Intravascular Imaging of Coronary Calcification and Its Clinical Implications

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

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• *Grant/Research/Fellowship Support*	• *Boston Scientific, Philips, InfraReDx, Abbott*
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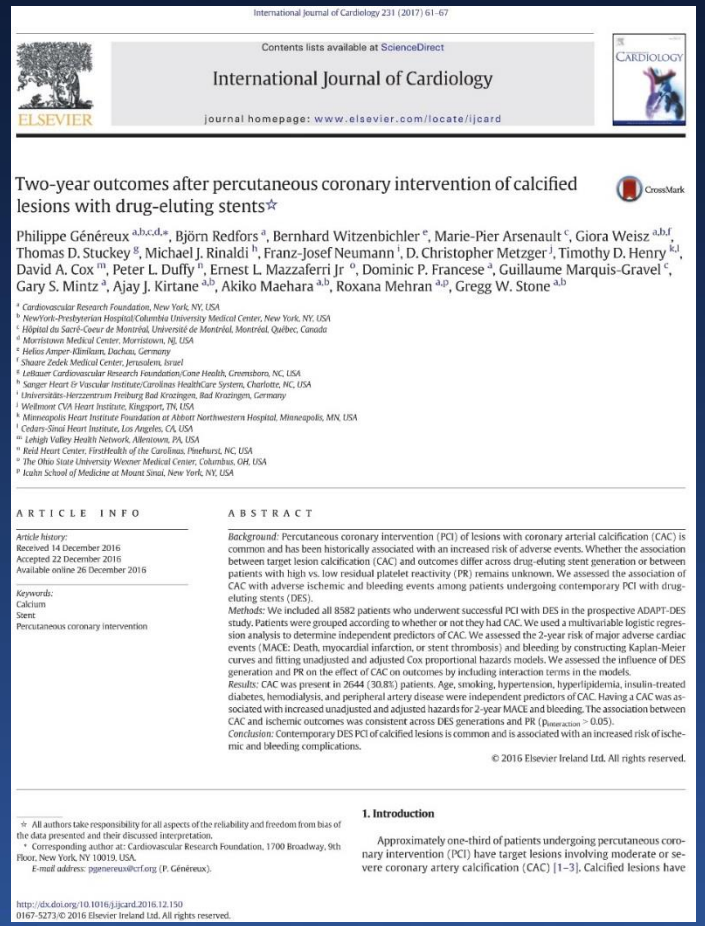
Angiographic Definitions

- **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***

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



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

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ABSTRACT

Background: Percutaneous coronary intervention (PCI) of lesions with coronary arterial calcification (CAC) is common and has been historically associated with an increased risk of adverse events. Whether the association between target lesion calcification (CAC) and outcomes differ across drug-eluting stent generation or between patients with high vs. low residual platelet reactivity (PR) remains unknown. We assessed the association of CAC with adverse ischemic and bleeding events among patients undergoing contemporary PCI with drug-eluting stents (DES).

Methods: We included all 8582 patients who underwent successful PCI with DES in the prospective ADAPT-DES study. Patients were grouped according to whether or not they had CAC. We used a multivariable logistic regression analysis to determine independent predictors of CAC. We assessed the 2-year risk of major adverse cardiac events (MACE: Death, myocardial infarction, or stent thrombosis) and bleeding by constructing Kaplan-Meier curves and fitting unadjusted and adjusted Cox proportional hazards models. We assessed the influence of DES generation and PR on the effect of CAC on outcomes by including interaction terms in the models.

Results: CAC was present in 2644 (30.8%) patients. Age, smoking, hypertension, hyperlipidemia, insulin-treated diabetes, hemodialysis, and peripheral artery disease were independent predictors of CAC. Having a CAC was associated with increased unadjusted and adjusted hazards for 2-year MACE and bleeding. The association between CAC and ischemic outcomes was consistent across DES generations and PR ($p_{\text{interaction}} > 0.05$).

Conclusion: Contemporary DES PCI of calcified lesions is common and is associated with an increased risk of ischemic and bleeding complications.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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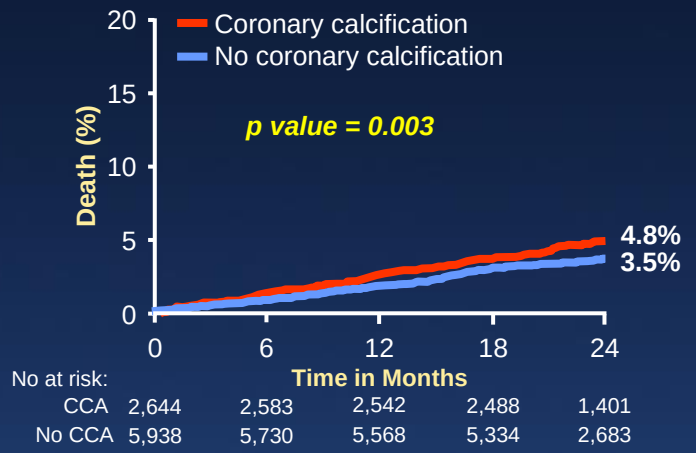
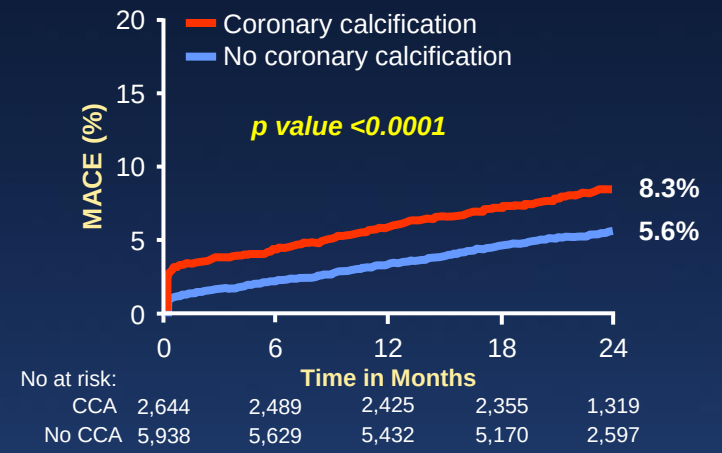
1. Introduction

Approximately one-third of patients undergoing percutaneous coronary intervention (PCI) have target lesions involving moderate or severe coronary artery calcification (CAC) [1–3]. Calcified lesions have

http://dx.doi.org/10.1016/j.ijcard.2016.12.150
0167-5273/



No at risk:					
CCA	2,644	2,583	2,542	2,488	1,401
No CCA	5,938	5,730	5,568	5,334	2,683



No at risk:					
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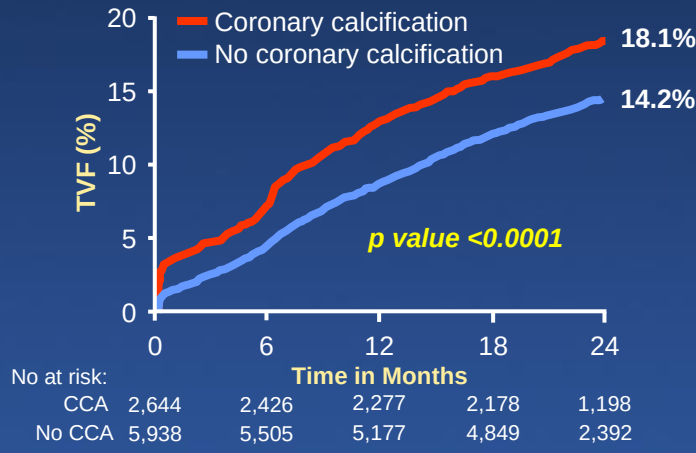
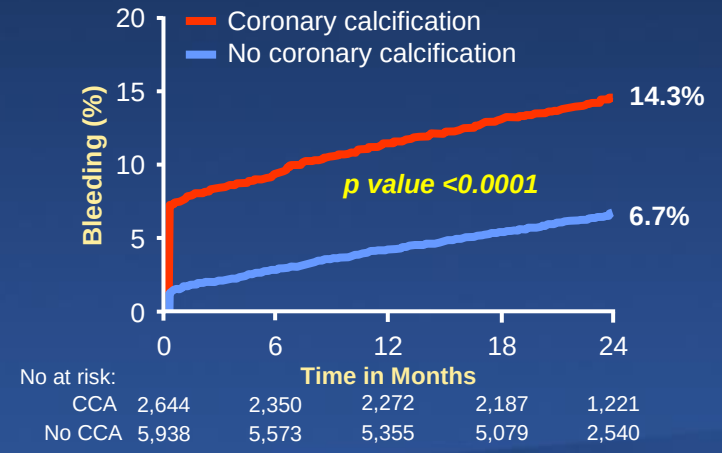
No CCA	5,938	5,629	5,432	5,170	2,597



No at risk:					
CCA	2,644	2,426	2,277	2,178	1,198
No CCA	5,938	5,505	5,177	4,849	2,392



No at risk:					
CCA	2,644	2,350	2,272	2,187	1,221
No CCA	5,938	5,573	5,355	5,079	2,540

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

Angiography is only moderately sensitive for detection of extensive lesion calcium (sensitivity 60% and 85% for three- and four-quadrant calcium)

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

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%): 306 (26%) moderate calcium and 134 (12%) severe. IVUS detected lesion calcium in 841 of 1155 (73%, $P<.0001$ versus angiography). The mean arc of lesion calcium measured 115±110°; 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±108°; 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±80°; 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 arcs, lengths, 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 (none/moderate/severe) of calcium in 62.8% of lesions.

Conclusions 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, 60% and 85% for three- and four-quadrant calcium, respectively), it is less sensitive for the presence of milder degrees. (***Circulation. 1995;91:1959-1965.***)

Key Words • coronary disease • calcium • ultrasonics • 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.[2-13]

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.

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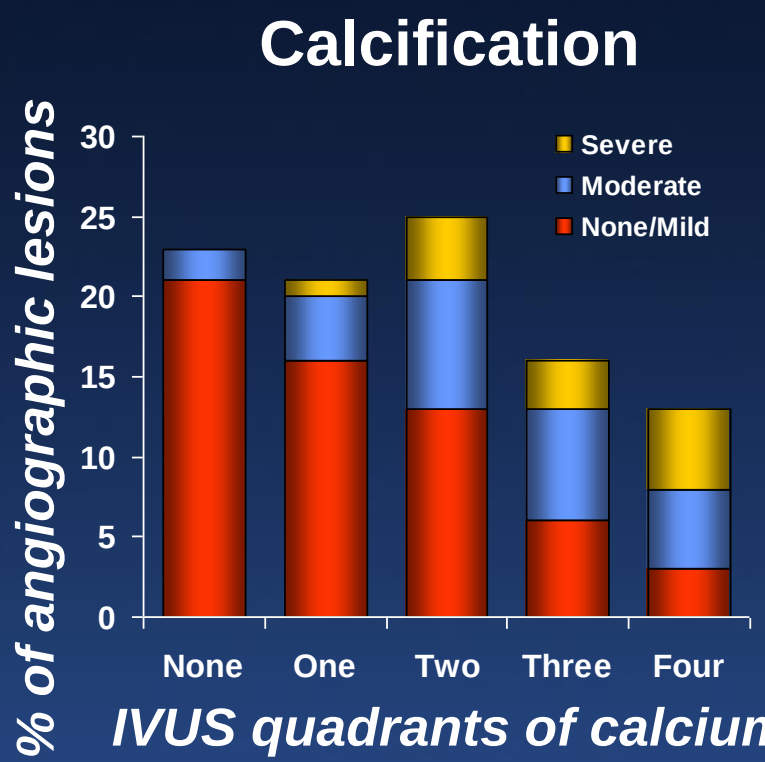
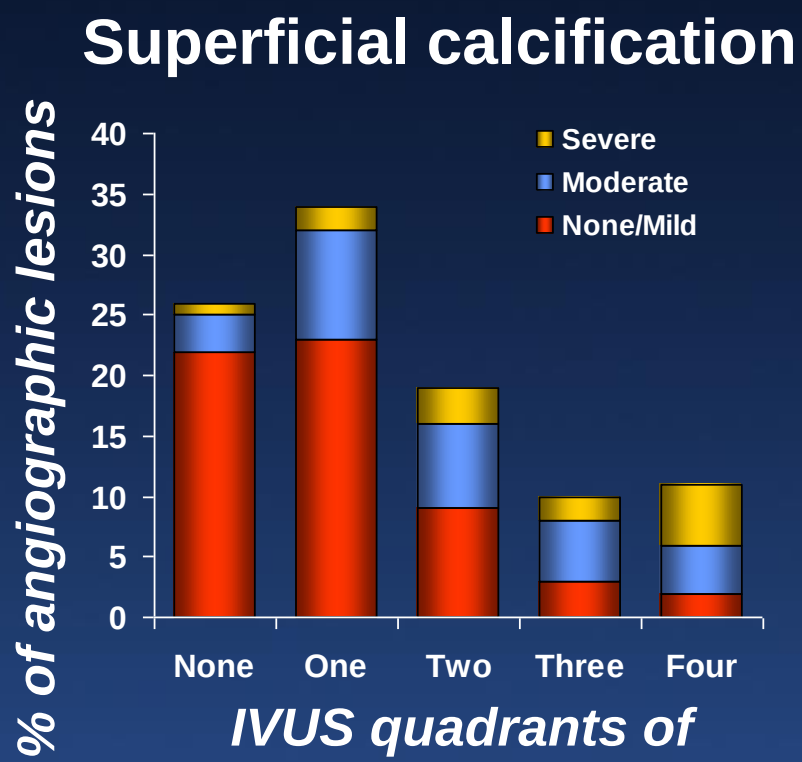
Methods

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 (thereby excluding vein graft and internal mammary lesions) and (2) ability to assess target lesion morphology by both IVUS and coronary angiography (therefore excluding lesions with previous stent placement). There were 862 men and 255 women 61±11 years old. Target lesion location was left main in 47, left anterior descending in 487, 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 ninety-six lesions were ostial 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





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*)*

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

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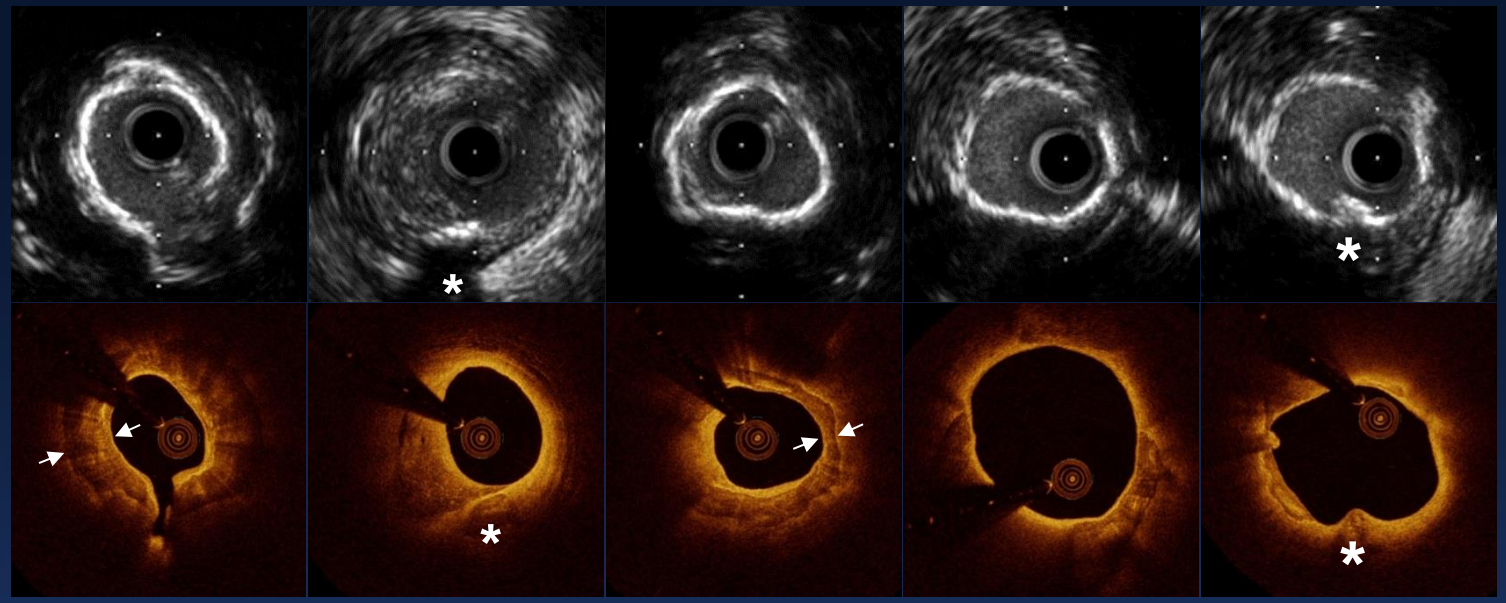
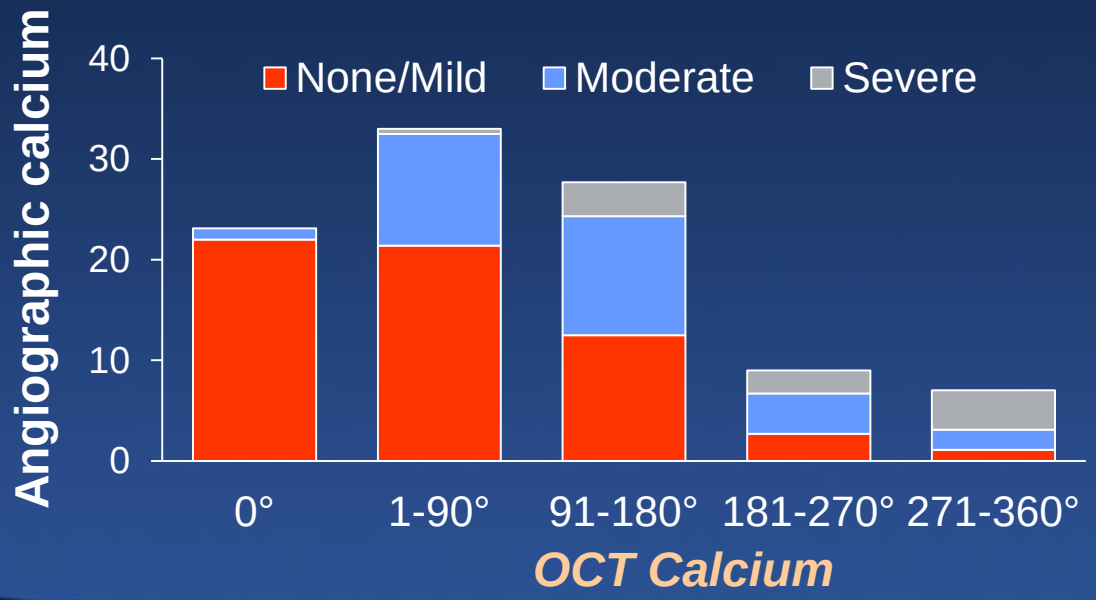
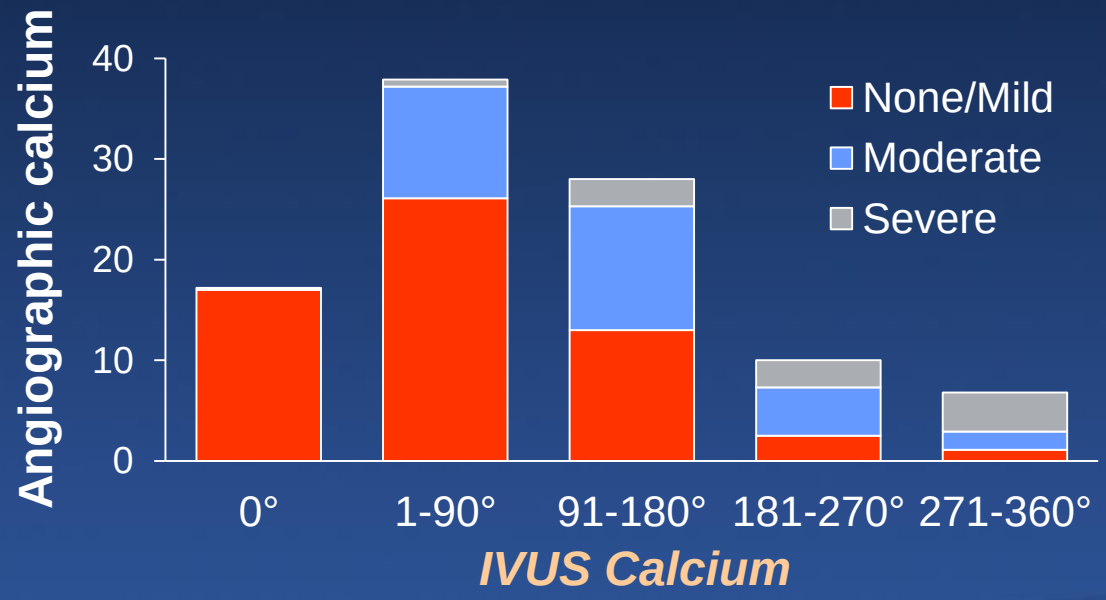


Arc Length

Arc Length Thickness Area Volume





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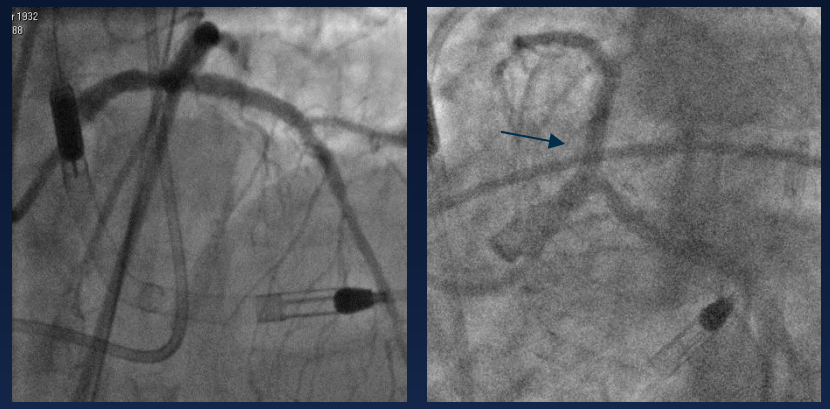
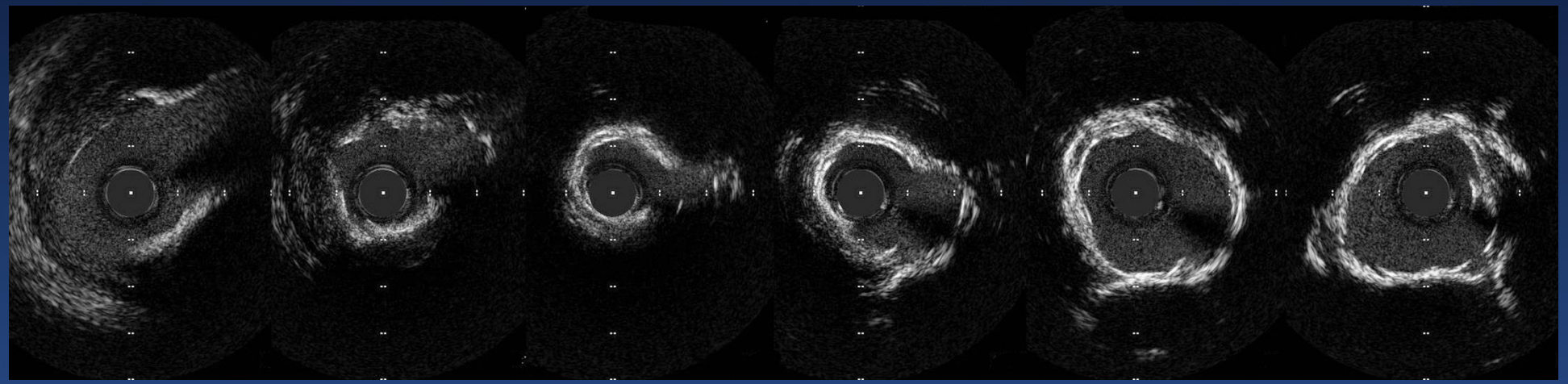
Wang et al. JACC Cardiovasc Imaging 2017;10:869-79
Mintz and Guagliumi. Lancet 2017;390:793-809



LMCA

LAD



0 → 2mm → 10mm

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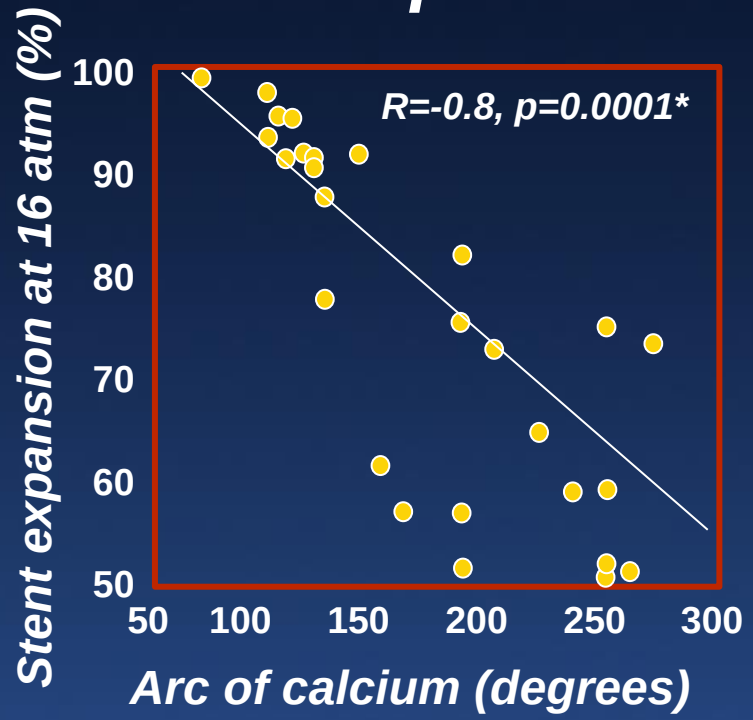
Mintz and Guagliumi. Lancet 2017;390:793-809

IVUS stent expansion is the strongest predictor of early ST or restenosis after BMS or DES

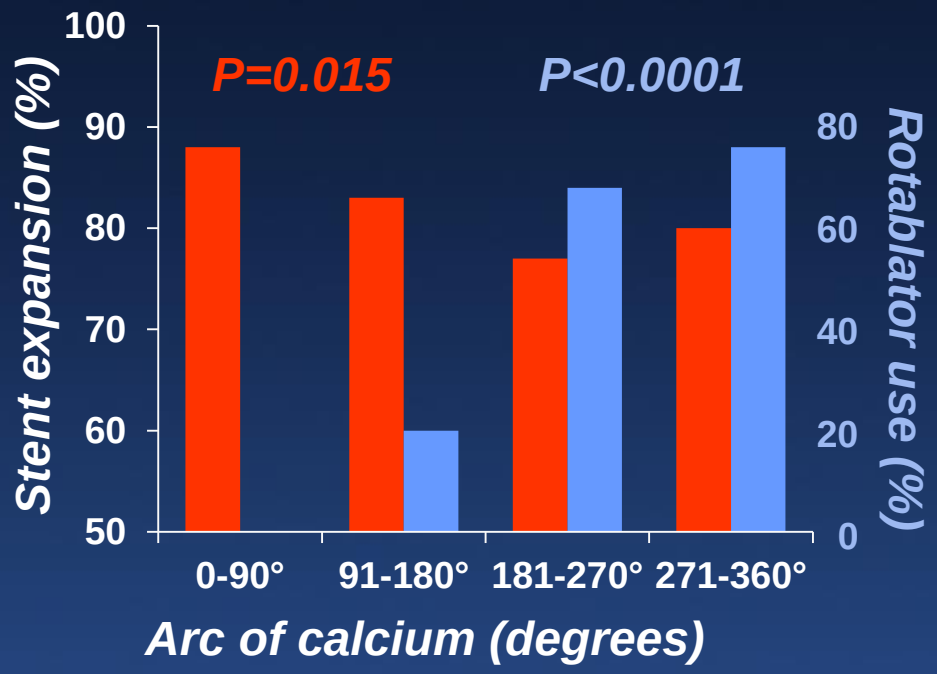
	Early Stent Thrombosis	Restenosis
BMS	•*Cheneau et al. Circulation 2003;108:43-7*	•*Kasaoka et al. J Am Coll Cardiol 1998;32:1630-5* •*Castagna et al. AHJ 2001;142:970-4* •*de Feyter et al. Circulation 1999;100:1777-83* •*Sonoda et al. J Am Coll Cardiol 2004;43:1959-63* •*Morino et al. Am J Cardiol 2001;88:301-3* •*Ziada et al. Am Heart J 2001;141:823-31* •*Doi et al. JACC Cardiovasc Interv. 2009;2:1269-75*
DES	•*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. Circulation Cardiovasc Interv. 20011;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* •*Hahn et al. J Am Coll Cardiol 2009;54:110-7* •*Kang et al. Circ Cardiovasc Interv 2011;4:9-14* •*Kang et al. Circ Cardiovasc Interv 2011;4:562-9* •*Choi et al. Am J Cardiol 2012;109:455-60* •*Song et al. Catheter Cardiovasc Interv. 2014;83:873-8*

In general, increasing amounts of IVUS-detected calcium was associated with increasing PCI dissections and decreased vessel expansion

- Fitzgerald et al. Circulation 1992;86:64-70
- Potkin et al. J Am Coll Cardiol 1992;20:942-51
- Kovach et al. J Am Coll Cardiol 1993;22:1024-32
- Mintz et al. Circulation 1995;92:3408-14
- Von Birgelen et al. Am J Cardiol 2003;92:5-10



**There was a similar, albeit less strong, correlation after 20 atm inflation (r=-0.58, p=0.0007)*



Vavarunakis et al. Catheter Cardiovasc Interv 2001;52:164-172
Hoffmann et al. Eur Heart J 1998;19:1224-31

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OCT-based calcium scoring system to predict stent under-expansion

Calcium score derived from pre- and post-stent OCT in a test cohort of 128 pts

Maximum calcium angle*	≤180°	0
	>180°	2
Maximum calcium thickness*	≤0.5mm	0
	>0.5mm	1
Calcium length*	≤5mm	0
	>5mm	1

***Largest calcium deposit**

Stent expansion vs calcium score in a validation cohort of 133 pts

	Calcium score (based on pre-PCI OCT)					
	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

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Fujino et al. EuroIntervention, in press

Correlates of IVUS Lesion Calcium

Patient Level

	N	Ca^{++}	p	Arc of Ca^{++}	P
Patient age					
21-40 yrs	44	55%	<0.0001	49°	<0.0001
41-60 yrs	603	67%		94°	
61-80 yrs	734	78%		126°	
>80 yrs	61	94%		186°	
Angina status					
Stable	1280	74%	0.0017	118°	0.0002
Unstable	162	62%		81°	
DM					
None	1062	70%	0.002	107°	0.0149
NIDDM	310	80%		123°	
IDDM	70	57%		98°	

Lesion Level

	N	Ca^{++}	p	Arc of Ca^{++}	P
Location					
Non-ostial	1837	72%	0.9	112°	0.0023
Aortoostial	126	72%		147°	
QCA DS (%)					
≤25	100	53%	0.041	77°	0.060
26-50	359	70%		106°	
51-75	998	72%		116°	
76-100	506	72%		115°	
Plaque burden					
≤50%	74	38%	<0.0001	29°	<0.0001
51-75%	272	62%		81°	
76-90%	826	74%		121°	

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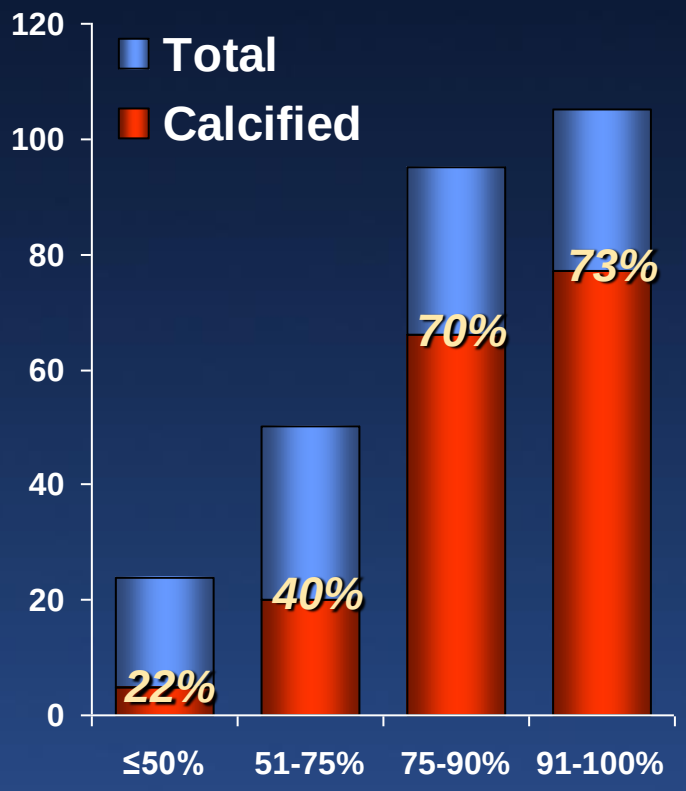
Mintz et al. J Am Coll Cardiol 1997;29:268-74

Calcium is an Index of Plaque Burden

IVUS arc of calcium (°)



IVUS plaque burden

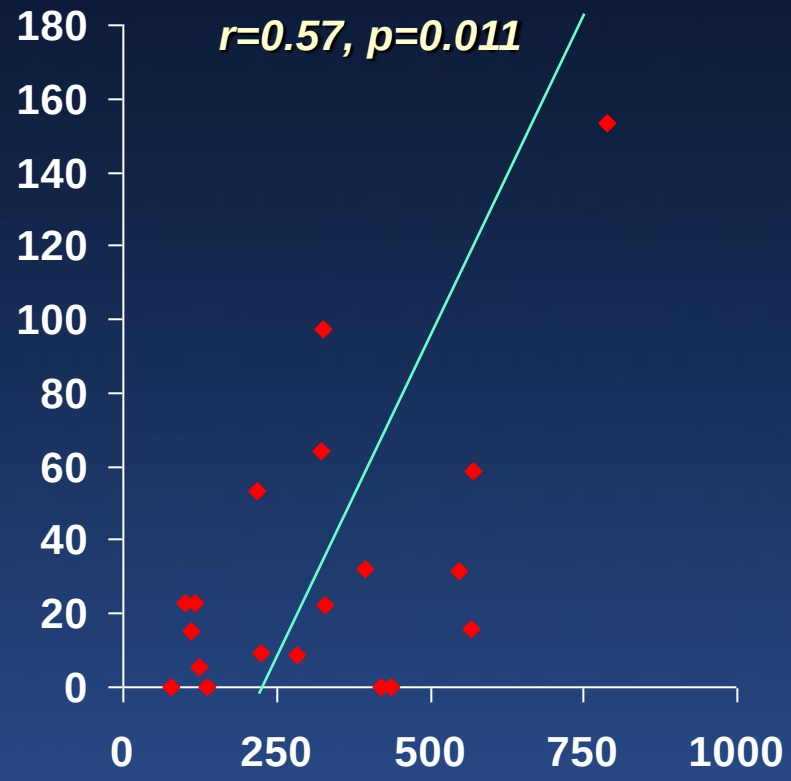
Mintz et al. J Am Coll Cardiol 1997;29:268-74

In 37 nondecalcified coronary arteries in 13 hearts

- **Significant correlation between calcium area and plaque area on a per-heart basis (r=0.87, p<0.0001), per-artery basis (LAD: r=0.89, p<0.0001; LCX: r=0.7, p<0.001; RCA: r=0.89, p<0.0001) and per-segment basis (r=0.52, p<0.0001).**
- **Poor correlation between residual lumen area and calcium area for individual hearts (r=0.48, p=NS), individual coronary arteries (LAD: r=0.59, p=NS; LCX: r=0.10, p=NS; RCA: r=0.59, p=NS) and coronary segments (r=0.07, p=NS).**

Sangiorgi et al. J Am Coll Cardiol 2000;31:126-33

Volumetric index of total calcium



Total plaque volume (mm^3)

Tinana et al. Am J Cardiol 2002;89:757-60

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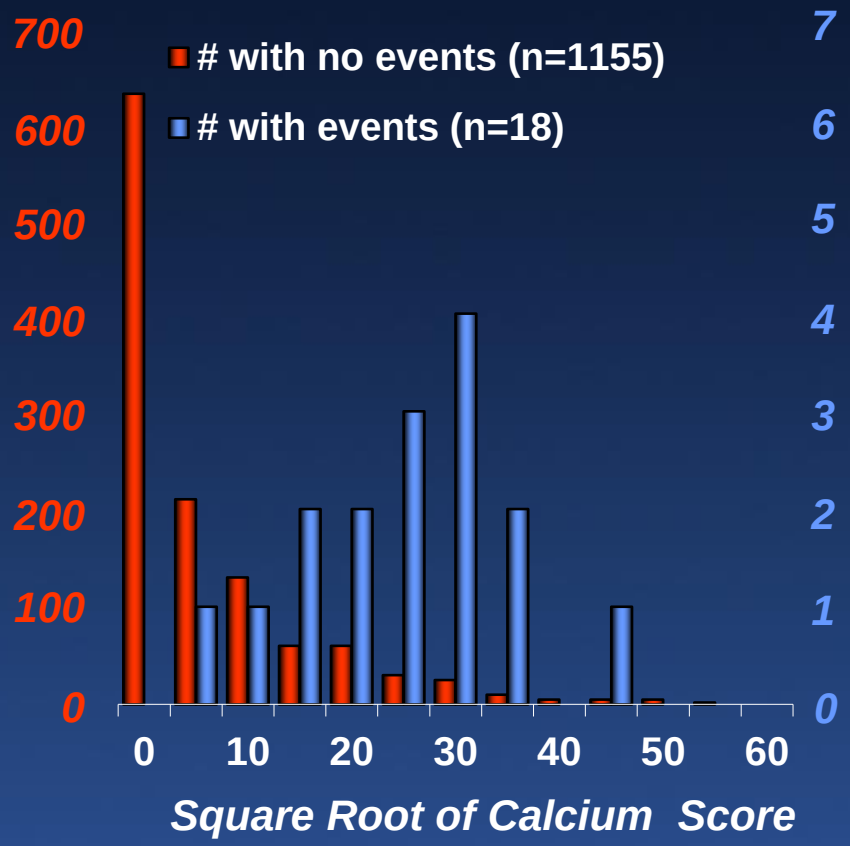
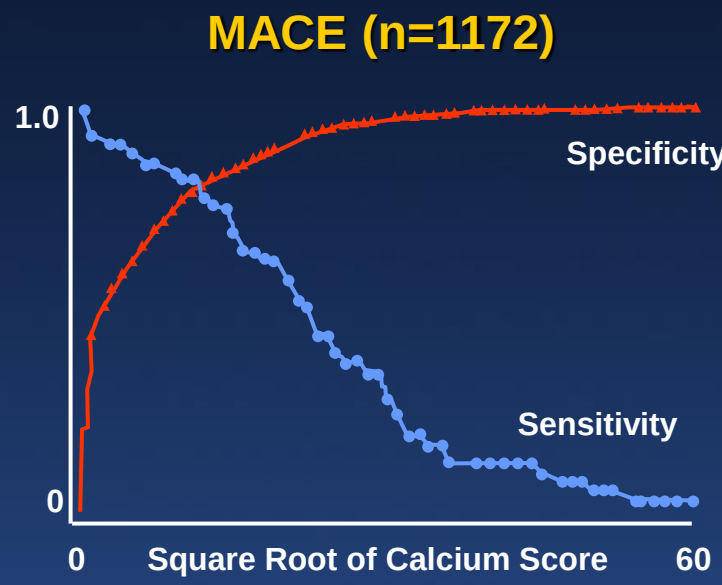
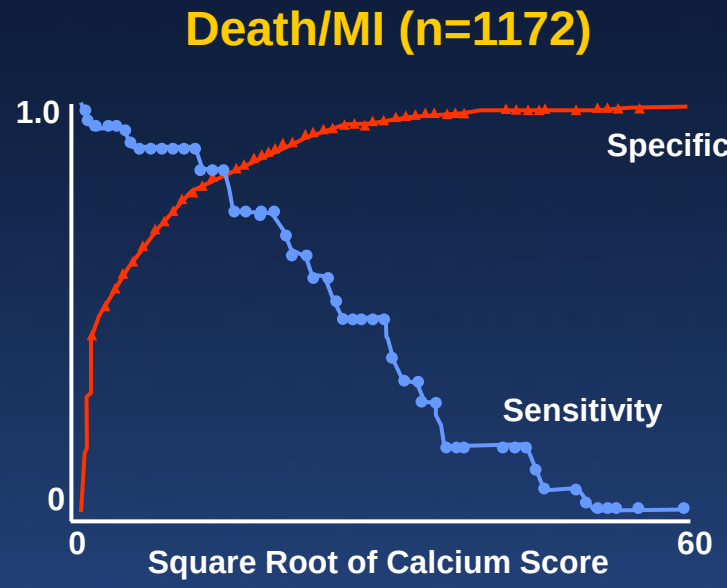
EBCT Calcium Score Predicts Acute Coronary Events at 1 yr







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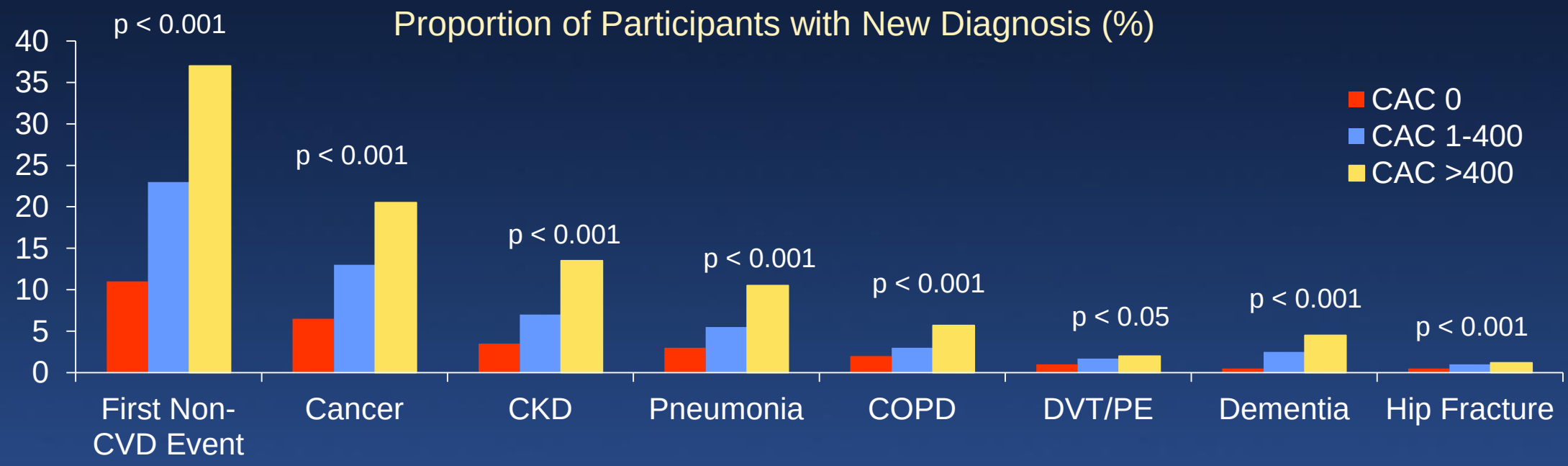
Arad et al. Circulation 1996;93:1951-3
Arad et al. J Am Coll Cardiol 2000;36:1253-60

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."

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

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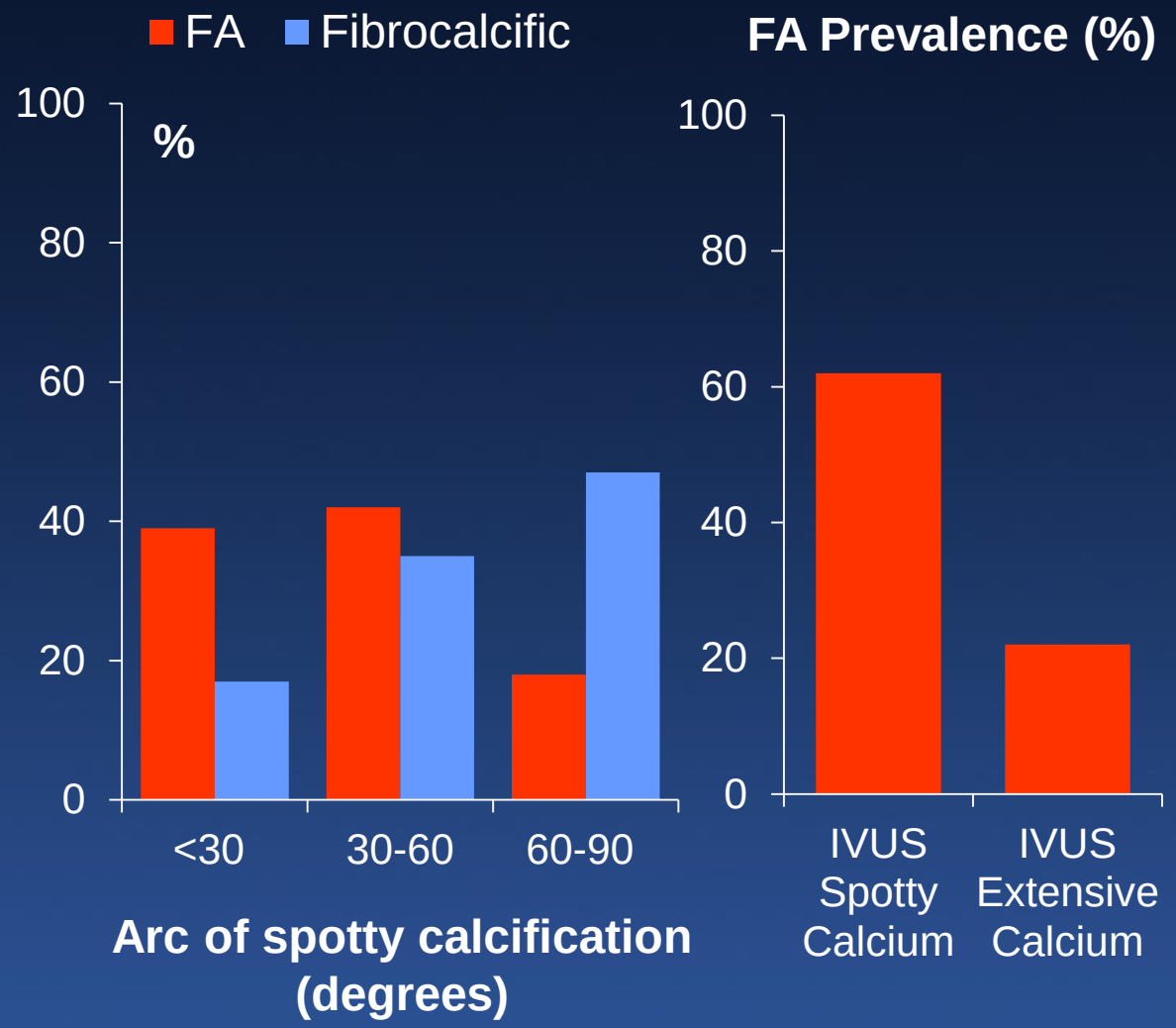
Ehara et al. Circulation 2004;110:3424-9

Prevalence of spotty calcification in histologic samples



- **72.6% of superficial spotty calcium was seen in FA with calcium deposits**
  - **45.3% late FA**
  - **27.3% early FA**
- **32.6% of deep spotty calcium was seen in FAs and only 12.5% were associated with a large NC**
- **67.4% of deep spotty calcium was seen in fibrocalcific plaque without a necrotic core**

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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

Kataoka et al. J Am Coll Cardiol 2012;59:1592-7

Original Article

Spotty calcification and plaque vulnerability *in vivo*: frequency-domain optical coherence tomography analysis

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Background: Spotty calcification is a morphological characteristic of a vulnerable plaque phenotype. While this calcium pattern is considered an active process, promoted by inflammation, it is unknown whether spotty calcification associates with development of microstructures observed in vulnerable plaques. As frequency-domain optical coherence tomography (FD-OCT) enables visualization of microstructures associated with plaque vulnerability, we investigated the association between spotty calcification and plaque microstructures by using FD-OCT.

Methods: A total of 300 patients with stable coronary artery disease (CAD), having clinical indication for percutaneous coronary intervention (PCI), were analyzed. Totally 280 non-culprit lipid plaques within the target vessel requiring PCI were evaluated by FD-OCT. Spotty calcification was defined as a presence of lesion <4 mm in length, containing an arc of calcification <90° on FD-OCT. Plaque microstructures were compared in non-culprit lipid-rich plaques with and without spotty calcification.

Results: Spotty calcification was observed in 39.6% of non-culprit lipid-rich plaques, with 30.6% of these plaques demonstrating multiple spotty calcifications. Plaques containing spotty calcification exhibited a greater lipid index (= averaged lipid arc × lipid length); 1,511.8±1,522.3 *vs.* 815.2±1,040.3 mm°, P<0.0001), thinner fibrous caps (89.0±31.6 *vs.* 136.5±32.5 μm, P=0.002) and a higher prevalence of microchannels (45.9% *vs.* 17.7%, P=0.007). A significant association was observed between the number of spotty calcifications per plaque and fibrous cap thickness (r=-0.40, P=0.006). Increased number of spotty calcification was also associated with a higher prevalence of microchannel within plaques (P=0.01).

Conclusions: In patients with stable CAD requiring PCI, the presence of spotty calcification imaged by FD-OCT was associated with features of greater plaque vulnerability.

Keywords: Calcification; plaque vulnerability; optical coherence tomography; plaque

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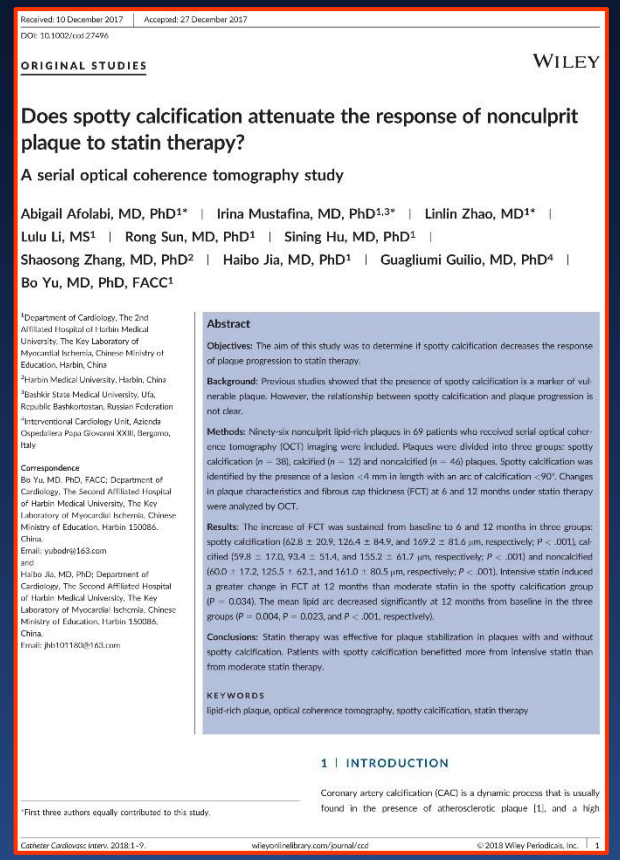
Introduction

Arterial calcification has been demonstrated to associate with an increased risk of cardiovascular events (1,2). Calcified plaque has been traditionally considered as a passive degenerative and quiescent form of disease, resulting from similar mechanisms to that of bone development (1). This concept has been supported by previous observations which plaque calcification is more prevalent in stable patients with coronary artery disease (CAD) (3-5) and is less likely to change despite anti-atherosclerotic medical therapies (6). However, recent molecular imaging studies have shown that arterial calcification can also reflect an active process stimulated by inflammation (7-11). Inflammatory cytokines contributed to early stages of

- **Plaques containing spotty calcification had more lipid, thinner fibrous caps, and a higher prevalence of microchannels.**
- **Patients with spotty calcification benefitted more from intensive statin than from moderate statin therapy.**



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ORIGINAL STUDIES

WILEY

Does spotty calcification attenuate the response of nonculprit plaque to statin therapy?

A serial optical coherence tomography study

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Abstract

Objectives: The aim of this study was to determine if spotty calcification decreases the response of plaque progression to statin therapy.

Background: Previous studies showed that the presence of spotty calcification is a marker of vulnerable plaque. However, the relationship between spotty calcification and plaque progression is not clear.

Methods: Ninety-six nonculprit lipid-rich plaques in 69 patients who received serial optical coherence tomography (OCT) imaging were included. Plaques were divided into three groups: spotty calcification ($n = 38$), calcified ($n = 12$) and noncalcified ($n = 46$) plaques. Spotty calcification was identified by the presence of a lesion <4 mm in length with an arc of calcification <90°. Changes in plaque characteristics and fibrous cap thickness (FCT) at 6 and 12 months under statin therapy were analyzed by OCT.

Results: The increase of FCT was sustained from baseline to 6 and 12 months in three groups: spotty calcification (62.8 ± 20.9, 126.4 ± 84.9, and 169.2 ± 81.6 μm, respectively; $P < .001$), calcified (59.8 ± 17.0, 93.4 ± 51.4, and 155.2 ± 61.7 μm, respectively; $P < .001$) and noncalcified (60.0 ± 17.2, 125.5 ± 62.1, and 161.0 ± 80.5 μm, respectively; $P < .001$). Intensive statin induced a greater change in FCT at 12 months than moderate statin in the spotty calcification group ($P = 0.034$). The mean lipid arc decreased significantly at 12 months from baseline in the three groups ($P = 0.004$, $P = 0.023$, and $P < .001$, respectively).

Conclusions: Statin therapy was effective for plaque stabilization in plaques with and without spotty calcification. Patients with spotty calcification benefitted more from intensive statin than from moderate statin therapy.

KEYWORDS
lipid-rich plaque, optical coherence tomography, spotty calcification, statin therapy

1 | INTRODUCTION

Coronary artery calcification (CAC) is a dynamic process that is usually found in the presence of atherosclerotic plaque (1), and a high

[1]First three authors equally contributed to this study.

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Kataoka et al. Cardiovasc Diagn Ther 2014;4:460-9
Afolabi et al. Catheter Cardiovasc Interv. 2018;91:582-590

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			
Total	985		52%	36%	3%	2%	9%

included all plaques with intact fibrous caps

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

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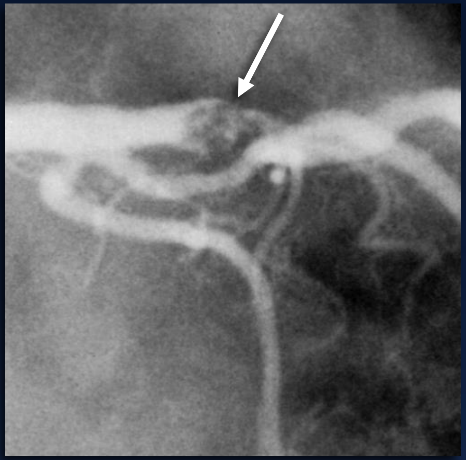

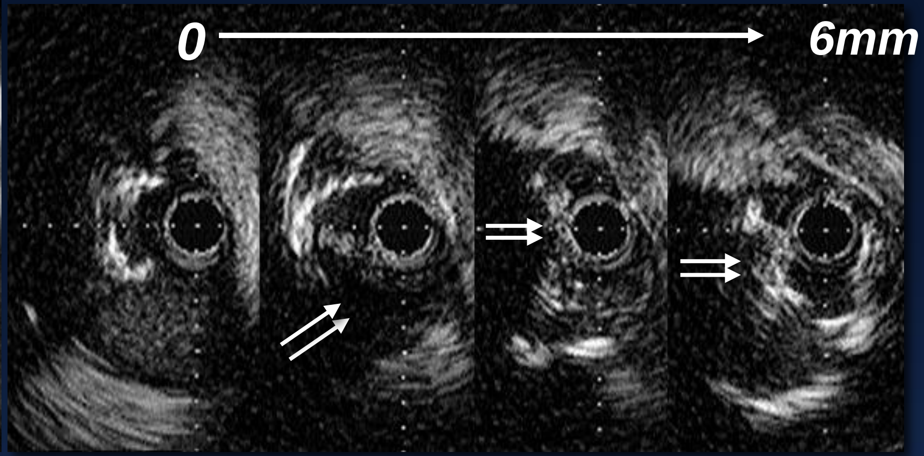

Volume 132, Number 3
American Heart Journal

Duissaillant et al. 687

Intravascular ultrasound identification of calcified intraluminal lesions misdiagnosed as thrombi by coronary angiography

Gaston R. Duissaillant, MD, Gary S. Mintz, MD, Augusto D. Pichard, MD, Kenneth M. Kent, MD, PhD, Lowell F. Satler, MD, Jeffrey J. Popma, MD, Jennifer Griffin, BS, and Martin B. Leon, MD
Washington, D.C.

Accurate identification of coronary atherosclerotic plaque composition is important for optimum patient management and transcatheter therapy. In particular, the presence of thrombus typically leads to protracted hospitalization, intravenous or intracoronary thrombolysis, prolonged systemic anticoagulation, and the use of transcatheter devices designed to remove thrombi. Furthermore, thrombi may be implicated in poor outcome after transcatheter therapy. Intraluminal filling defects are believed to be the most specific angiographic markers of thrombus. We report three patients with intracoronary filling defects initially diagnosed as thrombus; however, intravascular ultrasound (IVUS) imaging showed that these filling defects represented calcified nodules.

IVUS studies were performed with one of two commercially available systems. The first (Cardiovascular Imaging Systems Inc./InterTherapy Inc., Sunnyvale, Calif.) incorporated a single element 25-MHz transducer and an angled mirror mounted on the tip of a flexible shaft that was rotated at 1800 rpm within a 3.9F short monorail polyethylene imaging sheath to form planar cross-sectional images in real time. The second (Cardiovascular Imaging Systems) incorporated a single element 30-MHz beveled transducer within either a 2.9F long monorail imaging catheter having a common distal lumen design (the distal lumen alternatively accommodates the imaging core or the guide wire, but not both) or within a 3.2F short monorail imaging catheter. With both systems the imaging catheter was advanced 5 to 10 mm beyond the target lesion and the transducer was withdrawn automatically at 0.5 mm/sec within the imaging sheath to perform the imaging sequence. IVUS studies were recorded on ½-inch high resolution s-VHS tape for offline analysis.

Patient 1. A 78-year-old white man with a history of pneumoconiosis, gastrectomy for stomach cancer, congestive heart failure from dilated cardiomyopathy, and coronary artery disease was seen for progressive angina. A coronary angiogram showed a 95% ostial right coronary artery lesion with a round filling defect highly suggestive of thrombus. He was treated with heparin and sent home taking coumadin to dissolve the thrombus. However, he returned with worsening angina; coronary angiography still showed a large filling defect almost completely occluding the right coronary artery (Fig. 1). He was initially treated with an intracoronary urokinase infusion of 250,000 U followed by the use of a 2.2-mm transluminal extraction atherectomy cutter (Interventional Technologies, Inc., San Diego, Calif.) and 3.5-mm adjunct balloon

Fig. 1. Proximal right coronary artery filling defect *(arrow)* was initially thought to represent intracoronary thrombus. Patient was treated with prolonged system anticoagulation, intracoronary thrombolysis, and extraction atherectomy. IVUS imaging showed that filling defect was, in fact, calcified lesion protruding into lumen.

Fig. 2. Mid-right coronary artery filling defect *(arrow)* was initially thought to represent intracoronary thrombus. Patient was also treated with prolonged systemic anticoagulation. IVUS imaging showed that filling defect was, in fact, calcified lesion protruding into the lumen. Because of limited device availability, patient was referred for bypass graft surgery.

From the Intravascular Ultrasound Imaging and Cardiac Catheterization Laboratories, Washington Hospital Center.

Supported in part by the Cardiology Research Foundation, Washington, D. C.

Reprint requests: Martin B. Leon, MD, Washington Cardiology Center, 110 Irving St., NW, 4B-1, Washington, DC 20010.

Am Heart J 1996;132:687-9.

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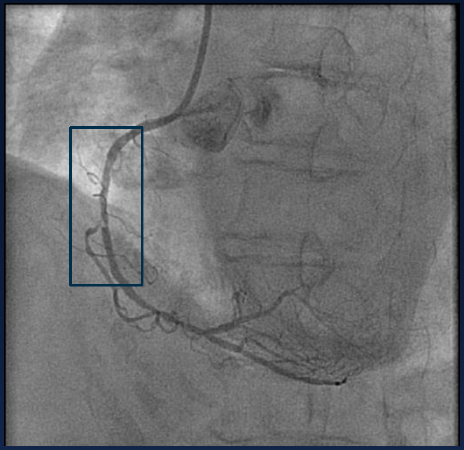
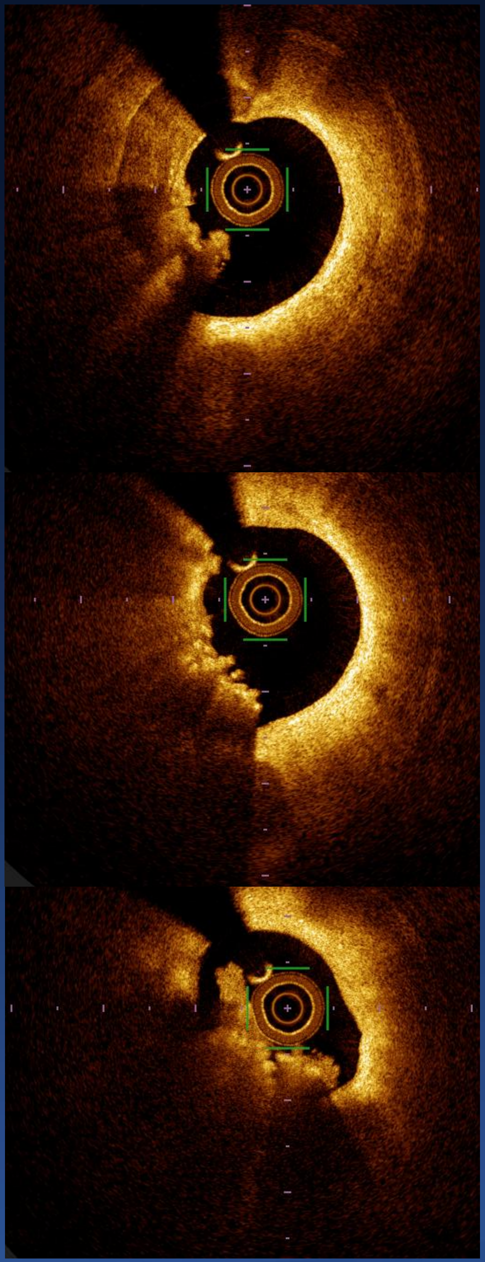
0002-8703/96/$5.00 + 0 4/4/71990

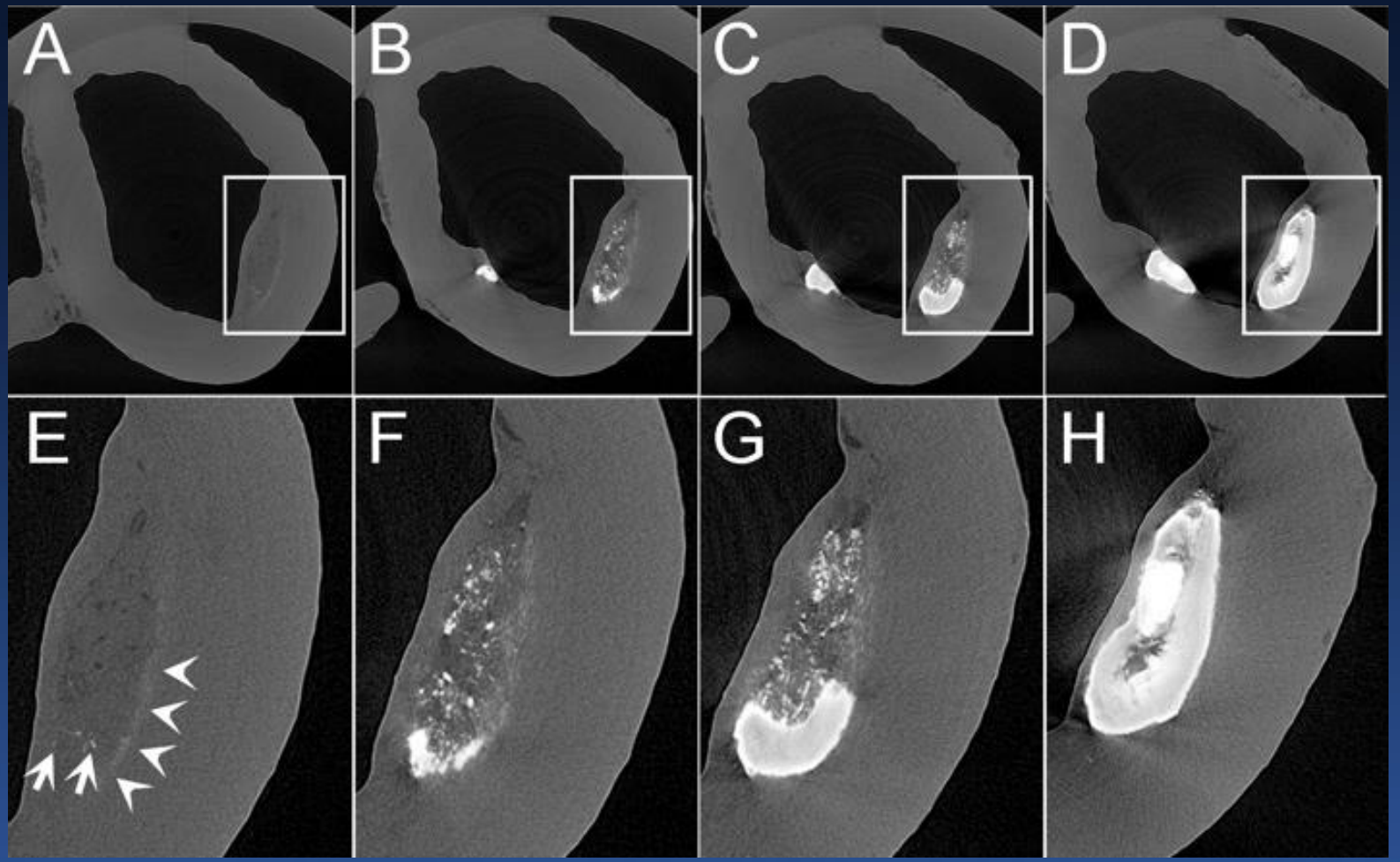
"We present three patients with classical angiographic features of intracoronary thrombus in whom IVUS imaging showed that the filling defects were not thrombi, but calcified (presumably atherosclerotic) masses."





Dussaillant et al. Am Heart J 1996;132:687-9
Jia et al. J Am Coll Cardiol 2013;62:1748-58

Ex Vivo High Resolution Micro-CT



Courtesy of Luis Cardoso and Sheldon Weinbaum
Department of Biomedical Engineering
City University of New York

Cardiovascular Research Foundation

Potential impact of 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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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

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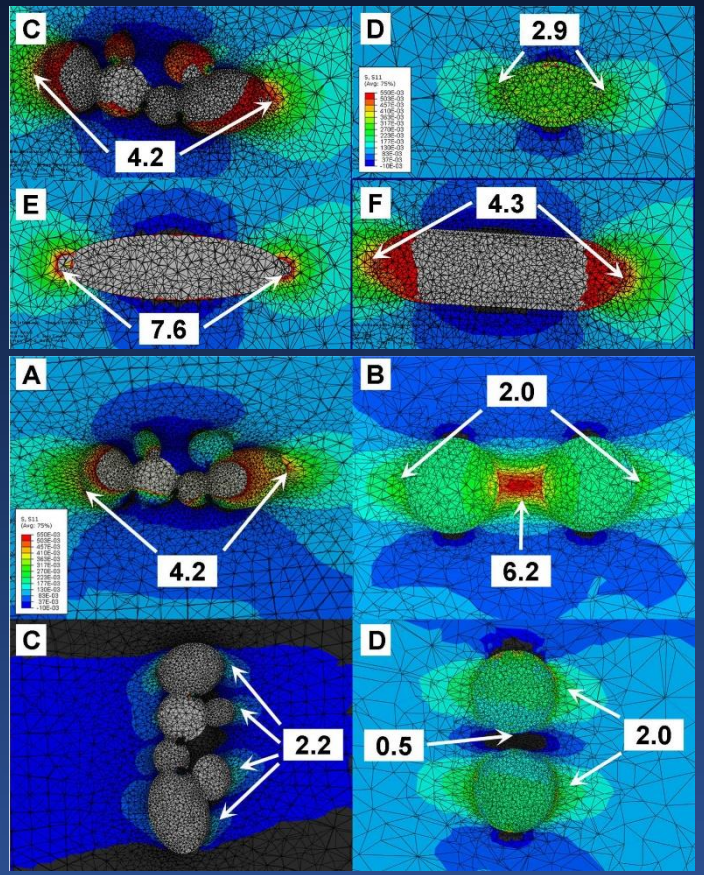
Conflict of interest
The authors have no conflict of interest.



Int J Cardiovasc Imaging (2015) 31:1079–1087
DOI 10.1007/s10554-015-0650-x

ORIGINAL PAPER

Imaging and analysis of microcalcifications and lipid/necrotic core calcification in fibrous cap atheroma

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Abstract The presence of microcalcifications (μCalcs) >5 μm within the cap of human fibroatheroma has been shown to produce a 200–700 % increase in peak circumferential stress, which can transform a stable plaque into a vulnerable one, whereas μCalcs < 5 μm do not appear to increase risk. We quantitatively examine the possibility to distinguish caps with μCalcs > 5 μm based on the gross morphological features of fibroatheromas, and the correlation between the size and distribution of μCalcs in the cap and the calcification in the lipid/necrotic core beneath it. Atherosclerotic lesions (N = 72) were imaged using HR-μCT at 2.1-μm resolution for detailed analysis of atheroma morphology and composition, and validated using non-decalcified histology. At 2.1-μm resolution one observes four different patterns of calcification within the lipid/necrotic core, and is able to elucidate the 3D spatial progression of the calcification process using these four patterns. Of the gross morphological features identified, only minimum cap thickness positively correlated with the existence of μCalcs > 5 μm in the cap. We also show that μCalcs in the cap accumulate in the vicinity of the lipid/necrotic core boundary with few on the lumen side of the cap. HR-μCT enables three-dimensional assessment of soft tissue composition, lipid content, calcification patterns within lipid/necrotic cores and analysis of the axial progression of calcification within individual atheroma. The distribution of μCalcs within the cap is highly non-uniform and decreases sharply as one proceeds from the lipid pool/necrotic core boundary to the lumen.

Keywords Microcomputed tomography · Vulnerable plaque · Microcalcifications · Fibrous cap rupture

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

Introduction

Approximately half of all cardiovascular deaths associated with acute coronary syndrome occur with the rupture of a vulnerable plaque, when a thin fibrous cap overlying a lipid rich core is ripped or fissured under the action of high blood pressure [1]. Criteria based on morphology and tissue composition such as fibrous cap thickness, vasa-vasorum, necrotic core size, and macrophage infiltration [2–4] have been found to be relevant, but insufficient, to identify vulnerable plaques and assess the risk of rupture. Calcification is also believed to be significant predictor of cardiovascular morbidity and mortality [5]. However, large calcifications have been shown to potentially stabilize a plaque [6]. In marked contrast, biomechanical analysis [7, 8] has shown that small microcalcifications (μCalcs) in close proximity within the fibrous cap itself can lead to a 200–700 % increase in local tissue stresses [9–12]. Such a stress accumulation in a region of cap thinning is more than sufficient to exceed the local tissue threshold required to explain the asymptomatic rupture of non-stenotic plaque [7–14].

The key role μCalcs might play in cap rupture was suggested in Vengrenyuk et al. [7] in which high resolution micro-computed tomography (HR-μCT) was used to observe cellular level μCalcs in the fibrous cap proper for the

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Cardoso et al. J Biomech. 2014;47:870-7
Maldonado et al. Int J Cardiovasc Imaging 2015;31:1079-87

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