

***What is the Definition of Moderate
to Heavy Calcification? Based on
Fluoroscopy or Intravascular
Imaging***

Gary S. Mintz, MD

Cardiovascular Research Foundation

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. Darano, BS, Martin B. Leon, MD

Background Target lesion calcium is a marker for significant coronary artery disease and a determinant of the success of transcatheter therapy.

Methods and Results Eleven hundred fifty-five native vessel target lesions in 1117 patients were studied by intravascular ultrasound (IVUS) and coronary angiography. The presence, magnitude, location, and distribution of IVUS calcium were analyzed and compared with the detection and classification (non/moderate/severe) by angiography. Angiography detected calcium in 440 of 1155 lesions (38%); 306 (26%) moderate calcium and 134 (12%) severe. IVUS detected lesion calcium in 841 of 1155 (73%; $P < .001$) versus angiography. The mean arc of lesion calcium measured $135 \pm 110^\circ$; the mean length measured 3.5 ± 3.7 mm. Target lesion calcium was only superficial in 48%, only deep in 28%, and both superficial and deep in 24%. The mean arc of superficial calcium measured $85 \pm 108^\circ$; the mean length measured 2.4 ± 3.4 mm. Three hundred seventy-three of 1155 reference segments (32%) contained calcium ($P < .0001$ compared with lesion site). The mean arc of reference calcium measured $42 \pm 80^\circ$; the mean

length measured 1.7 ± 3.6 mm. Only 44 (4%) had reference calcium in the absence of lesion calcium. Angiographic detection and classification of calcium depended on arc, length, location, and distribution of lesion and reference segment calcium. By discriminant analysis, the classification function for predicting angiographic calcium included the arc of target lesion calcium, the arc of superficial calcium, the length of reference segment calcium, and the location of calcium within the lesion. This model correctly predicted the angiographic detection of calcification in 74.4% of lesions and the angiographic classification (non/moderate/severe) of calcium in 62.8% of lesions.

Conclusion IVUS detected calcium in $> 50\%$ of lesions, significantly more often than standard angiography. Although angiography is moderately sensitive for the detection of extensive lesion calcium (sensitivity, 60% and 85% for three- and first-quadrant calcium, respectively), it is less sensitive for the presence of milder degrees. (Circulation. 1995;91:1959-1965.)

Key Words • coronary disease • calcium • ultrasonically • angiography

Selective coronary arteriography has been the "gold standard" for guiding revascularization in coronary artery disease. Despite its widespread acceptance, it has many inherent limitations, including its inability to assess plaque composition with negative contrast imaging. Recently, it has been suggested that coronary arteriography has a limited ability to detect and localize target lesion calcium.^{1,2} Target lesion calcium is both a marker for significant coronary artery disease and the major determinant of the success of various transcatheter therapies.³⁻⁷

Intravascular ultrasound (IVUS) provides transmural images of coronary arteries in vivo. The normal coronary arterial wall, the major components of the atherosclerotic plaque, and the changes that occur during the atherosclerotic disease process, after transcatheter therapy, and during restenosis can be studied in humans in a

manner previously not possible. The purpose of this study is (1) to use IVUS to evaluate the patterns (eg, magnitude, location, and distribution) of coronary artery calcium in a large number of patients undergoing transcatheter therapy for coronary artery disease and (2) to compare IVUS and coronary angiography in the evaluation of coronary artery calcification.

Methods

Patient Population

From July 1, 1993, to March 1, 1994, 1155 target lesions in 1117 patients were studied by IVUS and coronary angiography. These lesions met the following criteria: (1) native vessel location (thereby excluding vein graft and internal mammary lesions) and (2) ability to assess target lesion morphology by both IVUS and coronary angiography (thereby excluding lesions with previous stent placement). There were 862 men and 255 women 61 \pm 11 years old. Target lesion location was left main in 47, left anterior descending in 467, left circumflex in 180, and right coronary artery in 441. Diagonal branches were considered part of the left anterior descending, and marginal branches were considered part of the left circumflex artery. One hundred thirty-six lesions were occluded in location. No catheter-based intervention was performed in 149 lesions (21 of which were treated instead with operative revascularization), balloon angioplasty was performed in 127 lesions, directional coronary atherectomy (Devices for Vascular Intervention) in

Definition of Calcified Lesions – Angiography/Fluoroscopy

- Readily apparent densities noted within the vascular wall at the site of the stenosis
 - **Moderate:** Densities seen prior to contrast injection, but only during cardiac motion
 - **Severe:** Densities seen prior to contrast injection, but w/o cardiac motion and usually involve both sides of the arterial wall

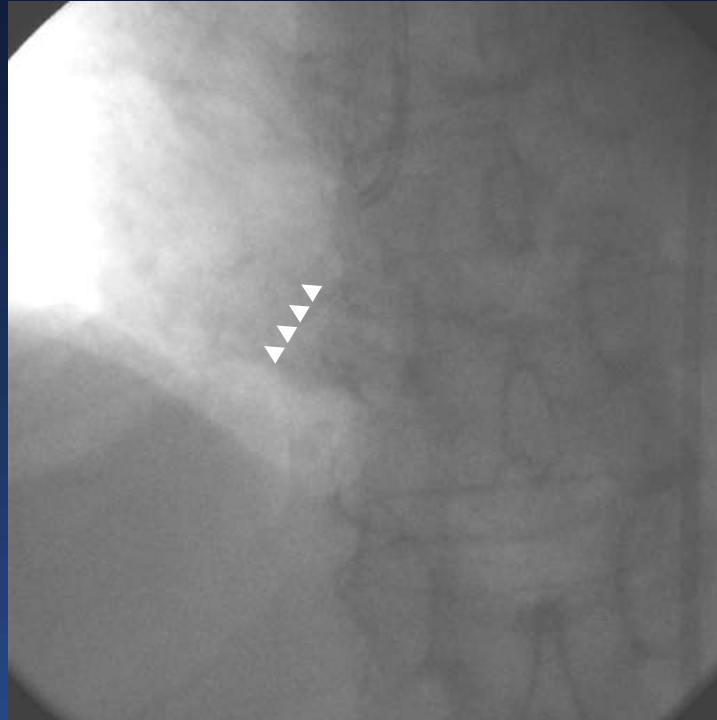
Received August 1, 1994; revision received October 12, 1994; revision accepted November 15, 1994.

From the Intravascular Ultrasound Imaging and Catheter Characterization Laboratories of the Washington Hospital Center, Washington, DC.

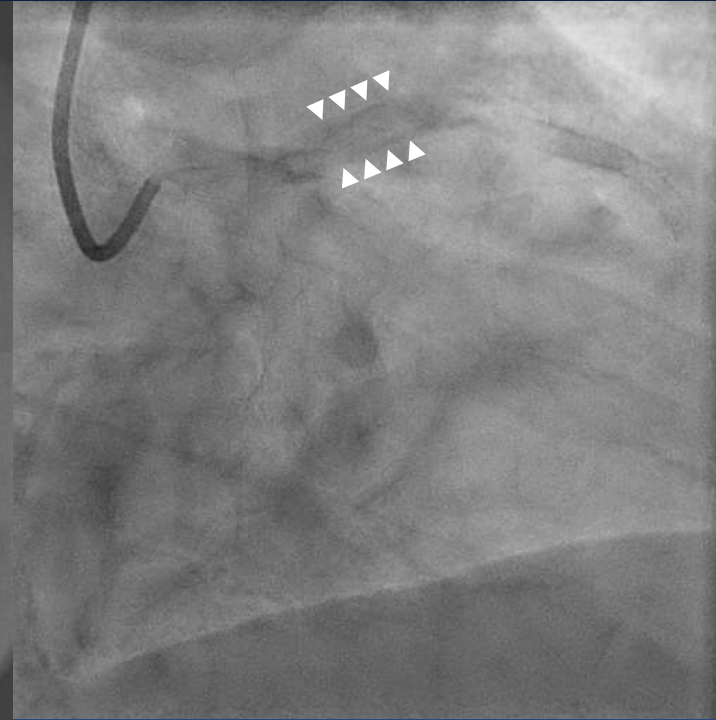
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Definition of Calcified Lesions – Angiography/Fluoroscopy



Moderate:
*Seen only during cardiac motion on
one side of vessel*



Severe:
*Seen without cardiac motion on
both sides of vessel*

Meta-analysis of 13 studies and 66,361 pts assessing the association between angiographic arget lesion calcification and adverse outcomes in pts undergoing DES implantation

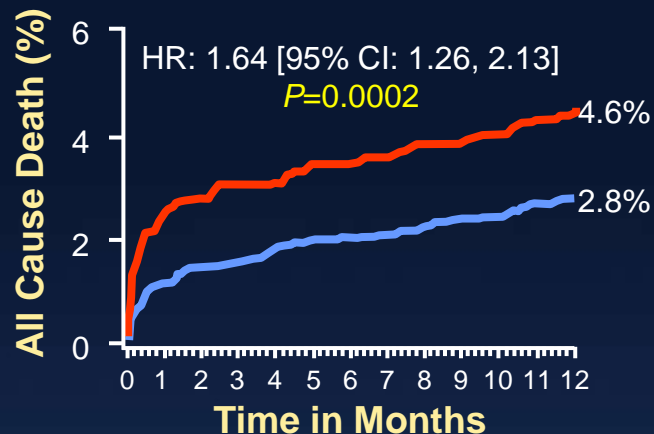
Endpoint	# of studies	HR
All cause mortality	4	1.41 (1.27-1.56)
Cardiac mortality	5	1.97 (1.68-2.31)
Myocardial infarction	6	1.33 (1.13-1.57)
MACE	5	1.37 (1.19-1.58)
TLR	8	1.47 (1.18-1.83)
Early TLR (<1 year)	7	1.63 (1.43-1.85)
Stent thrombosis	12	1.63 (1.36-1.96)
Early ST (<30 days)	5	1.69 (1.16-2.45)

10/13 studies compared moderate/severe calcium vs no/mild calcium

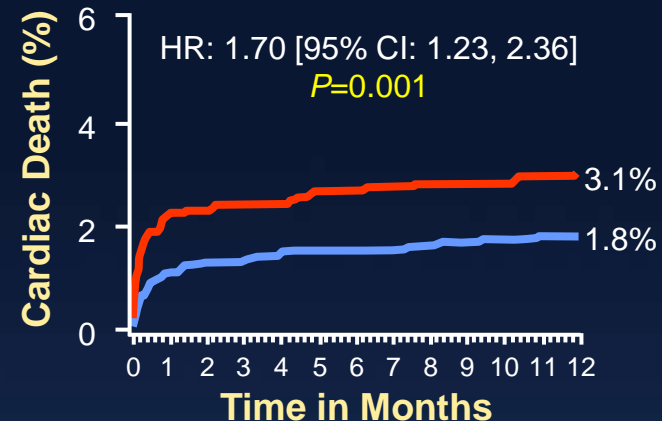
Ischemic Outcomes After PCI of Calcified Vessels in ACS Pts

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 ST (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)

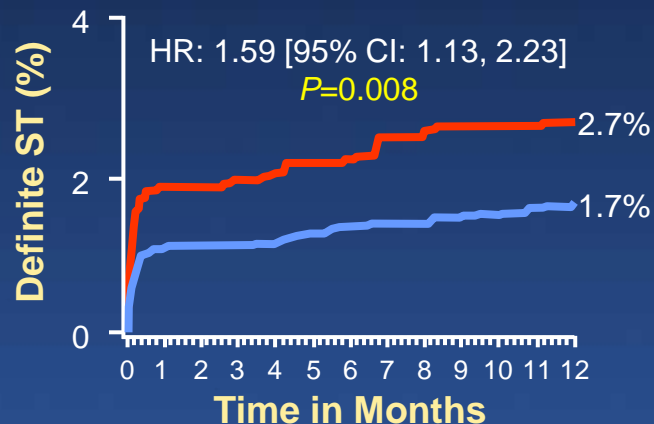


No. at risk		2190	2082	2049	1744
Moderate/severe		2190	2082	2049	1744
No/mild		4665	4460	4415	3588

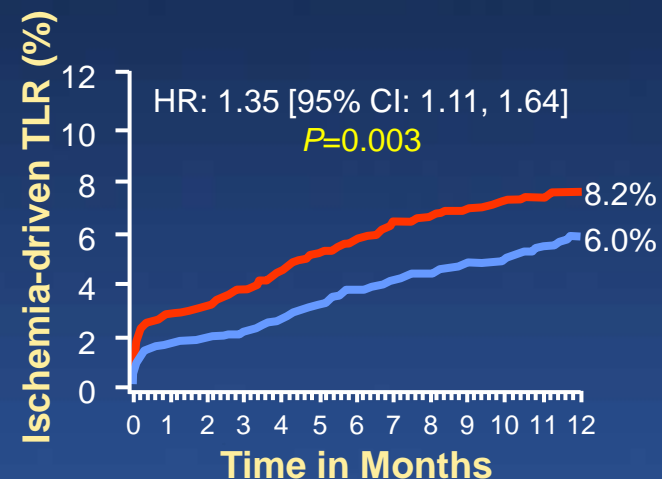


No. at risk		2190	2082	2049	1744
Moderate/severe		2190	2082	2049	1744
No/mild		4665	4460	4415	3588

— Moderate/severe target lesion calcification
— No/mild target lesion calcification



No. at risk		2139	2001	1961	1665
Moderate/severe		2139	2001	1961	1665
No/mild		4607	4358	4302	3588



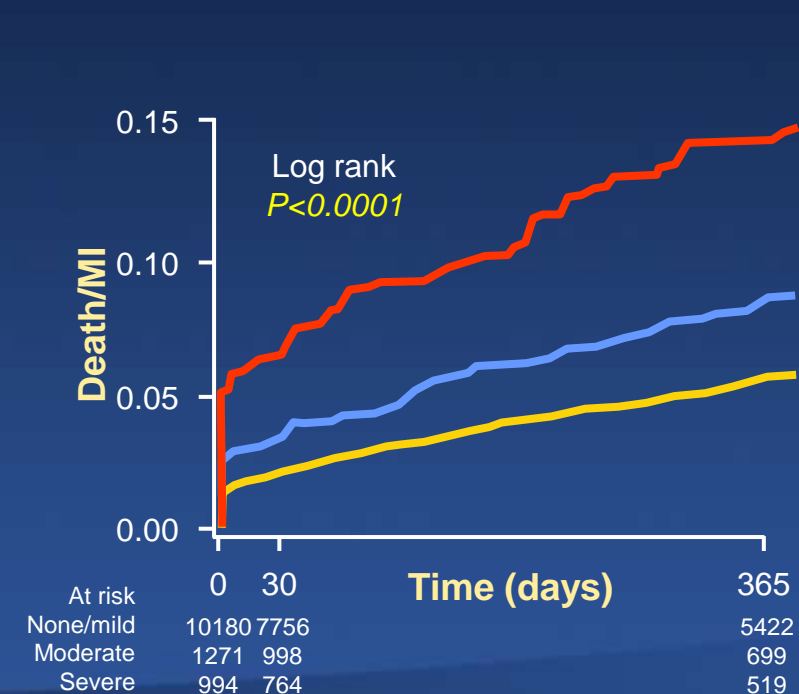
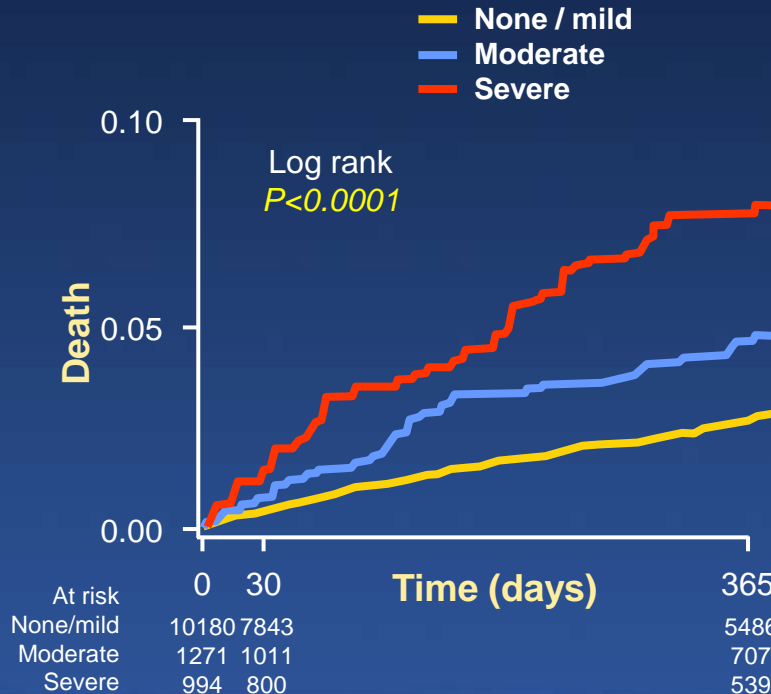
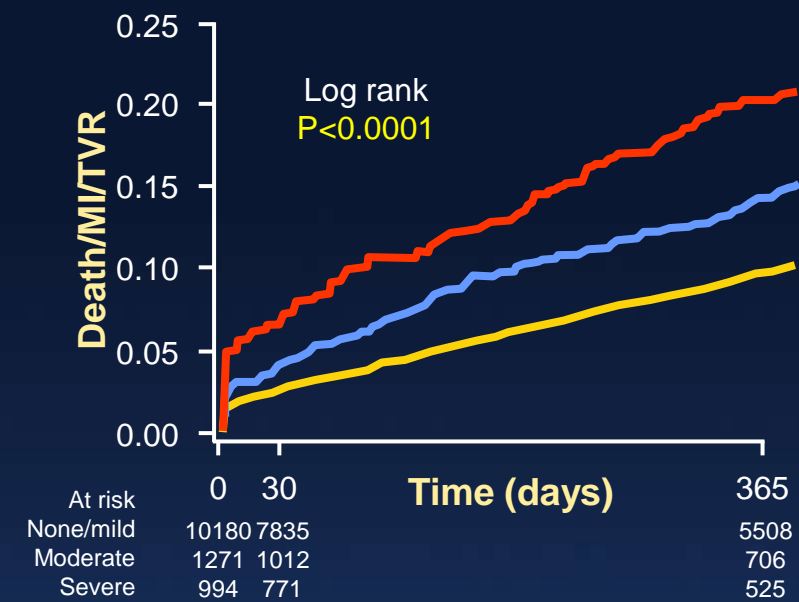
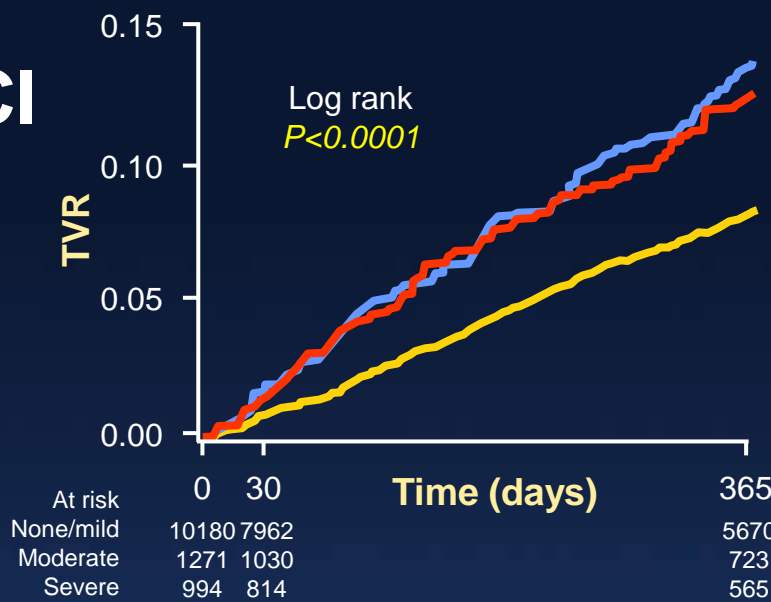
No. at risk		2190	1991	1921	1624
Moderate/severe		2190	1991	1921	1624
No/mild		4665	4349	4224	3388

Adverse Events Post-PCI And Calcification

Findings from a large multiethnic registry

The three strongest independent predictors of moderate to severe coronary calcification were lesion length, pt age, and LM location (c-statistic 0.73).

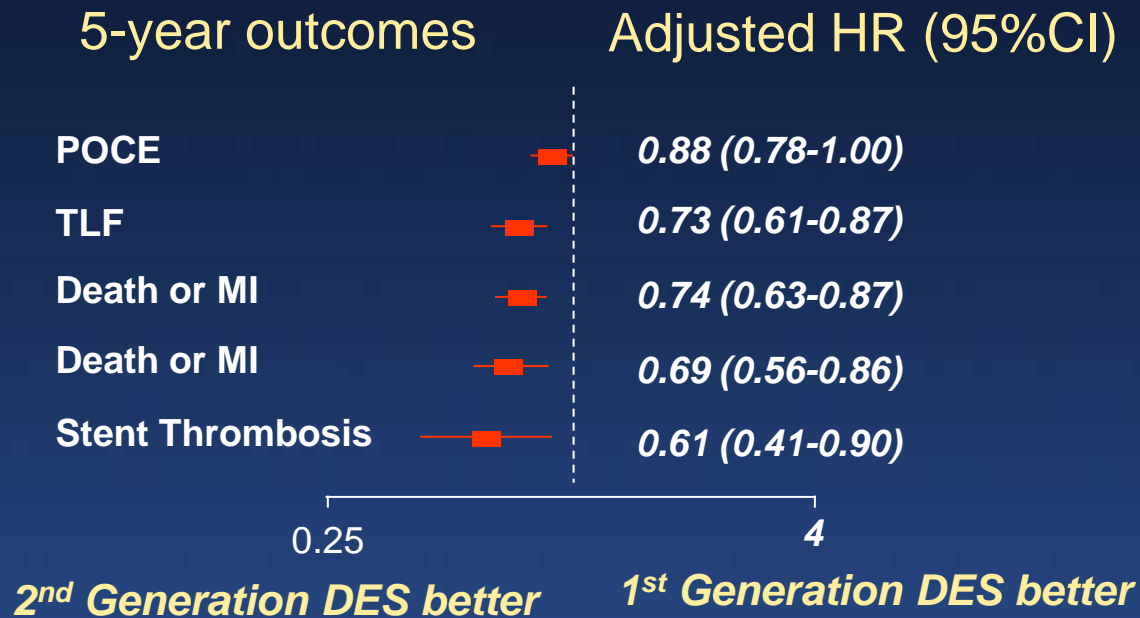
After adjusting for age, race, BMI, CKD, hypertension, smoking, prior MI or CABG, PAD, anemia, and lesion length, location, and angiographic characteristics, moderate or severe calcification remained associated with MACE (HR 1.63 [1.42, 1.86], $P < 0.001$) and mortality (HR 1.64 [1.26, 2.15], $P < 0.001$).



10-yr clinical outcomes: Pooled analysis of the ISAR-TEST 4 and 5 randomized trials

	No calcium	Mild calcium	Moderate calcium	Severe calcium	P-value
#	1212	2069	1276	396	
All cause mortality	25.3%	32.1%	41.7%	46.5%	0.004
TLR	17.4%	16.5%	19.8%	28.7%	0.001
MI	4.9%	5.9%	6.0%	10.5%	0.02
Definite/probable ST	1.3%	1.4%	1.8%	3.6%	0.6

Moderate/Severe Angiographic Coronary Calcification and Long-Term Outcomes According to DES Generation

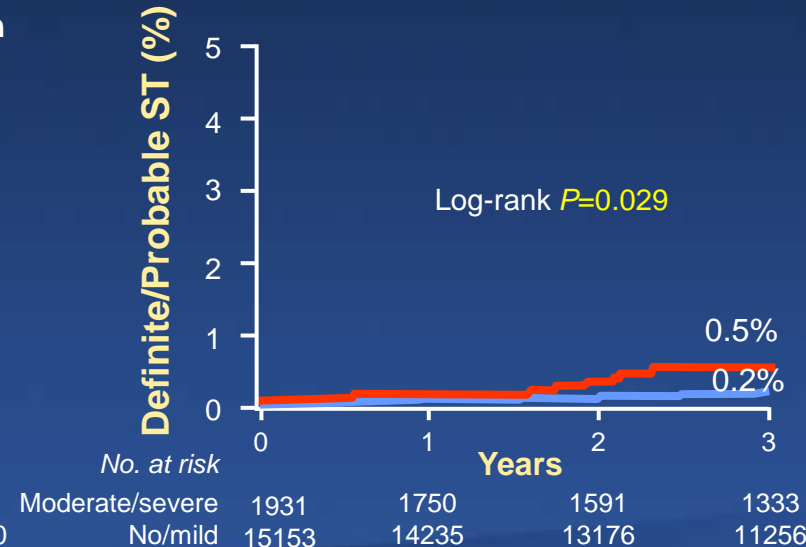
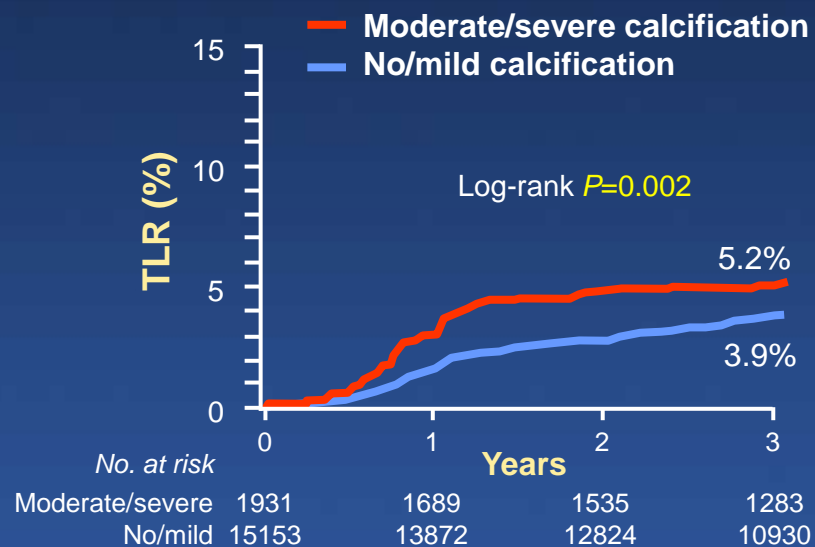
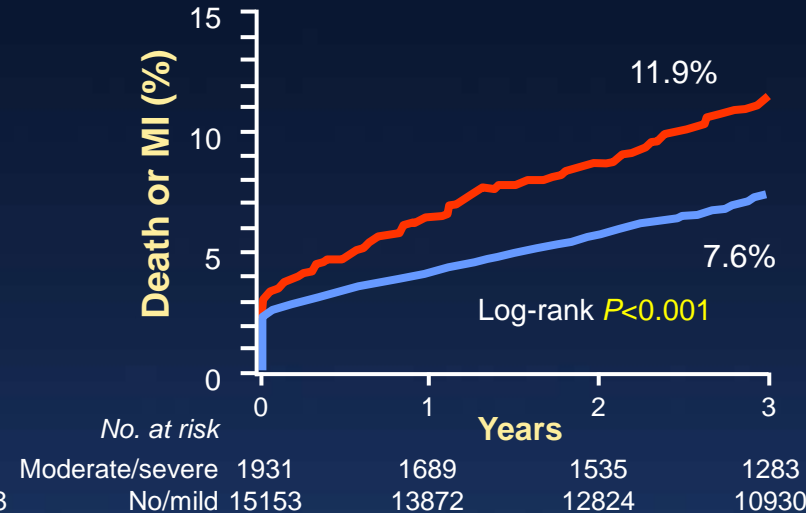
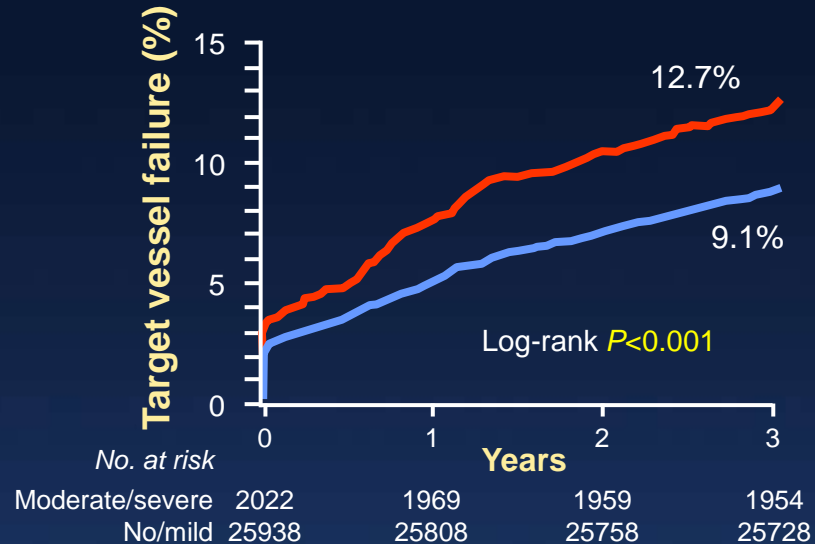


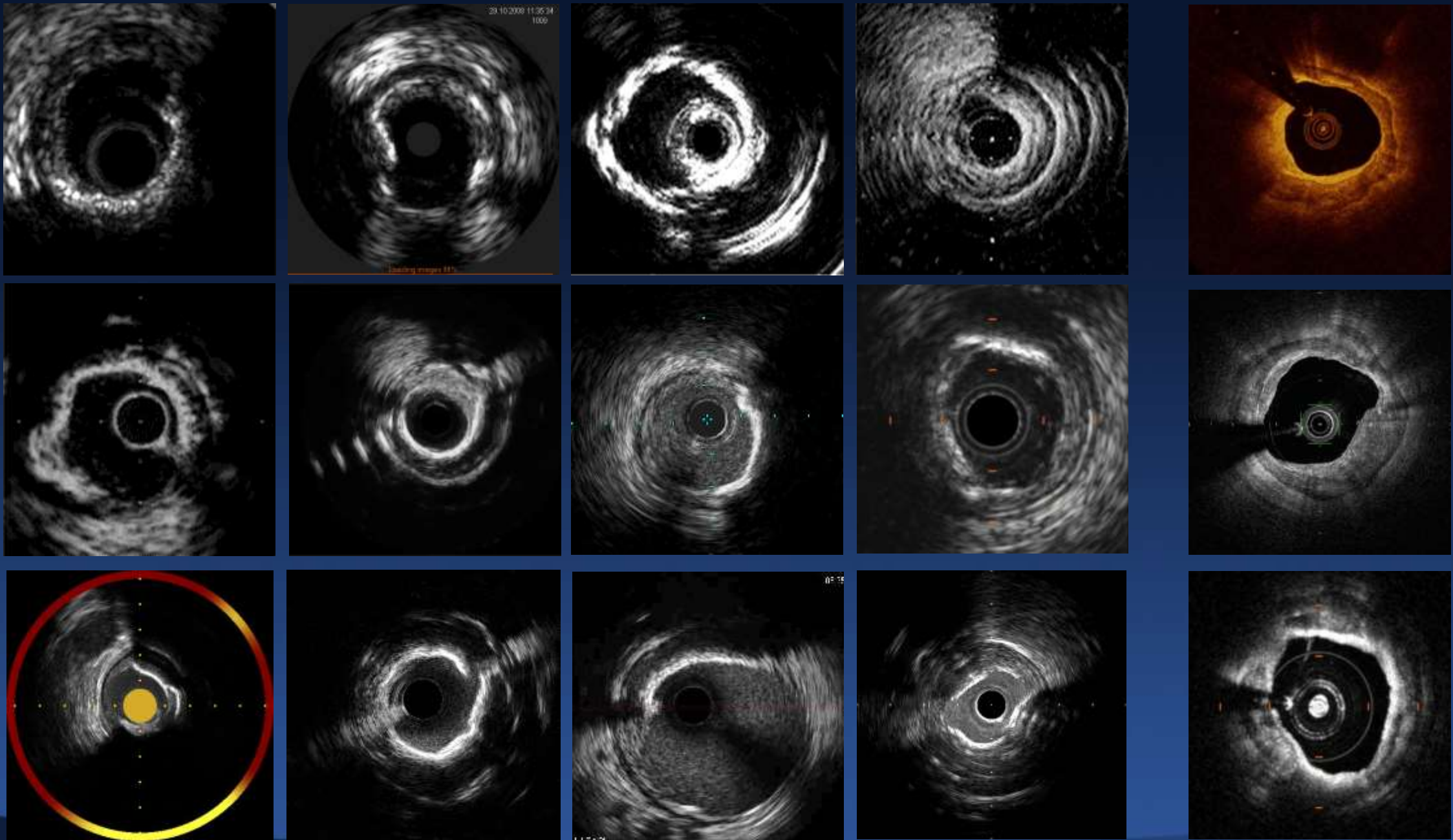
- Individual pt data were pooled from 18 RCT evaluating DES, categorized according to the presence of angiography core laboratory-confirmed moderate or severe coronary artery calcium.
- A total of 19,833 patients were included. Moderate or severe calcium was present in 1 or more target lesions in 6,211 patients (31.3%).
- Major endpoints were the patient-oriented composite endpoint (POCE; death, MI, or any revascularization) and the device-oriented composite endpoint of target lesion failure (cardiac death, target vessel MI, or ischemia-driven TLR).

IRIS-DES Registries (n=17,084 pts with 27,739 lesions)

The presence of moderate/severe coronary artery calcium was significantly associated with an adjusted risk of TVF at 3 yrs [hazard ratio, 1.37; 95% confidence interval (CI), 1.19-1.58; $P < 0.001$].

For severe calcium, optimal lesion preparation was associated with a lower 3-year rate of TVF (22.3vs. 12.8%) in the late F-U period of 1–3yrs (HR, 0.28; 95% CI, 0.12–0.69; $P=0.003$), but not in the early F-U period <1 yr (HR, 1.16; 95% CI, 0.37–3.71; $P=0.80$). However, post-dilation with a high-pressure noncompliant balloon had no effect on the outcome. There was no impact of technique on lesser amounts of calcium.





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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)

Patterns of Calcification in Coronary Artery Disease
A Statistical Analysis of Intravascular Ultrasound and Coronary Angiography in 1155 Lesions

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Background: Target lesion calcium is a marker for significant coronary artery disease and a determinant of the success of transcatheter therapy.

Methods and Results: Eleven hundred fifty-five native vessel target lesions in 1117 patients were studied by intravascular ultrasound (IVUS) and coronary angiography. The presence, magnitude, location, and distribution of IVUS calcium were analyzed and compared with the detection and classification (none/mild, moderate, and severe) by angiography. Angiography detected calcium in 440 of 1155 lesions (38%), 309 (26%) moderate calcium and 131 (12%) severe. IVUS detected lesion calcium in 841 of 1155 (73%), 60 (5%) severe angiographic lesions. The mean arc of lesion calcium measured 115° (13°), the mean length measured 3.7 (3.7) mm. Target lesion calcium was only superficial in 48%, only deep in 26%, and both superficial and deep in 26%. The mean arc of superficial calcium measured 82° (36°), the mean length measured 2.4 (3.4) mm. Three hundred seventy-three of 1155 reference segments (32%) contained calcium (P<.001) compared with lesions (84%). The mean arc of reference calcium measured 42° (30°), the mean length measured 1.7 (3.6) mm. Only 44 (4%) had reference calcium in the absence of lesion calcium. Angiographic detection and classification of calcium depended on arc, length, location, and distribution of lesion and reference segment calcium. In discriminant analysis, the classification function for predicting angiographic calcium included the arc of target lesion calcium, the arc of superficial calcium, the length of reference segment calcium, and the location of calcium within the lesion. The model correctly predicted the angiographic detection of calcification in 74.4% of lesions and the angiographic classification (mean sensitivity) of calcium in 82.9% of lesions.

Conclusion: IVUS detected calcium in ~70% of lesions, significantly more often than standard angiography. Although angiography is moderately sensitive for the detection of extensive lesion calcium (sensitivity, 90% and 80% for three- and four-quadrant calcium, respectively), it is less sensitive for the presence of milder degrees of calcification. **Keywords:** IVUS, angiography, coronary disease, calcium, stenosis, angiography.

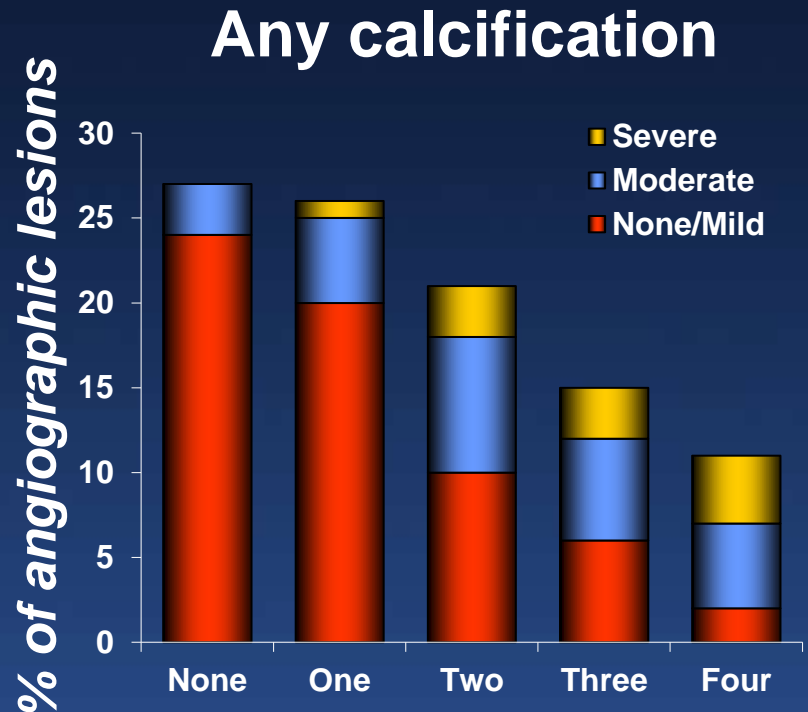
Selective coronary arteriography has been the "gold standard" for guiding revascularization in coronary artery disease. Despite its widespread acceptance, it has many inherent limitations, including its inability to assess plaque composition with negative contrast imaging. Recently, it has been suggested that coronary arteriography has a limited ability to detect and localize target lesion calcium.^{1,2} Target lesion calcium is both a marker for significant coronary artery disease and the major determinant of the success of various transcatheter therapies.³⁻⁵

Intravascular ultrasound (IVUS) provides transmural images of coronary arteries in vivo. The normal coronary arterial wall, the major components of the atherosclerotic plaque, and the changes that occur during the atherosclerotic disease process, after transcatheter therapy, and during restenosis can be studied in humans in a manner previously not possible. The purpose of this study is (1) to use IVUS to evaluate the patterns (eg, magnitude, location and distribution) of coronary artery calcium in a large number of patients undergoing transcatheter therapy for coronary artery disease and (2) to compare IVUS and coronary angiography in the evaluation of coronary artery calcification.

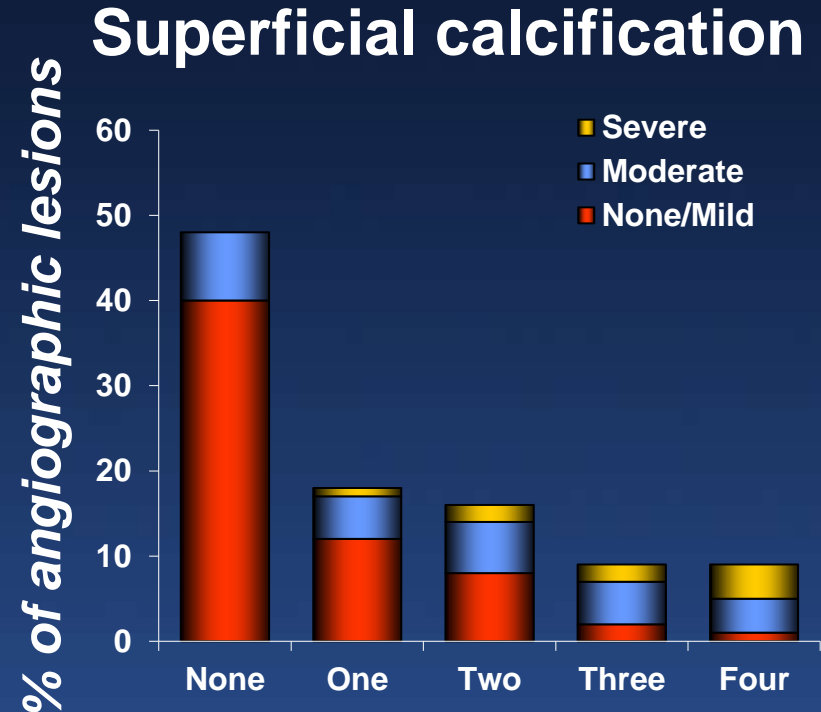
Methods

Patient Population

From July 1, 1991, to March 1, 1994, 1155 target lesions in 1117 patients were studied by IVUS and coronary angiography. These lesions met the following criteria: (1) native vessel location (excludes saphenous vein graft and internal mammary artery) and (2) ability to assess target lesion morphology by both IVUS and coronary angiography (that is, excludes lesions with previous stent placement). There were 962 men and 25 women (2.1%) years old. Target lesion location was left main in 37, left anterior descending in 487, left circumflex in 180, and right coronary artery in 451. Diagonal branches were considered part of the left anterior descending, and marginal branches were considered part of the left circumflex artery. The handed coronary system was either left or right. Non-catheter-based intervention was performed in 103 lesions (9% of which were treated instead with operative revascularization). Follow-up angiography was performed in 125 lesions. Distal coronary arteriography (Detours for Vascular Intervention) in



IVUS quadrants of calcium



IVUS quadrants of superficial calcium

IVUS	Angiographic Calcification		
	None/Mild	Moderate	Severe
#	715	306	134
Target lesion Ca⁺⁺	61%	90%	98%
Arc of lesion Ca⁺⁺ (°)	71 ± 83	165 ± 106	238 ± 104
Superficial lesion Ca⁺⁺	37%	72%	92%
Arc of Superficial lesion Ca⁺⁺ (°)	44 ± 74	124 ± 110	215 ± 119
Arc of reference Ca⁺⁺ (°)	25 ± 63	61 ± 93	87 ± 98
Total length of Ca⁺⁺ (mm)	3.6 ± 4.4	7.2 ± 6.4	9.7 ± 6.4

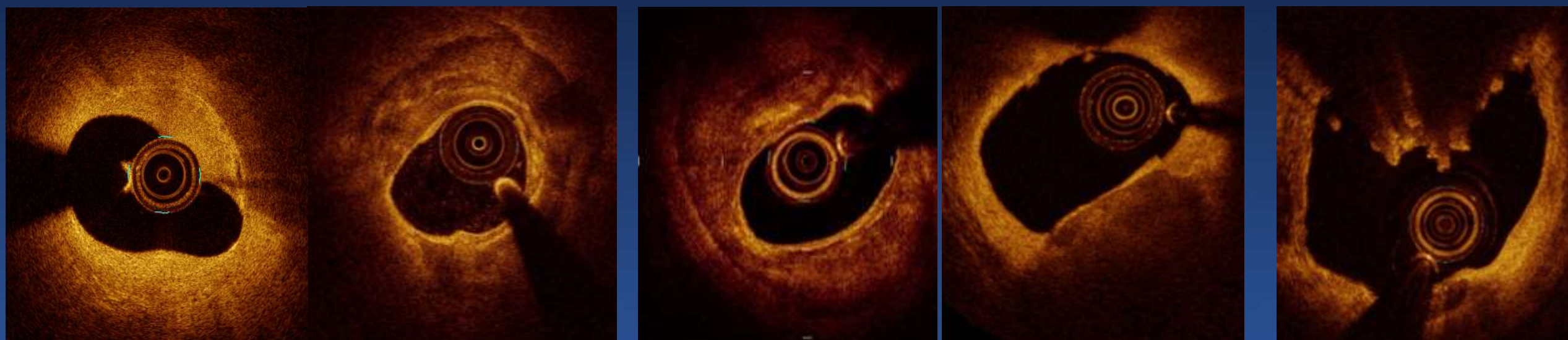
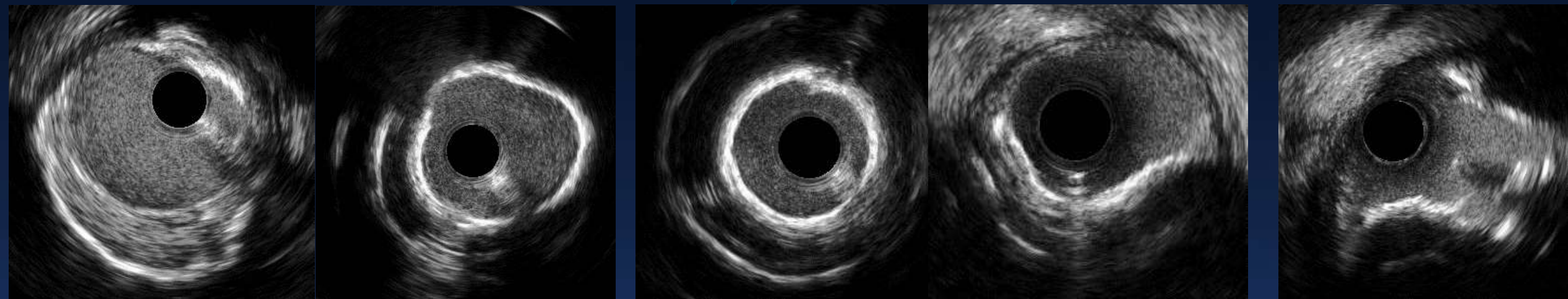
Deep calcium

Superficial calcium

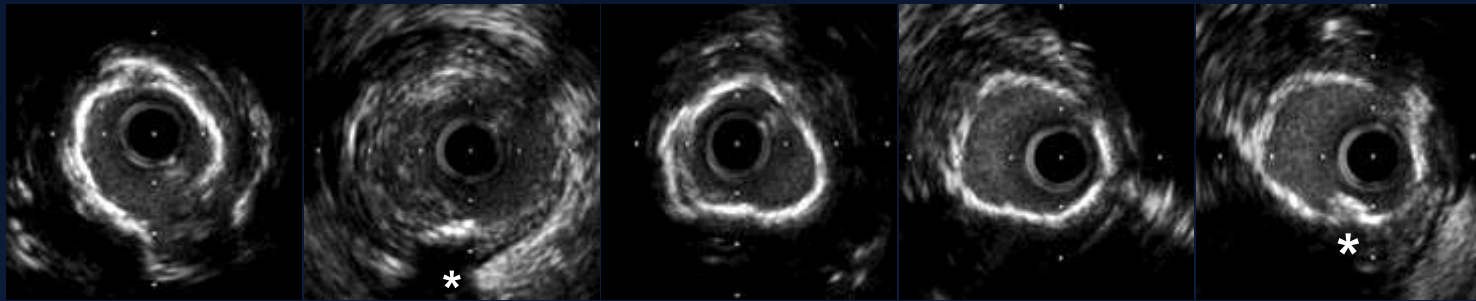
Concentric calcium

Eccentric calcium

Calcified nodule

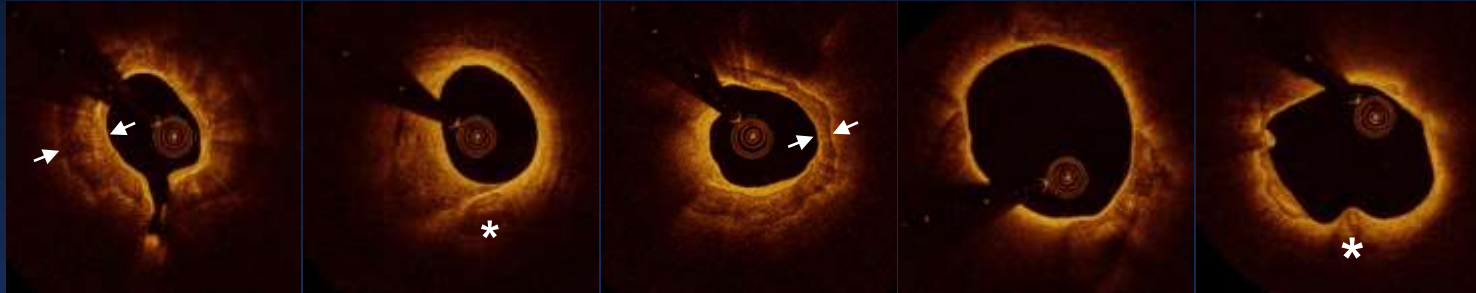


IVUS

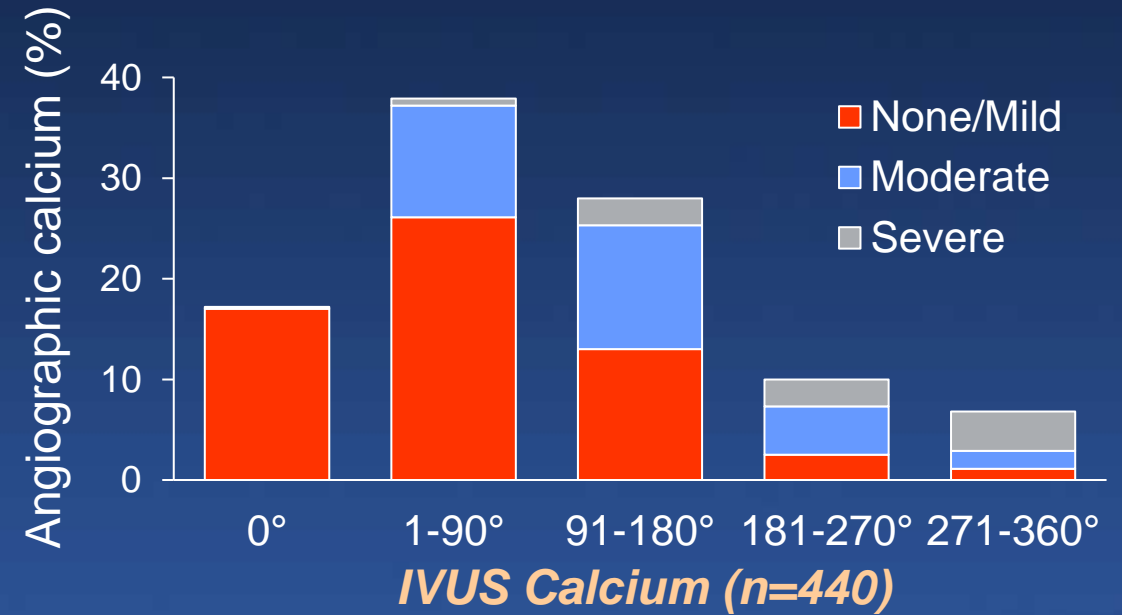
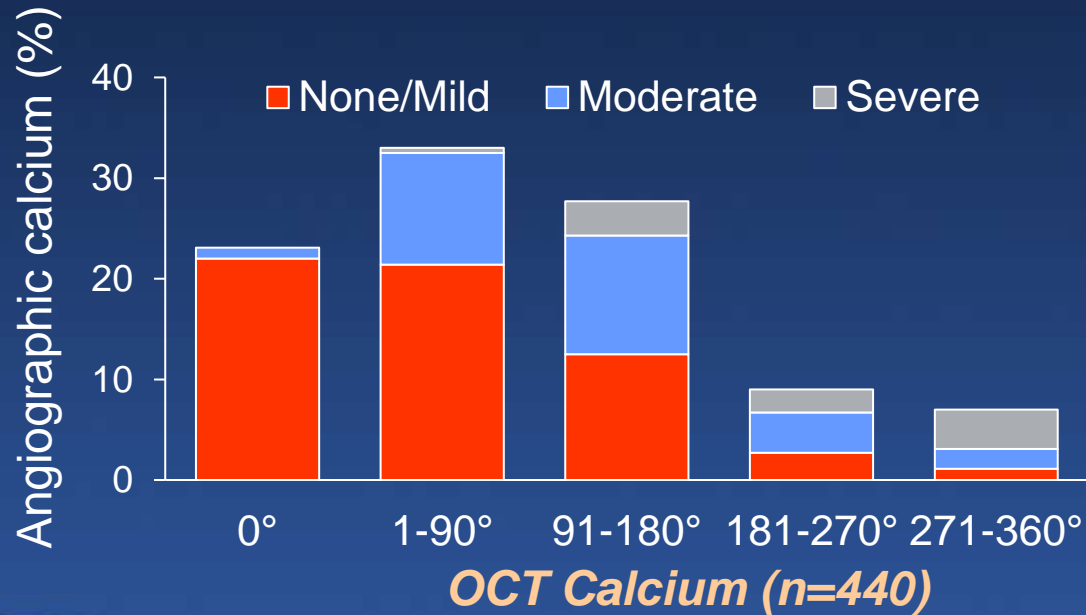


Arc Length

OCT



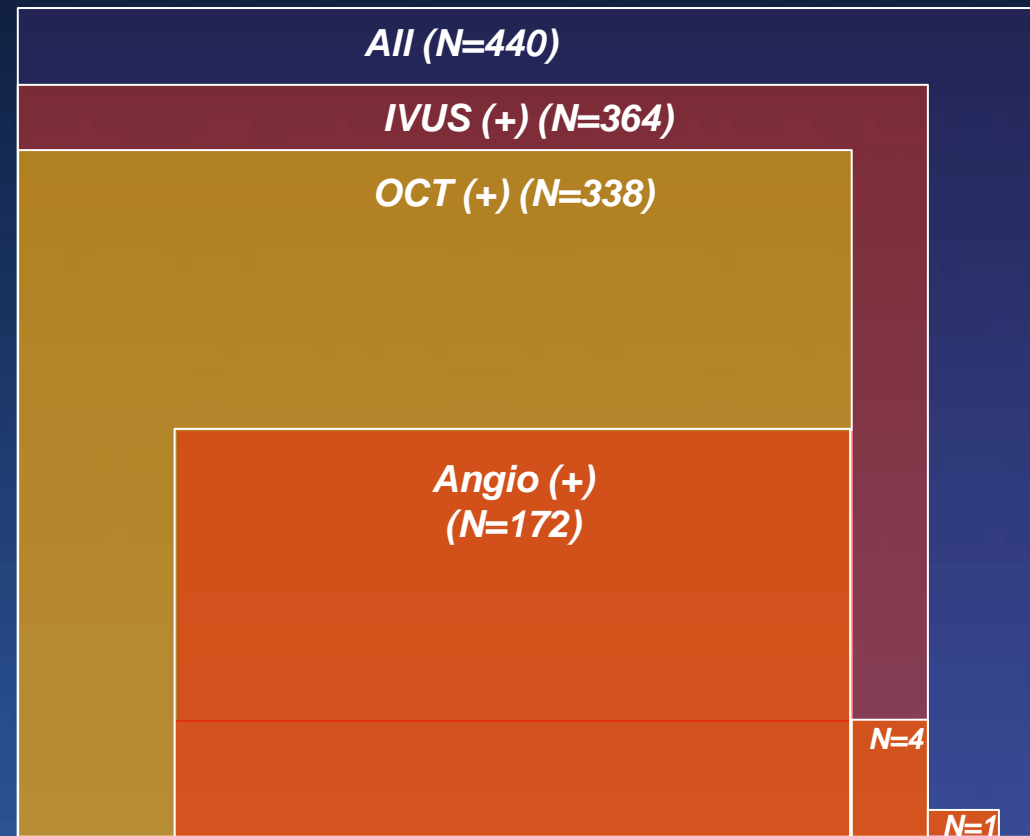
Arc Length
Thickness
Area
Volume



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

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

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



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

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.

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.

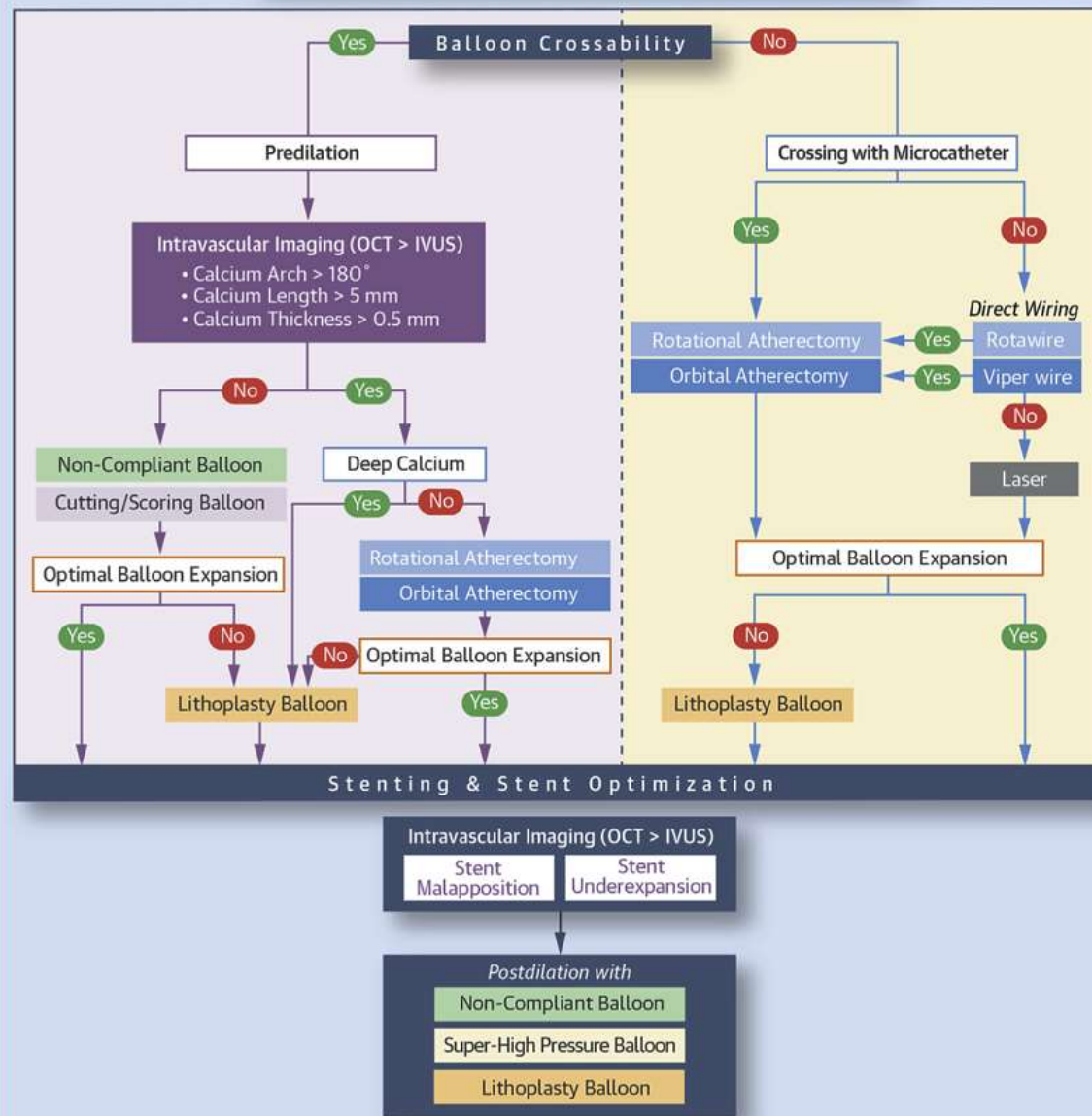
From the Oxford Heart Centre, Oxford University Hospitals, NHS Trust, Oxford, United Kingdom. *Dr. De Maria and Scarsini contributed equally to this paper. Dr. De Maria has received a speaker fee from Miracor Medical SA. Dr. Scarsini has received an educational grant from EAPCI. Dr. Banning has received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

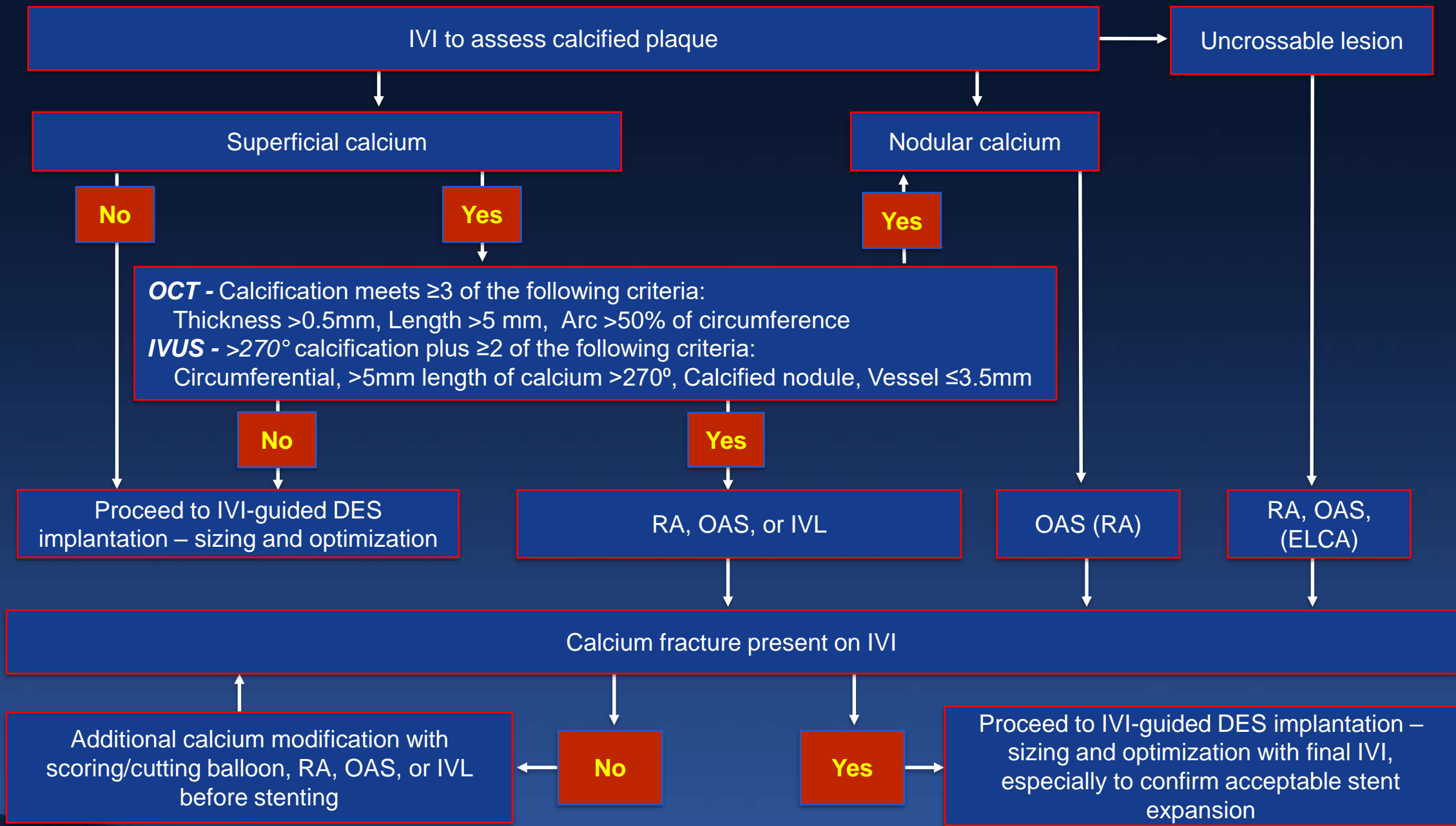
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Lesion with High Calcium Content on Coronary Angiogram

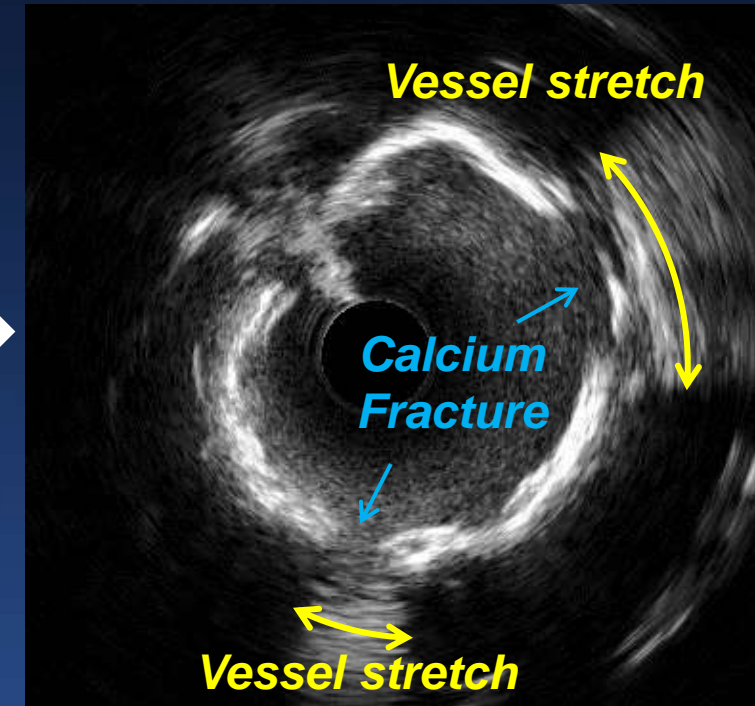
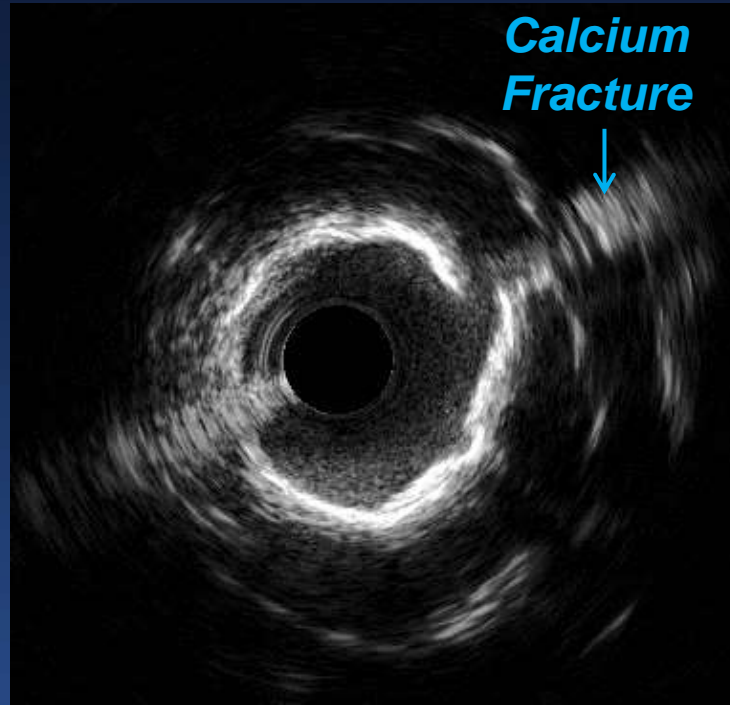
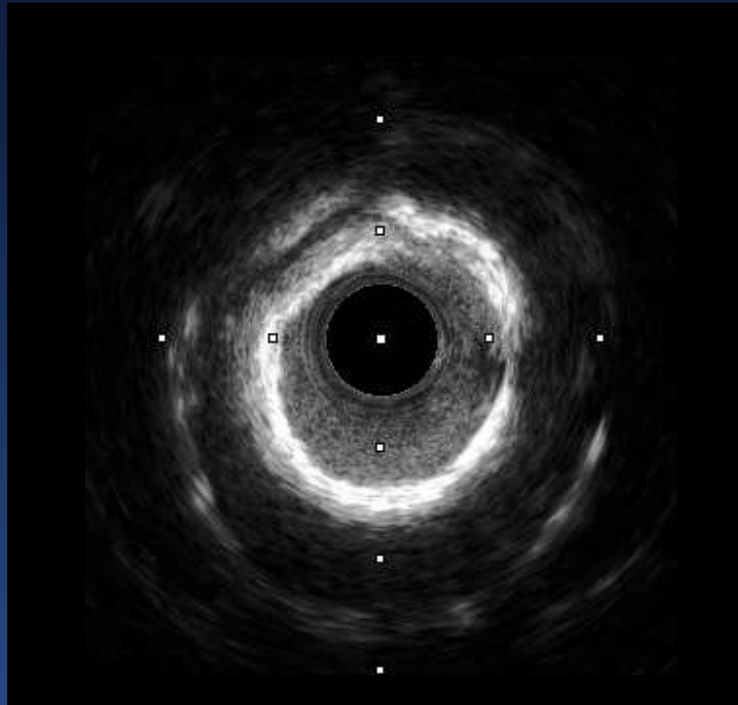




Detection of Calcium Fracture

Post-Balloon

Post-Stent Final



Question

Is the definition of Moderate to Heavy Calcification based on fluoroscopy or intravascular imaging

Answer

Both. It depends on the situation.