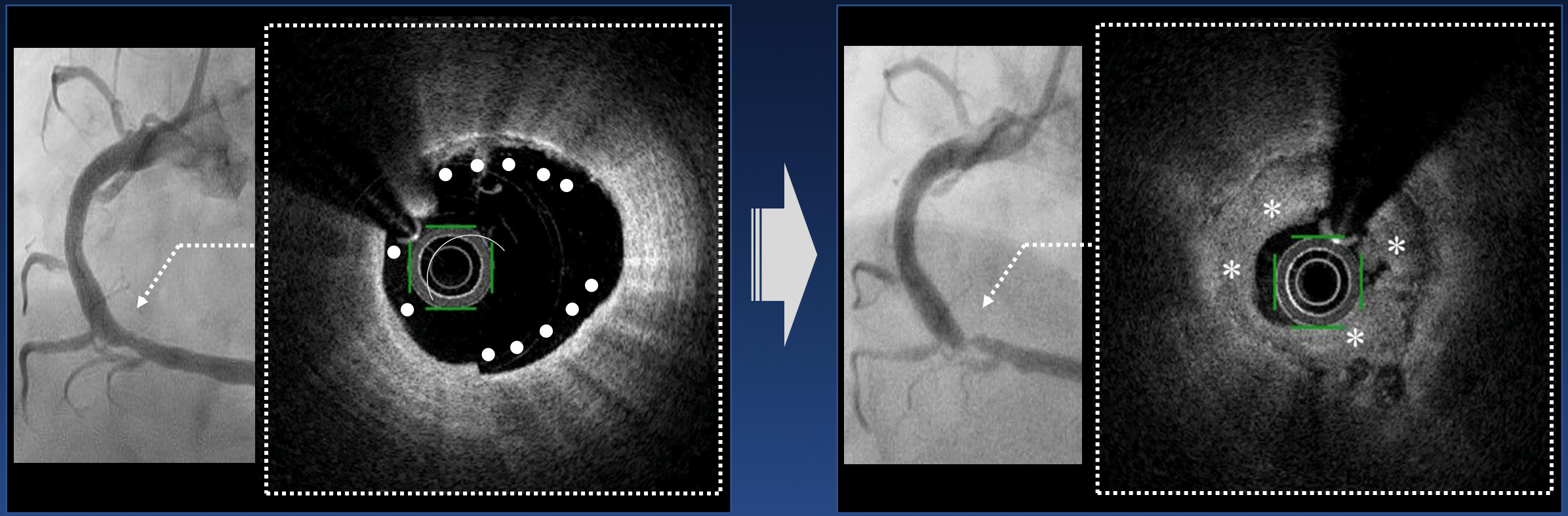
Baseline

8 months follow-up



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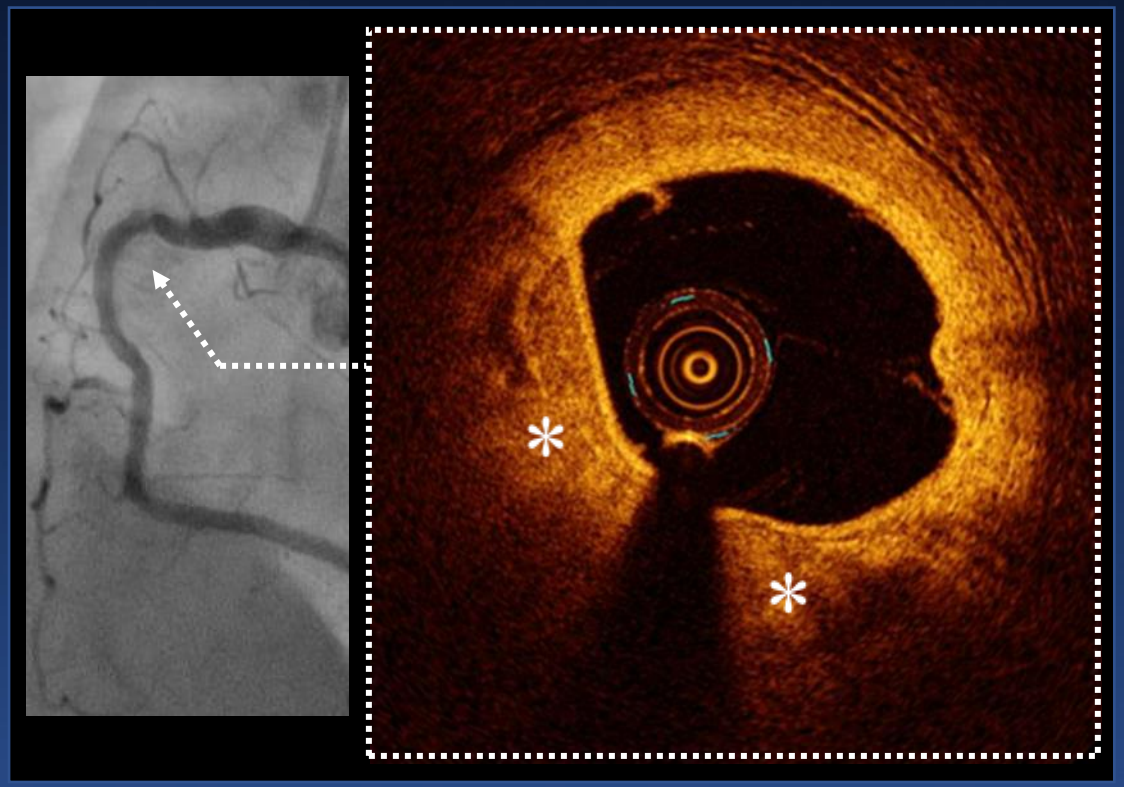
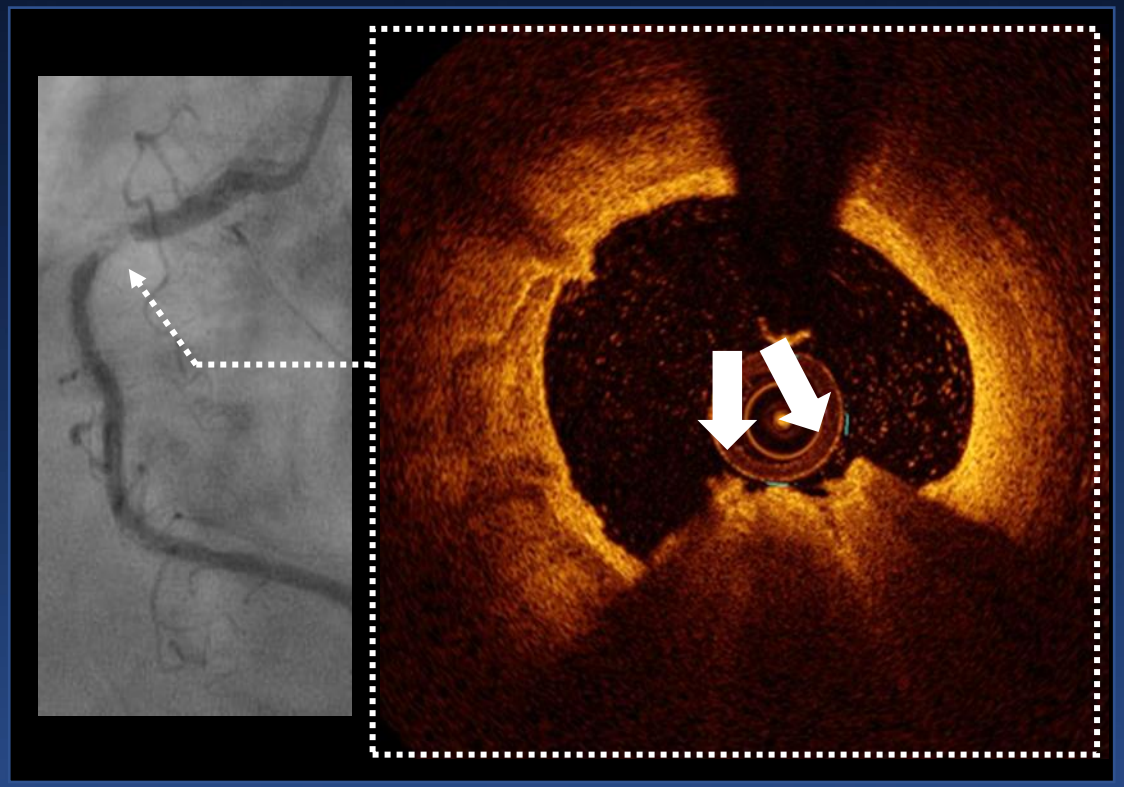
Baseline

9 months follow-up





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I remain skeptical. For many reasons, PREVENT has not changed my mind. My questions about the diagnosis and treatment of vulnerable plaque persist. However, it is time to re-open the discussion to plan the next chapter in vulnerable plaque diagnosis and treatment, especially large scale clinical trials.