Intracoronary Calcium: From Spotty Calcium to Calcified Nodules to In-stent Restenosis

Gary S. Mintz, MD

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Spotty Calcium

Spotty Calcification in ACS/MI

	MI (n=61)	ACS (n=70)	Stable Angina (n=47)
No calcium	26%	41%	21%
Spotty calcium	51%	40%	30%
Intermediate calcium	15%	16%	11%
Extensive calcium	8%	3%	38%

p<0.0001

- ***Spotty calcification = only small calcium deposits <90°***
- ***Intermediate calcification = 90-180° in at least 1cross-section***
- ***Extensive calcificaiton = >180° in at least 1 cross-section***

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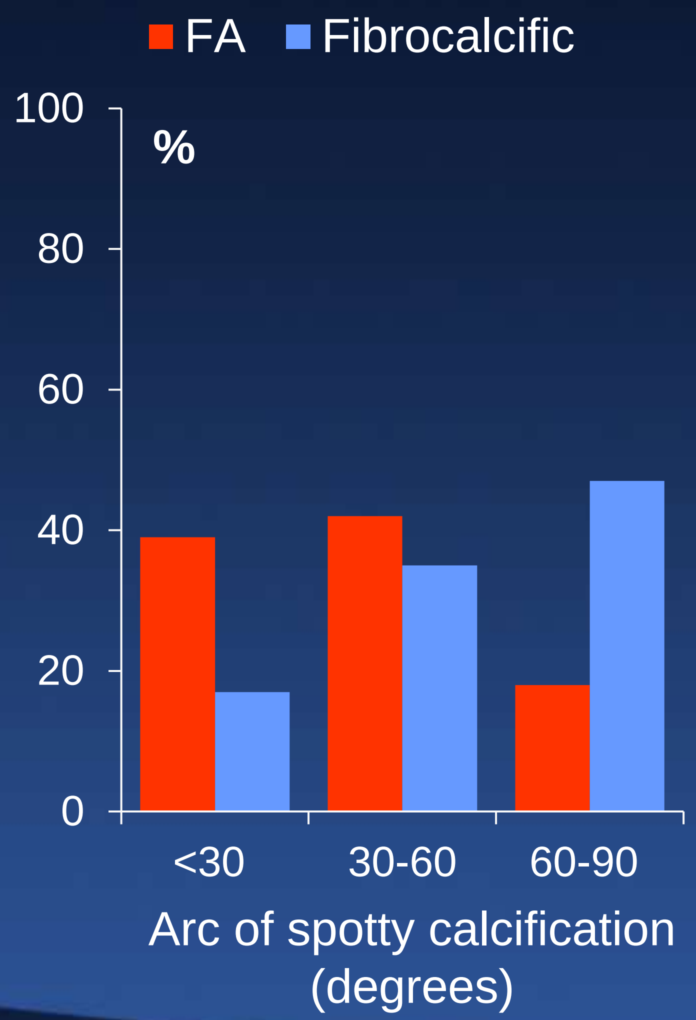
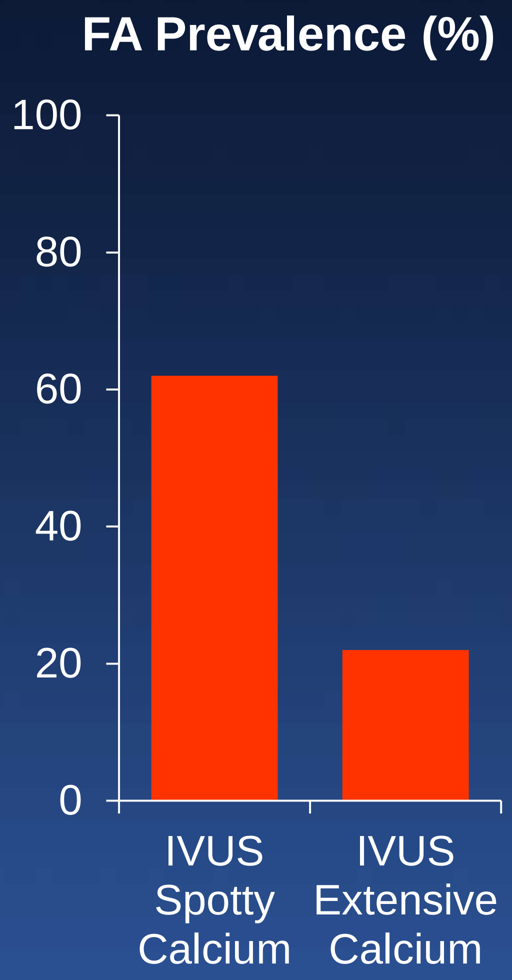
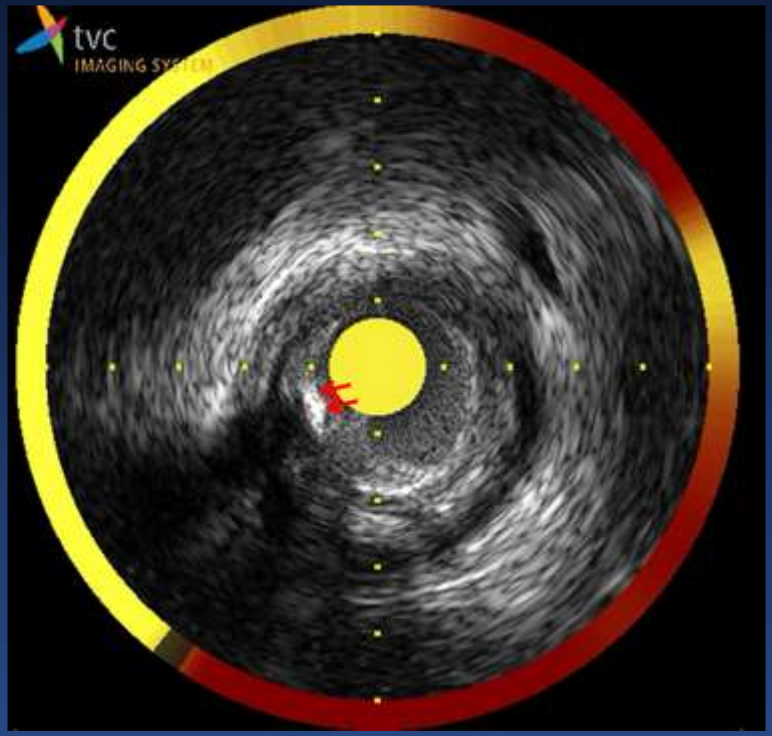
Ehara et al. Circulation 2004;110:3424-9

Prevalence of spotty calcification and fibroatheromas in histologic samples







Pu et al. J Am Coll Cardiol 2014;63:2220-3

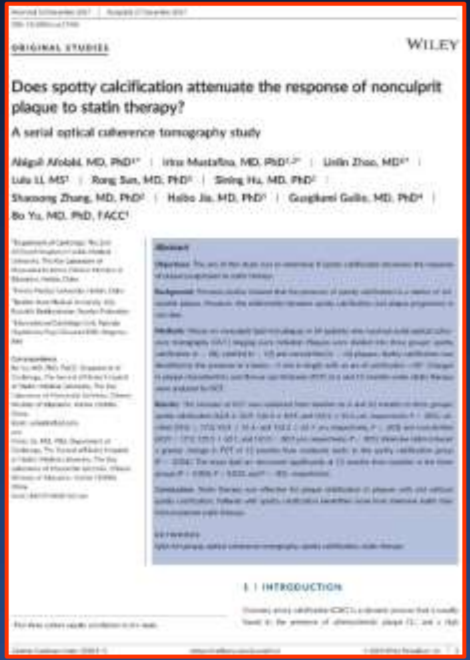
Spotty Calcium and Atherosclerosis Progression

From the Cleveland Clinic Core Laboratory

	Spotty Calcium	No Calcium	P-value
Patients	922	425	
Baseline PAV	36.0±7.5%	29.0±8.5%	<0.001
ΔPAV	0.43±0.07%	0.02±0.10%	0.002
Adjusted ΔPAV	0.68±0.12%	0.05±0.17%	0.002

adjusted for clinical characteristics, LDL and HDL, statin use, and baseline PAV

In OCT studies


ORIGINAL STUDIES
WILEY
Does spotty calcification attenuate the response of nonculprit plaque to statin therapy?
A serial optical coherence tomography study
Abigail Afolabi, MD, PhD | Irina Mustafina, MD, PhD | Linlin Zhao, MD | Lulu Li, MS | Rong Sun, MD, PhD | Sining Hu, MD, PhD | Shaosong Zhang, MD, PhD | Haibo Jia, MD, PhD | Bo Yu, MD, PhD, FACC
Abstract
1 | INTRODUCTION

Pts with spotty calcification benefitted more from intensive statin than from moderate statin therapy.

Kataoka et al. J Am Coll Cardiol 2012;59:1592-7
Afolabi et al. Catheter Cardiovasc Interv. 2018;91:582-590

Microcalcification as a stress concentrator increasing fibrous cap instability and promoting rupture

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Effect of tissue properties, shape and orientation of microcalcifications on vulnerable cap stability using different hyperelastic constitutive models

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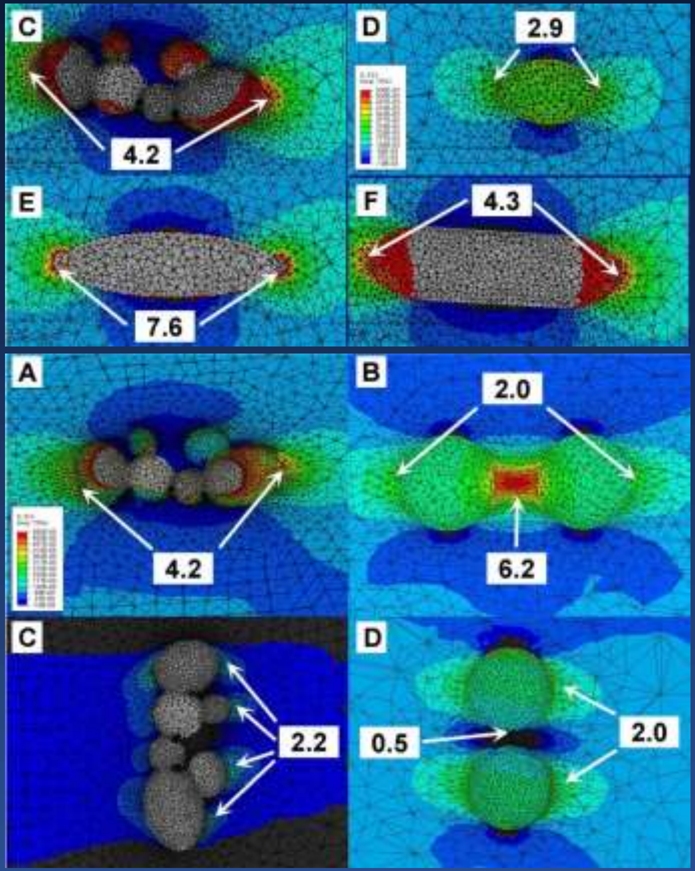
[2]The Graduate Center of The City University of New York, New York, NY, USA

Abstract

Approximately half of all cardiovascular deaths associated with acute coronary syndrome occur when the thin fibrous cap tissue overlying the necrotic core in a coronary vessel is torn, ripped or fissured under the action of high blood pressure. From a biomechanics point of view, the rupture of an atheroma is due to increased mechanical stresses in the lesion, in which the ultimate stress (i.e. peak circumferential stress (PCS) at failure) of the tissue is exceeded. Several factors including the cap thickness, morphology, residual stresses and tissue composition of the atheroma have been shown to affect the PCS. Also important, we recently demonstrated that microcalcifications (μCalcs) > 5 μm are a common feature in human atheroma caps, which behave as local stress concentrators, increasing the local tissue stress by at least a factor of two surpassing the ultimate stress threshold for cap tissue rupture. In the present study, we used both idealized μCalcs with spherical shape and actual μCalcs from human coronary atherosclerotic caps, to determine their effect on increasing the circumferential stress in the fibroatheroma cap using different hyperelastic constitutive models. We have found that the stress concentration factor (SCF) produced by μCalcs in the fibroatheroma cap is affected by the material tissue properties, μCalcs spacing, aspect ratio and their alignment relative to the tensile axis of the cap.

Keywords

micro computed tomography; vulnerable plaque; microcalcifications; fibrous cap rupture



- Microcalcifications >5µm are a common feature in human fibroatheroma caps.
- The stress concentration factor produced by microcalcifications is affected by the spacing, aspect ratio, and alignment relative to the tensile axis of the cap.

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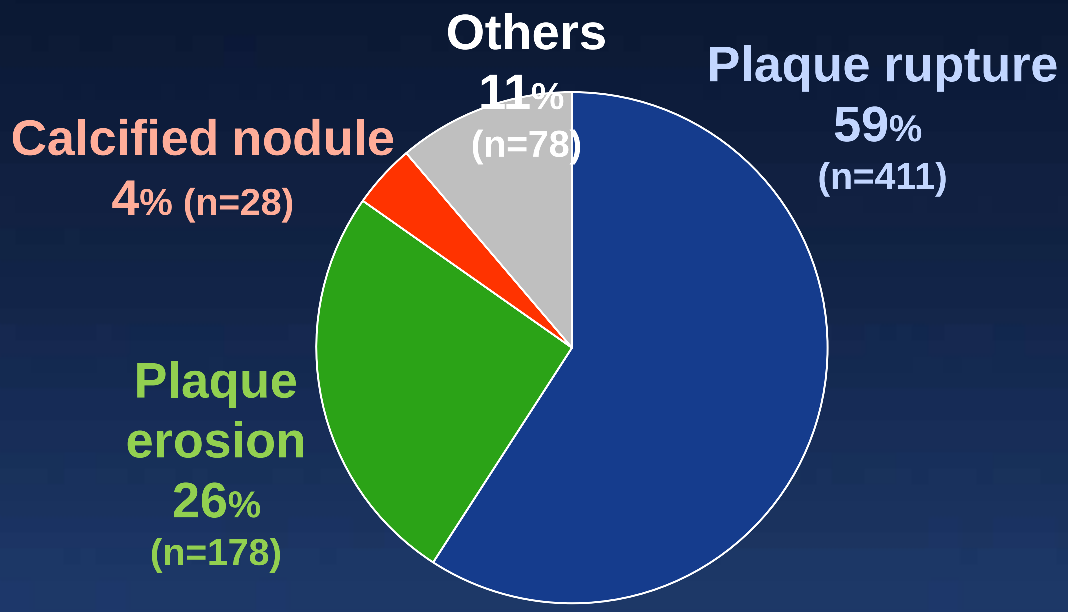
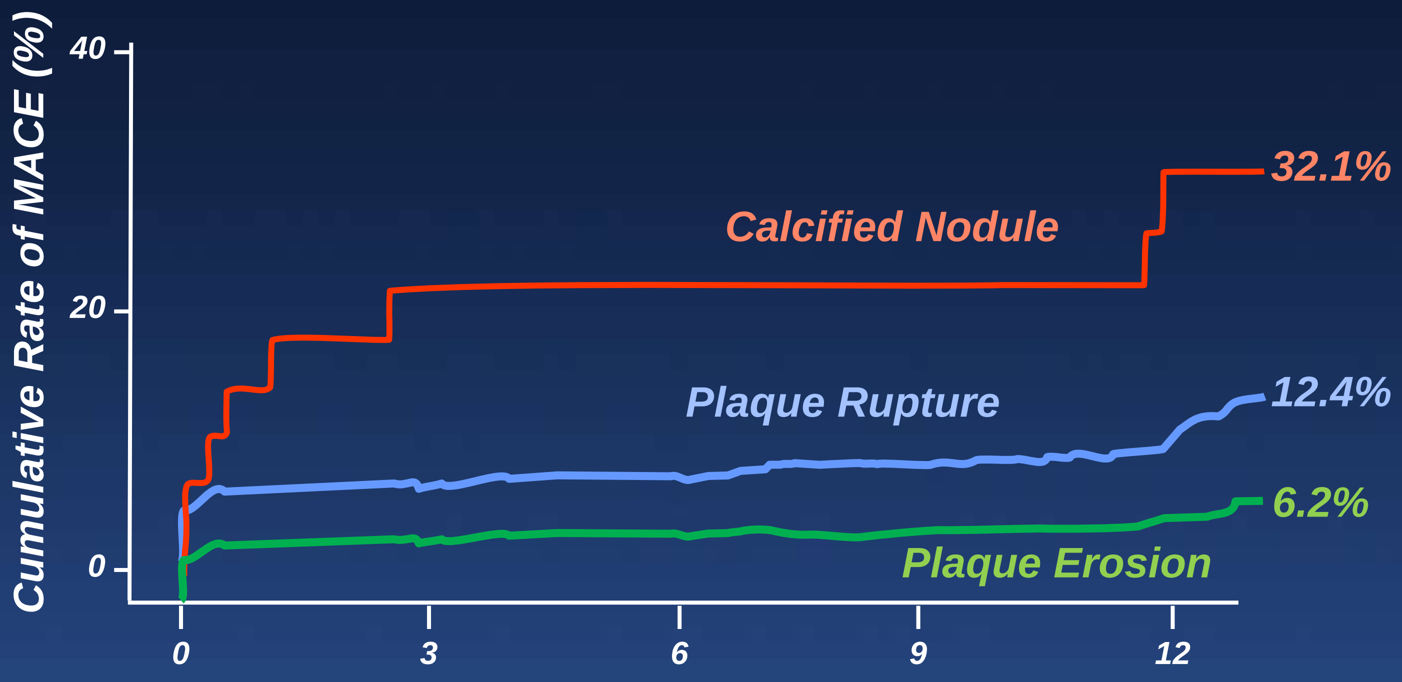
Cardoso et al. J Biomech. 2014;47:870-7

Calcified Nodule

MACE Stratified by ACS Causes in TACTICS Registry



Others	
Significant stenosis	64 (9.1%)
Coronary spasm	7 (1.0%)
Ectasia	3 (0.4%)
Embolism	3 (0.4%)
Spontaneous coronary dissection	1 (0.1%)



Number at Risk

	0	3	6	9	12
Calcified Nodule	28	20	20	20	15
Plaque Rupture	411	382	375	371	289
Plaque Erosion	178	171	171	170	151

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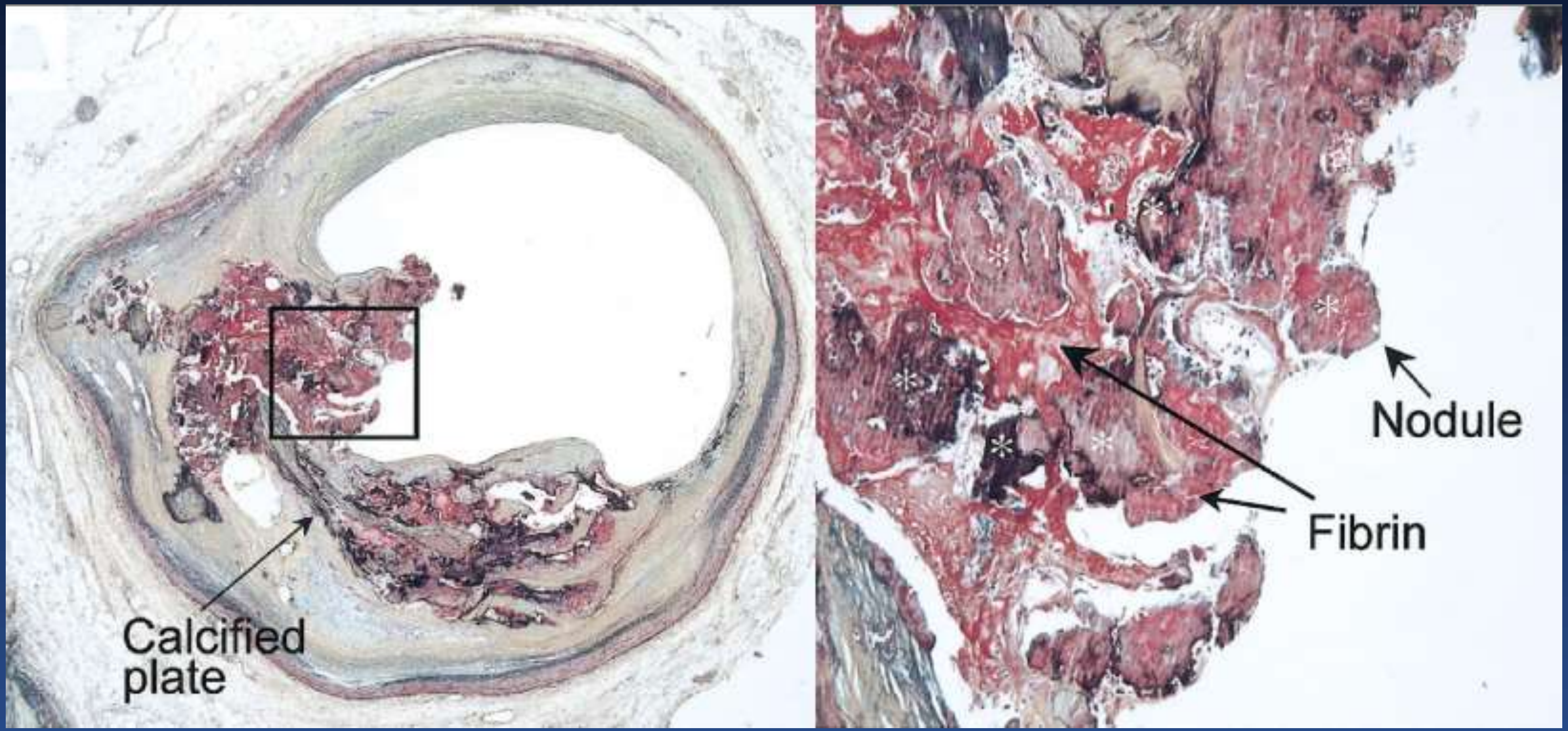
Shinke. TCT2022



Virmani et al. J Am Coll Cardiol 2006;:C13-8

Eruptive calcified nodule

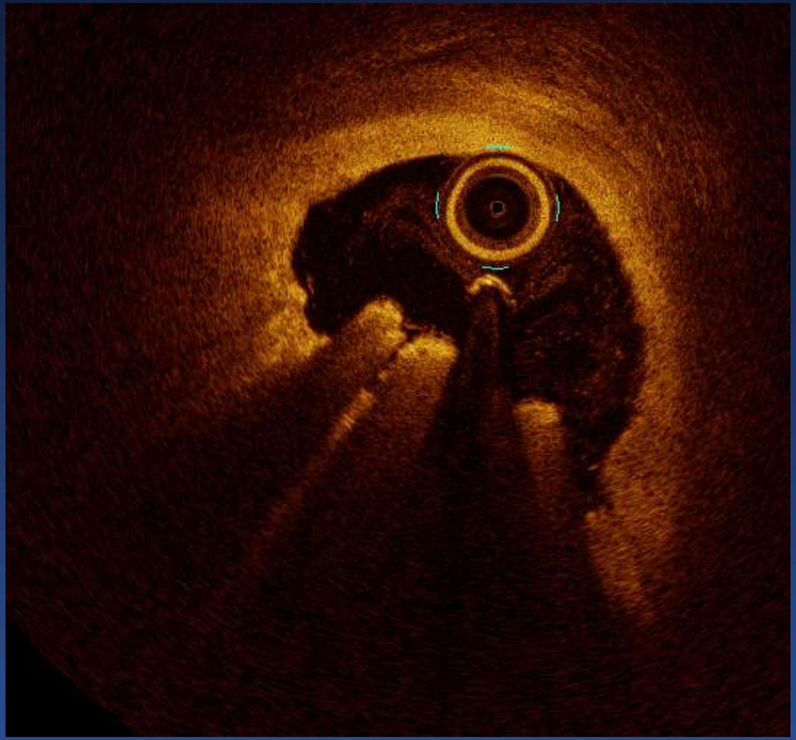
- **Fibrous cap disruption and protruding into the luminal space**
- **Absence of endothelium and overlying platelet/fibrin thrombus**
- Third most common cause of an acute coronary syndrome
- Clustering of smaller calcified nodules
- (Thought to be initiated through fragmentation of necrotic core calcifications and associated with a healed fibroatheroma and intraplaque hemorrhage

Non-eruptive nodular calcium

- **Occurs within the plaque, is related to the extent of underlying calcification, does not involve disruption of the fibrous cap, and (therefore) does not involve contact with the lumen**
- **No thrombus**
- Nodules covered by an intact fibrous cap
- Areas of nodular calcification of varying sizes

Virmani et al. Arterioscler Thromb Vasc Biol. 2000;20:1262–75
Virmani et al. J Am Coll Cardiol. 2006;47:C13–C18
Burke et al. Herz. 2001;26:239–44
Sato et al. Atherosclerosis. 2021;318:40-42

Eruptive calcified nodule



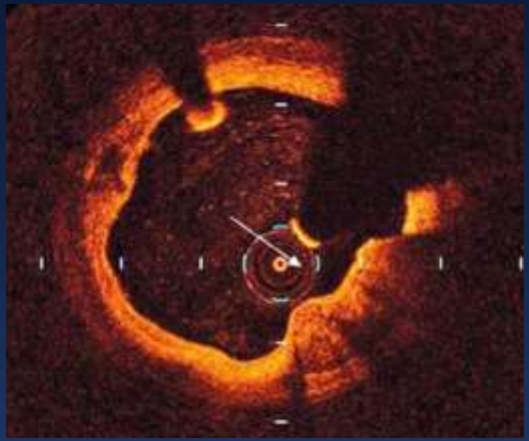
Non-eruptive nodular calcium

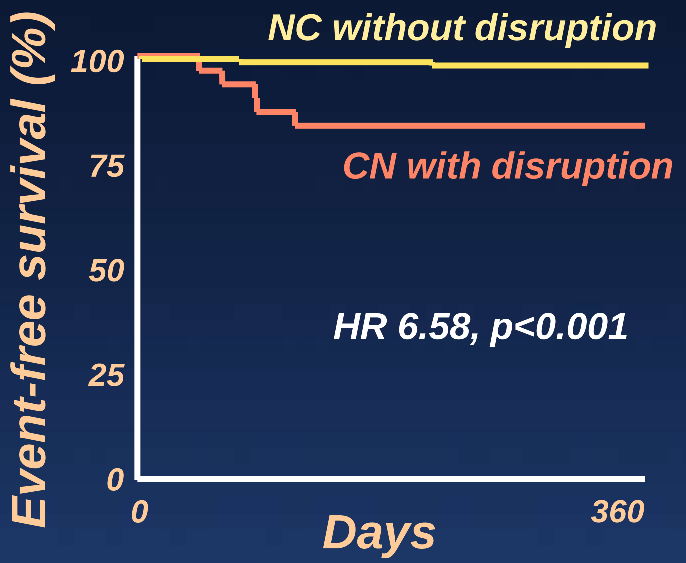
Using standard resolution IVUS, it is difficult to identify thrombus or an intact versus a ruptured fibrous cap. Thus, it is likely that published articles employing standard resolution IVUS used the term calcified nodule indiscriminately to include eruptive CN, non-eruptive NC, or both. At most, the clinical scenario of patients included in some of these articles may be used to infer the underlying morphology *particularly if a study is limited to ACS patients*.

Unlike standard resolution IVUS (and there are currently no studies using high definition IVUS), OCT can differentiate an eruptive CN from non-eruptive NC.

Clinical outcomes of 222 calcified nodules detected by OCT in 1776 non-culprit LAD plaques in 180 pts

Nodular calcium without fibrous cap disruption





After correction for baseline clinical differences and single or combined presence of the 4 CLIMA features of plaque vulnerability, an CN with disruption was confirmed as an independent predictor of events

Calcified nodule with fibrous cap disruption

	CN with disruption	NC without disruption	P-value
#	30	150	
Cardiac death +TV MI	20.0%	2.7%	<0.001
Cardiac death	13.3%	2.0%	0.001
TV MI	6.7%	10.7%	0.022
TVR	6.7%	0.7%	0.108

Prati et al. EuroIntervention 2020;16:380-6

Stent Underexpansion

Predictors of DES Early ST, Restenosis, MACE, or DoCE

	IVUS		OCT
	Early ST	Restenosis/MACE	Restenosis/MACE/DoCE
Small MSA or underexpansion in stable lesions Small MLA in ACS/MI lesions	•Fujii et al. J Am Coll Cardiol 2005;45:995-8 •Okabe et al. Am J Cardiol. 2007;100:615-20 •Liu et al. JACC Cardiovasc Interv. 2009;2:428-34 •Choi et al. Circ Cardiovasc Interv 2011;4:239-47	•Sonoda et al. J Am Coll Cardiol 2004;43:1959-63 •Hong et al. Eur Heart J 2006;27:1305-10 •Doi et al JACC Cardiovasc Interv. 2009;2:1269-75 •Fujii et al. Circulation 2004;109:1085-1088 •Kang et al. Circ Cardiovasc Interv 2011;4:9-14 •Choi et al. Am J Cardiol 2012;109:455-60 •Song et al. Catheter Cardiovasc Interv 2014;83:873-8 •Kang et al. PLoS One 2015;10(10):e0140421 •Hong et al. JAMA 2015;314(:2155-63. •Lee et al. Rev Esp Cardiol 2017;70:88-95 •Katagiri et al. Catheter Cardiovasc Interv. 2019 Jan 31. doi: 10.1002/ccd.28105. •Kim et al. EuroIntervention. 2020;16:e480-e488 •Park et al. JACC Cardiovasc Interv 2020;13:1403-13 •Ladwiniec et al. EuroIntervention 2020;16:201-9 •Sugane et al. Atherosclerosis 2021;318:70-5 •Kwon et al. EuroIntervention 2021;17:e639-e646 •Cha et al. Coron Artery Dis 2021;32:1541-8 •Fujimura et al. JACC Cardiovasc Interv 2021;14:1639-50 •Lee et al. Circ Cardiovasc Interv. 2021;14:e011124. •Komaki et al. Int J Cardiol 2021;334:31-36	•Prati et al. JACC Cardiovasc Imaging 2015;8:1297-305 •Prati et al. Circ Cardiovasc Interv. 2016;9. pii: e003726. •Soeda et al. Circulation 2015;132:1020-9 •Matsuo et al. Cathet Cardiovasc Interv 2015;87:E9-14 •Prati et al. EuroIntervention 2018;14:e443-e451 •Katsura et al. Catheter Cardiovasc Interv 2020;96:E501-E507 •Kim et al. JACC Cardiovasc Imaging 2021:S1936-878X(21)00268-0. doi: 10.1016/j.jcmg.2021.03.008
Edge problems (geographic miss, secondary lesions, large plaque burden, dissections, etc)	•Fujii et al. J Am Coll Cardiol 2005;45:995-8 •Okabe et al., Am J Cardiol. 2007;100:615-20 •Liu et al. JACC Cardiovasc Interv. 2009;2:428-34 •Choi et al. Circ Cardiovasc Interv 2011;4:239-47	•Sakurai et al. Am J Cardiol 2005;96:1251-3 •Liu et al. Am J Cardiol 2009;103:501-6 •Costa et al, Am J Cardiol, 2008;101:1704-11 •Kang et al. Am J Cardiol 2013;111:1408-14 •Kobayashi et al. Circ Cardiovasc Interv. 2016;9:e003553 •Calvert et al. Catheter Cardiovasc Interv 2016;88:340-7 •Park et al. JACC Cardiovasc Interv 2020;13:1403-13	•Prati et al. JACC Cardiovasc Imaging 2015;8:1297-305 •Prati et al. Circ Cardiovasc Interv. 2016;9. pii: e003726. •Ino et al. Circ Cardiovasc Interv. 2016;9:e004231 •Prati et al. EuroIntervention 2018;14:e443-e451 •van Zandvoort et al. Circ Cardiovasc Interv. 2020;13:e008685
Protrusion in ACS/MI **Irregular Protrusion**	•Choi et al. Circ Cardiovasc Interv 2011;4:239-47 •Hong et al. Int J Cardiol 2013;168:1674-5		•Prati et al. Circ Cardiovasc Interv. 2016;9. pii: e003726. •Soeda et al. Circulation 2015;132:1020-9
Stent length (>40mm)		•Hong et al. Eur Heart J 2006;27:1305-10	
Asymmetry/Eccentricity		•Suwannasom et al. JACC Cardiovasc Interv 2016;9:1231-42 (not significant at long term follow-up: JACC Cardiovasc Interv 2018;11:1013-5)	
Acute malapposition			•Souteyrand et al. Eur Heart J. 2016;37:1208-16 •**Kim et al. JACC Cardiovasc Imaging** 2021 May 11;S1936-878X(21)00268-0. doi: 10.1016/j.jcmg.2021.03.008

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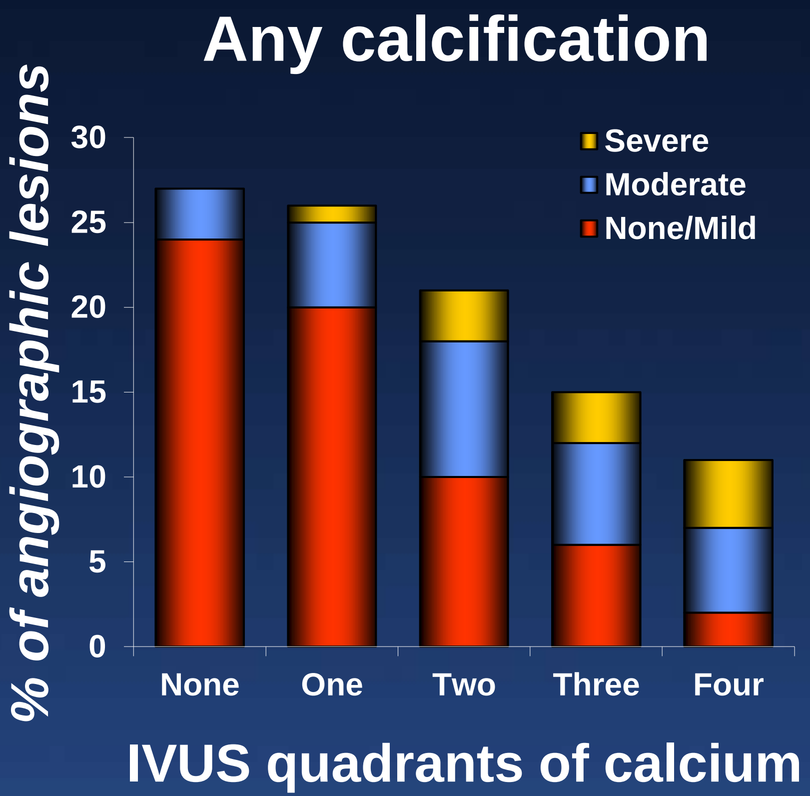
Angiography is only moderately sensitive for detection of extensive lesion calcium (sensitivity 60% and 85% for 3- and 4-quadrant calcium, n=1155)

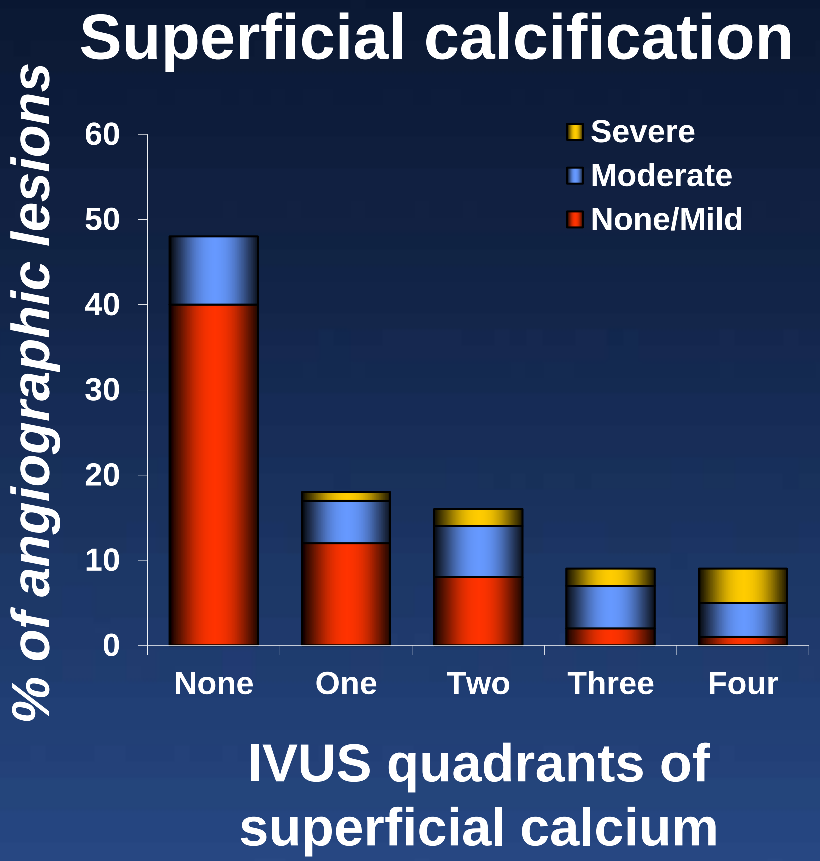
1959

Patterns of Calcification in Coronary Artery Disease

A Statistical Analysis of Intravascular Ultrasound and Coronary Angiography in 1155 Lesions

Gary S. Mintz, MD; Jeffrey J. Popma, MD; Augusto D. Pichard, MD; Kenneth M. Kent, MD, PhD; Lowell F. Satler, MD; Ya Chien Chuang, PhD; Christine J. Ditrano, BS; Martin B. Leon, MD





The only predictor of IVUS calcium was angiographic calcification elsewhere in the coronary tree.

(Tuzcu et al. *J Am Coll Cardiol* 1996;27:832-8)

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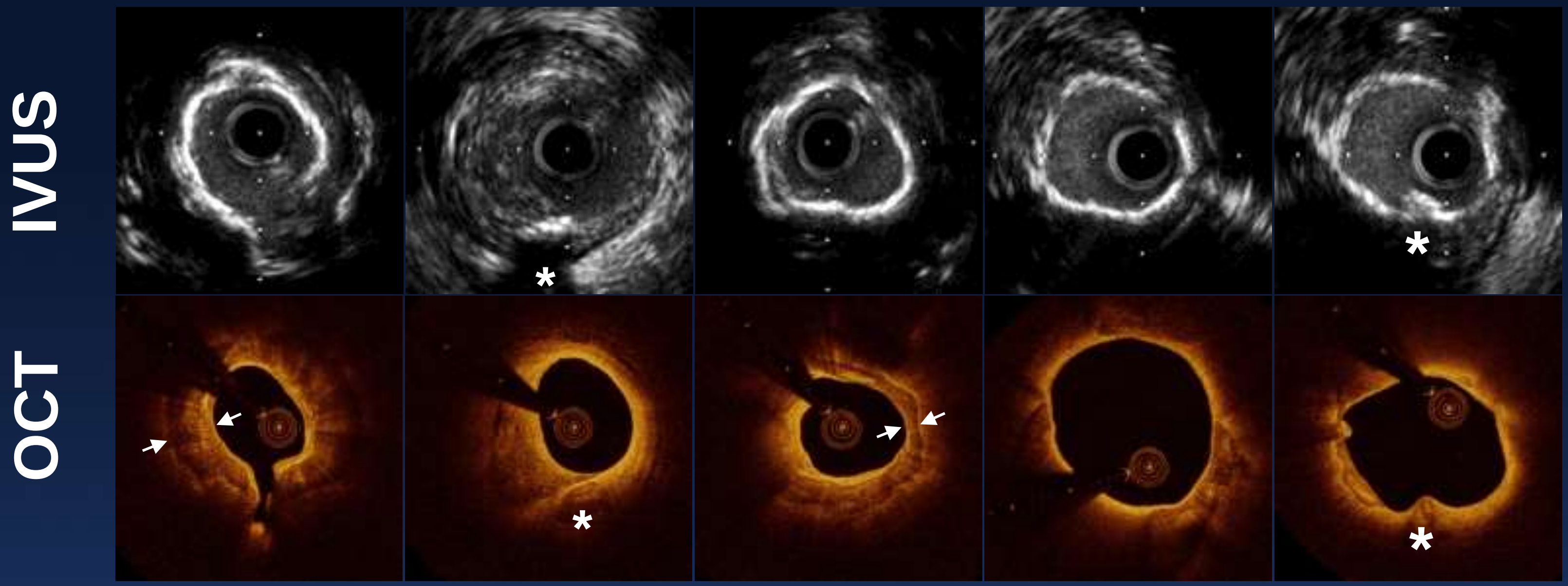
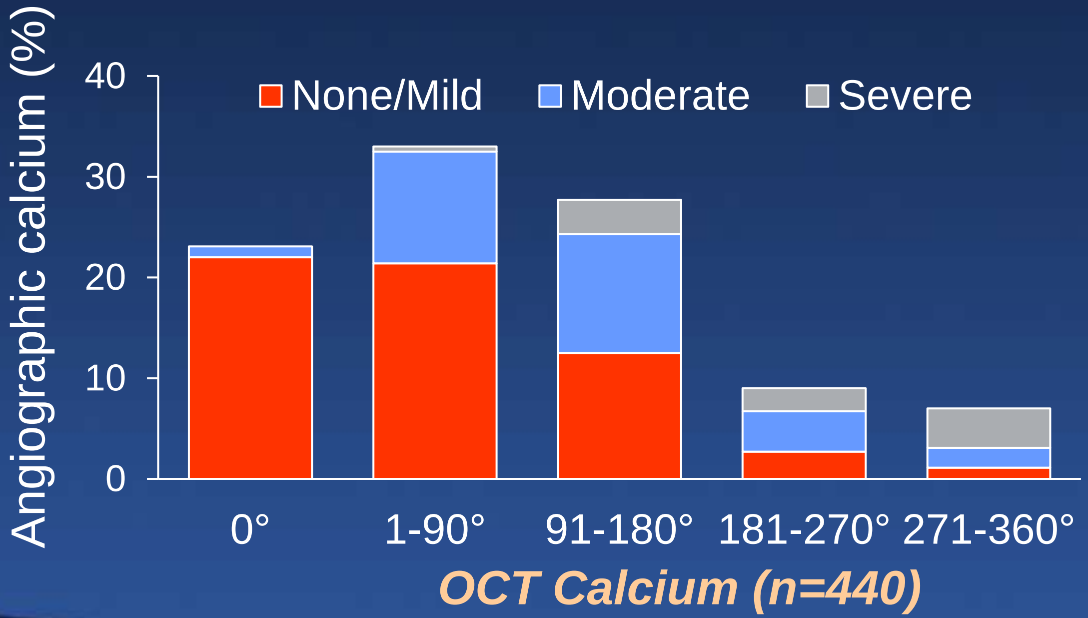
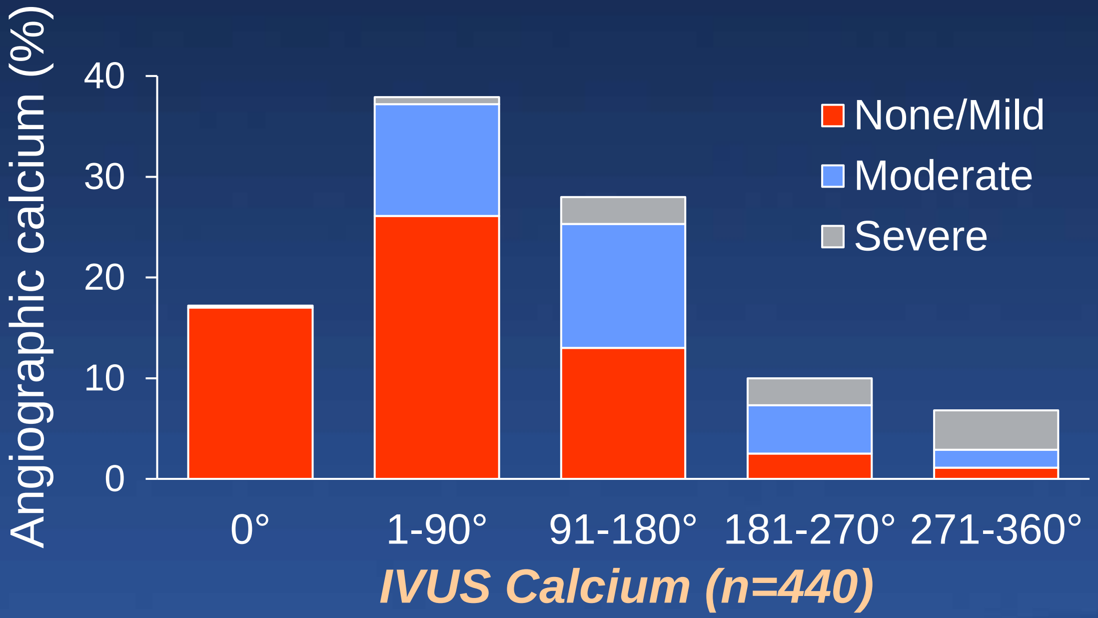
Mintz et al. Circulation 1995;91:1959-65.



Arc
Length

Arc
Length
Thickness
Area
Volume





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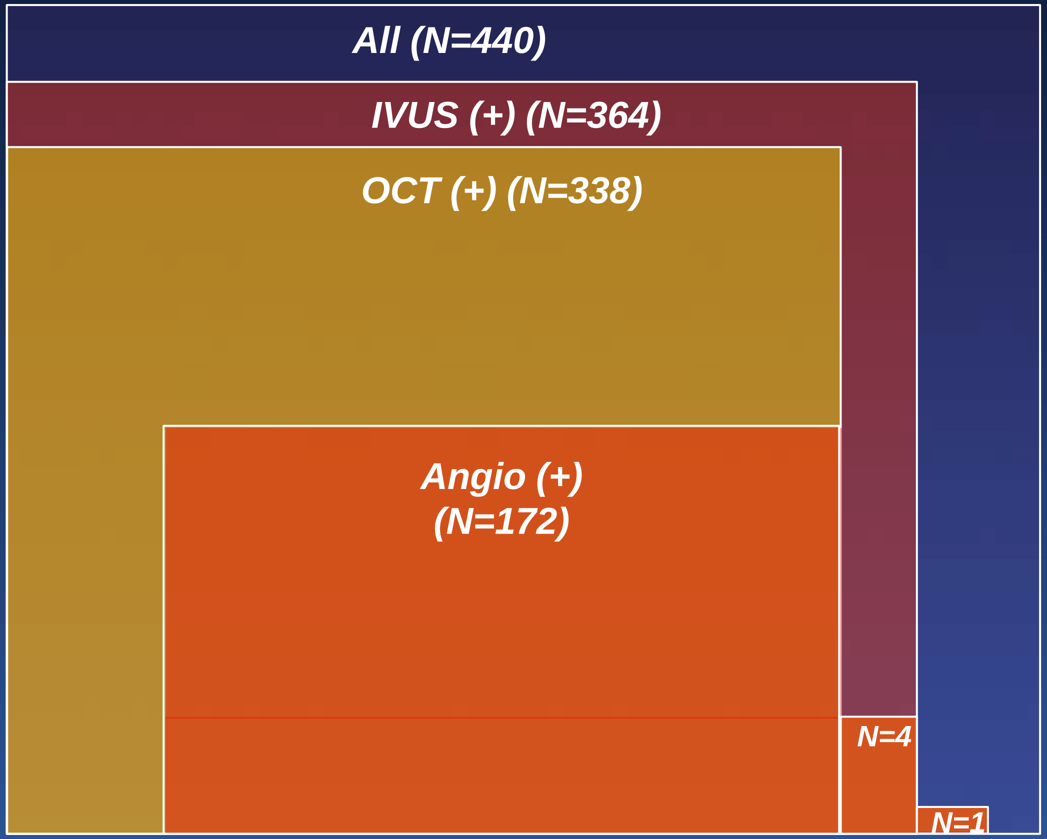
Wang et al. JACC Cardiovasc Imaging 2017;10:869-79
Mintz and Guagliumi. Lancet 2017;390:793-809

	IVUS (+)	IVUS (-)
Angio (+)	176	1
Angio (-)	188	75

	OCT (+)	OCT (-)
Angio (+)	172	5
Angio (-)	166	97

	OCT (+)	OCT (-)
IVUS (+)	338	26
IVUS (-)	0	76



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Wang et al. JACC Cardiovasc Imaging 2017;10:869-79

Pre and post-OCT calcium scoring system predicting stent expansion

Test cohort of 128 pts

	Regression Coefficient	95% CI	P-value	Calcium Score		
Maximum calcium angle (per 180°)	-7.43	-12.6 to -2.21	<0.01	**Maximum calcium angle**	**≤180°**	**0**
					>180°	**2**
Maximum calcium thickness (per 0.5 mm)	-3.40	-6.35 to -0.45	0.02	**Maximum calcium thickness**	**≤0.5mm**	**0**
					>0.5mm	**1**
Calcium length (per 5 mm)	-3.32	-4.09 to -0.55	0.01	**Calcium length**	**≤5mm**	**0**
					>5mm	**1**

Validation cohort of 133 pts

Score	0 (n=27)	1 (n=45)	2 (n=34)	3 (n=3)	**4 (n=24)**	P-value
MSA, mm^2	7.2 (5.4, 9.2)	6.3 (5.2, 8.4)	5.9 (4.8, 8.0)	6.7 (5.8, 7.1)	**5.7 (4.4, 7.4)**	0.21
Stent expansion at target lesion calcium, %	99 (93, 108)	98 (86, 109)	86 (77, 100)	98 (83, 104)	**78 (70, 86)**	<0.01
Stent expansion at MSA, %	91 (84, 95)	85 (78, 93)	80 (73, 93)	80 (73, 85)	**69 (60, 77)**	<0.01

Fujino et al. EuroIntervention 2018;13(18):e2182-e2189

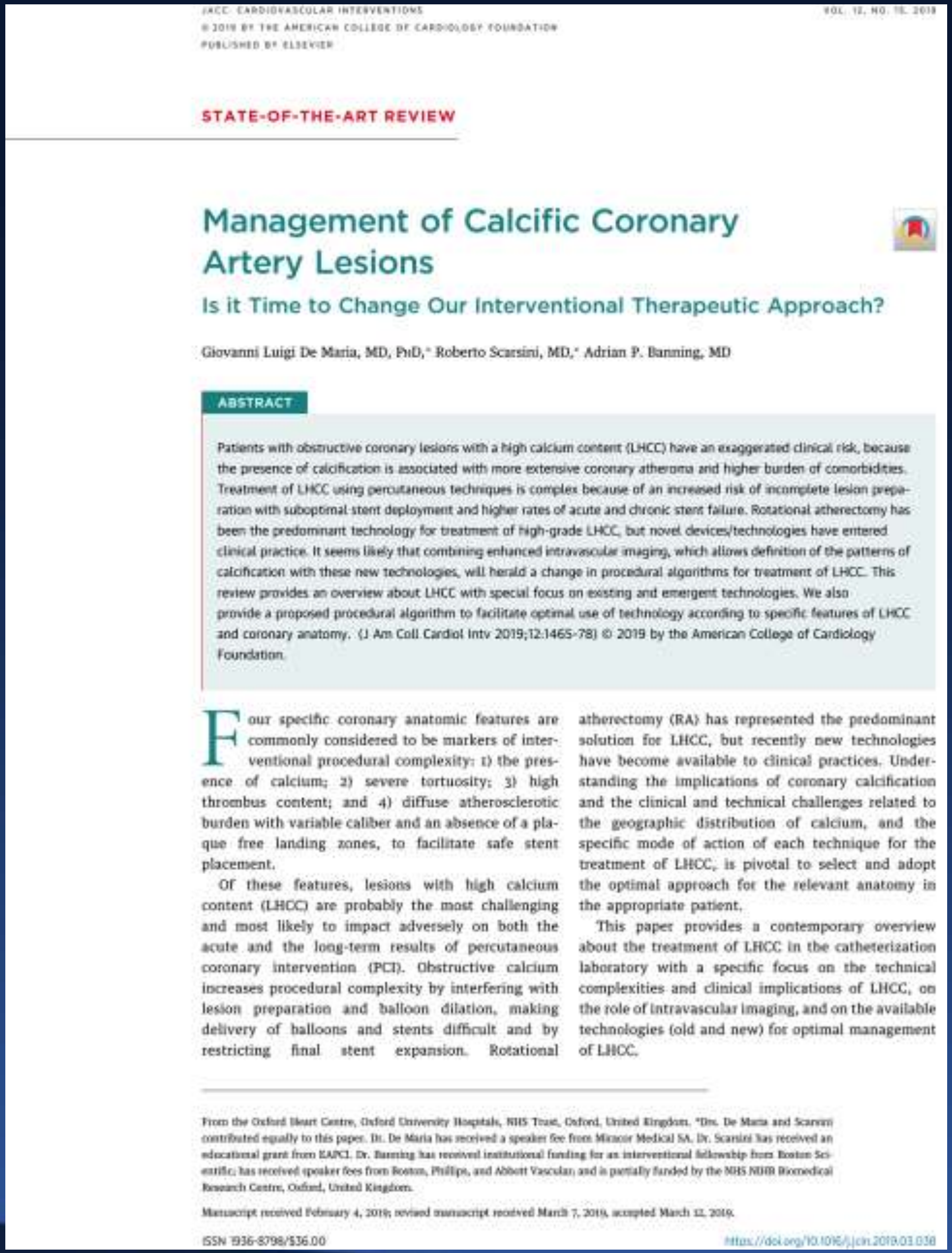
IVUS calcium score predicting stent expansion (as a continuous variable) in lesions with calcium >270°

Test cohort of 97 pts						
	Regression Coeff	95% CI	P-value	Cut-off	Calcium Score	
Length of calcium >270° (per 5mm)	-5.5	-9.7, -1.2	0.01	5.0	≤5mm	0
					>5mm	1
Calcium Nodule	-10.2	-16.3 to -4.2	0.0009		absent	0
					present	1
Vessel diameter (per 1mm)	8.6	2.7 to 14.4	0.004	3.5	>3.5mm	0
					≤3.5mm	1
Circumferential calcium	-14.3	-25.0 to -3.5	0.009		absent	0
					present	1

Stent underexpansion (<70%) in the validation cohort of 97 pts						
	Cut-off	C-statistics	Sensitivity	Specificity	PPV	**NPV**
Score	≥2	0.85 [0.77, 0.93]	89%	63%	48%	94%

In 67 lesions without angiographically visible calcium, but with a maximum IVUS angle of superficial calcium >270°, there were none with a calcium score of 4 and only 1 with stent underexpansion.

Zhang et al. Circ Cardiovasc Interv. 2021;14:e010296. doi: 10.1161/CIRCINTERVENTIONS.120.010296


JACC: CARDIOVASCULAR INTERVENTIONS VOL. 12, NO. 15, 2019

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STATE-OF-THE-ART REVIEW

Management of Calcific Coronary Artery Lesions

Is it Time to Change Our Interventional Therapeutic Approach?

Giovanni Luigi De Maria, MD, PhD,* Roberto Scarsini, MD,* Adrian P. Banning, MD

ABSTRACT

Patients with obstructive coronary lesions with a high calcium content (LHCC) have an exaggerated clinical risk, because the presence of calcification is associated with more extensive coronary atheroma and higher burden of comorbidities. Treatment of LHCC using percutaneous techniques is complex because of an increased risk of incomplete lesion preparation with suboptimal stent deployment and higher rates of acute and chronic stent failure. Rotational atherectomy has been the predominant technology for treatment of high-grade LHCC, but novel devices/technologies have entered clinical practice. It seems likely that combining enhanced intravascular imaging, which allows definition of the patterns of calcification with these new technologies, will herald a change in procedural algorithms for treatment of LHCC. This review provides an overview about LHCC with special focus on existing and emergent technologies. We also provide a proposed procedural algorithm to facilitate optimal use of technology according to specific features of LHCC and coronary anatomy. (J Am Coll Cardiol Intv 2019;12:1465-78) © 2019 by the American College of Cardiology Foundation.

Four specific coronary anatomic features are commonly considered to be markers of interventional procedural complexity: 1) the presence of calcium; 2) severe tortuosity; 3) high thrombus content; and 4) diffuse atherosclerotic burden with variable caliber and an absence of a plaque free landing zones, to facilitate safe stent placement.

Of these features, lesions with high calcium content (LHCC) are probably the most challenging and most likely to impact adversely on both the acute and the long-term results of percutaneous coronary intervention (PCI). Obstructive calcium increases procedural complexity by interfering with lesion preparation and balloon dilation, making delivery of balloons and stents difficult and by restricting final stent expansion. Rotational atherectomy (RA) has represented the predominant solution for LHCC, but recently new technologies have become available to clinical practices. Understanding the implications of coronary calcification and the clinical and technical challenges related to the geographic distribution of calcium, and the specific mode of action of each technique for the treatment of LHCC, is pivotal to select and adopt the optimal approach for the relevant anatomy in the appropriate patient.

This paper provides a contemporary overview about the treatment of LHCC in the catheterization laboratory with a specific focus on the technical complexities and clinical implications of LHCC, on the role of intravascular imaging, and on the available technologies (old and new) for optimal management of LHCC.

From the Oxford Heart Centre, Oxford University Hospitals, NHS Trust, Oxford, United Kingdom. *Drs. De Maria and Scarsini contributed equally to this paper. Dr. De Maria has received a speaker fee from Miracor Medical SA. Dr. Scarsini has received an educational grant from EAPCI. Dr. Banning has received institutional funding for an interventional fellowship from Boston Scientific; has received speaker fees from Boston, Phillips, and Abbott Vascular; and is partially funded by the NHS NIHR Biomedical Research Centre, Oxford, United Kingdom.

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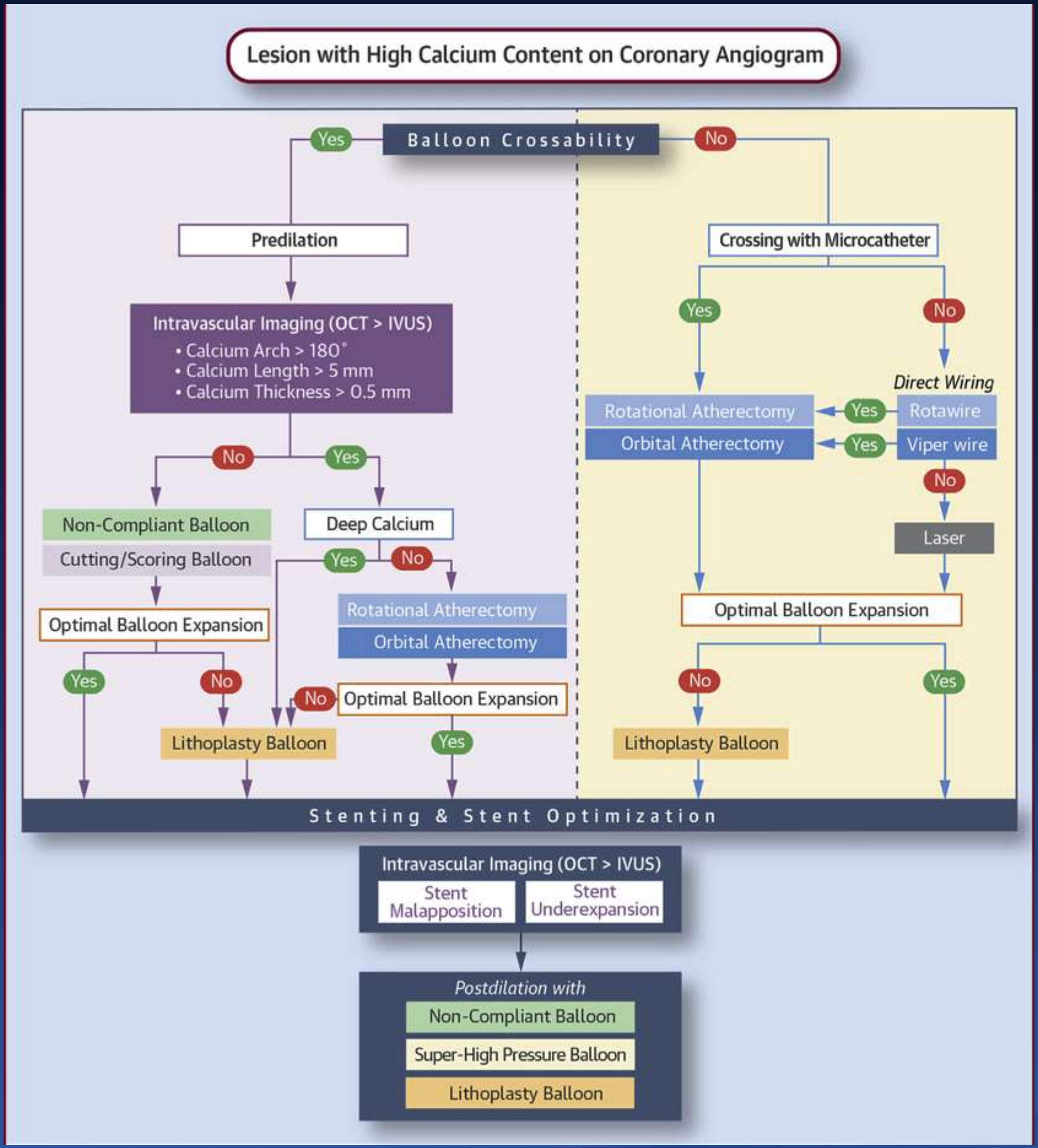
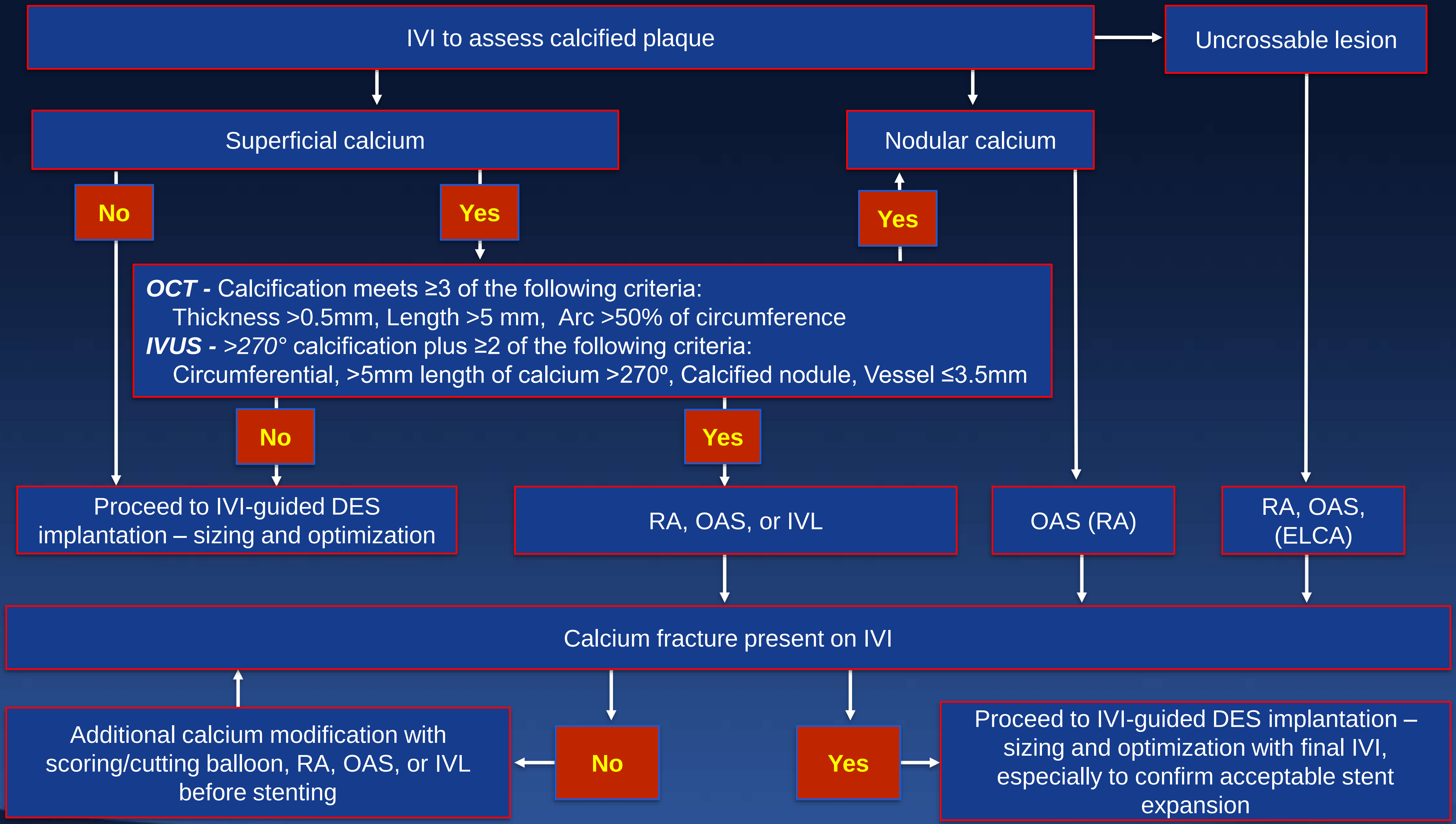


DeMaria et al. J Am Coll Cardiol Intv 2019;12:1465–78



Mintz et al. Heart 2021;107:755-64

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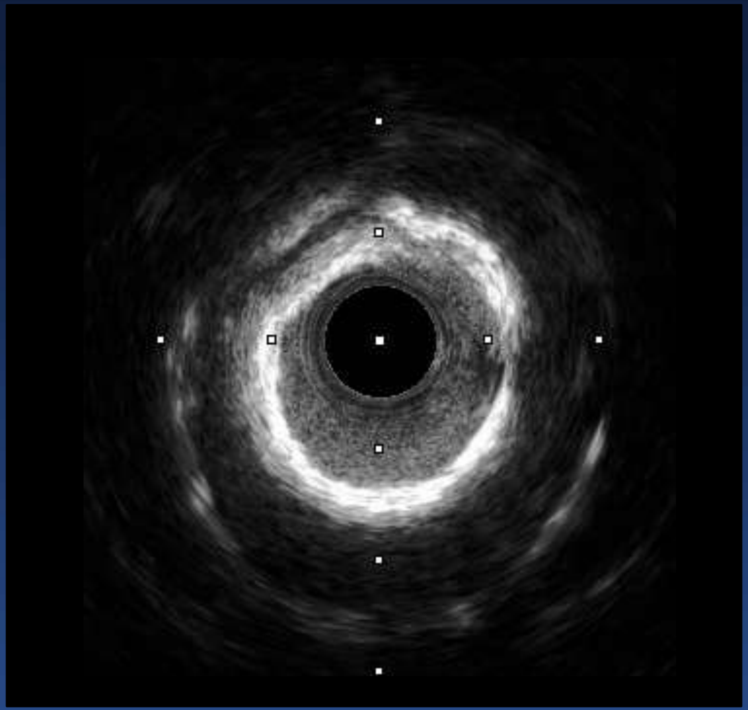
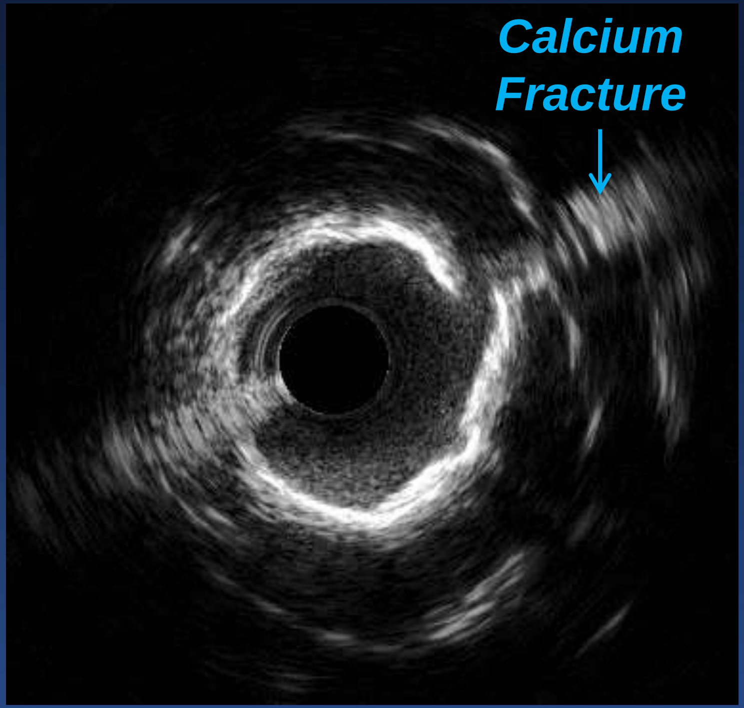
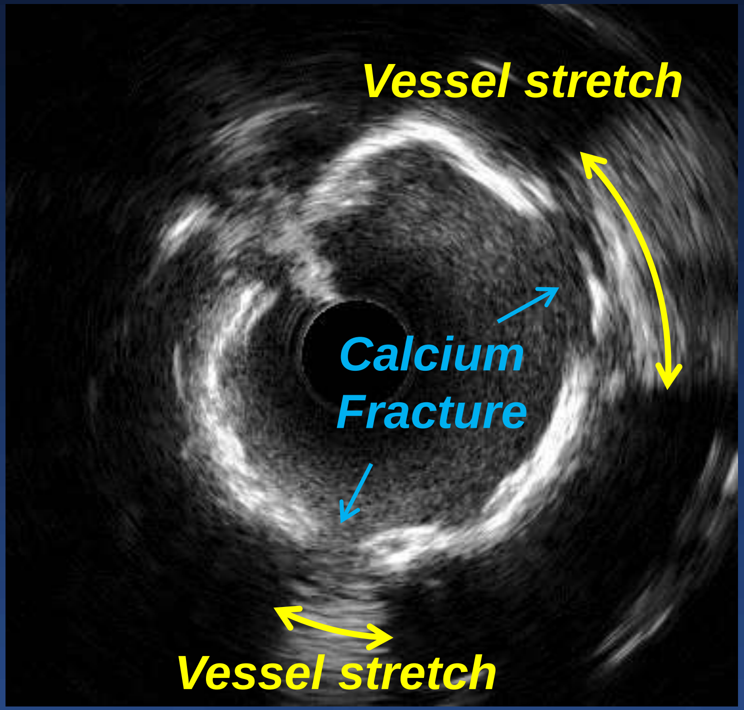
Detection of Calcium Fracture



Post-Balloon



Post-Stent Final



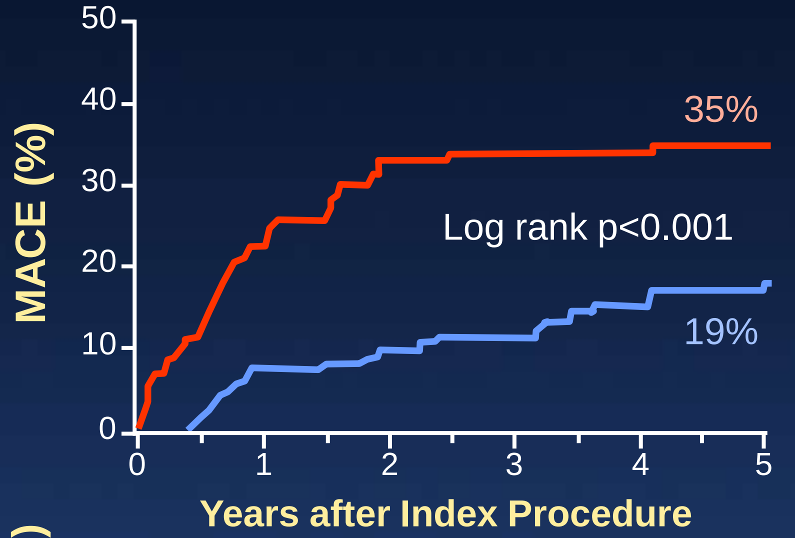
Prevalence of Calcified Nodule within Severely Calcified Lesions

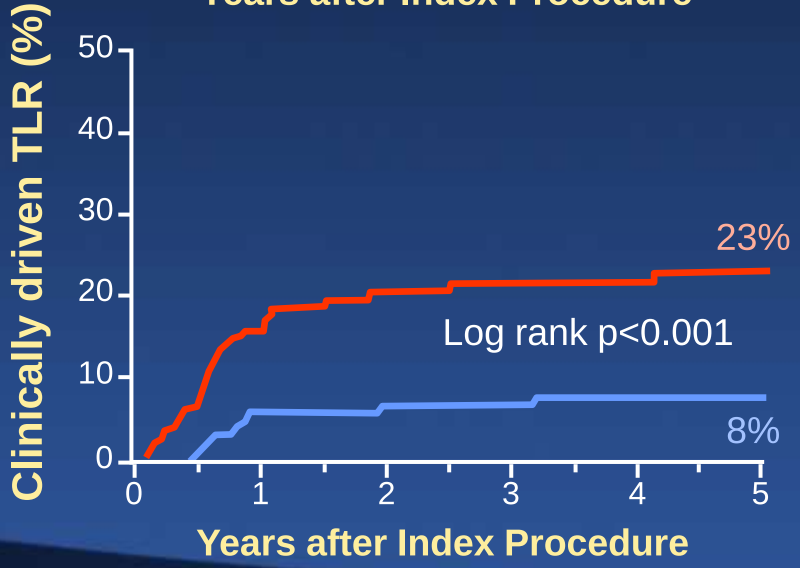
	Dialysis	# Severely calcified	Prevalence
Morofuji et al. Cathet Cardiovasc Interv 2021;97:10-19	Yes	77	58%
	No	187	44%
Jinnouchi et al. J Atheroscler Thromb. 2022 Aug 24.doi: 10.5551/jat.63667.	Yes	65	60%
	No	174	34%
Okamura et al. Heart Vessels 2022;37:1662-1668	Yes	51	59%

	ACS	# Severely calcified	Prevalence
Lee et al. JACC Cardiovasc Imaging. 2017;10:883-91	All	72 *	32%
	Yes	ACS	43%
	No	SAP	27%

* Hemodialysis, angiographic hinge-point between diastole and systole, and maximum calcium arc were independently associated with the presence of a CN.

CN (n=128) vs no CN (n=144) in heavily calcified lesions treated with RA+stenting

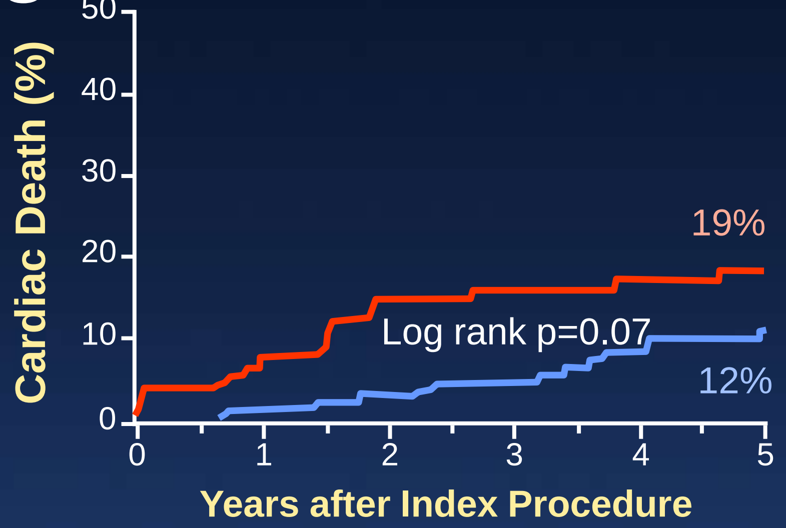


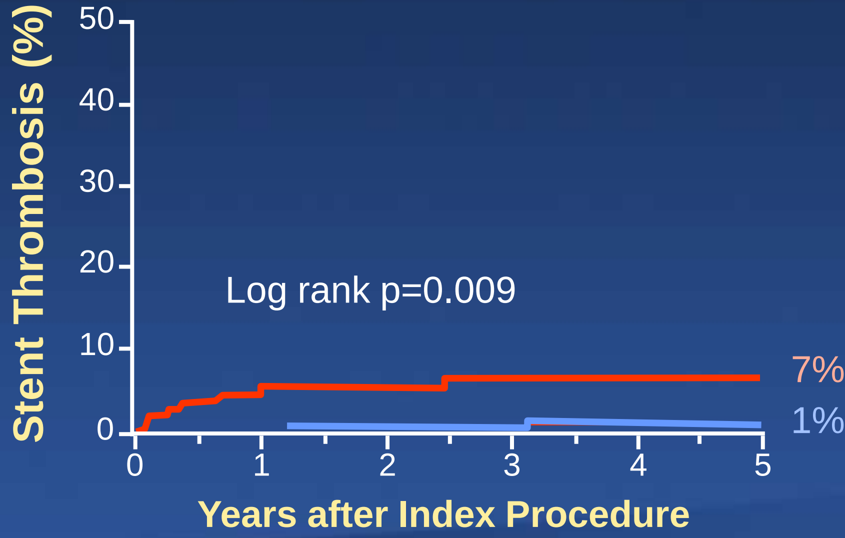


CN
No CN

IPW Adjustment		
	HR	P-value
MACE	2.52	<0.001
CD-TLR	4.13	<0.001
ST	8.53	0.04
Cardiac death	1.49	0.3

Independent risk factors of 5 yr MACE included hemodialysis, CN, ostial or RCA lesion, and LVEF



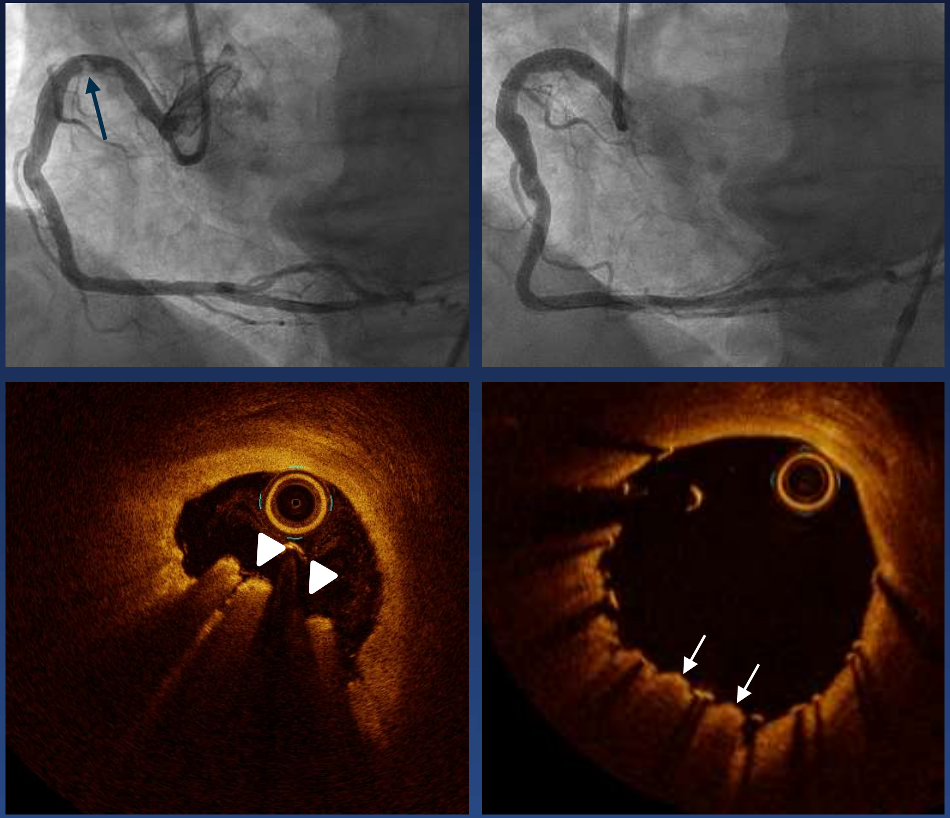


Morofuji et al. Cathet Cardiovasc Interv 2021;97:10-19

Impact of eruptive CN (n=126) versus non-eruptive NC (n=104) morphology on acute and long-term outcomes after stenting

Eruptive CN

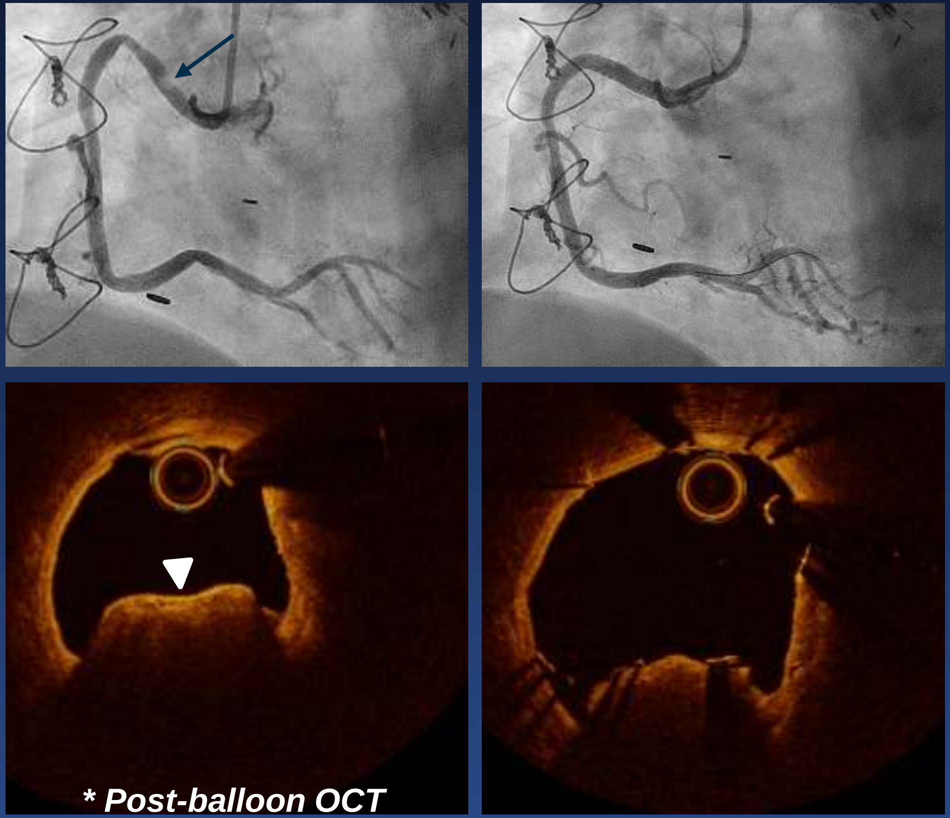
Pre-PCI *Final*



Post-PCI, there was stent-related deformation of the Eruptive-CN, but not of Non-eruptive NC which was associated with better stent expansion: 89.2 ± 18.7 vs. 81.5 ± 18.9%, p=0.003.

Non-Eruptive NC

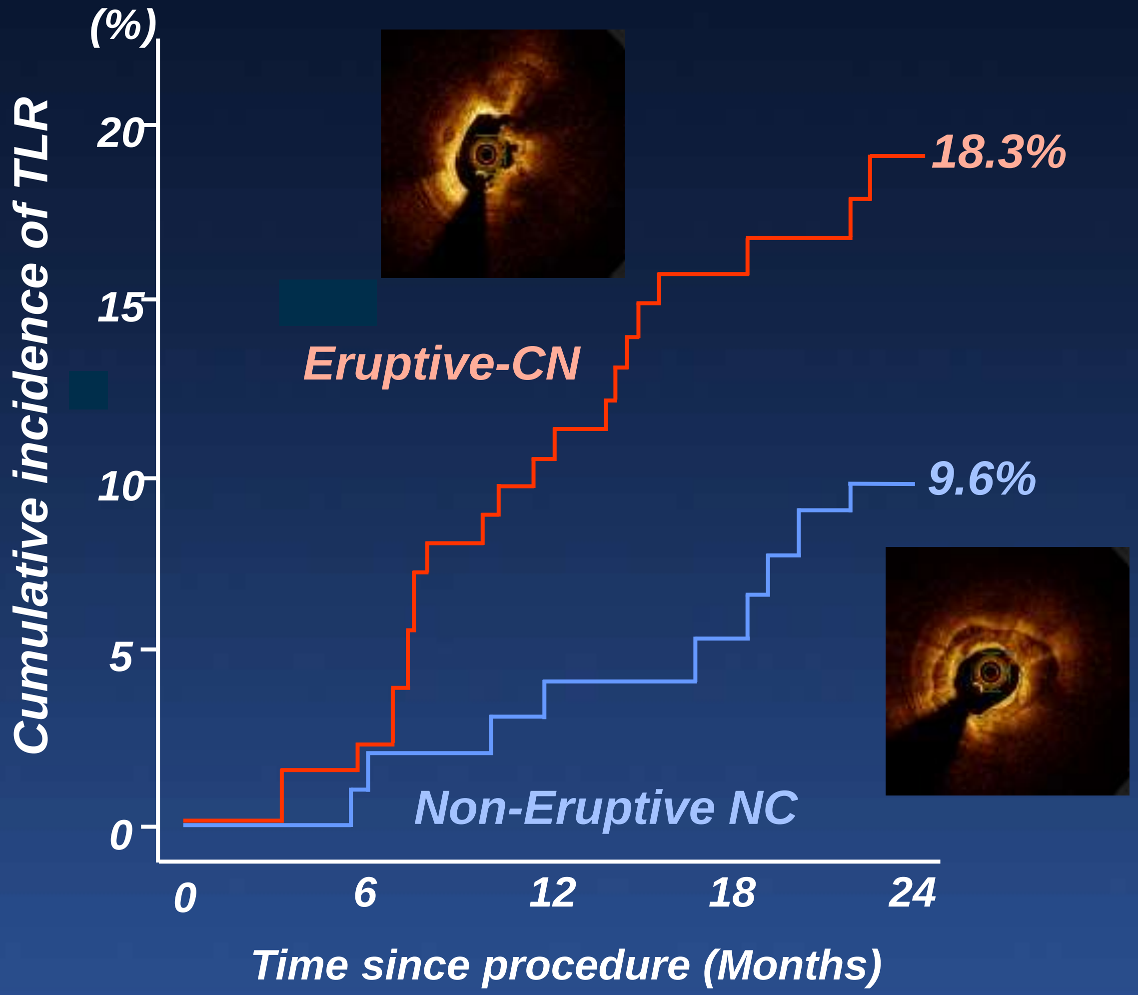
Pre-PCI *Final*



**** Post-balloon OCT image***

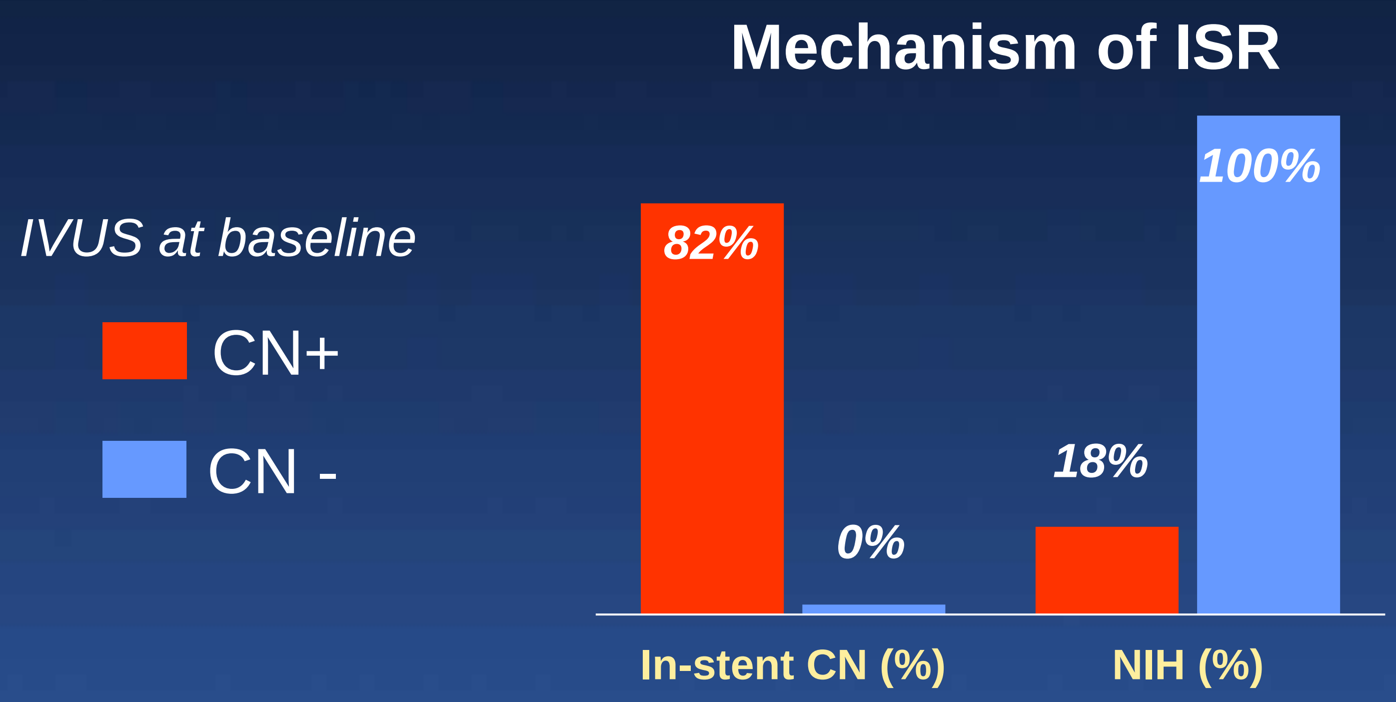
Sato et al. JACC Cardiovasc Interv, in press

However, at 2 years, Eruptive-CN trended toward more TLF compared with Non-eruptive NC (Kaplan-Meier estimates, 19.8 versus 12.5%, p=0.11) and significantly more TLR (18.3 vs. 9.6%, p=0.04). In the adjusted model, Eruptive-CN was independently associated with 2-year TLF, hazard ratio 2.07 (95% confidence interval, 1.01, 4.50), p=0.048



Sato et al. JACC Cardiovasc Interv, in press

Over 80% of TLR was driven by its re-appearance of the calcified nodule within the implanted DES.



Sugane et al. Atherosclerosis 2021;318:70-75

Calcium and In-stent Restenosis

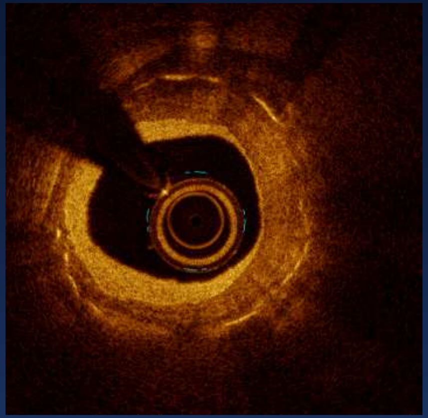
Predictors of Lipidic or Calcified NA

	Lipidic NA		Calcified NA	
	Odds ratio (95%CI)	*P* value	Odds ratio (95%CI)	*P* value
Age, year	1.00 (0.98-1.03)	0.77	1.00 (0.97-1.03)	0.83
Male	0.86 (0.50-1.46)	0.57	2.07 (0.98-4.38)	0.06
Diabetes mellitus	1.48 (0.91-2.41)	0.12	1.49 (0.78-2.86)	0.23
eGFR<60 ml/min/1.73 mm^2	2.92 (1.80-4.73)	<0.001	1.60 (0.81-3.15)	0.18
LDL cholesterol, per 10mg/dL	1.12 (1.05-1.20)	<0.001	0.99 (0.98-1.00)	0.08
Time from stent implantation, year	1.10 (1.01-1.20)	0.03	1.87 (1.63-2.15)	<0.001
Statin treatment	0.71 (0.37-1.35)	0.29		
ACEI/ARB treatment	0.72 (0.45-1.17)	0.19		

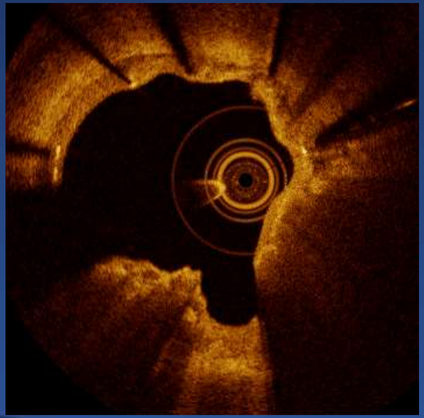
Chen et al. Circ Cardiovasc Interv. 2022;15:e011693. doi: 10.1161/CIRCINTERVENTIONS.121.011693.

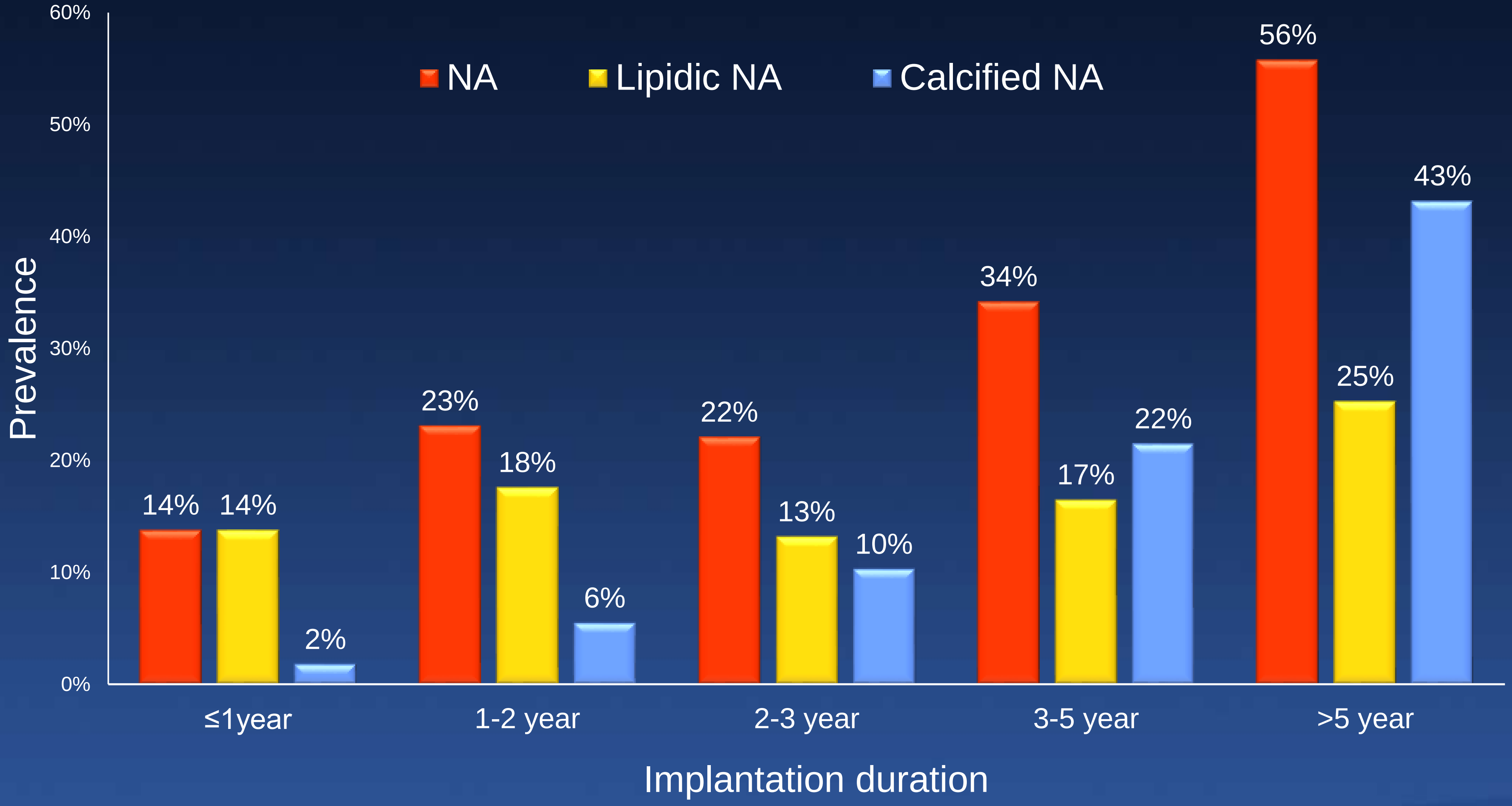
Prevalence of calcified neoatherosclerosis (NA) in 512 2nd generation DES

Neointimal calcified plate



Neointimal calcified nodule

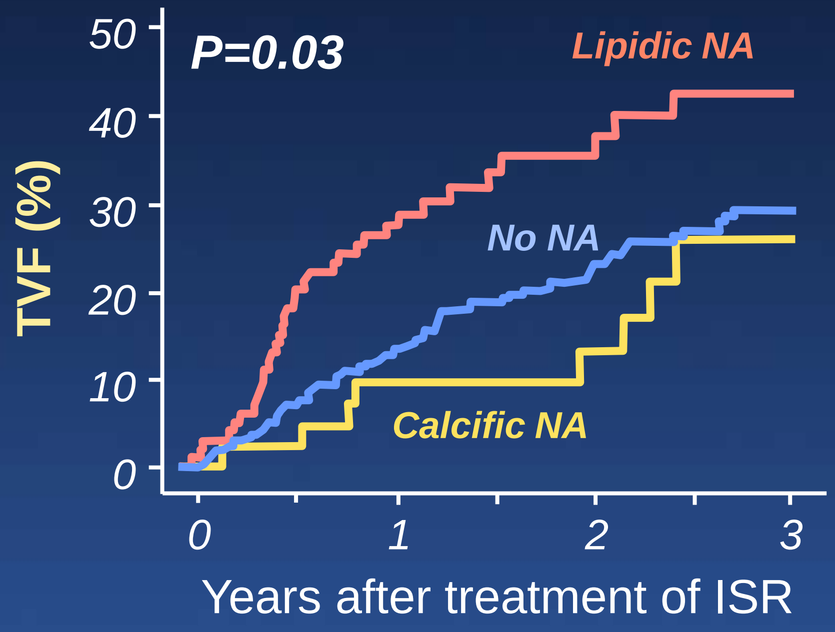




Chen et al. Circ Cardiovasc Interv. 2022;15:e011693. doi: 10.1161/CIRCINTERVENTIONS.121.011693.

Impact of neoatherosclerosis on long-term follow-up after treatment of ISR:

512 second generation DES ISR lesions treated and followed for a minimum of 6 mos.



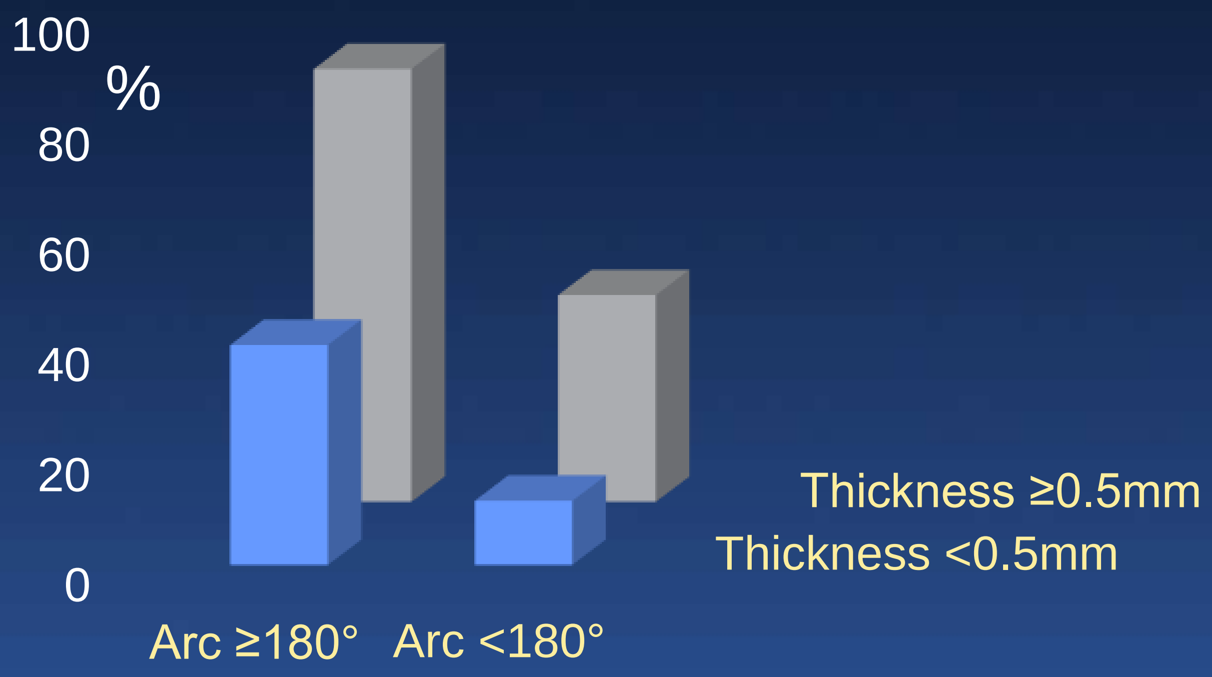
Lipid neoatherosclerosis, but not neointimal calcium was an independent predictor of TVF. Final MLD affected TVF in calcific, but not lipidic neoatherosclerosis

Cardiovascular Research Foundation

Chen et al. Circ Cardiovasc Interv. 2022;15:e011693. doi: 10.1161/CIRCINTERVENTIONS.121.011693.

ISR and New Stent Underexpansion
(n=143 ISR lesions, 5.8±4.8 yrs post implantation)

Frequency of MSA <4.5mm² and stent expansion <70% vs lesion calcium*

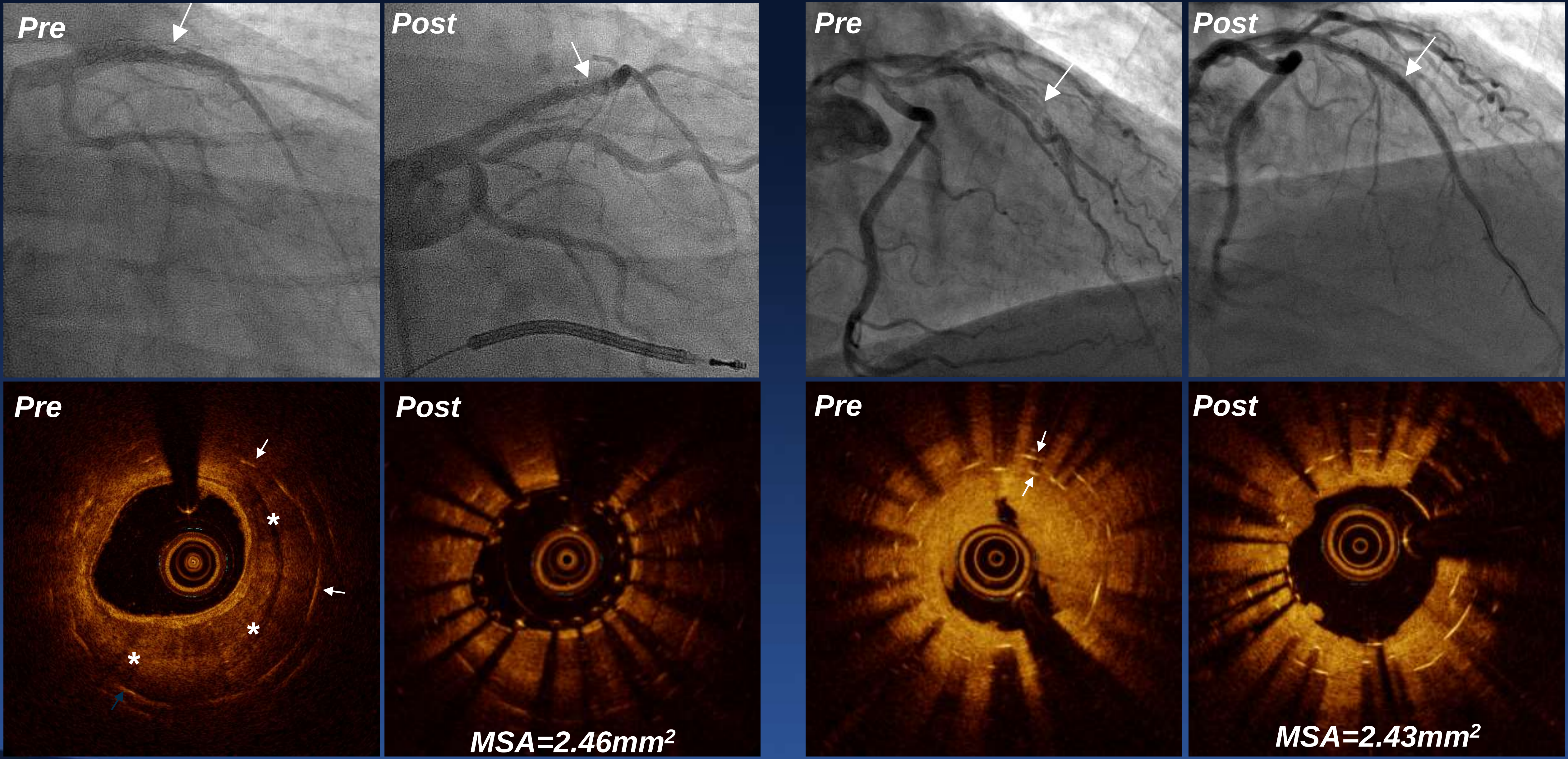


includes peri-stent and neointimal calcium

Old stent under-expansion (OR; 7.67, 95%CI: 2.19-26.9; p=0.001), calcium* angle (per 90°) (OR: 2.0, 95%CI: 1.37-2.90; p<0.001), and multiple layers of old stent (OR: 7.32, 95%CI: 2.43-22.0; p<0.001) were independently associated with new stent under-expansion (MSA <4.5mm² and MSA/mean reference lumen <70%).

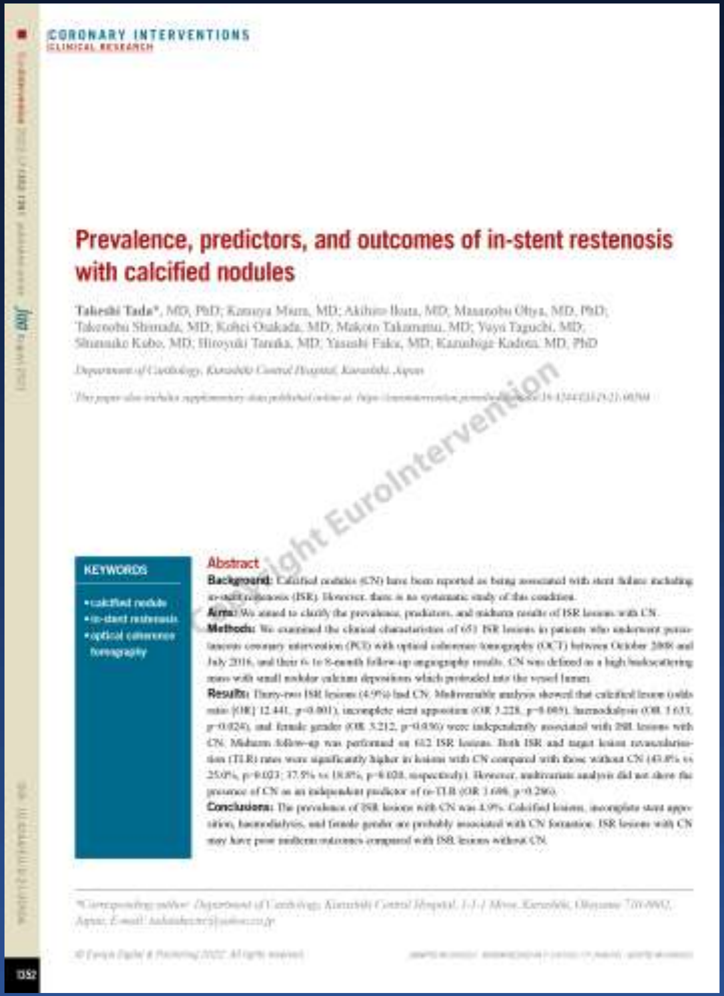
Cardiovascular Research Foundation

Yin et al. EuroIntervention. 2020;16:e335-e343



Yin et al. EuroIntervention. 2020;16:e335-e343

First-time ISR/TLR in lesions with/without CN and Treatment



CORONARY INTERVENTIONS
CLINICAL RESEARCH

Prevalence, predictors, and outcomes of in-stent restenosis with calcified nodules

Takeshi Tada*, MD, PhD; Kazuya Miura, MD; Akihiro Ikuta, MD; Masanobu Ohya, MD, PhD; Takenobu Shimada, MD; Kohei Osakada, MD; Makoto Takamatsu, MD; Yuya Taguchi, MD; Shunsuke Kubo, MD; Hiroyuki Tanaka, MD; Yasushi Fuku, MD; Kazushige Kadota, MD, PhD

Department of Cardiology, Kurashiki Central Hospital, Kurashiki, Japan

KEYWORDS
- calcified nodule
- in-stent restenosis
- optical coherence tomography

Abstract

Background: Calcified nodules (CN) have been reported as being associated with stent failure including in-stent restenosis (ISR). However, there is no systematic study of this condition.

Aims: We aimed to clarify the prevalence, predictors, and midterm results of ISR lesions with CN.

Methods: We examined the clinical characteristics of 651 ISR lesions in patients who underwent percutaneous coronary intervention (PCI) with optical coherence tomography (OCT) between October 2008 and July 2016, and their 6- to 8-month follow-up angiography results. CN was defined as a high backscattering mass with small nodular calcium depositions which protruded into the vessel lumen.

Results: Thirty-two ISR lesions (4.9%) had CN. Multivariable analysis showed that calcified lesion (odds ratio [OR] 12.441, p<0.001), incomplete stent apposition (OR 3.228, p=0.005), haemodialysis (OR 3.633, p=0.024), and female gender (OR 3.212, p=0.036) were independently associated with ISR lesions with CN. Midterm follow-up was performed on 612 ISR lesions. Both ISR and target lesion revascularisation (TLR) rates were significantly higher in lesions with CN compared with those without CN (43.8% vs 25.0%, p=0.023; 37.5% vs 18.8%, p=0.028, respectively). However, multivariate analysis did not show the presence of CN as an independent predictor of re-TLR (OR 1.698, p=0.286).

Conclusions: The prevalence of ISR lesions with CN was 4.9%. Calcified lesions, incomplete stent apposition, haemodialysis, and female gender are probably associated with CN formation. ISR lesions with CN may have poor midterm outcomes compared with ISR lesions without CN.

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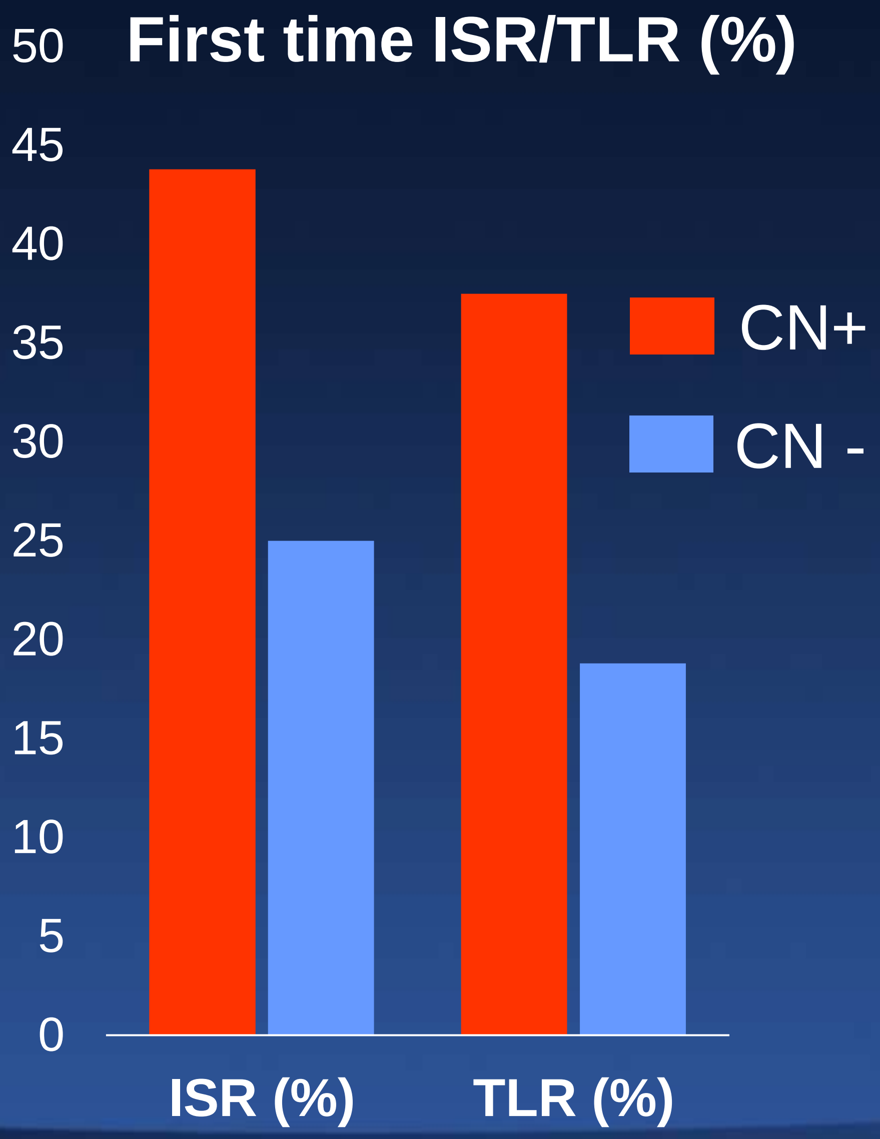
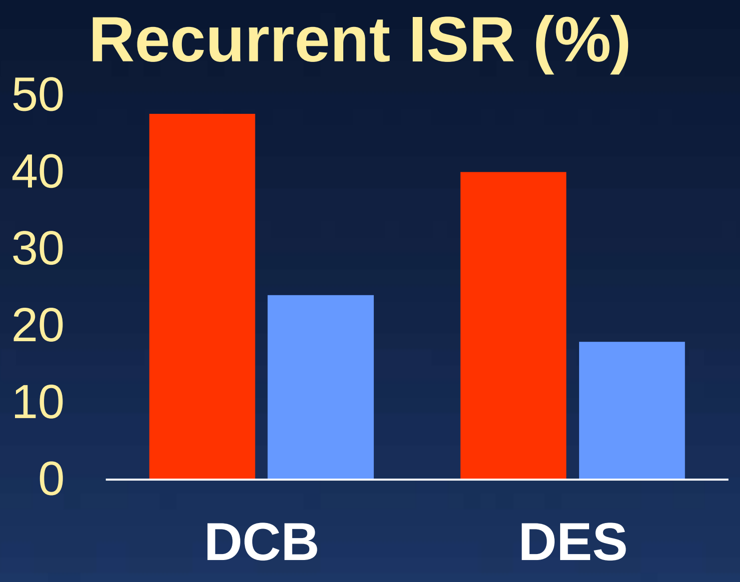
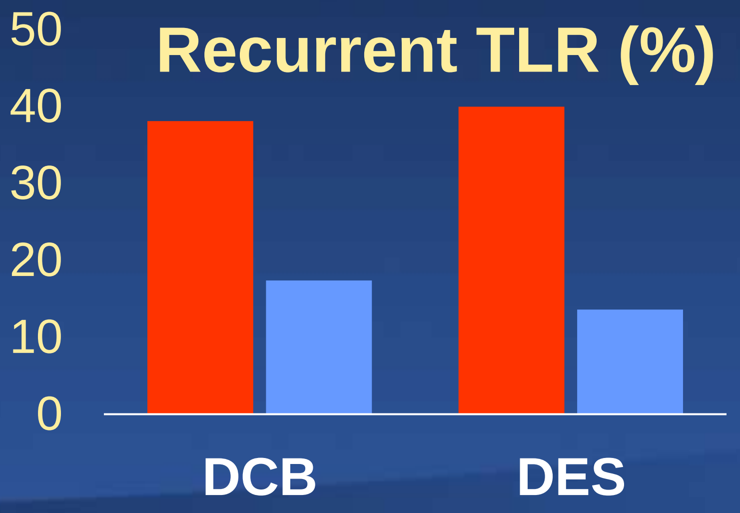


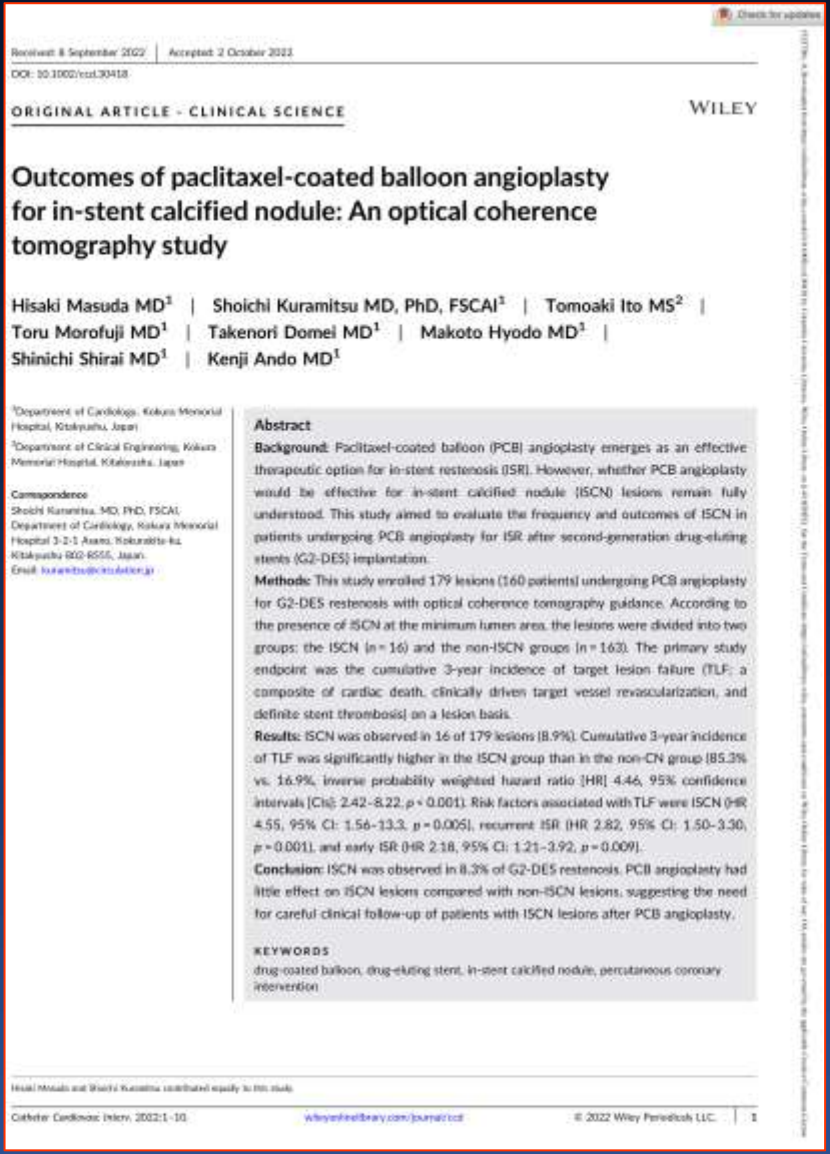




Cardiovascular Research Foundation

Tada et al. EuroIntervention 2022;17:1352-1361

Outcomes of paclitaxel-coated balloon angioplasty for in-stent calcified nodule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Received: 8 September 2022 | Accepted: 2 October 2022
DOI: 10.1002/ccd.30418

ORIGINAL ARTICLE - CLINICAL SCIENCE

WILEY

Outcomes of paclitaxel-coated balloon angioplasty for in-stent calcified nodule: An optical coherence tomography study

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Abstract

Background: Paclitaxel-coated balloon (PCB) angioplasty emerges as an effective therapeutic option for in-stent restenosis (ISR). However, whether PCB angioplasty would be effective for in-stent calcified nodule (ISCN) lesions remain fully understood. This study aimed to evaluate the frequency and outcomes of ISCN in patients undergoing PCB angioplasty for ISR after second-generation drug-eluting stents (G2-DES) implantation.

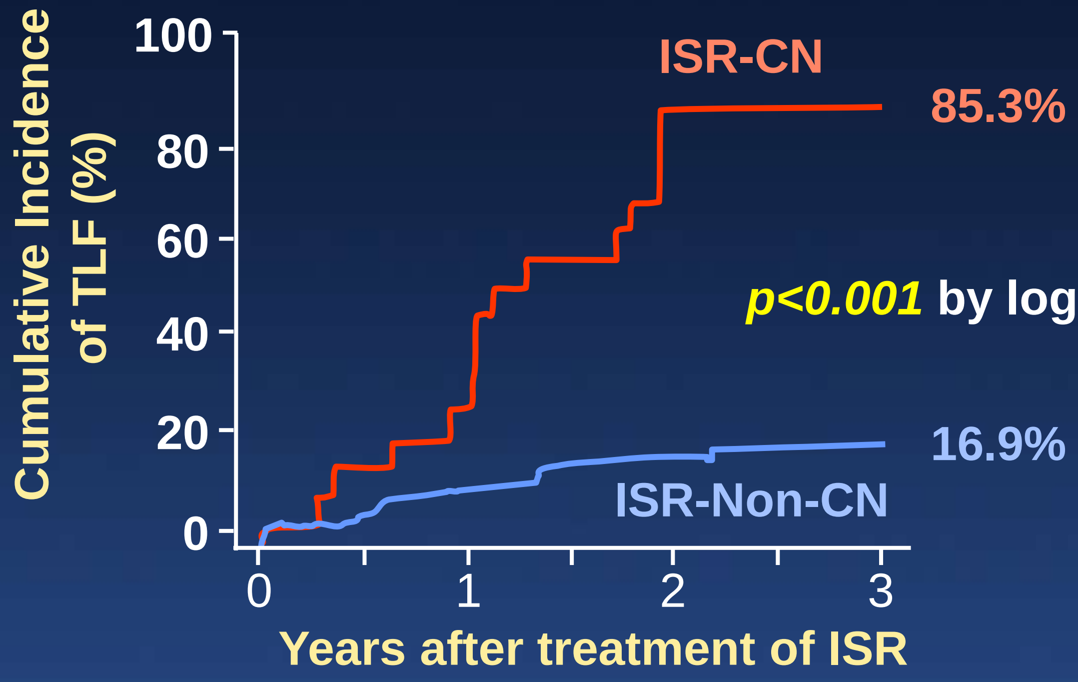
Methods: This study enrolled 179 lesions (160 patients) undergoing PCB angioplasty for G2-DES restenosis with optical coherence tomography guidance. According to the presence of ISCN at the minimum lumen area, the lesions were divided into two groups: the ISCN (n = 16) and the non-ISCN groups (n = 163). The primary study endpoint was the cumulative 3-year incidence of target lesion failure (TLF; a composite of cardiac death, clinically driven target vessel revascularization, and definite stent thrombosis) on a lesion basis.

Results: ISCN was observed in 16 of 179 lesions (8.9%). Cumulative 3-year incidence of TLF was significantly higher in the ISCN group than in the non-CN group (85.3% vs. 16.9%, inverse probability weighted hazard ratio [HR] 4.46, 95% confidence intervals [CIs]: 2.42–8.22, p < 0.001). Risk factors associated with TLF were ISCN (HR 4.55, 95% CI: 1.56–13.3, p = 0.005), recurrent ISR (HR 2.82, 95% CI: 1.50–3.30, p = 0.001), and early ISR (HR 2.18, 95% CI: 1.21–3.92, p = 0.009).

Conclusion: ISCN was observed in 8.3% of G2-DES restenosis. PCB angioplasty had little effect on ISCN lesions compared with non-ISCN lesions, suggesting the need for careful clinical follow-up of patients with ISCN lesions after PCB angioplasty.

KEYWORDS
drug-coated balloon, drug-eluting stent, in-stent calcified nodule, percutaneous coronary intervention

Hisaki Masuda and Shoichi Kuramitsu contributed equally to this study.



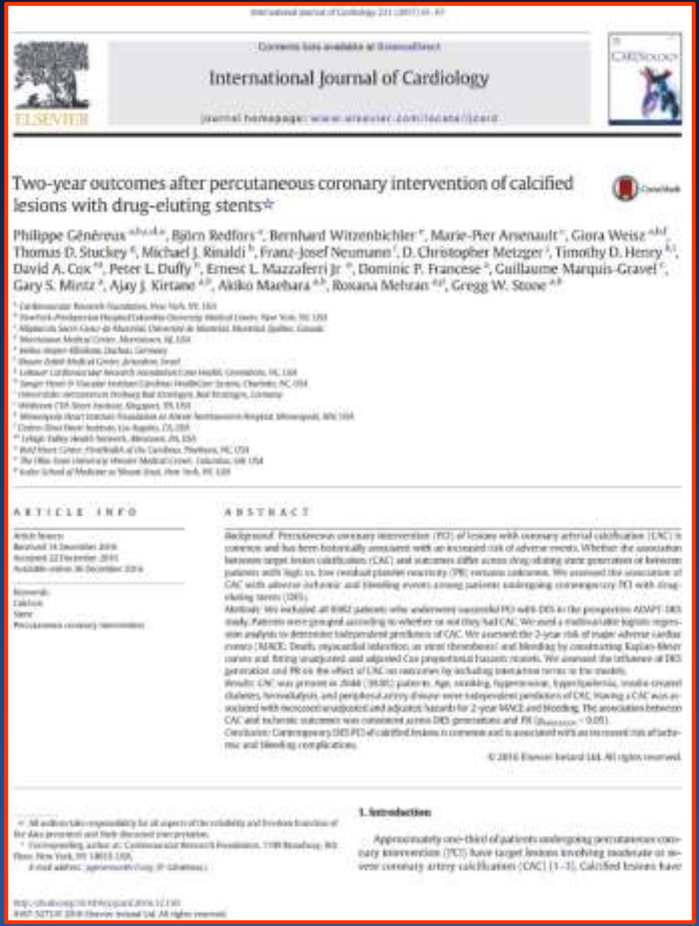
	0	1	2	3
ISR-CN				
# of lesions at risk	16	12	2	2
Cumulative incidence	0.0%	26.6%	85.3%	85.3%
ISR-NoCN				
# of lesions at risk	163	140	98	67
Cumulative incidence	0.0%	7.7%	15.8%	16.9%

Cardiovascular Research Foundation

Masuda et al. Catheter Cardiovasc Interv. 2022 Oct 13. doi: 10.1002/ccd.30418.

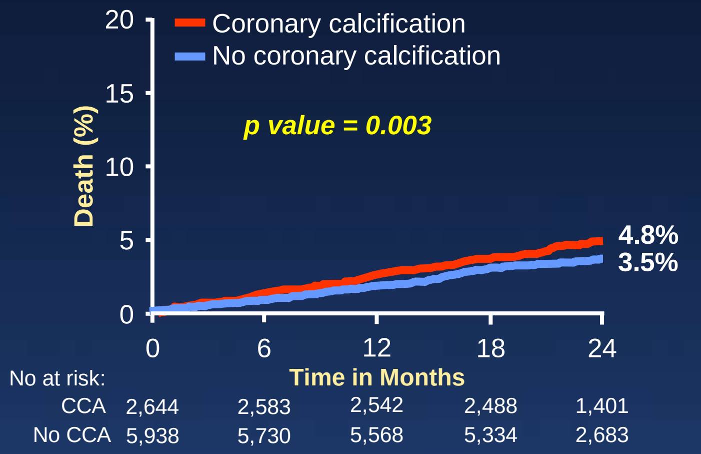
Calcium and Patient Outcomes

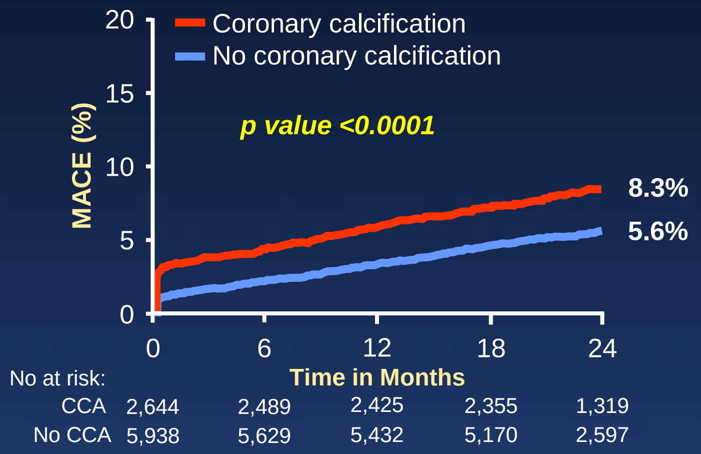
In the ADAPT-DES database of unselected pts undergoing PCI with DES, calcium was seen in approximately one-third of the target lesions and was independently and consistently associated with an increased risk of both ischemic events and bleeding events across 1st and 2nd generation DES

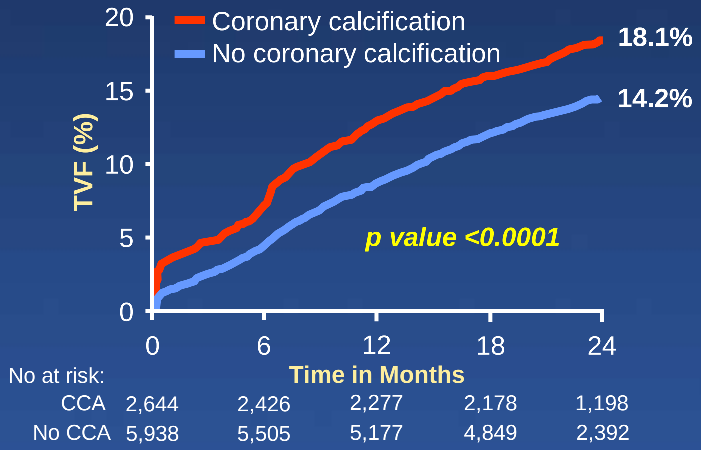

International Journal of Cardiology

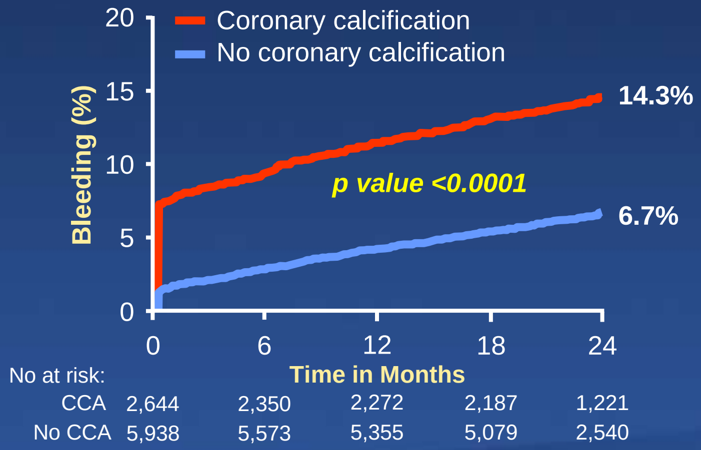
Two-year outcomes after percutaneous coronary intervention of calcified lesions with drug-eluting stents

Philippe Généreux, Björn Redfors, Bernhard Witzenbichler, Marie-Pier Arsenault, Giora Weisz, Thomas D. Stuckey, Michael J. Rinaldi, Franz-Josef Neumann, D. Christopher Metzger, Timothy D. Henry, David A. Cox, Peter L. Duffy, Ernest L. Mazzaferri Jr, Dominic P. Francese, Guillaume Marquis-Gravel, Gary S. Mintz, Ajay J. Kirtane, Akiko Maehara, Roxana Mehran, Gregg W. Stone









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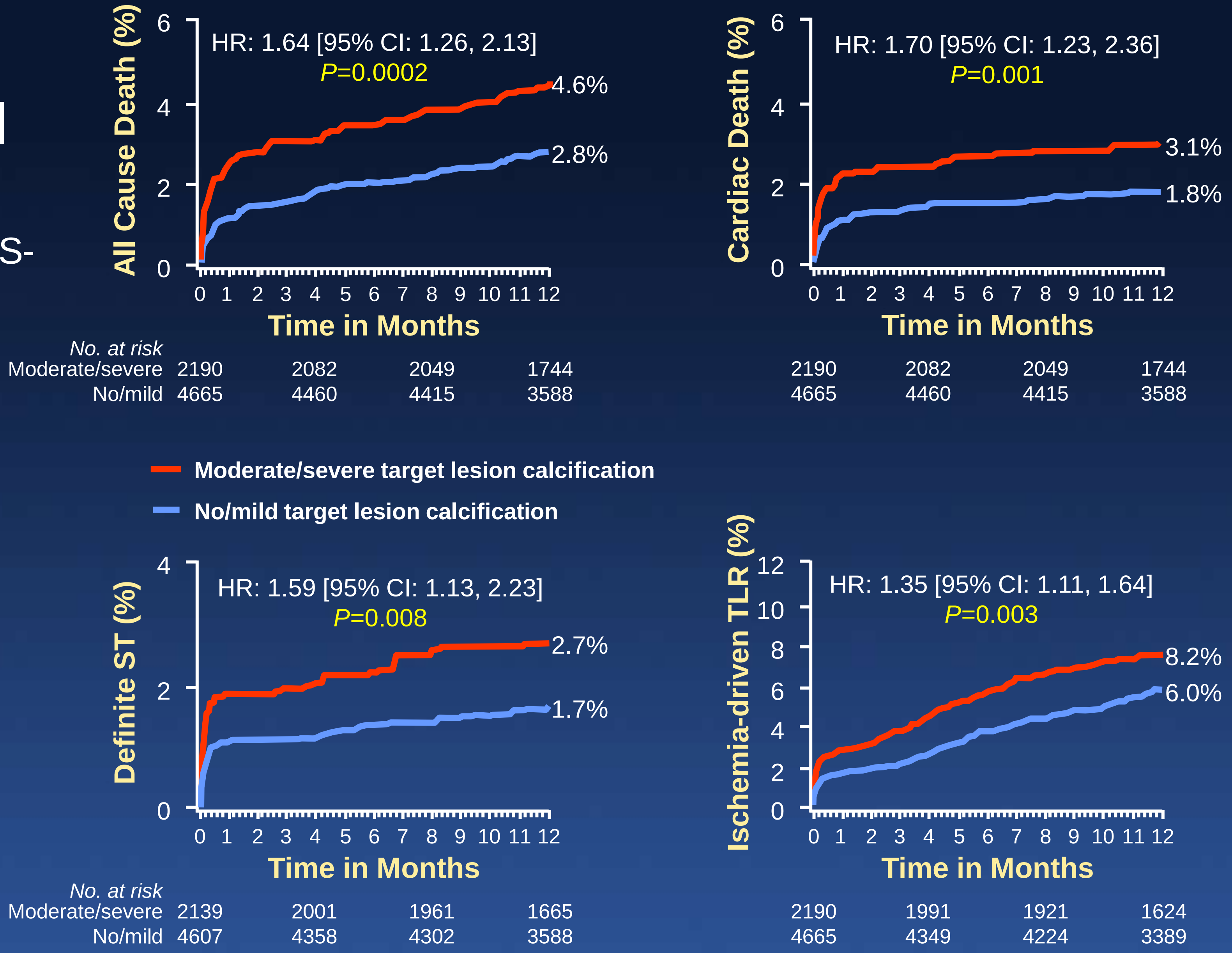
Genereux et al. Int J Cardiol. 2017;231:61-67

Ischemic Outcomes After PCI of Calcified Vessels in ACS Pts

Pooled Analysis from the HORIZONS-AMI and ACUITY Trials

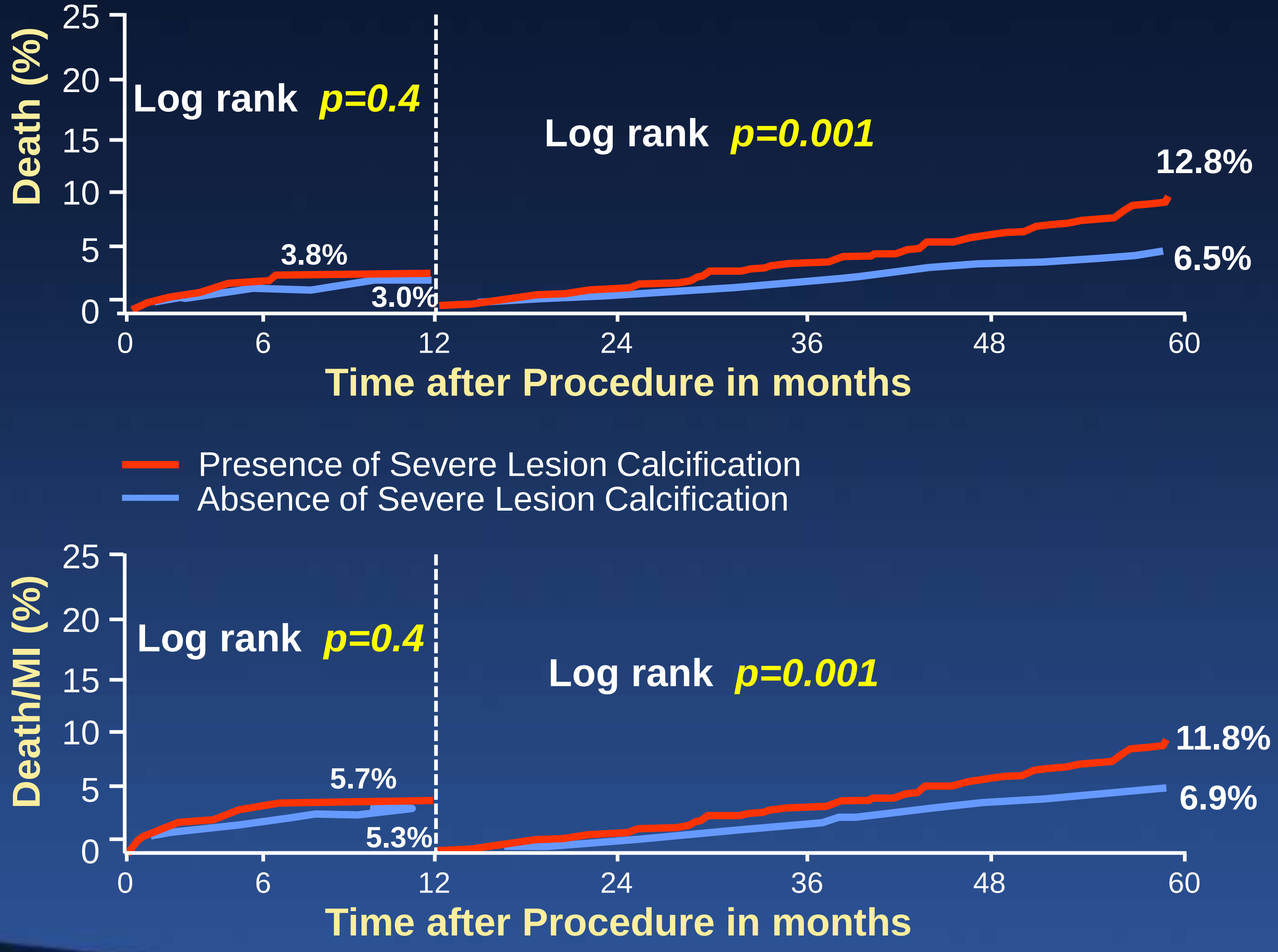


The presence of moderate/severe target lesion calcification was an independent predictor of 1-year definite STis (hazard ratio [HR]: 1.62; 95% confidence interval [CI]: 1.14 to 2.30; p=0.007) and ischemic TLR (HR: 1.44; 95% CI: 1.17 to 1.78; p=0.0007)

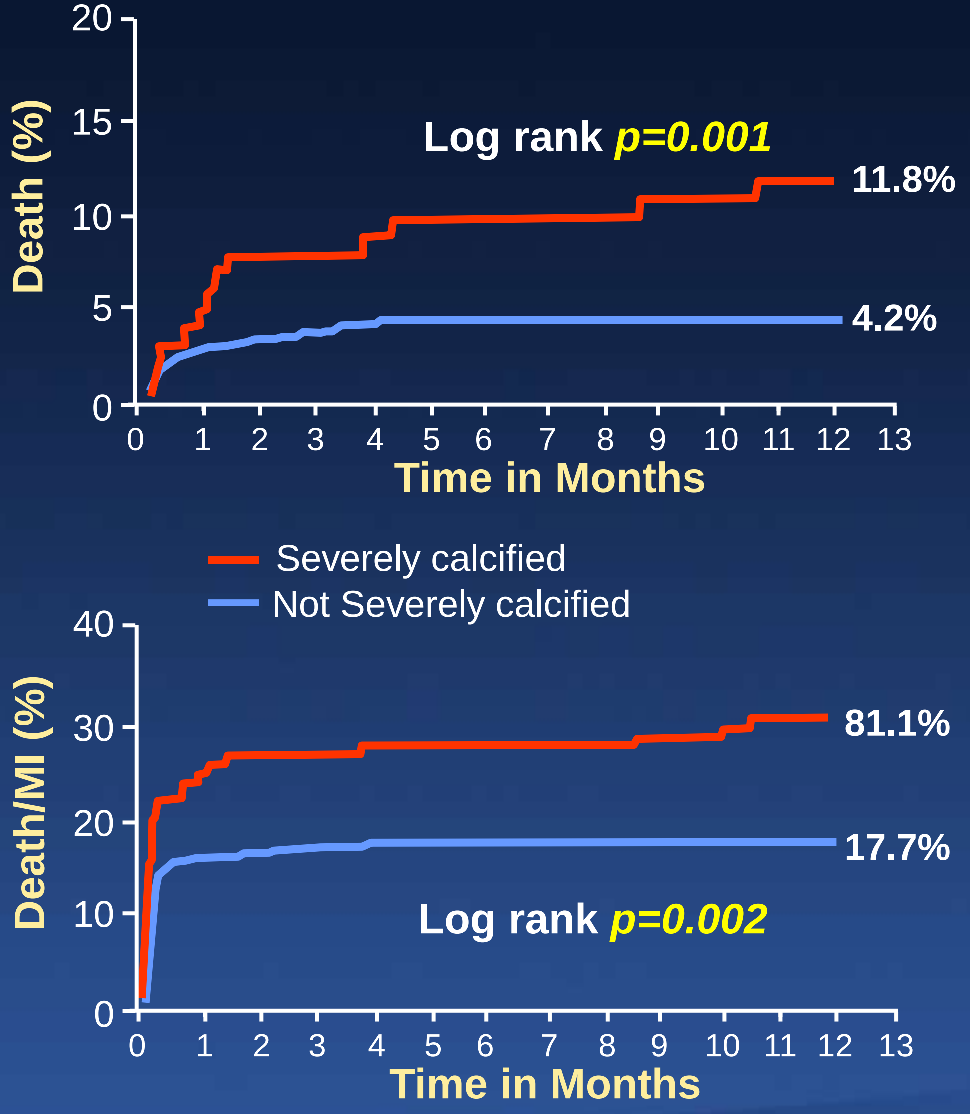
Cardiovascular Research Foundation

Genereux et al. J Am Coll Cardiol 2014;63:1845-54

Patients Undergoing CABG in SYNTAX



Patients Undergoing CABG in ACUITY



Bourantas et al. Cathet Cardiovasc Interv 2015;85:199-206
Ertelt et al. Am J Cardiol 2013;112;1730-37

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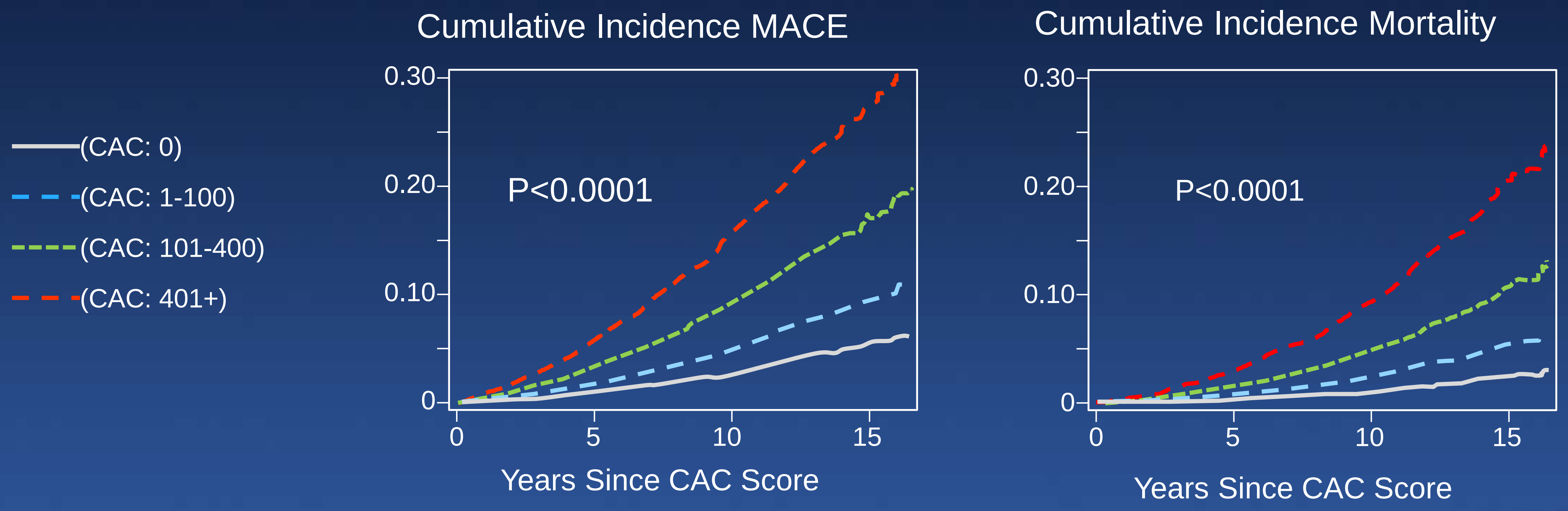
Coronary Artery Calcium and Long-Term Risk of Death, MI, and Stroke: The Walter Reed Cohort Study

(23,637 consecutive pts without atherosclerotic cardiovascular disease who underwent coronary artery calcium (CAC) scoring by CT were assessed for MI, stroke, MACE, and all-cause mortality)

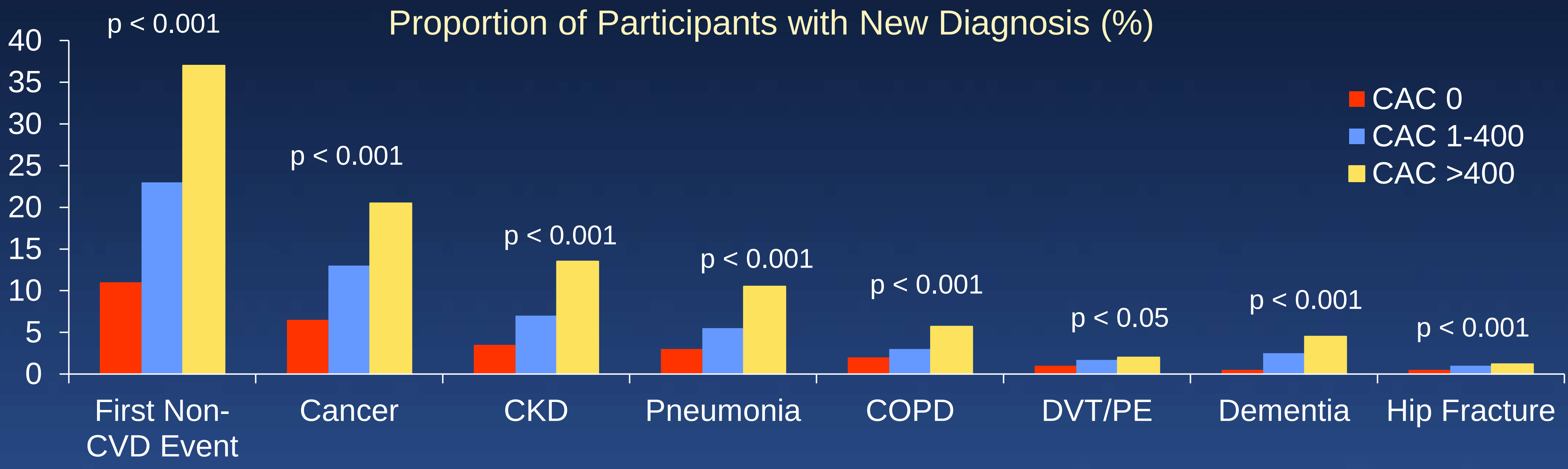


Mitchell et al. JACC Cardiovasc Imaging 2018;11:1799-1806

Cardiovascular Research Foundation

Association of Coronary Artery Calcium With Non-Cardiovascular Disease

(n=6814 pts followed for 10.2 yrs [median])



Participants with elevated CAC were at increased risk of cancer, CKD, COPD, and hip fractures. Those with CAC = 0 are less likely to develop common age-related comorbid conditions, and represent a unique population of "healthy agers."

Cardiovascular Research Foundation

Handy CE et al. J Am Coll Cardiol Img 2016;9:568-76.

Conclusions

- **Calcium is ubiquitous in coronary artery disease and is a risk factor for coronary and non-coronary events.**
- **Regardless of its size and appearance, calcium can be problematic**

Microscopic amounts	Fibrous cap destabilization – depending on particle size and orientation
Spotty	Marker for a fibroatheroma and disease progression
Calcified nodule	Causes ACS and is associated with worse outcomes whether treated medically or with PCI
Large amounts	Inhibit stent expansion and treatment of instent restenosis