Pathology of PAD: Implications for Device and Medical Therapies

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Disclosure

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

Consultant: Cook, and W.L. Gore.

Employment in industry: No

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Owner of a healthcare company: No

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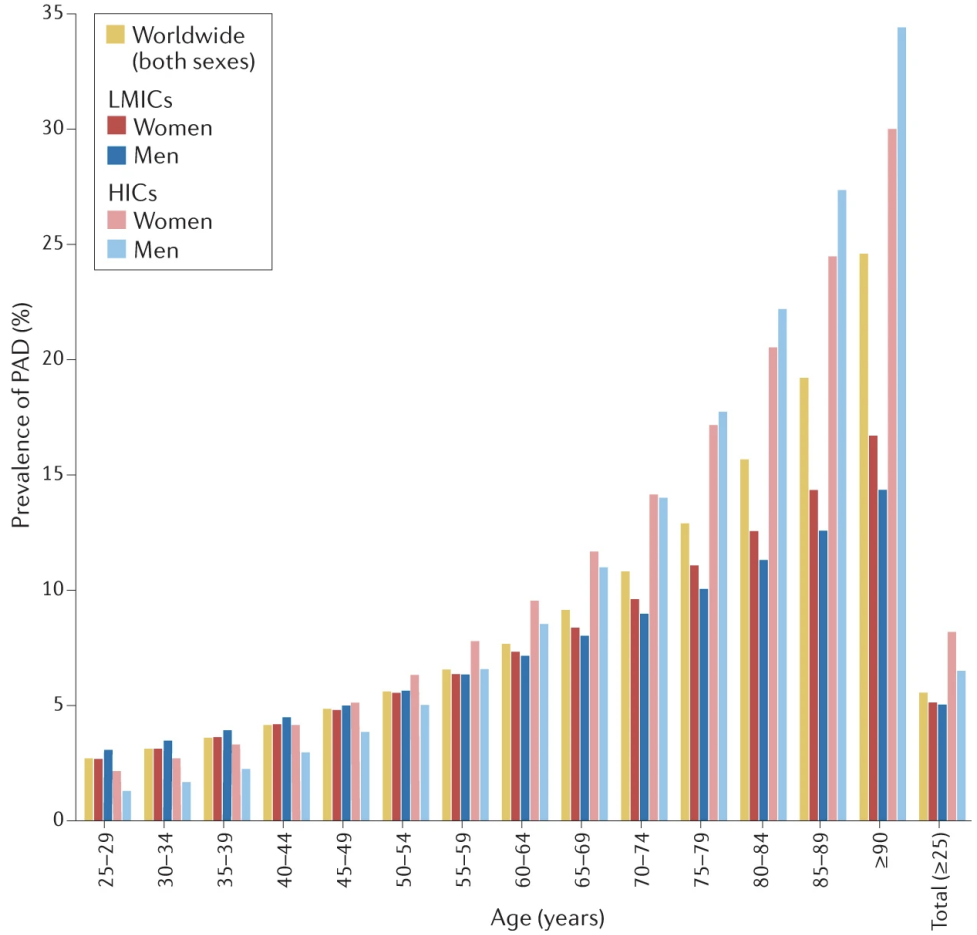
Prevalence of PAD (by Age and Income)

Fig. 1: Prevalence of PAD in relation to age and country income.

From: Update on the pathophysiology and medical treatment of peripheral artery disease



The prevalence of peripheral artery disease (PAD) increases with age, particularly in high-income countries (HICs) compared with low-income and middle-income countries (LMICs). Prevalence of PAD reported as percentage. The graph was generated using data from ref.[5].

The prevalence of PAD increased with age, and this age-related rise was more marked in HICs than in LMICs

The prevalence of PAD in women was greater than in men for many age ranges

Gollege J. Nature Reviews Cardiology 2022

Pathology of PAD: What is Known?

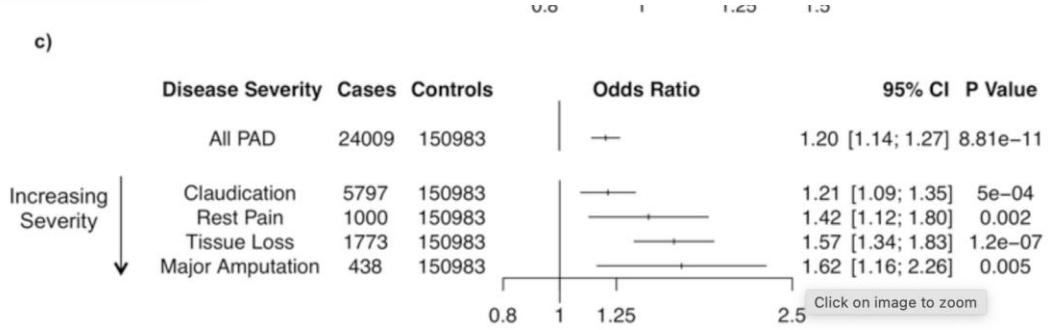
- PAD is primarily caused by atherosclerosis or thrombotic occlusion of arteries that supply blood to lower limbs and associated microvascular dysfunction promoted by risk factors
- Pathologic studies of human arteries shows atherosclerosis has progressive stages involving accumulation of lipids, smooth muscle and inflammatory cells into the lesion
- Plaques advance through processes such cap thinning, necrotic core expansion and inflammatory cell infiltration leading to plaque rupture or in some cases erosion
- Most of this work has been done in coronary arteries and its relevance to PAD is unclear

Pathology (cont.)

- Only a very few histological studies have been performed on samples of peripheral arteries from subject with symptomatic PAD
- No report has described serially sectioned pathologic characterization of PAD

PAD and CAD: Same Disease or Different?

- GWAS Studies have shed some light on this
  - 19 PAD loci were found after analysis of Million Veteran Program (32 million DNA variants among 31K cases and 211K controls)
  - 11/19 loci were associated with disease in 3 vascular beds (coronary, cerebral, peripheral) and included LDLR, LPL, Lp(a), and SORT1 suggesting these targets as therapeutic for all 3 atherosclerotic phenotypes
  - 4/19 variants were exclusive to PAD (RP11-359M6.3, HLA-B, CHRNA3) and included F5p.R506Q (Factor V Leiden), highlighting role of thrombosis
    - This risk seemed to be specific for PAD (no association with CAD) as the F5 variants effect estimate increase with PAD (20% increased risk) and its severity with carriers have 62% increased risk of undergoing PAD-related major amputation
    - The variants significance for PAD seem to increase in the presence of smoking suggest synergism

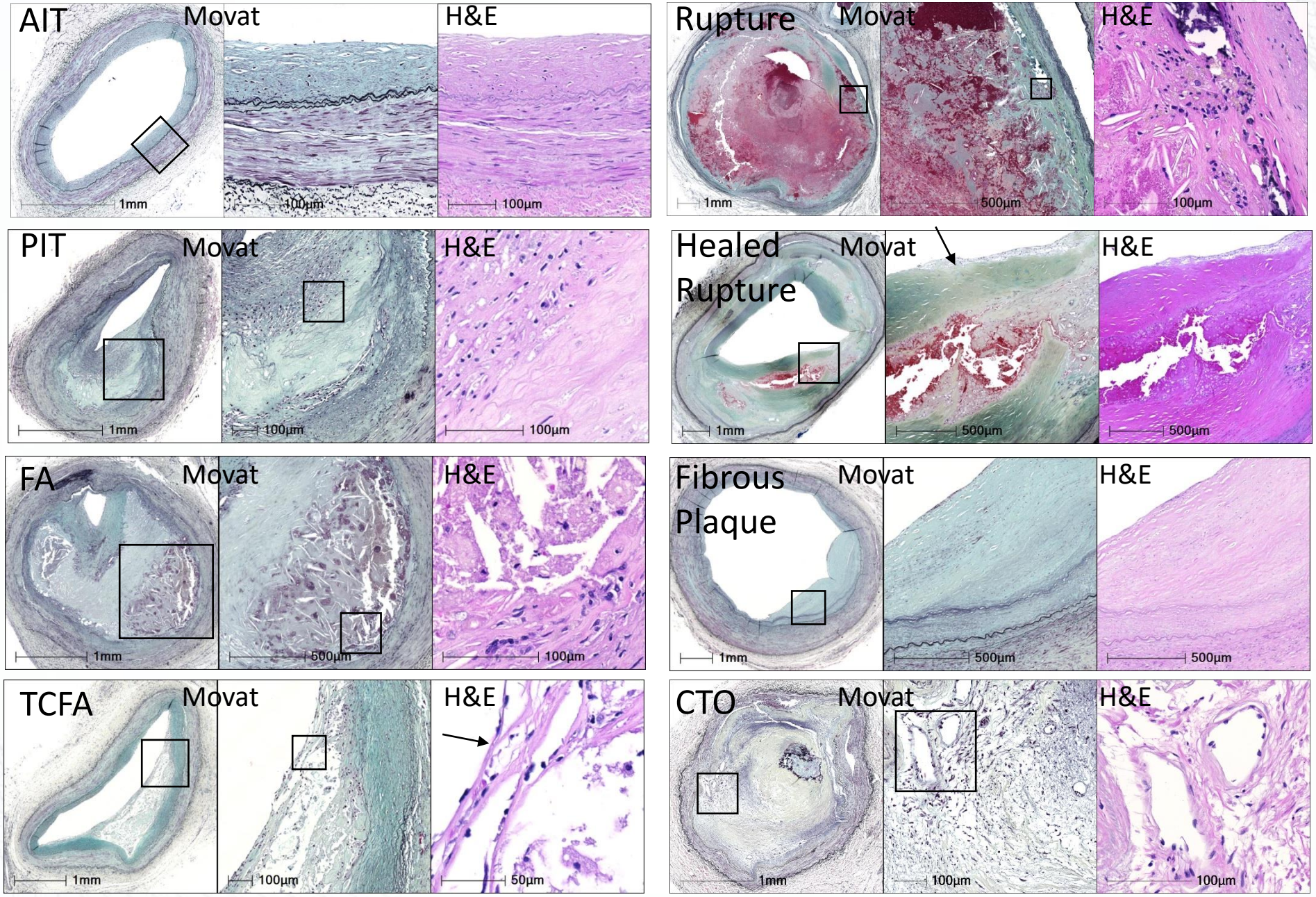


Klarin D. Nat Med. 2019

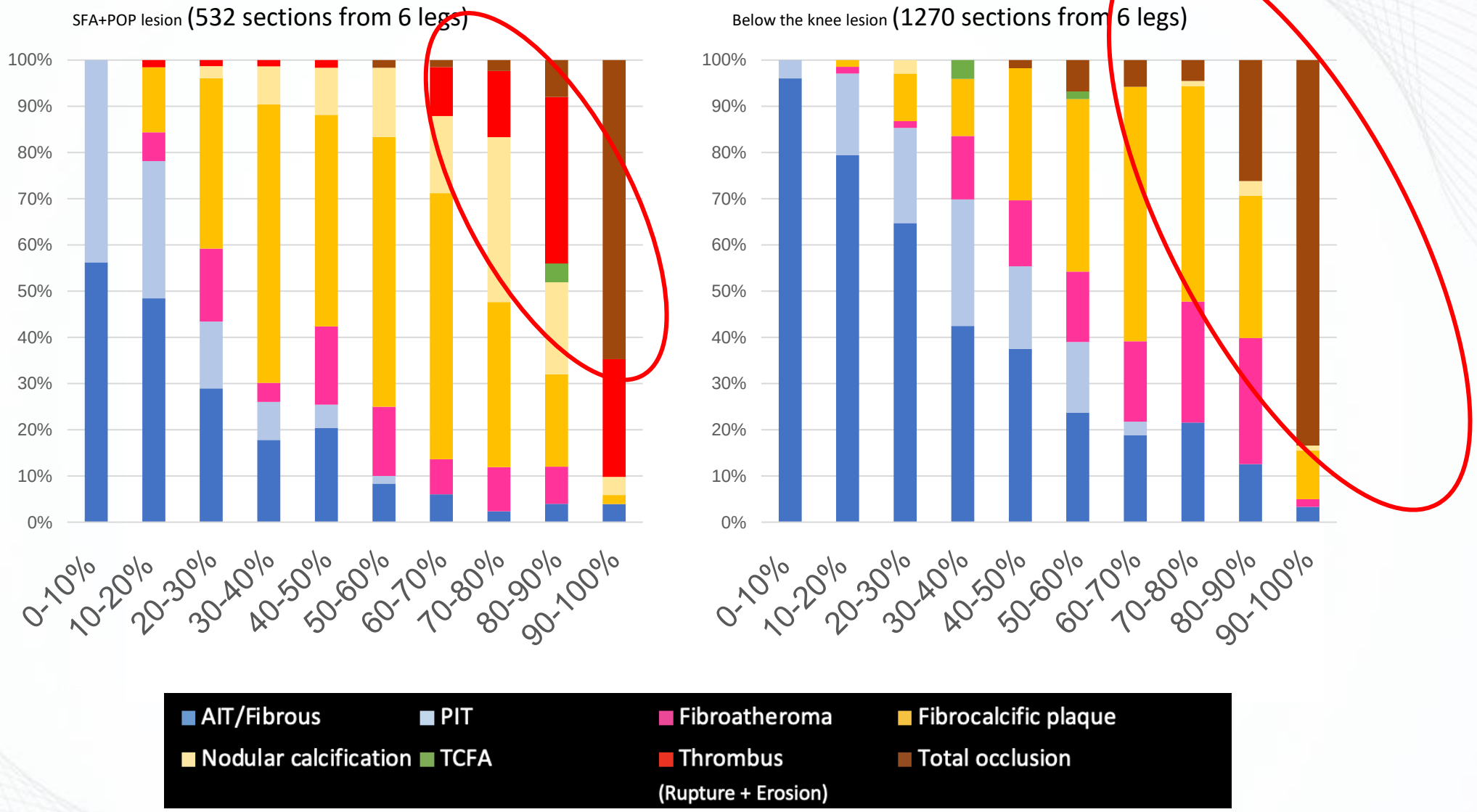
Methods

- 12 legs from 8 cadavers were obtained from donors through Science Care
- Subjects were >70 yo with known histories of smoking, DM, HTN, HLD, DM and CKD and calcification by XRAY to enrich population for PAD
- Subjects with history of vascular intervention were excluded
- Lower extremity arteries were dissected along entire length
- 6/12 vessels were decalcified and sequentially cut at 3-4 mm intervals, embedded in paraffin and sectioned at 4-5 uM intervals
- Remaining 6 vessels were not decalcified and segments with heavy calcification were embedded in Spurr resin and subjected to EXACT technique to make 30-60uM sections

Atherosclerotic Plaque Progression in Peripheral Arteries



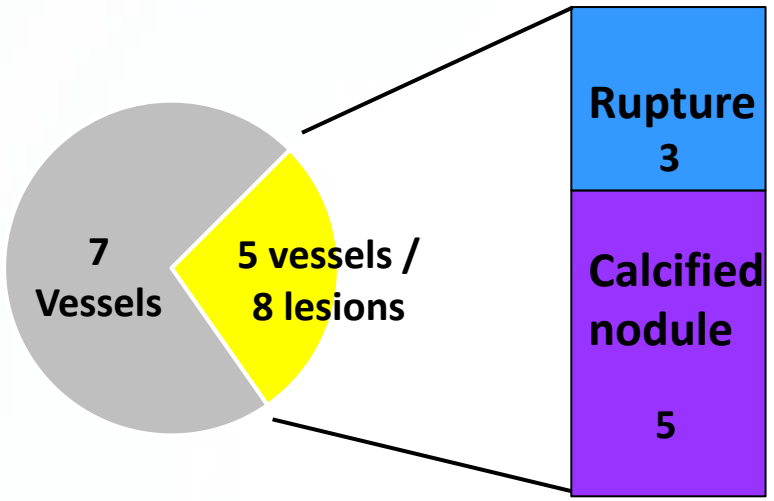
The relationship between % stenosis and plaque type



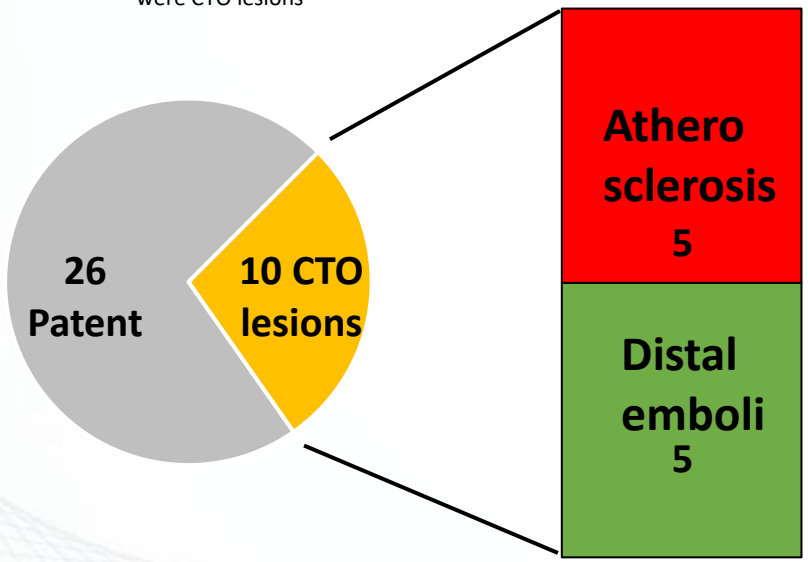
Plaque type was significantly different between AK and BK arteries; athero lesions were more common AK with higher incidence of lipid rich plaque (PIT and FA) and plaque rupture. Acute thrombotic plaques exclusively observed AK (8 lesions (5 CN, 3 PR).

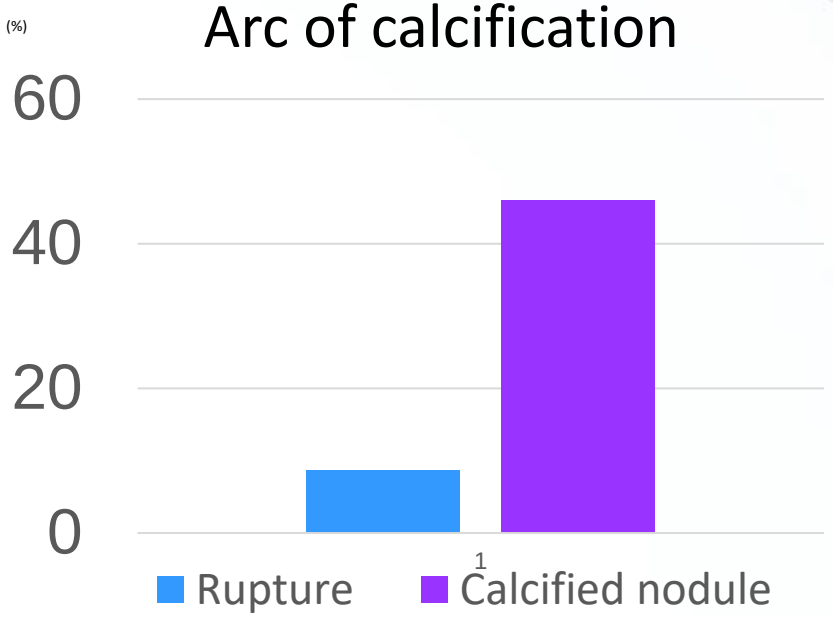
Why vessels below the knee occlude?

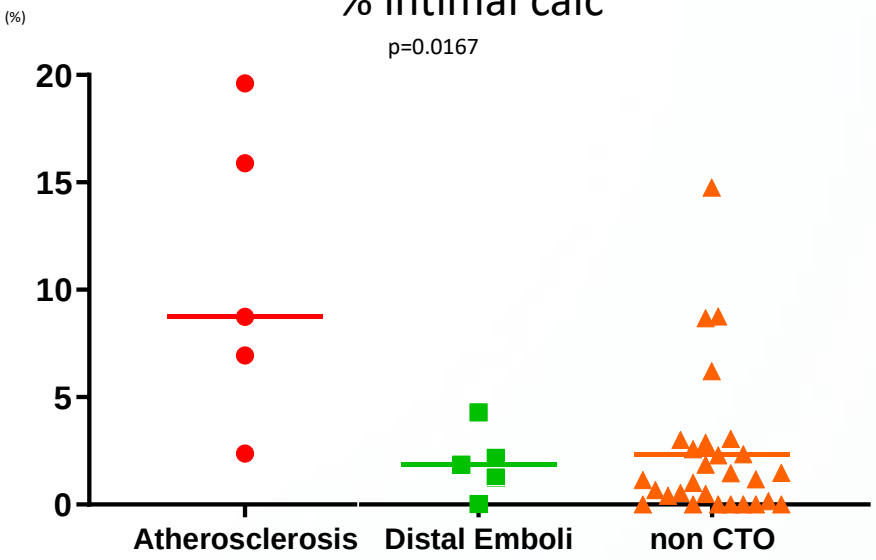
5 vessels in 12 **AK** vessels (40%)
had culprit thrombotic lesions



10 in 36 **BK** vessels (27.8%)
were CTO lesions







Torii S, J Am Coll Cardiol Img 2018.

Pathology in Patients Presenting with CLI: Amputation Data (121 Amputations 95 patients)

TABLE 1 Vessel Pathology in Patients Presenting With CLI

	Stenosis ≥70% (n = 165)				All Stenosis (n = 239)			
	FEM-POP (n = 31)	INFRA-POP (n = 134)	Odds Ratio*	p Value*	FEM-POP (n = 34)	INFRA-POP (n = 205)	Odds Ratio*	p Value*
Insignificant atherosclerosis	9 (29.0)	72 (53.7)	3.3	0.0262	10 (29.4)	121 (59.02)	5.47	0.00284
Atherosclerotic lesions	21 (67.7)	60 (44.8)			23 (67.6)	79 (38.5)		
PIT	0 (0.0)	1 (1.7)			1 (4.3)	8 (10.1)		
Fibroatheroma	9 (42.9)	20 (33.3)			9 (39.1)	24 (30.4)		
Fibrocalcific lesions	12 (57.1)	39 (65.0)			13 (56.5)	47 (59.5)		
Restenotic lesions	1 (3.2)	2 (1.5)			1 (2.9)	5 (2.4)		
	FEM-POP (n = 31)	INFRA-POP (n = 134)	Odds Ratio*	p Value*	FEM-POP (n = 34)	INFRA-POP (n = 205)	Odds Ratio*	p Value*
No medial calcification	13 (41.9)	37 (27.6)			14 (41.2)	55 (26.8)		
Medial calcification	18 (58.1)	97 (72.4)	2.38	0.16457	20 (58.8)	150 (73.2)	2.89	0.0799
	FEM-POP (n = 31)	INFRA-POP (n = 134)	Odds Ratio†	p Value†	FEM-POP (n = 34)	INFRA-POP (n = 205)	Odds Ratio†	p Value†
Medial calcification, extent								
No calcification	13 (41.9)	37 (27.6)	3.94	0.00589	14 (41.2)	55 (26.8)	3.35	0.00632
<25% of circumference	9 (29.0)	22 (16.4)			10 (29.4)	30 (14.6)		
≥25 to <50% of circumference	4 (12.9)	14 (10.4)			4 (11.8)	19 (9.3)		
≥51 to <75% of circumference	2 (6.5)	18 (13.4)			2 (5.9)	26 (12.7)		
≥75% of circumference	3 (9.7)	43 (32.1)			4 (11.8)	75 (36.6)		

Incidence of significant lesions was higher AK than BK; where insignificant athero was the opposite even in Vessels with > 70% luminal stenosis

Narula N. JACC 2018

Vessel Pathology of CLI >70% Luminal Stenosis

TABLE 2 Vessel Wall Pathology of CLI in ≥70% Luminal Stenosis, FEM-POP, and INFRA-POP Arteries, Acute or Chronic Thrombi

	FEM-POP (n = 31)	INFRA-POP (n = 134)	OR*	p Value
Chronic thrombi	12 (38.7)	77 (57.5)		
Chronic thrombi with insignificant atherosclerosis	5 (41.7)	62 (80.5)	16.71	<0.0001
Chronic thrombi with significant atherosclerosis	7 (58.3)	15 (19.5)		
Chronic thrombi with PIT	0 (0)	1 (1.3)		
Chronic thrombi with FA	3 (25.0)	3 (3.9)		
Chronic thrombi with FC	4 (33.3)	11 (14.3)		
Acute thrombi	12 (38.7)	19 (14.2)		
Acute thrombi with insignificant atherosclerosis	4 (33.3)	10 (52.6)	0.71	0.41
Acute thrombi with significant atherosclerosis	8 (66.6)	9 (47.4)		
Acute thrombi with PIT	0 (0)	0 (0.0)		
Acute thrombi with FA	4 (33.3)	5 (26.3)		
Acute thrombi with FC	4 (33.3)	4 (21.1)		

Values are n (%). *Computed with generalized linear mixed model hierarchical regression with a logistic link function, controlling for fixed effects age, sex, diabetes, hypertension, hyperlipidemia, congestive heart failure, cerebrovascular disease, ischemic heart disease, and smoking status.

Odds for Thrombi	Groups	Adjusted OR†	95% CI	p Value
Chronic thrombi	Insignificant vs. significant atherosclerosis	16.7	(5.3–50.4)	0.0002
Acute thrombi	Insignificant vs. significant Atherosclerosis	0.71	(0.3–1.6)	0.41
Chronic thrombi	INFRA-POP vs. FEM-POP	2.14	(1.4–3.3)	0.0041
Acute thrombi	INFRA-POP vs. FEM-POP	0.27	(0.1–0.7)	0.0067

Acute or chronic thrombi observed in 72.7% of arteries with >70% stenosis with 67.5% demonstrating Insignificant atherosclerosis.

Narula N. JACC 2018

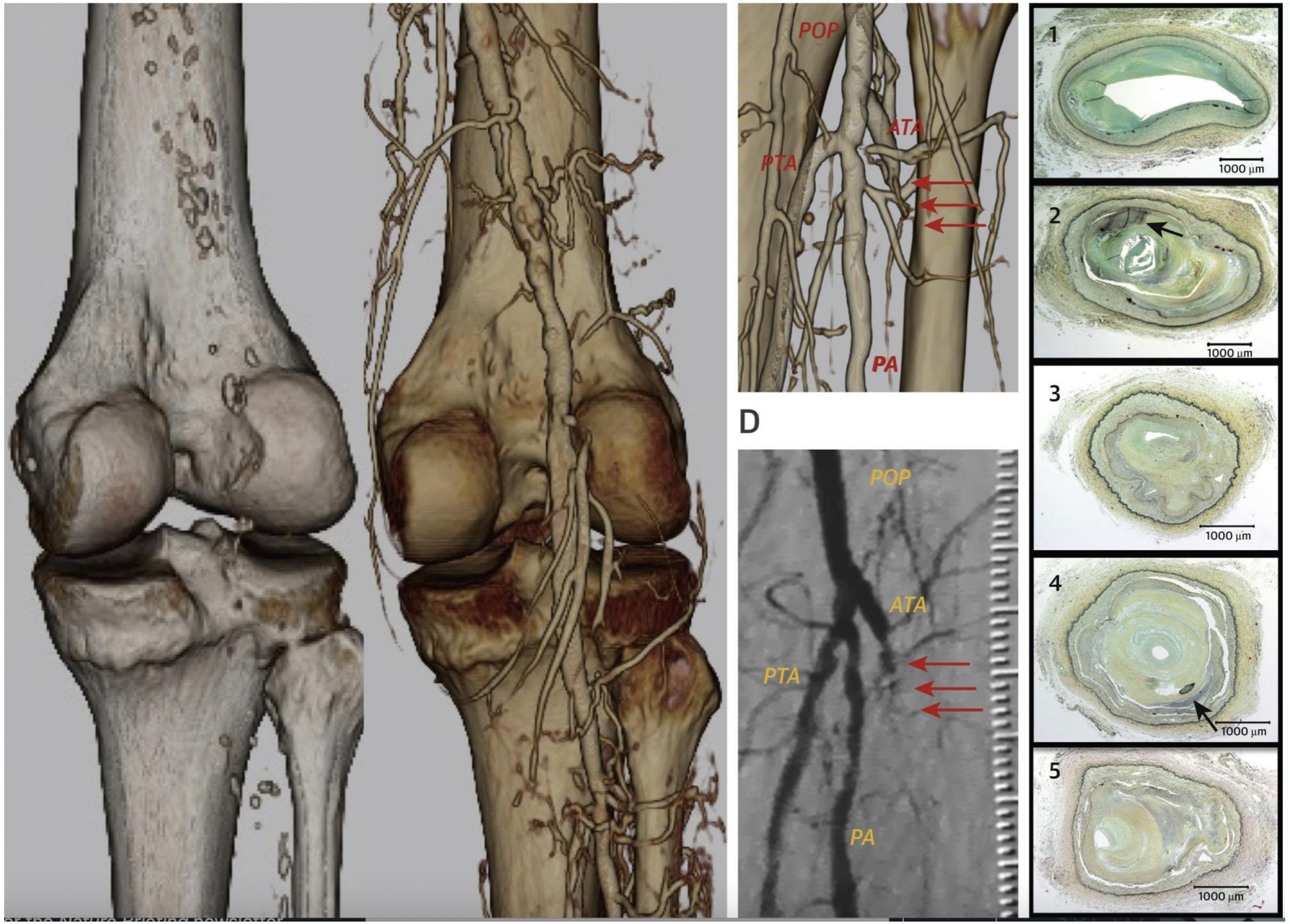
Comparison Between AK and BTK Arteries

	AK Arteries	BK Arteries	P value
Prevalence of atherosclerotic lesions	95.6 (88.9-100.0)	56.8 (44.1-66.4)	<0.0001
Percent stenosis	52.0 (36.6-58.0)	40.1 (29.9–49.4)	0.03
Circumferential intimal Calcification (%)	15.1 (9.6–17.6)	1.6 (0.2–10.6)	0.04
Circumferential Medial Calcification (%)	2.4 (1.0–4.8)	2.3 (1.2–4.0)	0.71
Bone Formation	10 (83.3)	4 (33.3)	0.02

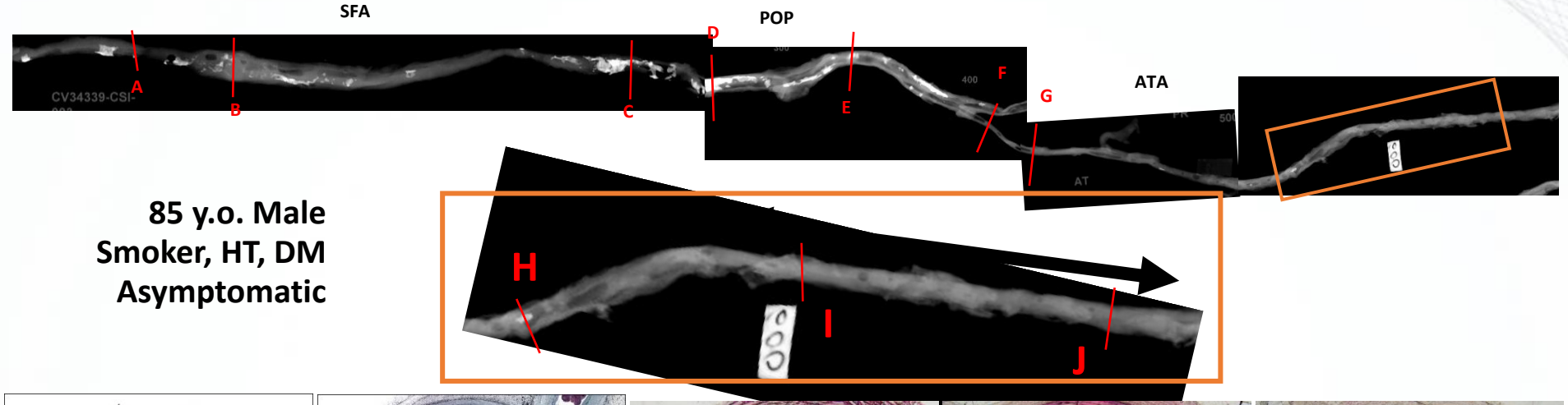
Torii S, J Am Coll Cardiol Img 2018.

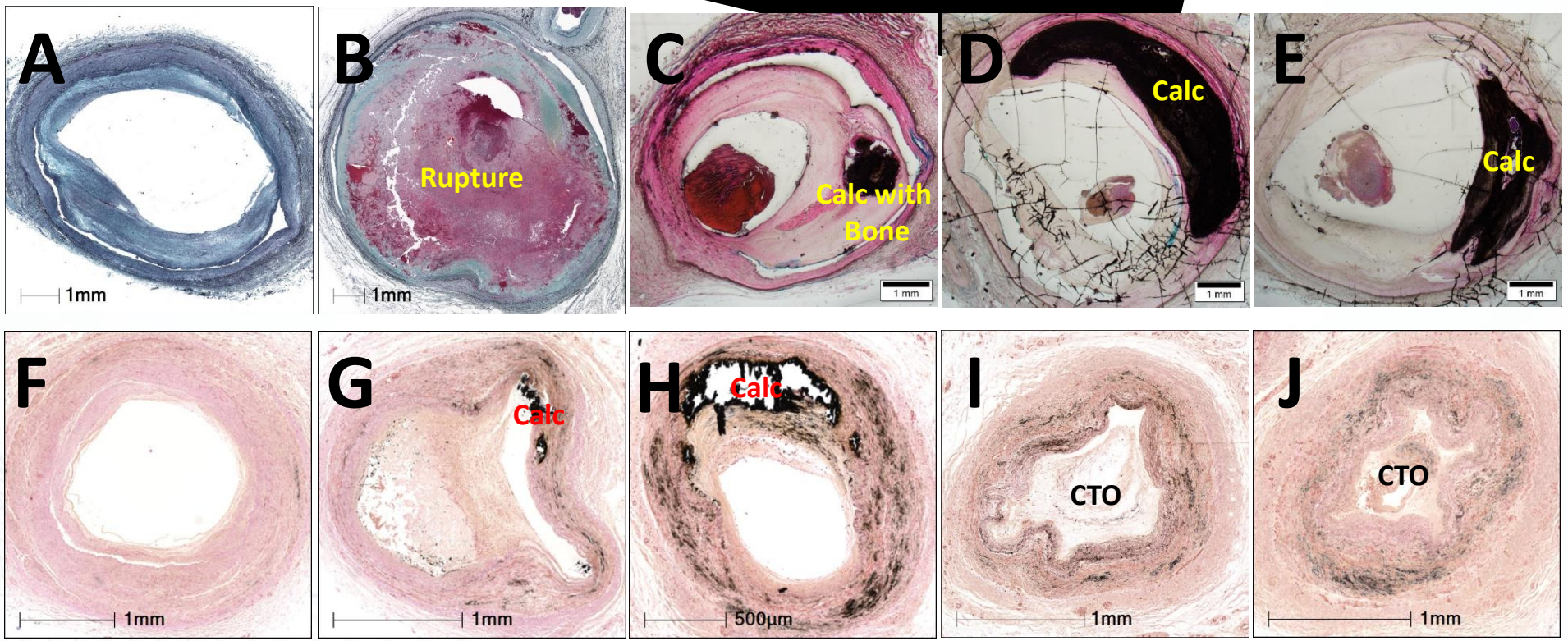
CTO of Anterior Tibial Artery with Negative Remodeling and Minimal Ca

85-year-old woman with a history of smoking, hypertension, and hyperlipidemia. Chronic total occlusion (CTO) of the proximal region of the anterior tibial artery (ATA) is demonstrated in **C and D (red arrows)**. Note negative remodeling with focal minimal calcification in the occluded ATA in histological sections **(2 to 5)**. A calcified nodule with occlusive thrombus was observed in the proximal SFA (not shown); the etiology of CTO was considered to be “embolic CTO” because no necrotic core or significant atherosclerosis was observed in these sections.

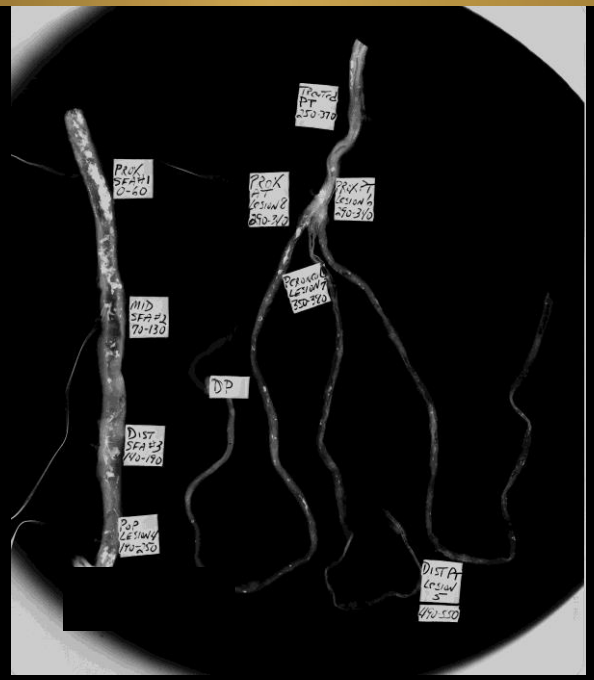


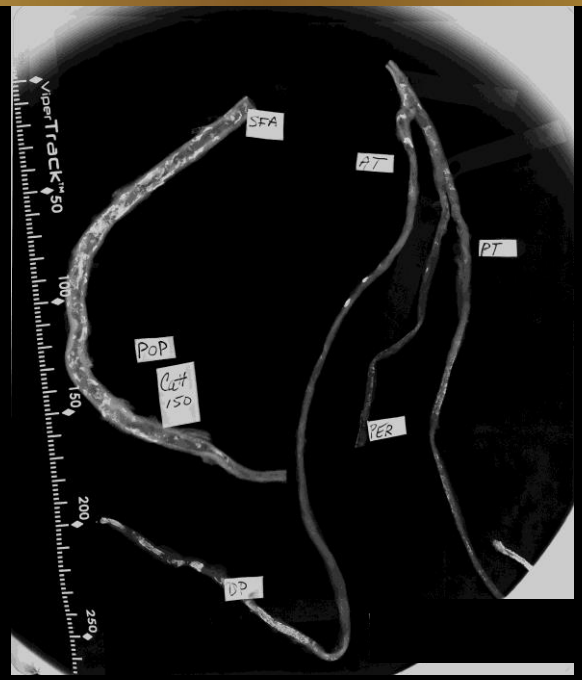
CTO secondary to distal emboli

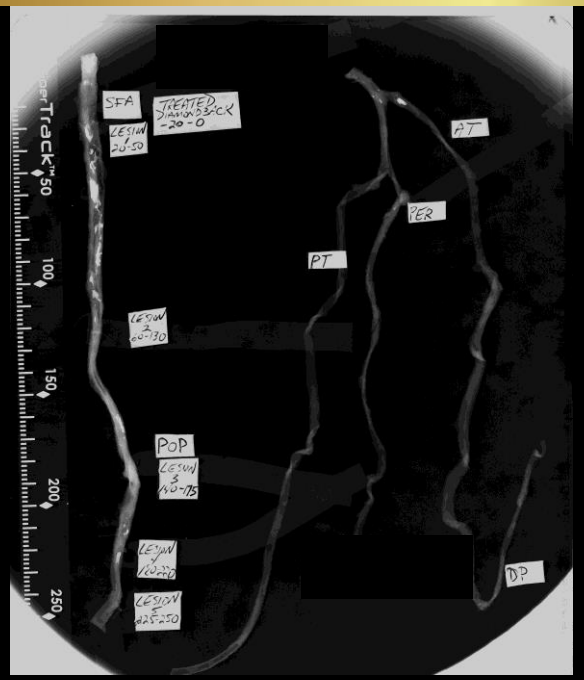




Atherosclerosis and calcification in human peripheral arteries







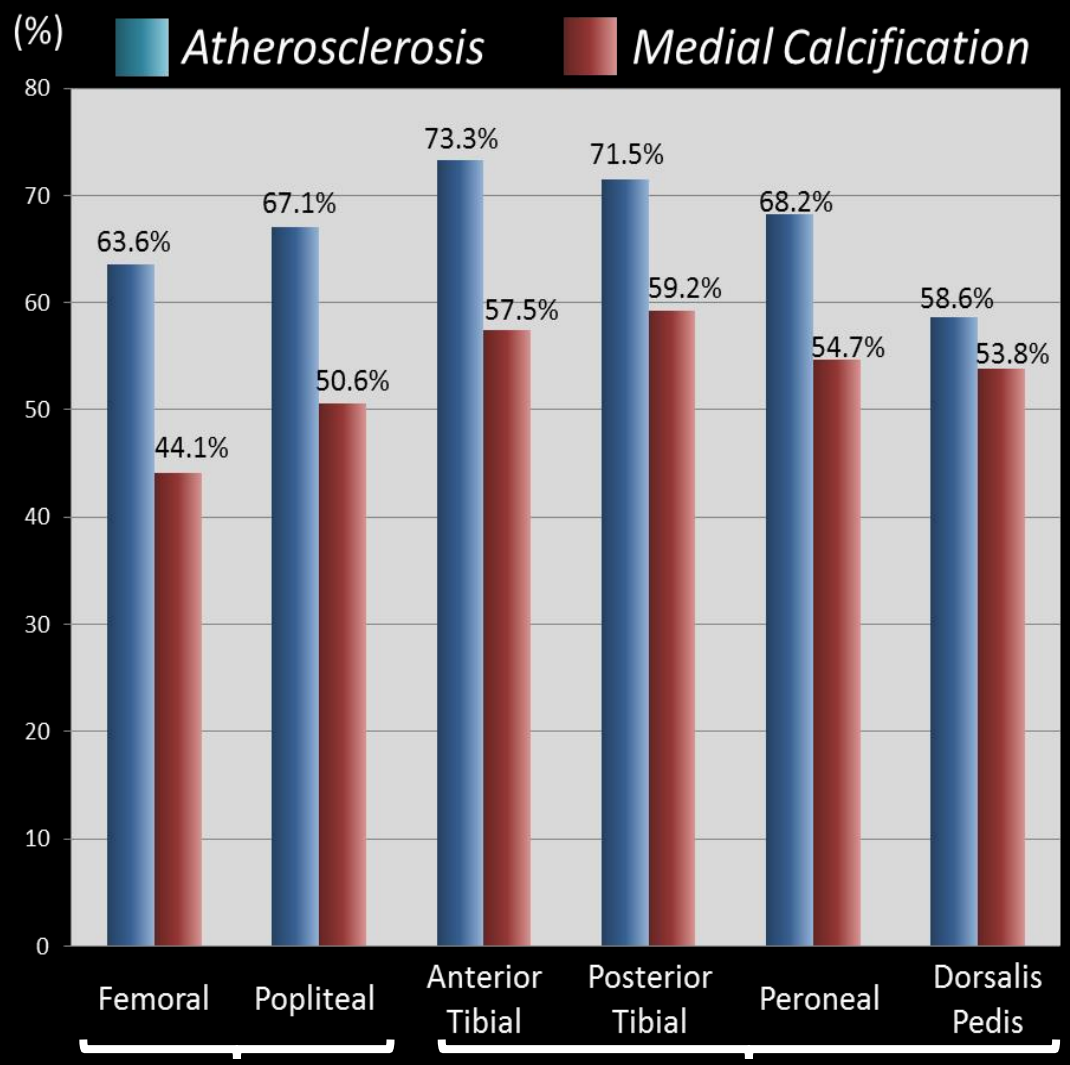
- Type of calcification
- Intimal vs. Medial calcification

16 asymptomatic legs (**3069** histologic sections) from 12 patients

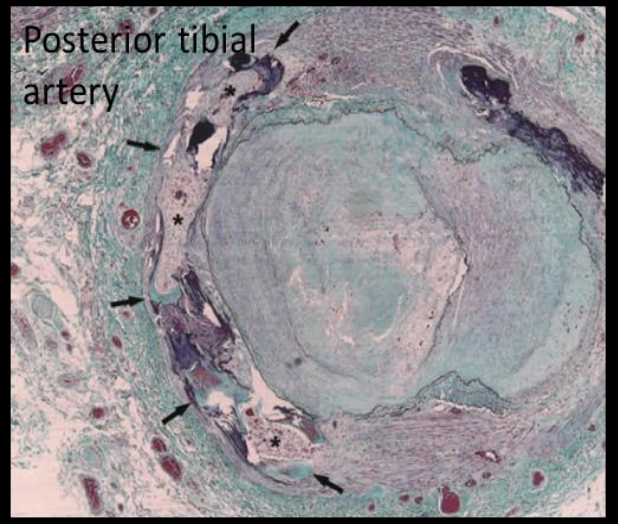
Mean age 82±4, Male 70%

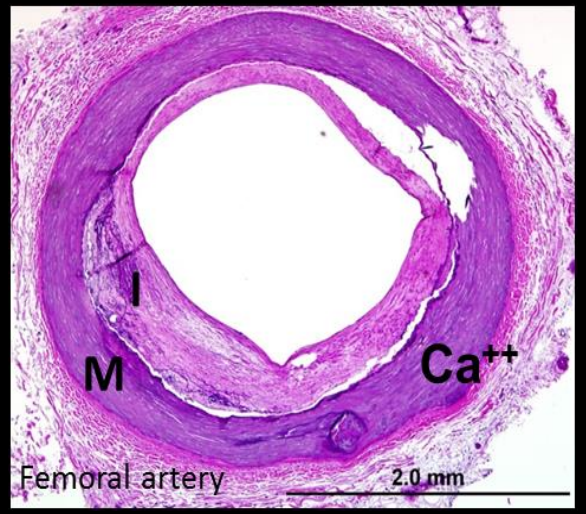
Torii S. JACC Imaging 2018 Dec 6.

Extent of Atherosclerosis and Medial Calcification in Critical Limb Ischemia patients undergoing amputation



Ossification: 19% of arteries

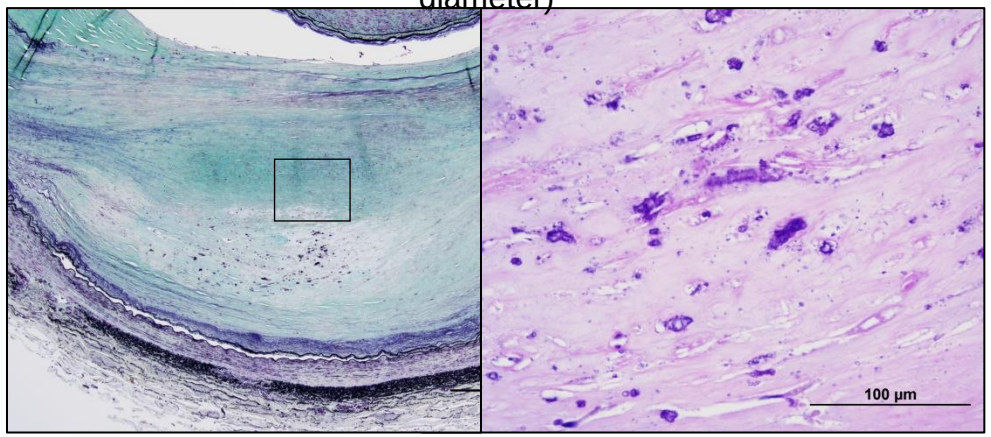




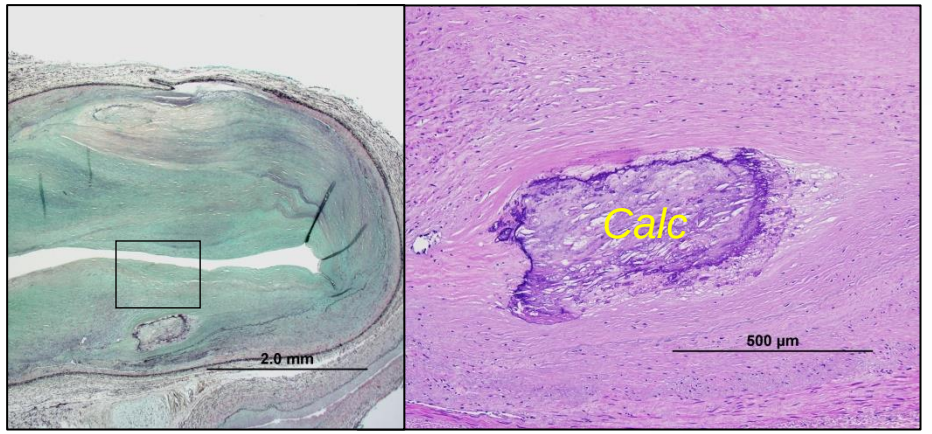
Soor GS, et al. Pathology 2008;40:385-391

Intimal calcification in peripheral arteries

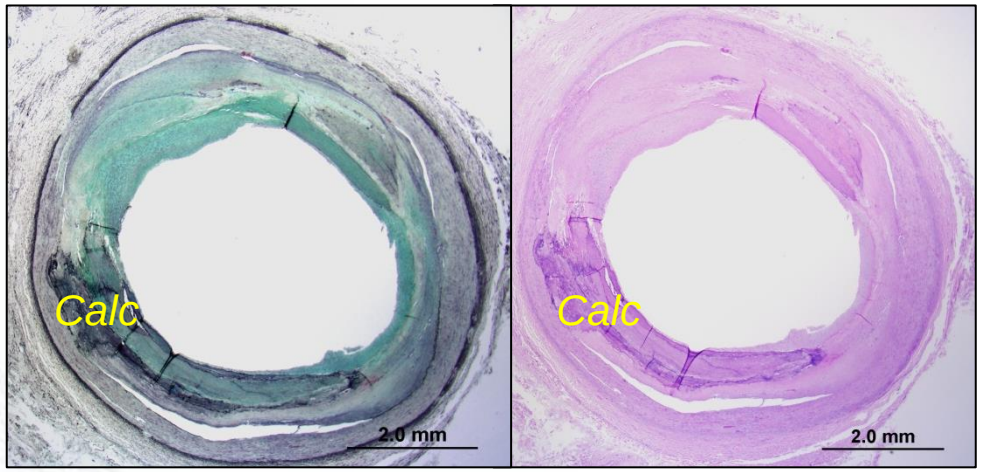
Microcalcification (calcium particles varying from ≥0.5 but <15 μm in diameter)



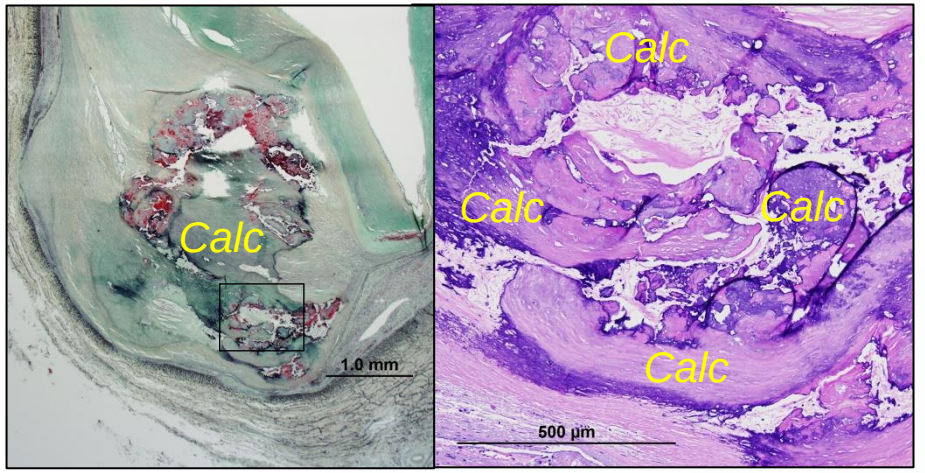
Fragmented calcification (≥1 mm)



Sheet calcification (>1 quadrant of the vessel demonstrated calcification)

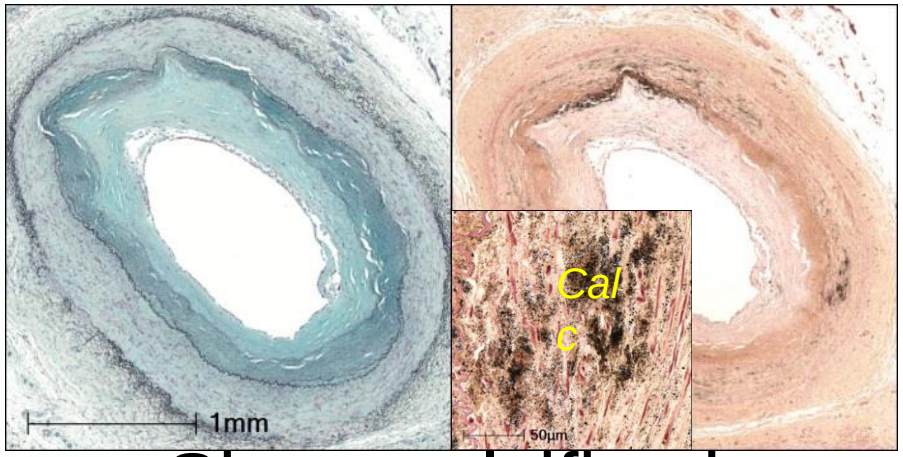


Nodular calcification (not penetrating though lesion surface)

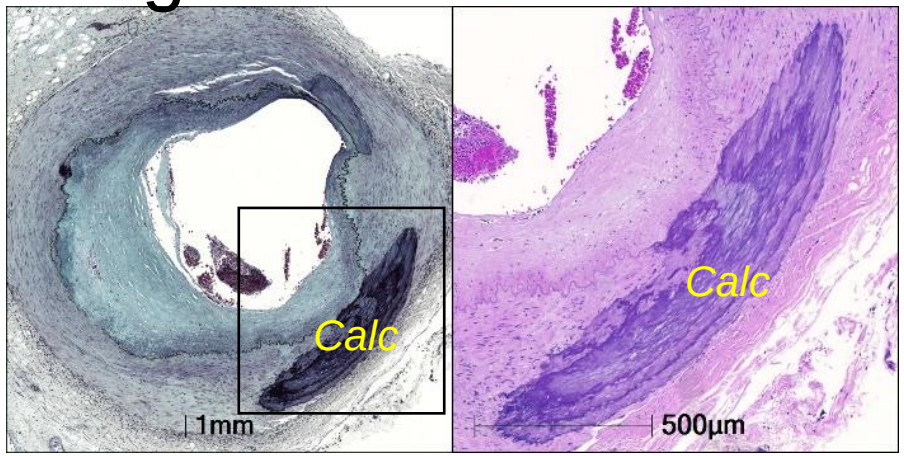


Medial calcification in peripheral arteries

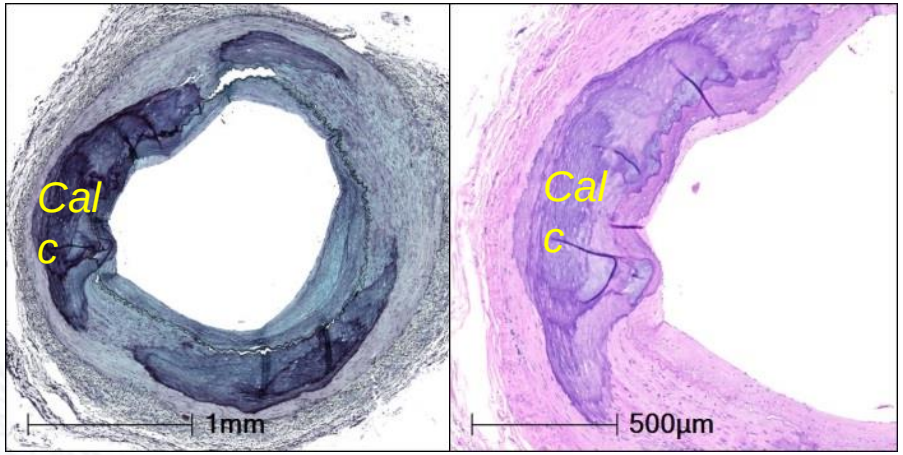
Microcalcification



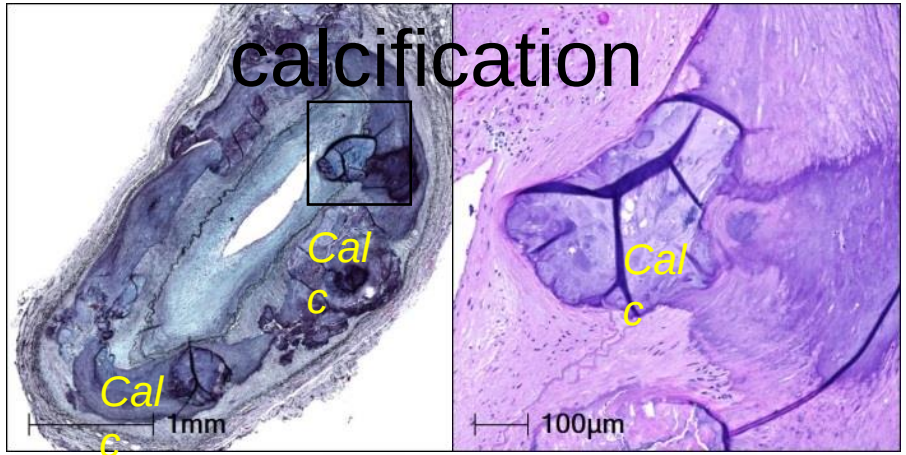
Fragmented calcification



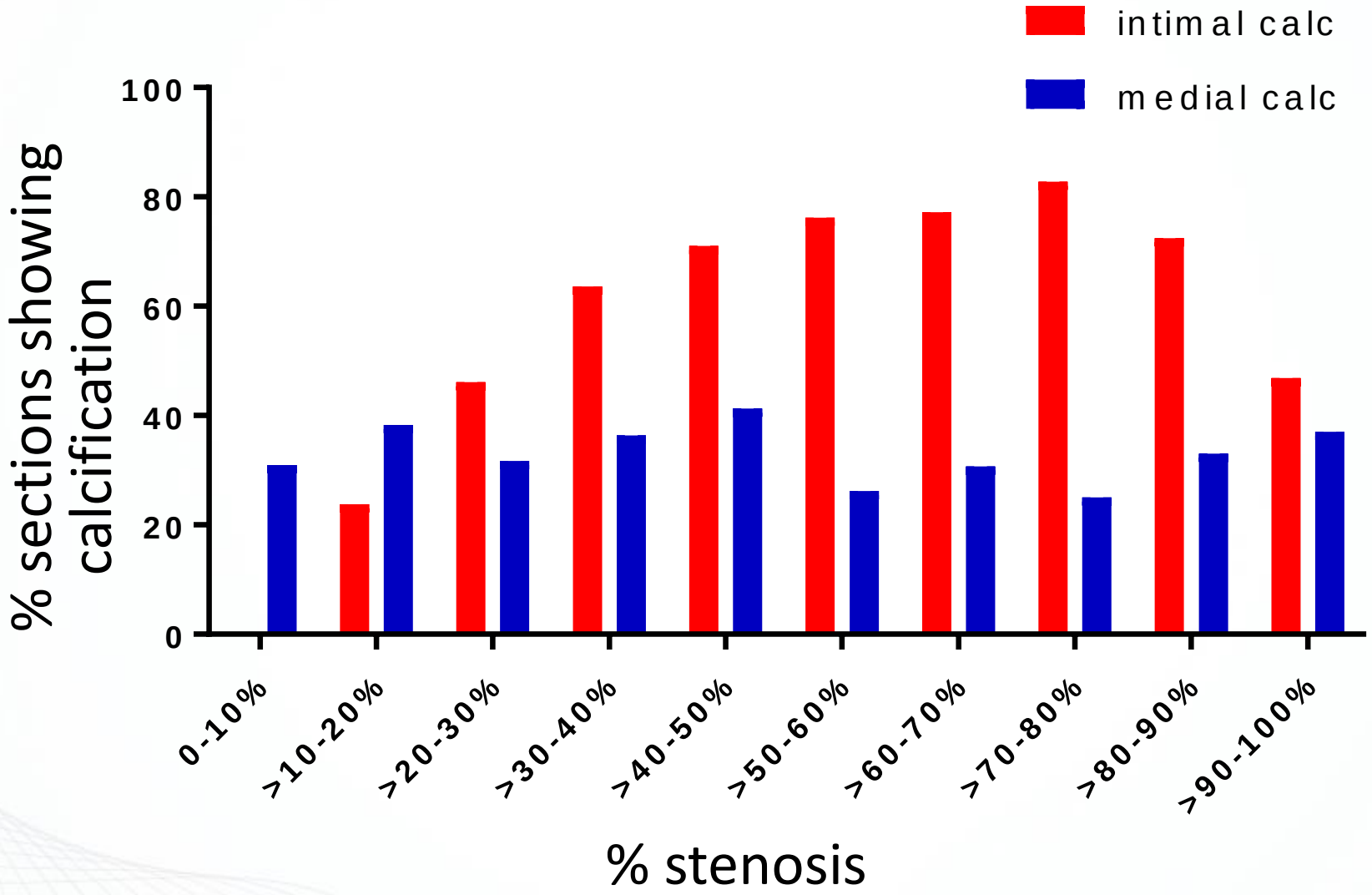
Sheet calcification



Sheet + Nodular calcification

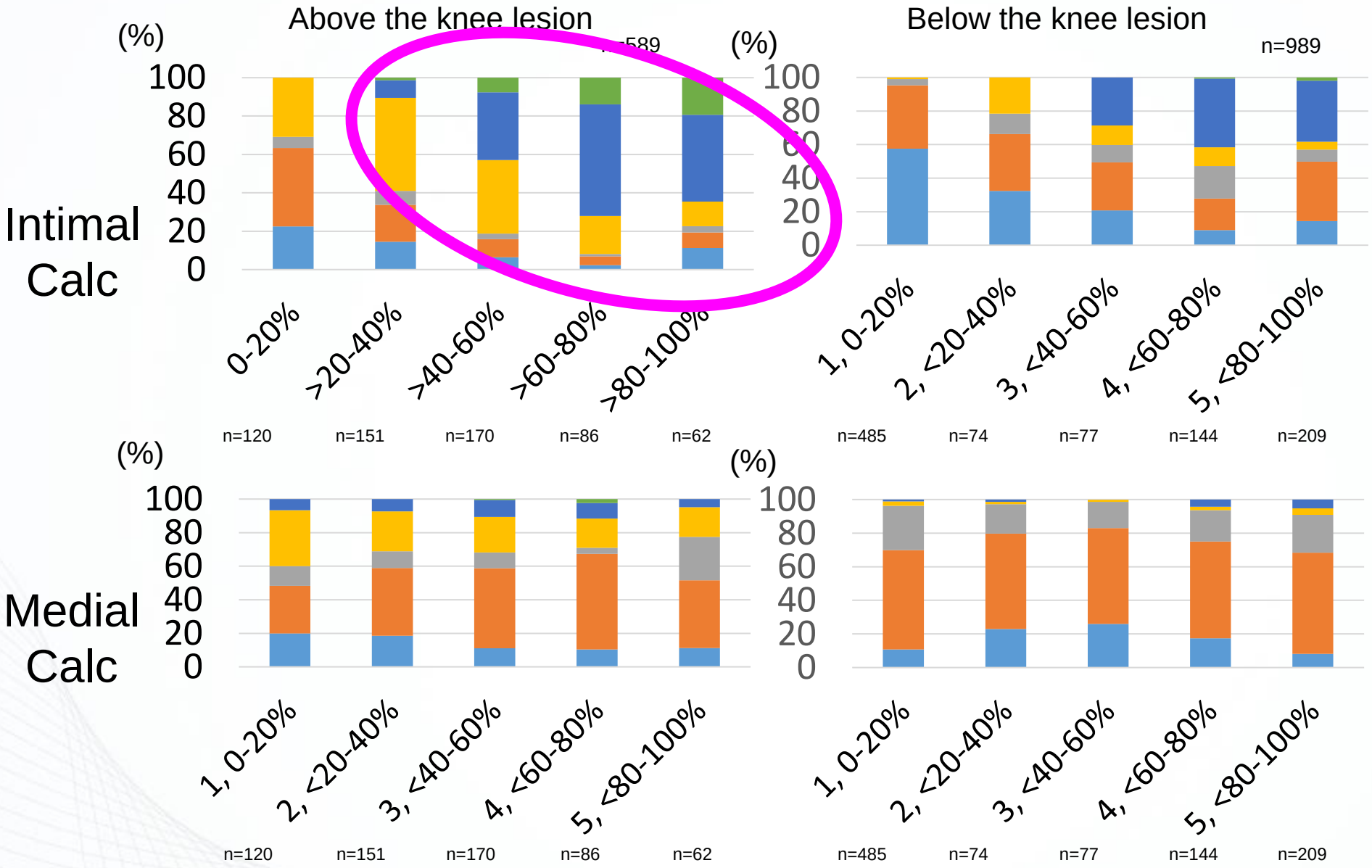


Correlation between calcification and %stenosis



Torii S. et al. JACC 2018

The relationship between % stenosis and Calcification



intimal calcification assessed was significantly higher in AK arteries compared with BK arteries

extent of medial calcification was similar in AK and BK

Summary

- Intimal Calcification is frequently observed in both coronary and lower extremities, and is more common in above the knee.
- Medial calcification is observed in lower extremities, and calcification is especially high in diabetic and renal failure patients.
- In patients with asymptomatic PAD, thrombotic events (calcified nodule and rupture) are exclusively seen in AK.
- BK vessels with CTO lesions frequently occur secondary to both atherosclerosis and distal emboli.
- Medial and intimal calcification do not allow good vessel preparation and the penetration of the drug, is often hampered after DCB usage.
- Use of systemic anti-coagulation in subjects with PAD especially CLI may a useful therapeutic option but is associated with increased risk of bleeding
- Better risk stratification of individuals at risk is needed to prevent atherothrombotic events before they occur perhaps using genetic risk scores