Pathological Features of Peripheral Atherosclerosis: Implication for Device Development

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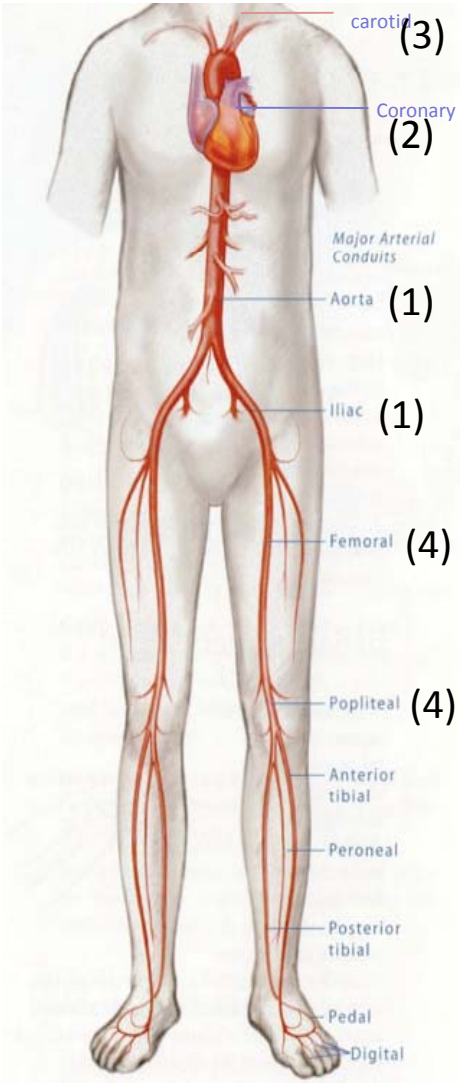
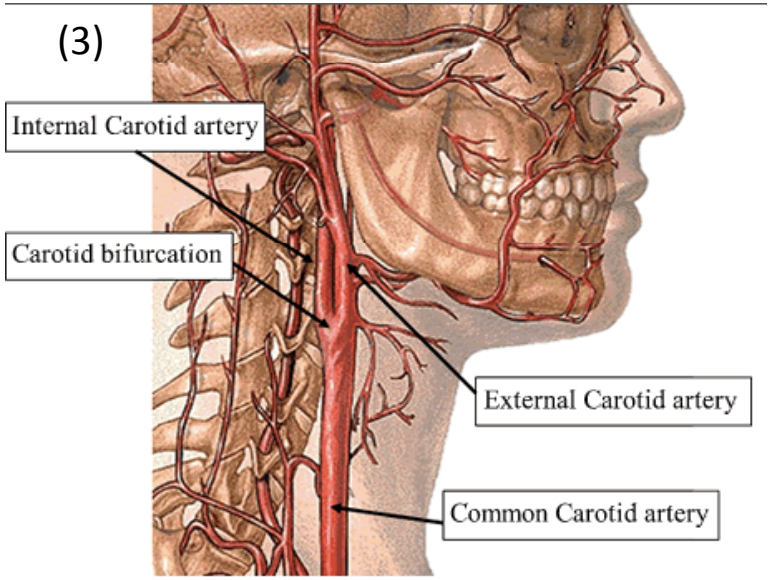
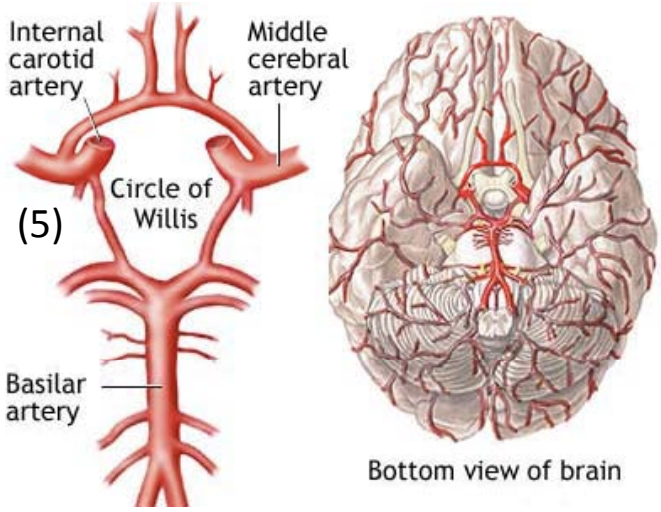
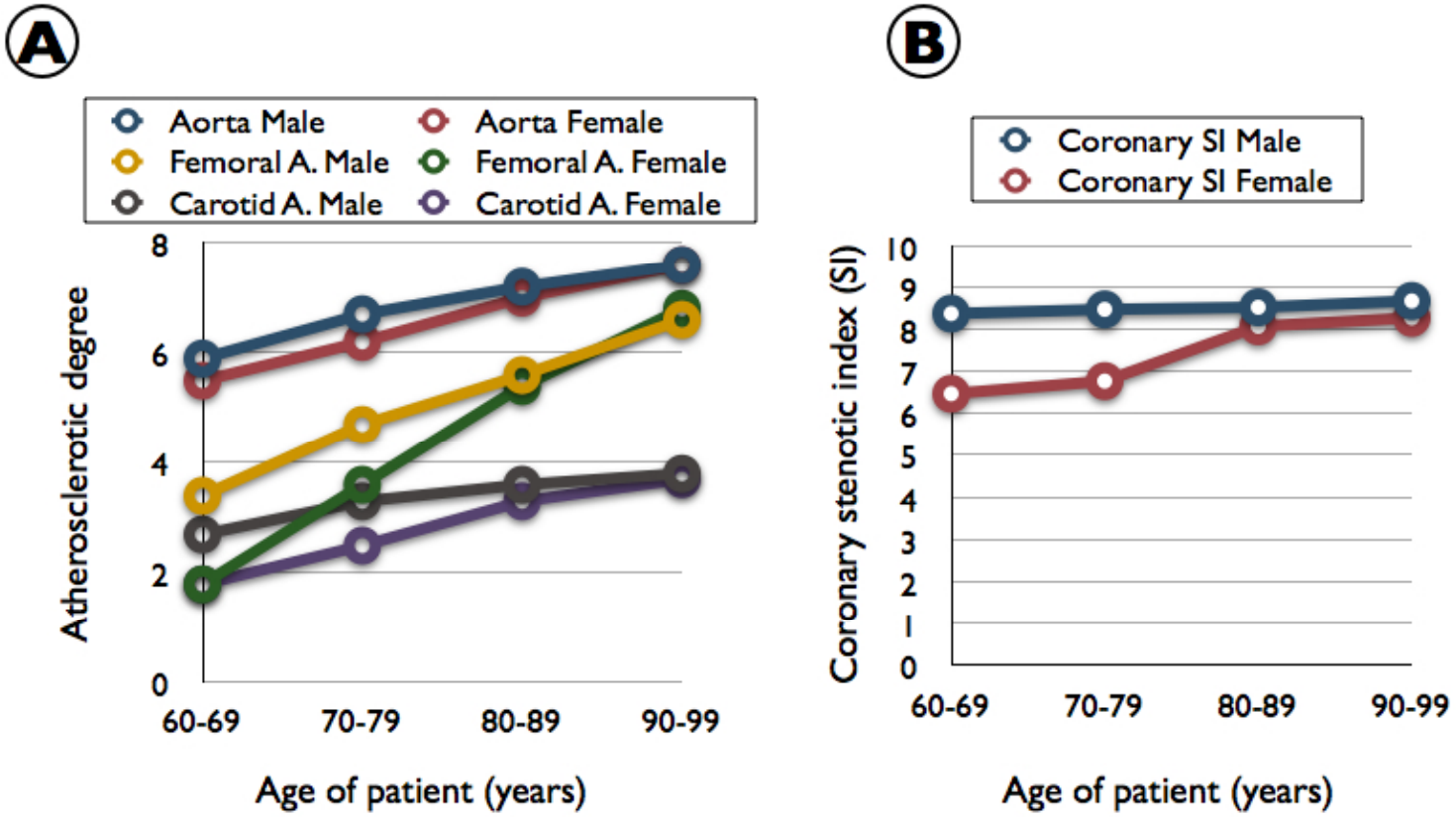
Sites of Atherosclerosis In order of Frequency







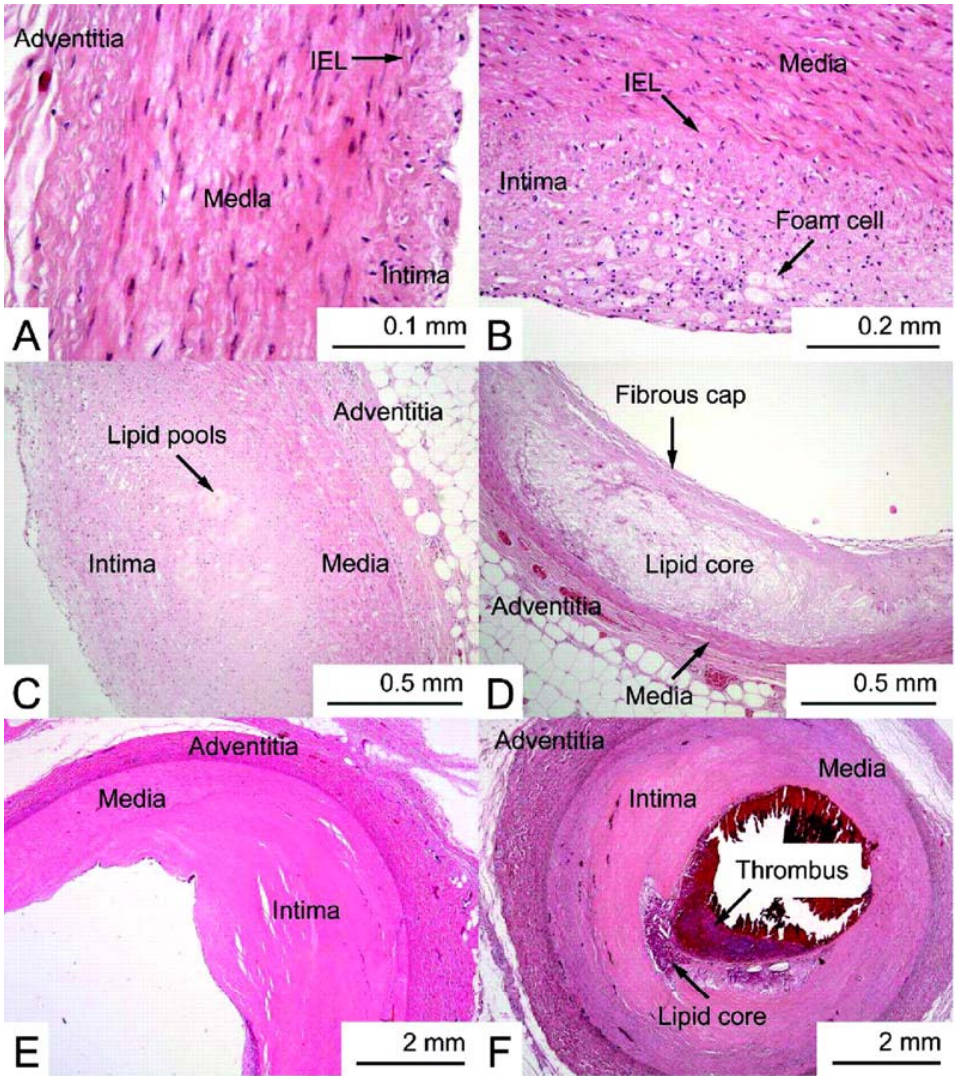
Gender- Age- and Atherosclerosis



Atherosclerosis in the large arteries was semi-quantitatively scored on a scale of 0–8 according to the ratio of the atheroma-occupied area to the entire surface area: negligible (0 point, ratio = 0–1/20), minimal (2 points, 1/20–1/6), mild (4 points, 1/6–1/3), moderate (6 points, 1/3–2/3), and severe (8 points, 2/3–1) where as for coronary arteries it was based on stenosis.

Sawabe M, et al. Atherosclerosis 2006:186:374-379

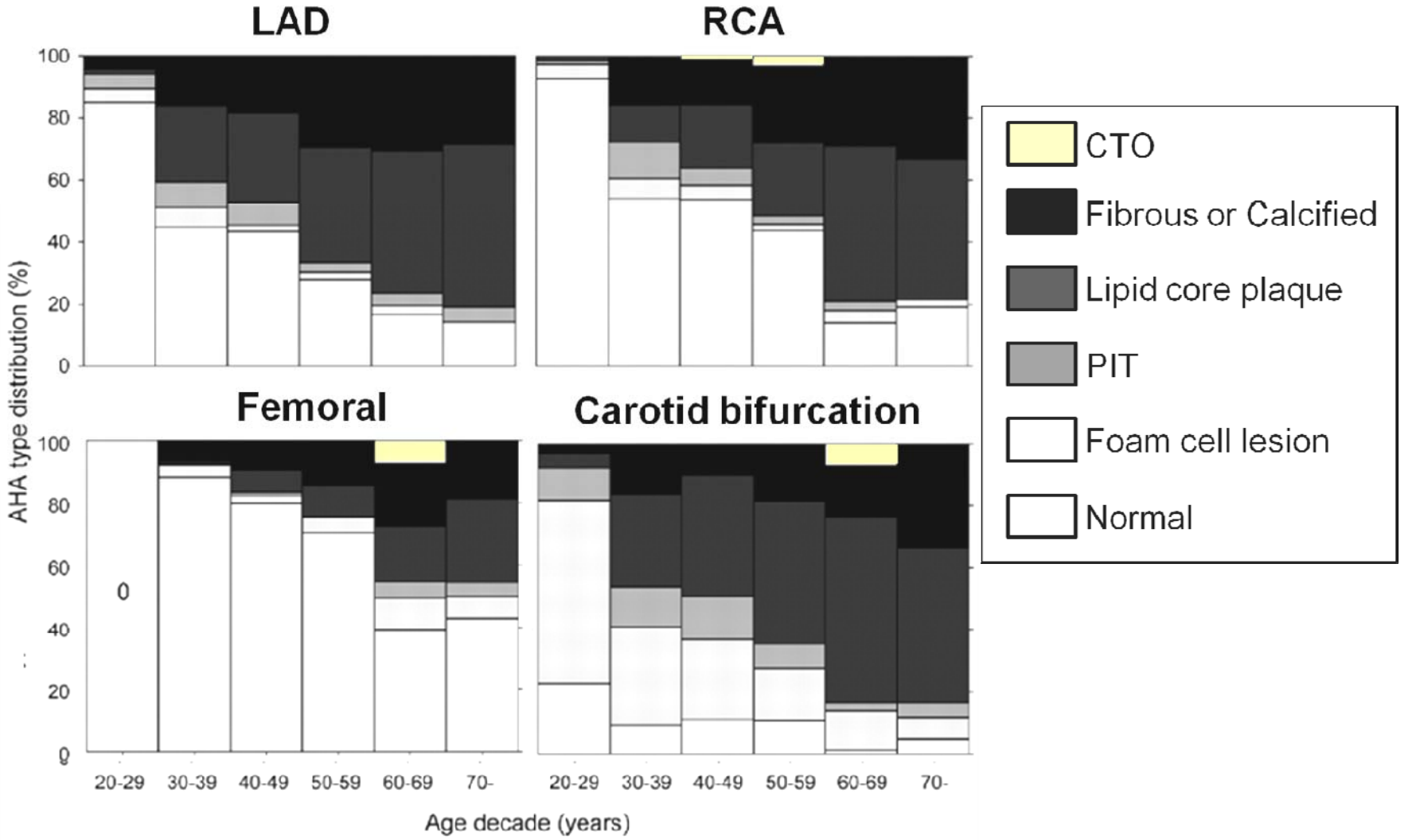
Histological examples Coronary vs. Femoral



A, B, C, and D are Coronary plaques and E and F are Femoral arteries

Dalager, S. et al. Stroke 2007;38:2698-2705

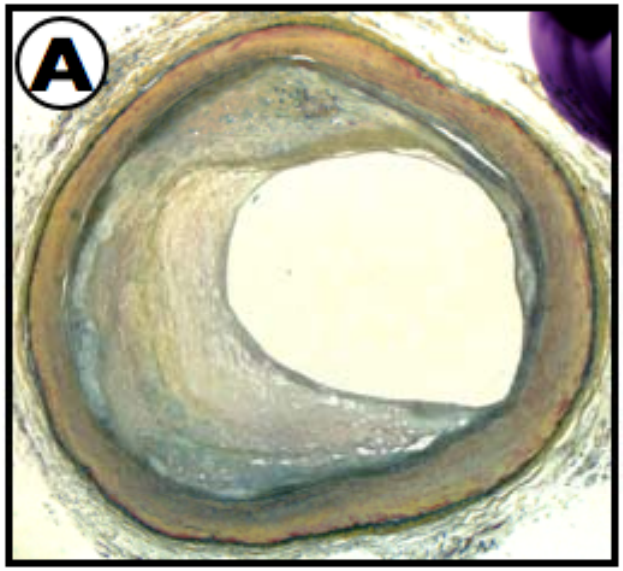
Percentage distribution of AHA lesion types in the different arteries stratified by age decade



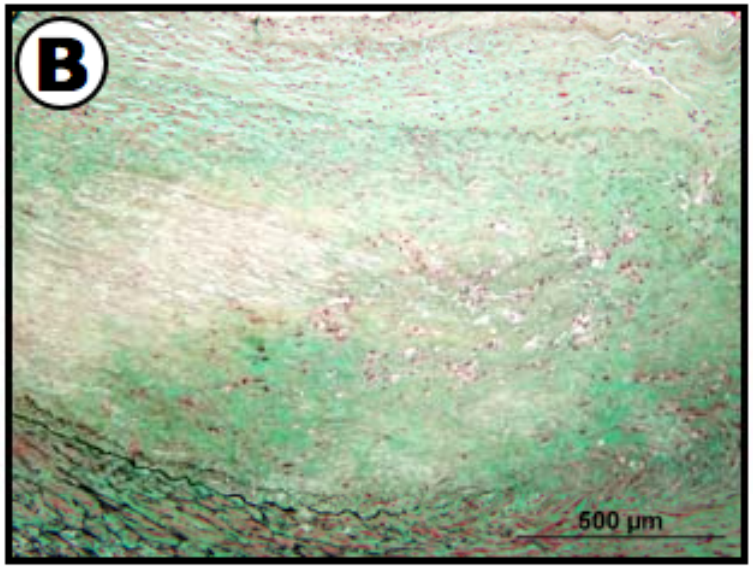
Dalager, S. et al. Stroke 2007;38:2698-2705

Eccentric Fibrous plaque

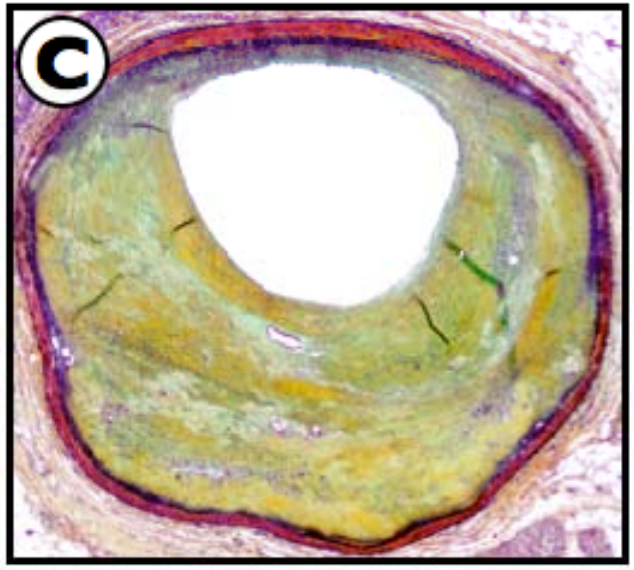
Femoral



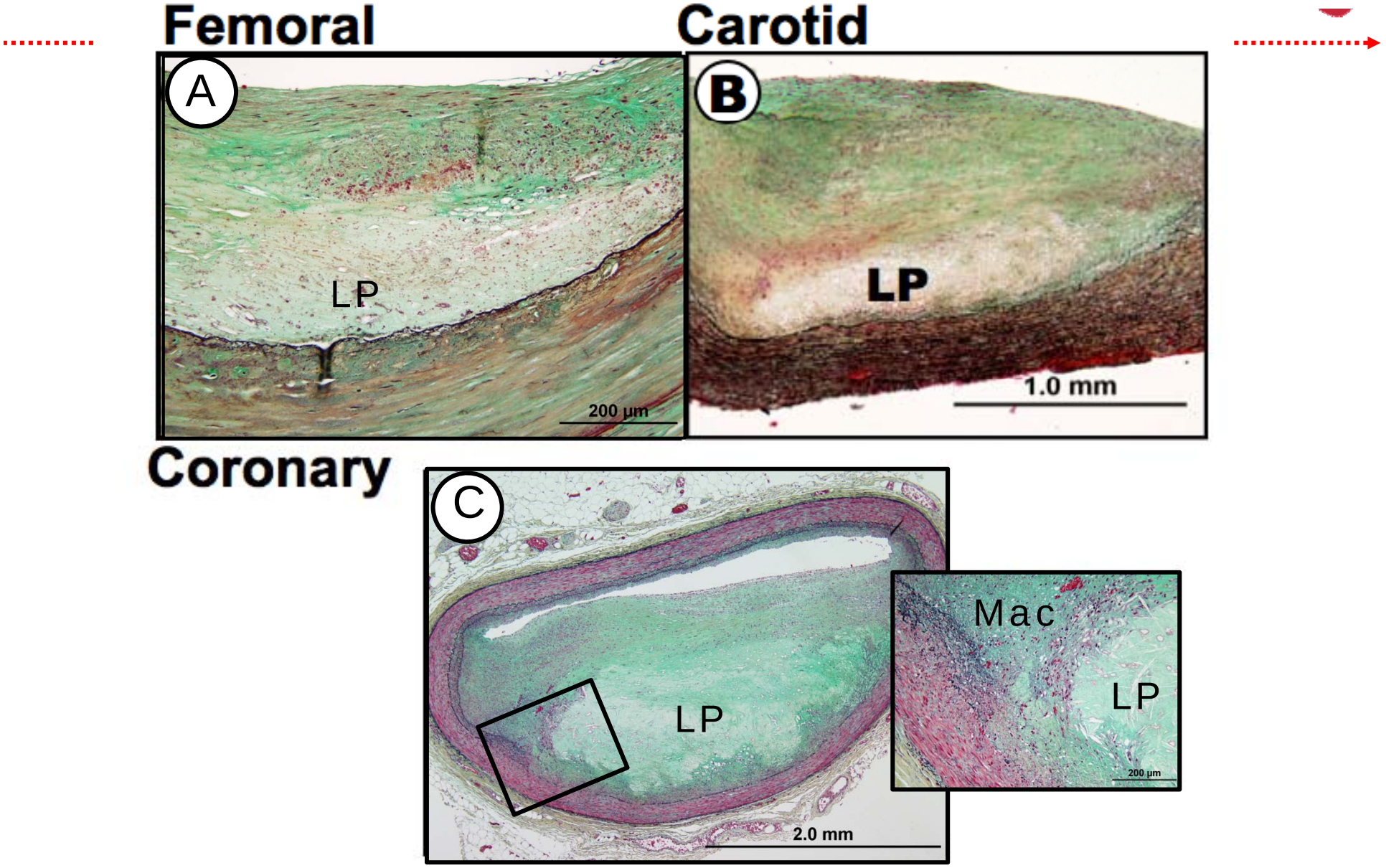
Carotid



Coronary



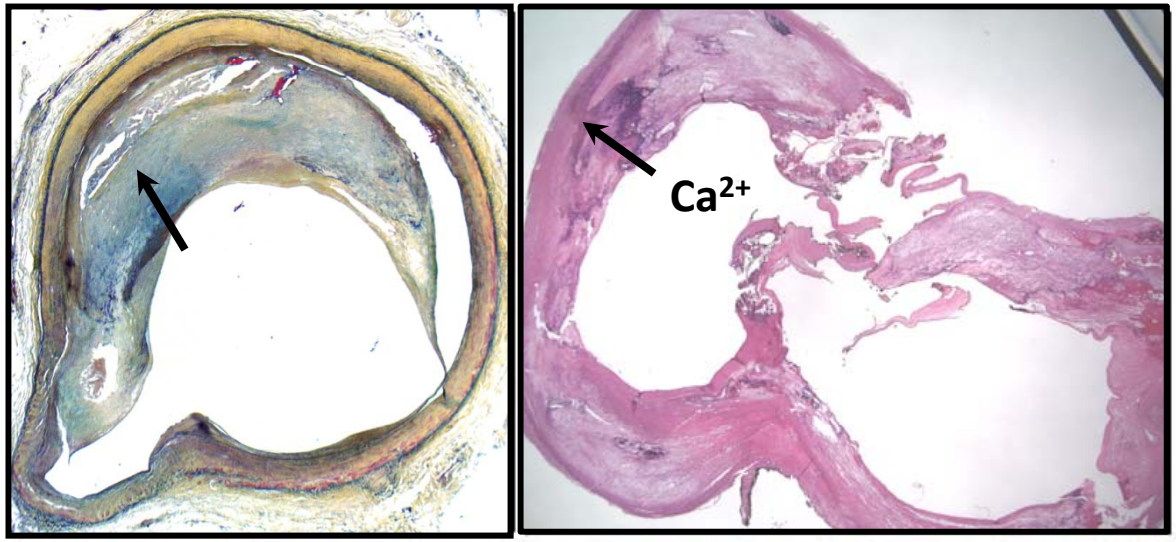
Early phase of atherosclerosis in different types of artery: Pathologic Intimal Thickening



Eccentric Fibrous Plaque with Calcified Necrotic Core

Femoral

Carotid



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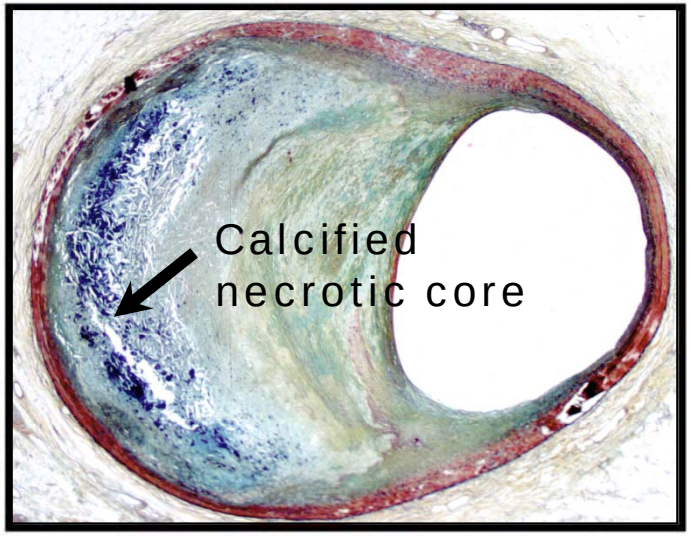
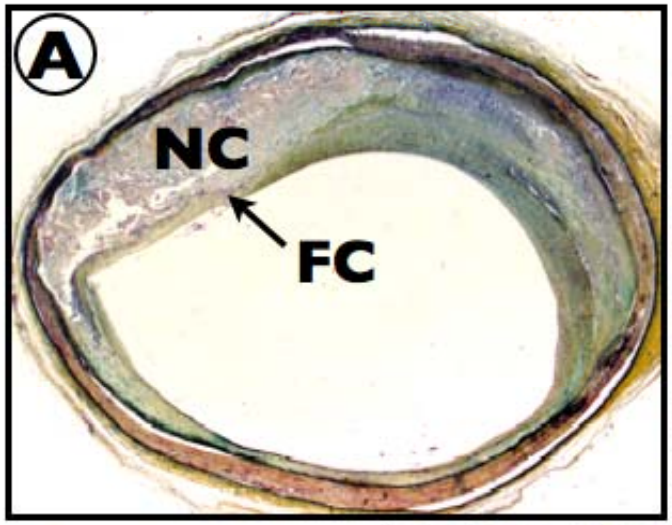


Eccentric Plaque with Large lipid Core and Thin Cap Fibroatheroma in 3 different beds

Femoral



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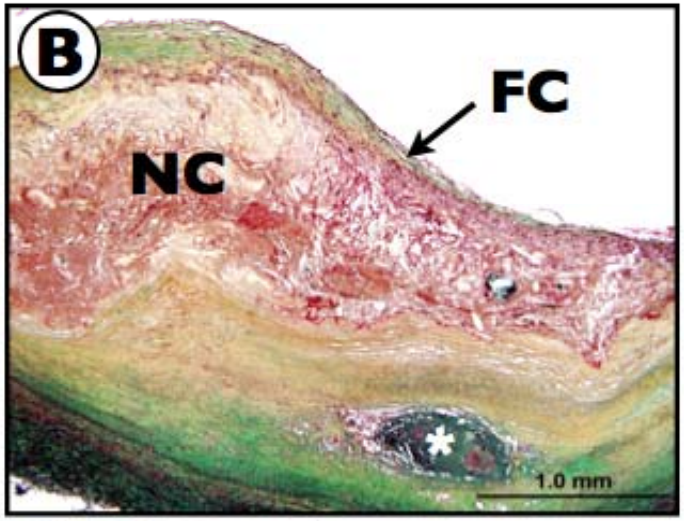

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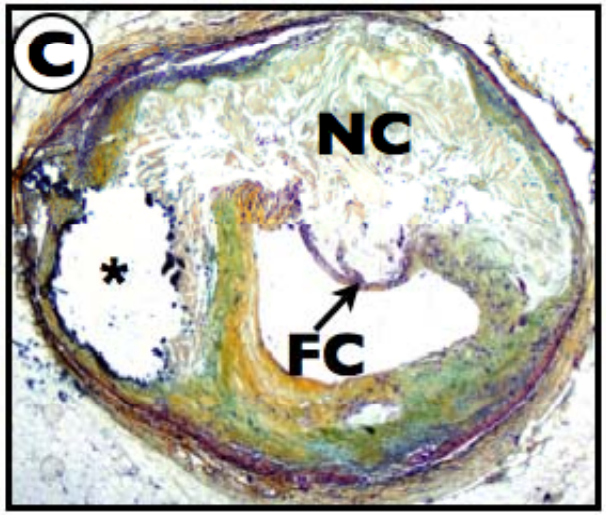
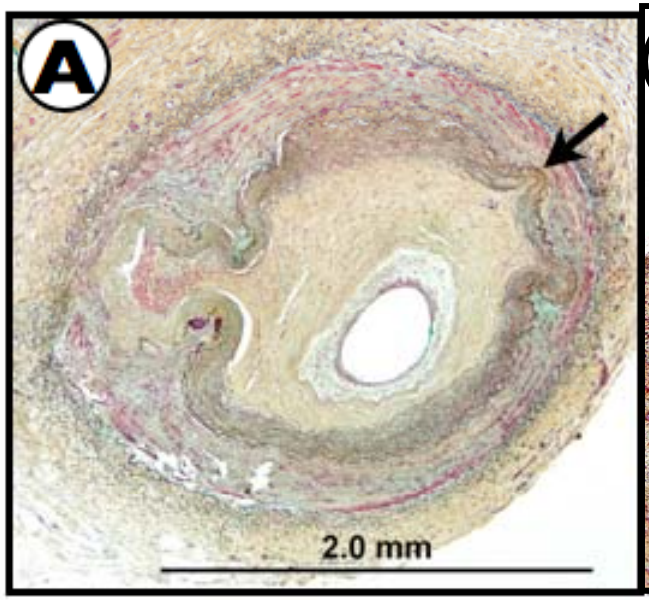


Chronic Total Occlusion

Femoral



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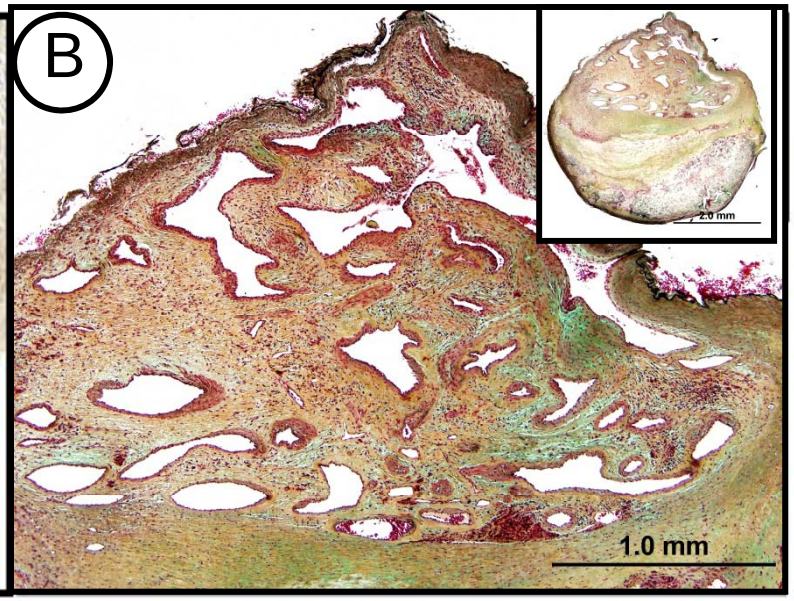
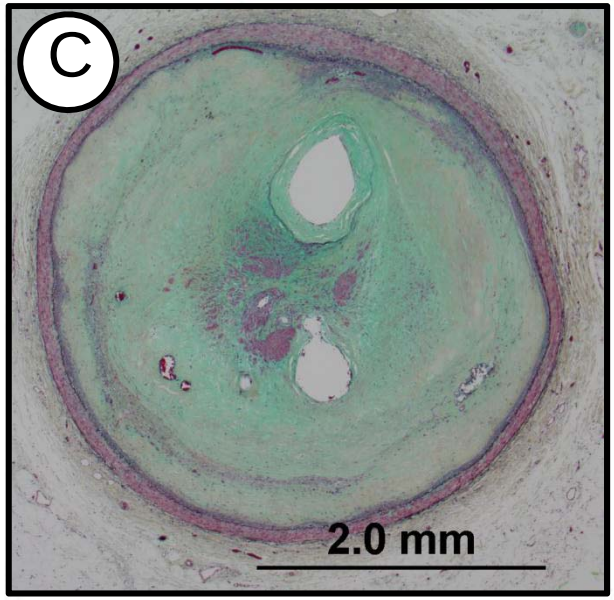
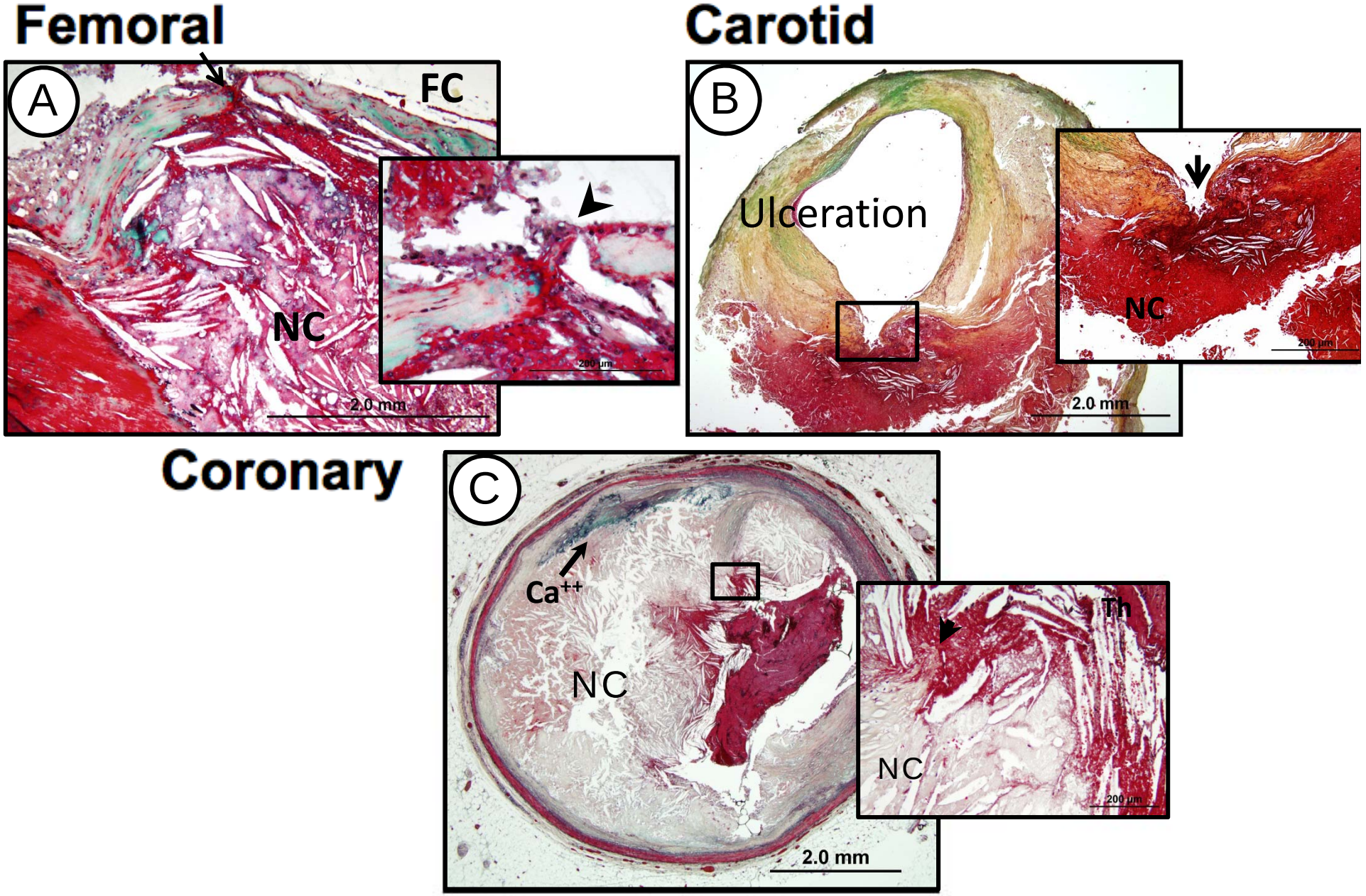


Coronary

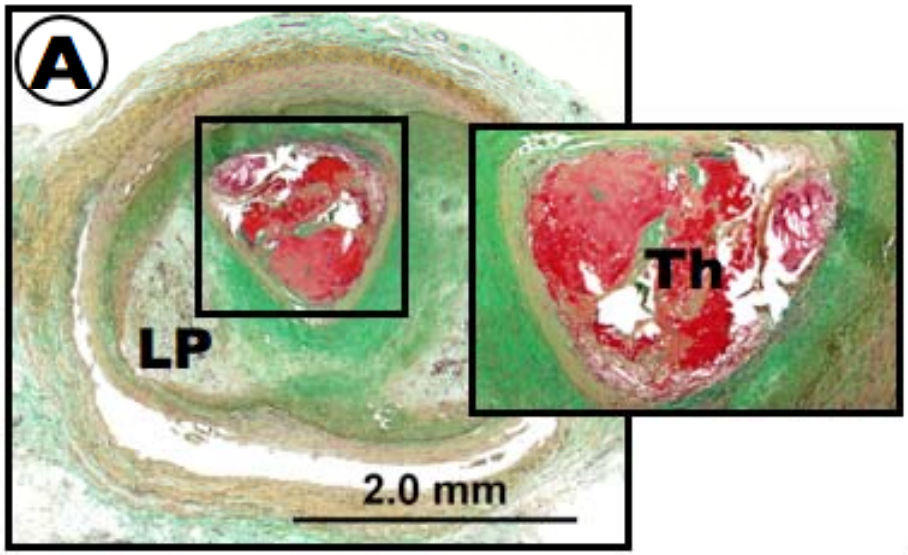


Plaque Rupture

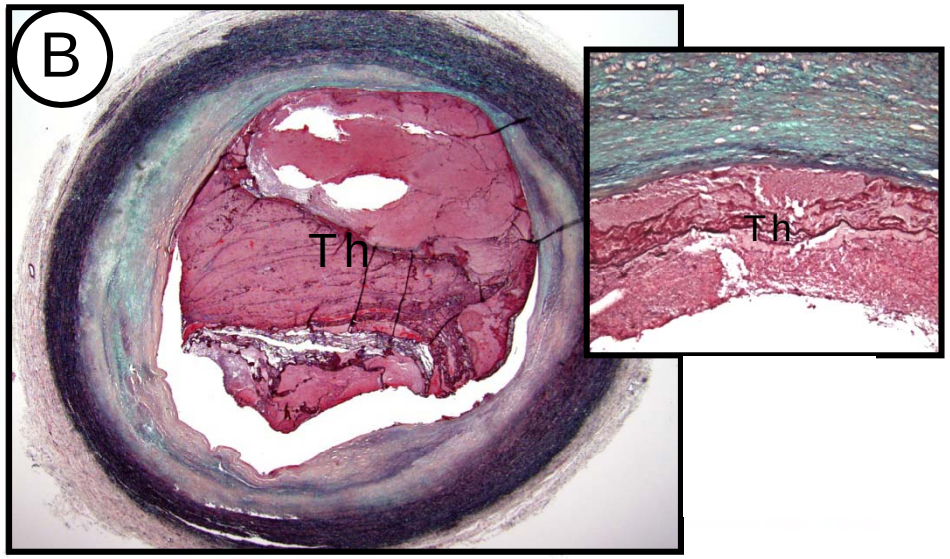


Plaque Erosion

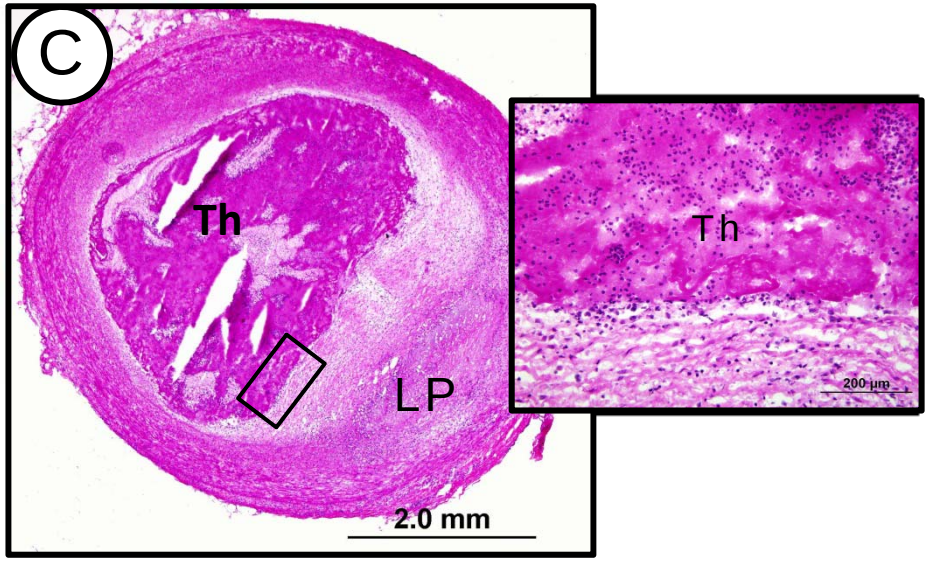
Femoral



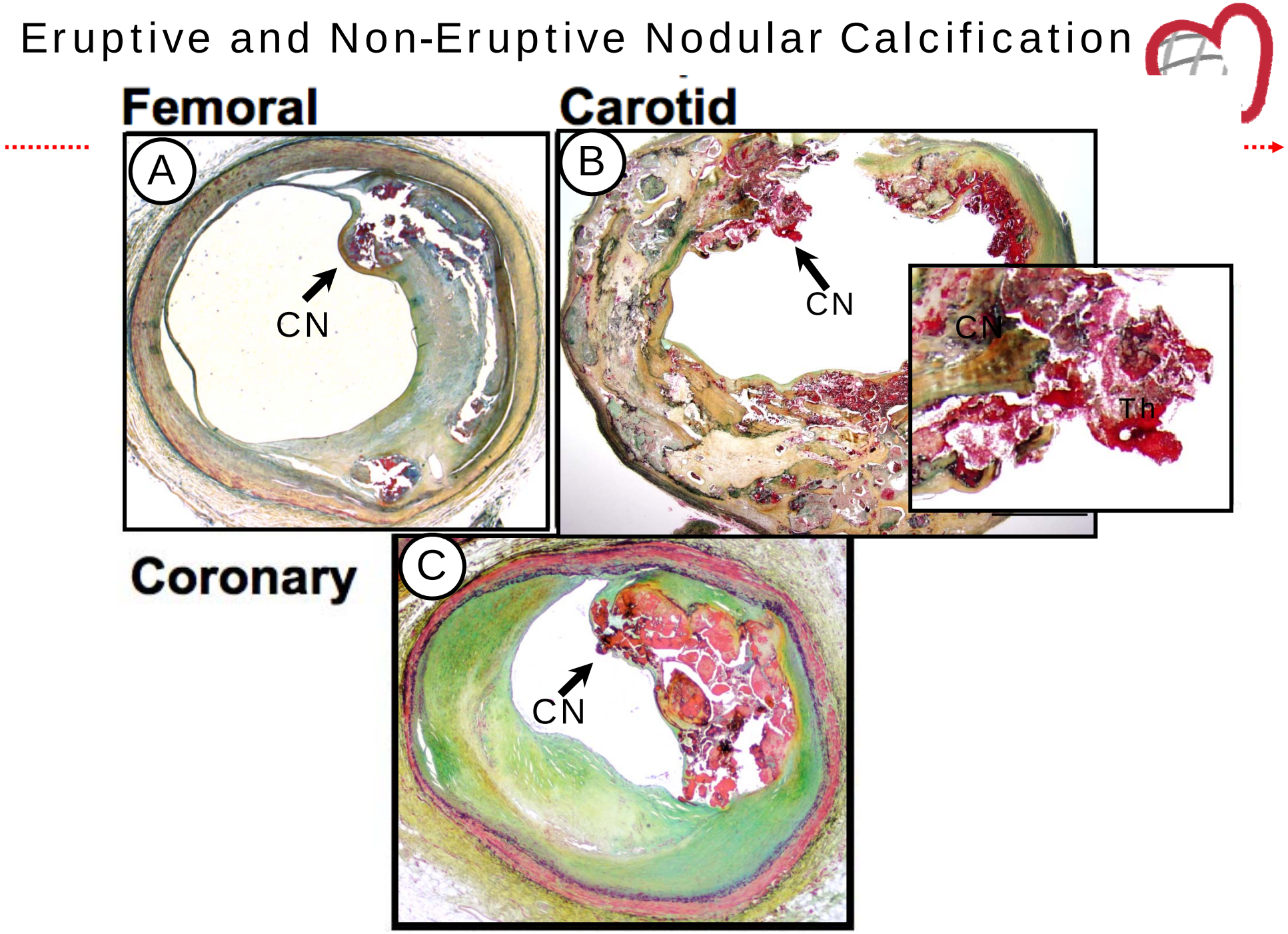
Carotid



Coronary

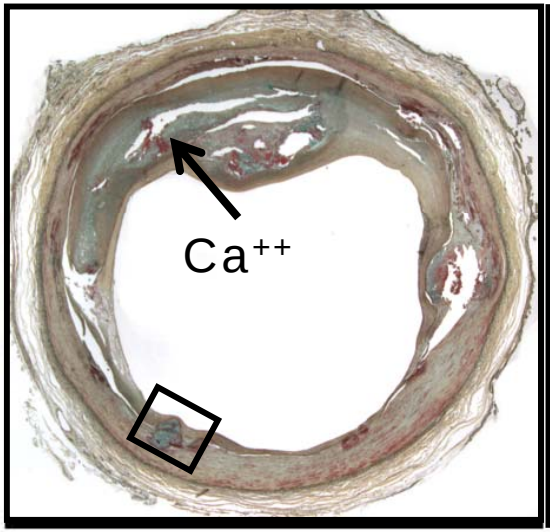


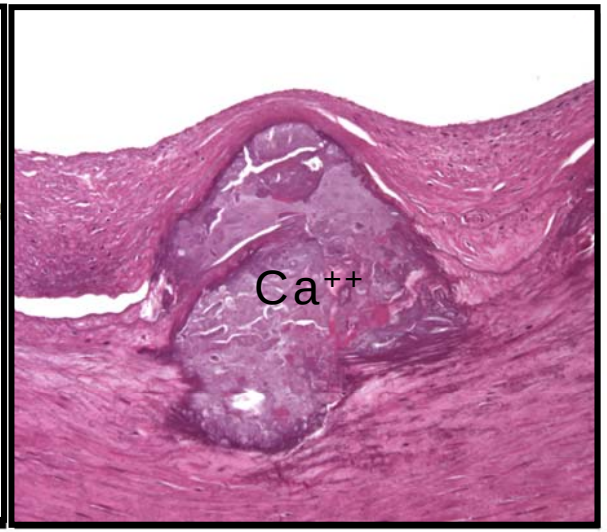
Eruptive and Non-Eruptive Nodular Calcification

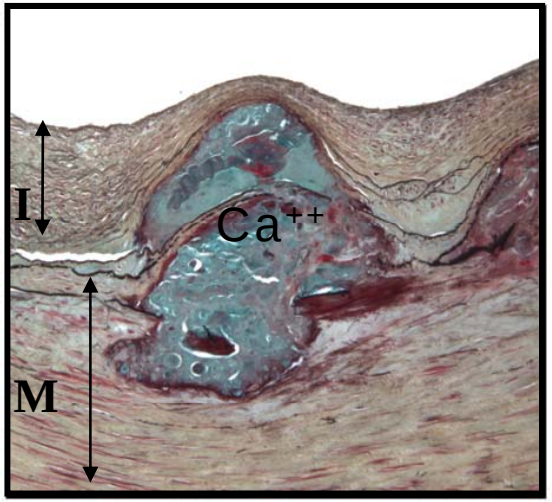


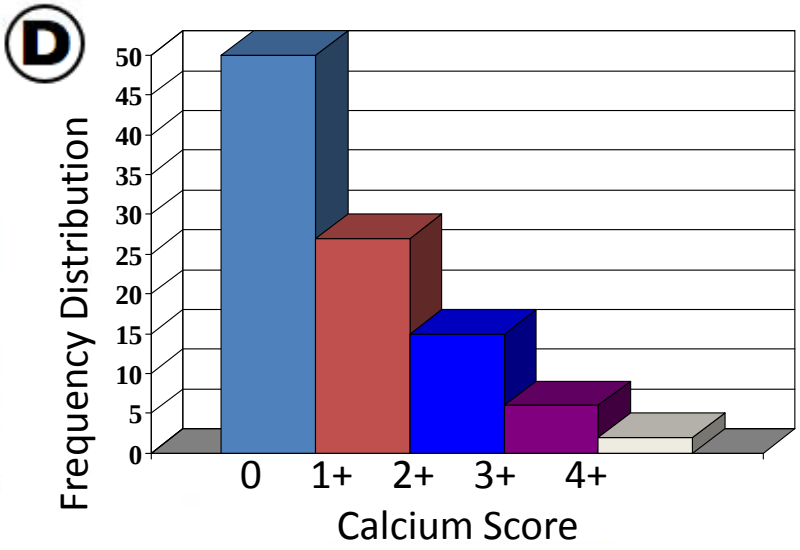
Calcification in Lower Extremity Artery

Mönckeberg's Medial Calcification from Asymptomatic PVD Patients

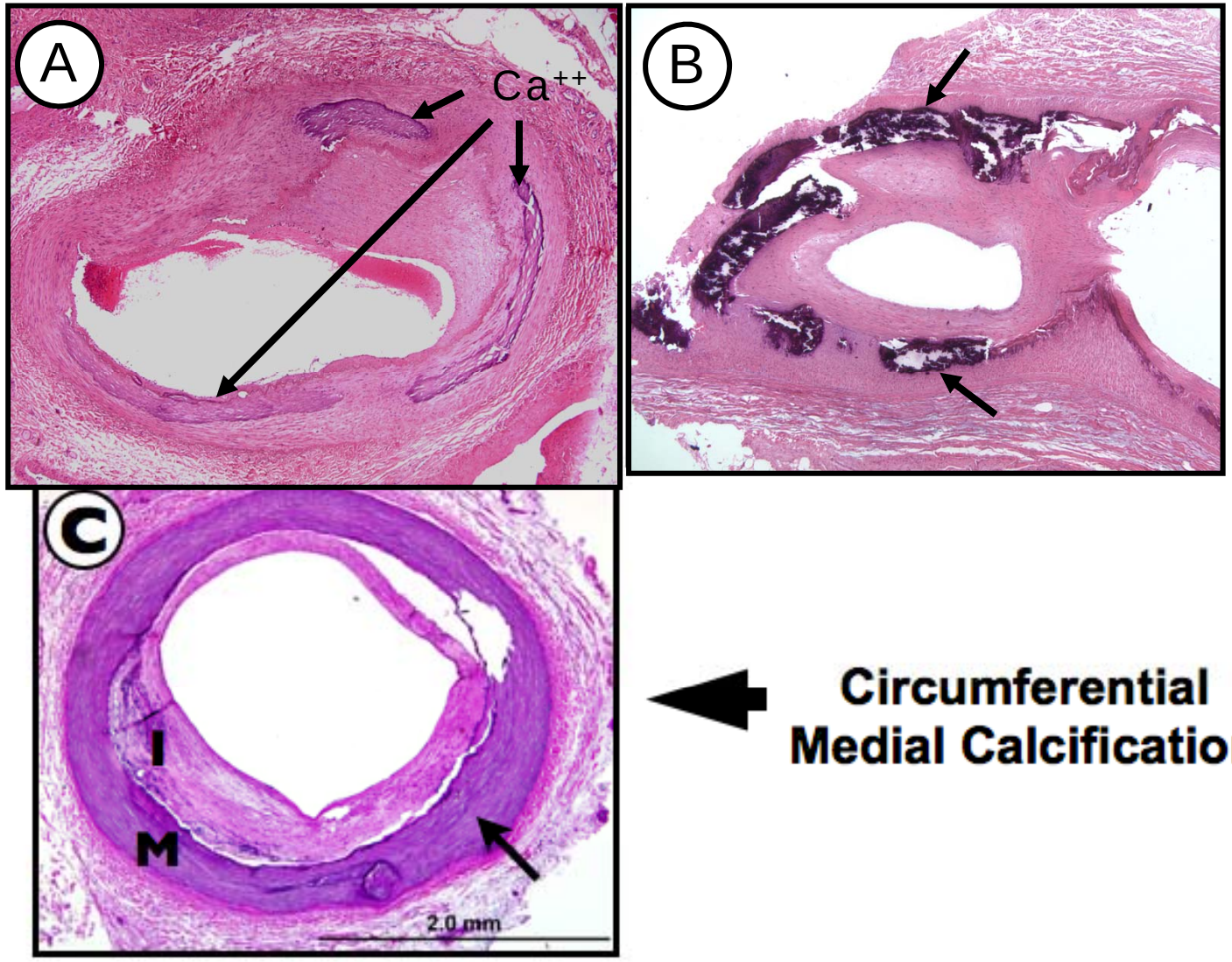








Monckeberg's Medial Calcification from Symptomatic PVD Patients Requiring Ampuatation



Circumferential Medial Calcification

Differences and Similarities Between Coronary and Peripheral Atherosclerosis

- The stages of atherosclerosis described in the coronary, carotid and aortic disease are also applicable in the peripheral arteries
- Peripheral arteries have a high frequency of Mönckeberg's medial calcification, a feature not present in coronary or carotid artery disease
- Lipid cores in femoral arteries are not as large as those in the coronary or carotid disease

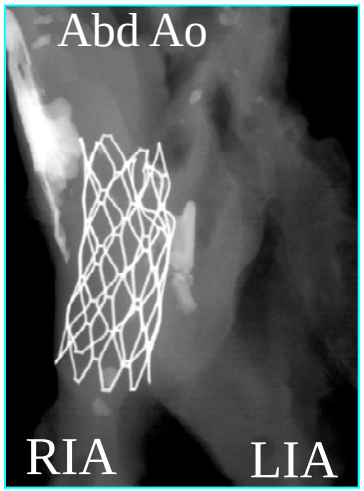
Limitations of Current Technology for the treatment of PAD

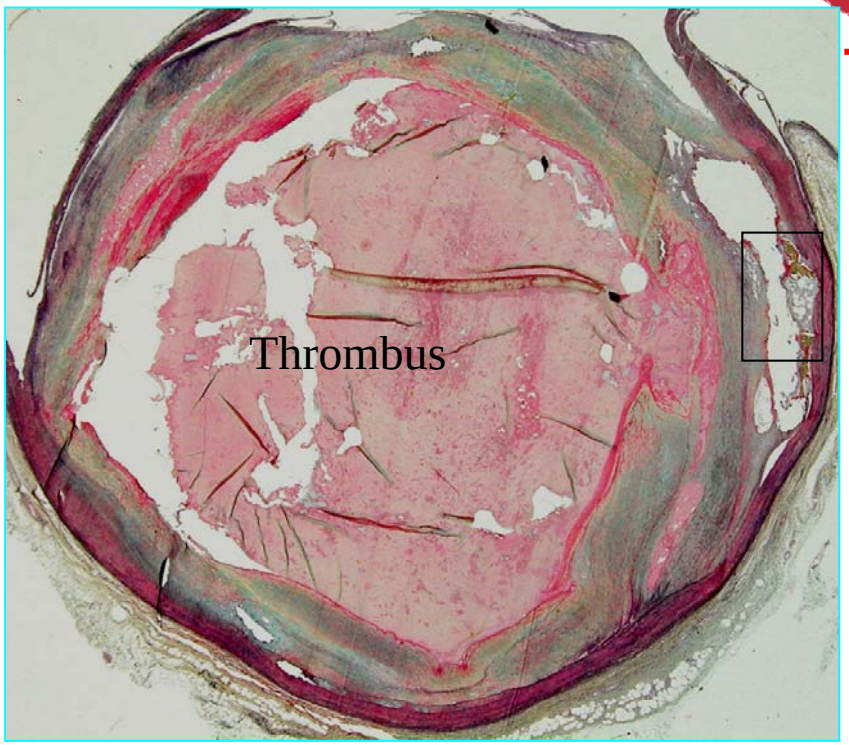
Restenosis Rates after Percutaneous Interventions

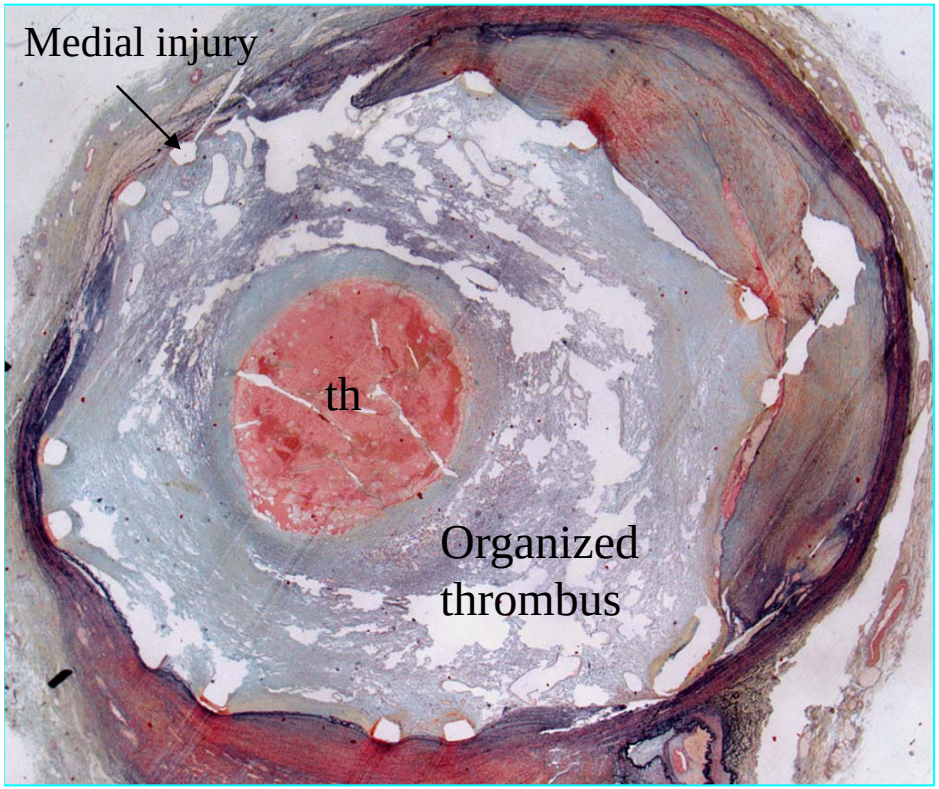
Artery	*Restenosis at 6 -12 months*
Coronary	
BMS	18 - 30 %
DES	0 -10 %
Carotid	5 - 8 % (BMS)
Iliac	
Balloon angioplasty	6 - 41 %
BMS	3 - 32 %
SFA, Poplitial	
BMS	8 - 44 %
DES	0 - 10 % (23% at 2 years)
Below the knee	
BMS	21 - 79 %
DES	4 - 37 (SES), 77 (PES) %

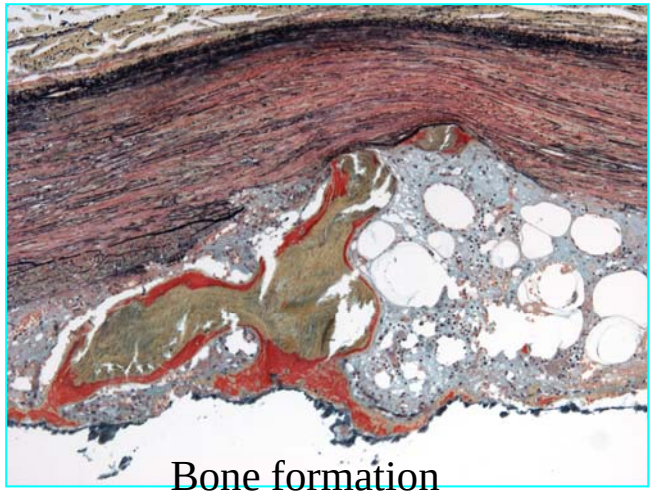
Modified from Deiter RS, and Laird JR. Endovascular Today 2004

45 yrs WF with Left common iliac artery stent placement 2.5 yrs before death









Lower Extremity Artery Stenting

Procedure

- ✓ Long lesion (require overlapping stent)
- ✓ Under-expansion or incomplete apposition due to calcification

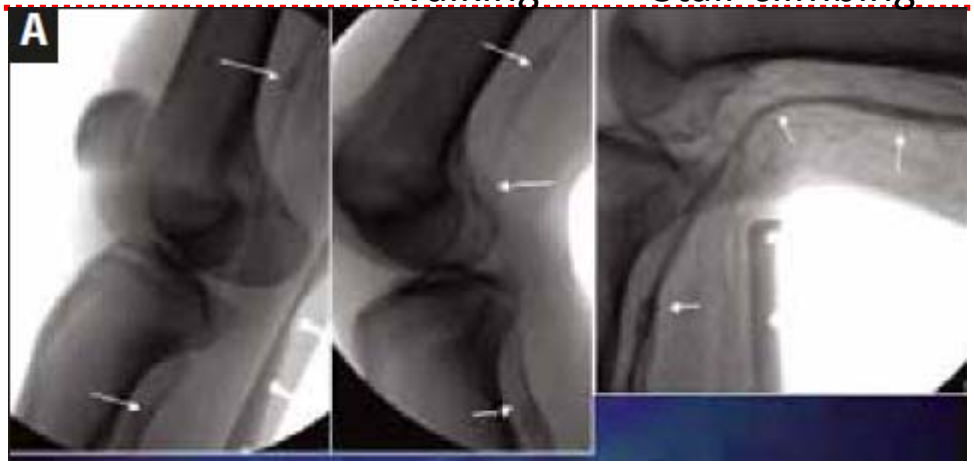
Results

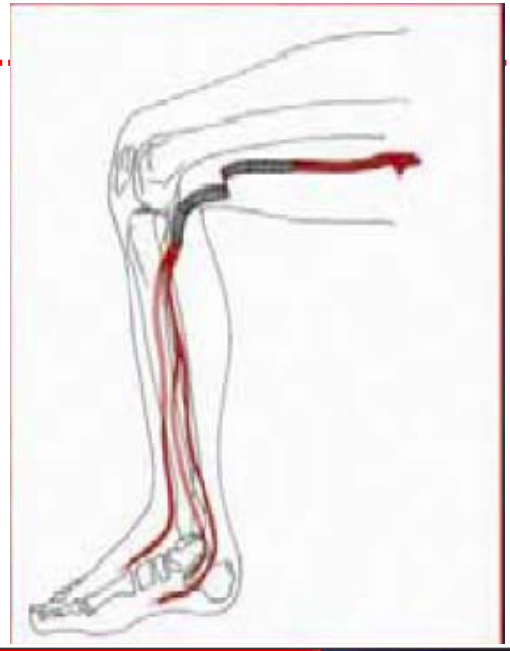
- ✓ Enhanced delayed healing
- ✓ High incidence of restenosis or re-occlusion

Biomechanical forces in the femoropopliteal stenting

Hip flexion/Knee bending (degree)

0/0 70/20 Walking 90/90 Stair climbing

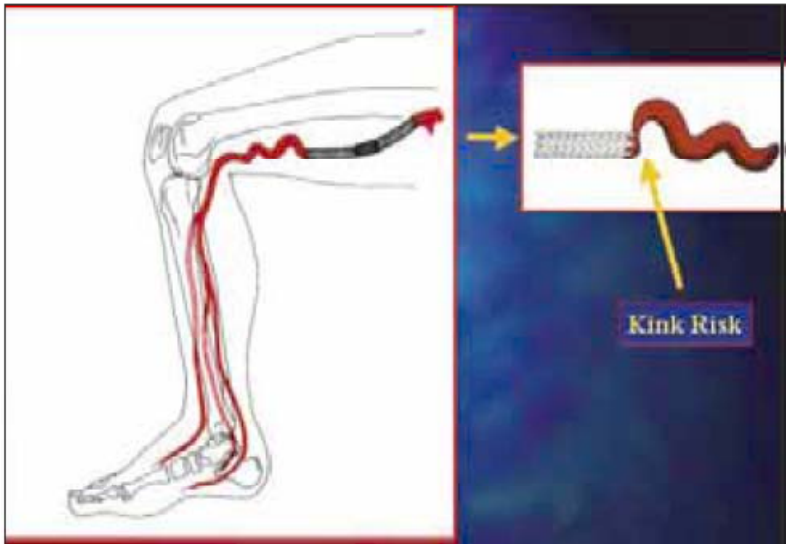




- No elongation
- Torsion was not critically evaluated - not observed
- Shortening and bending - major changes

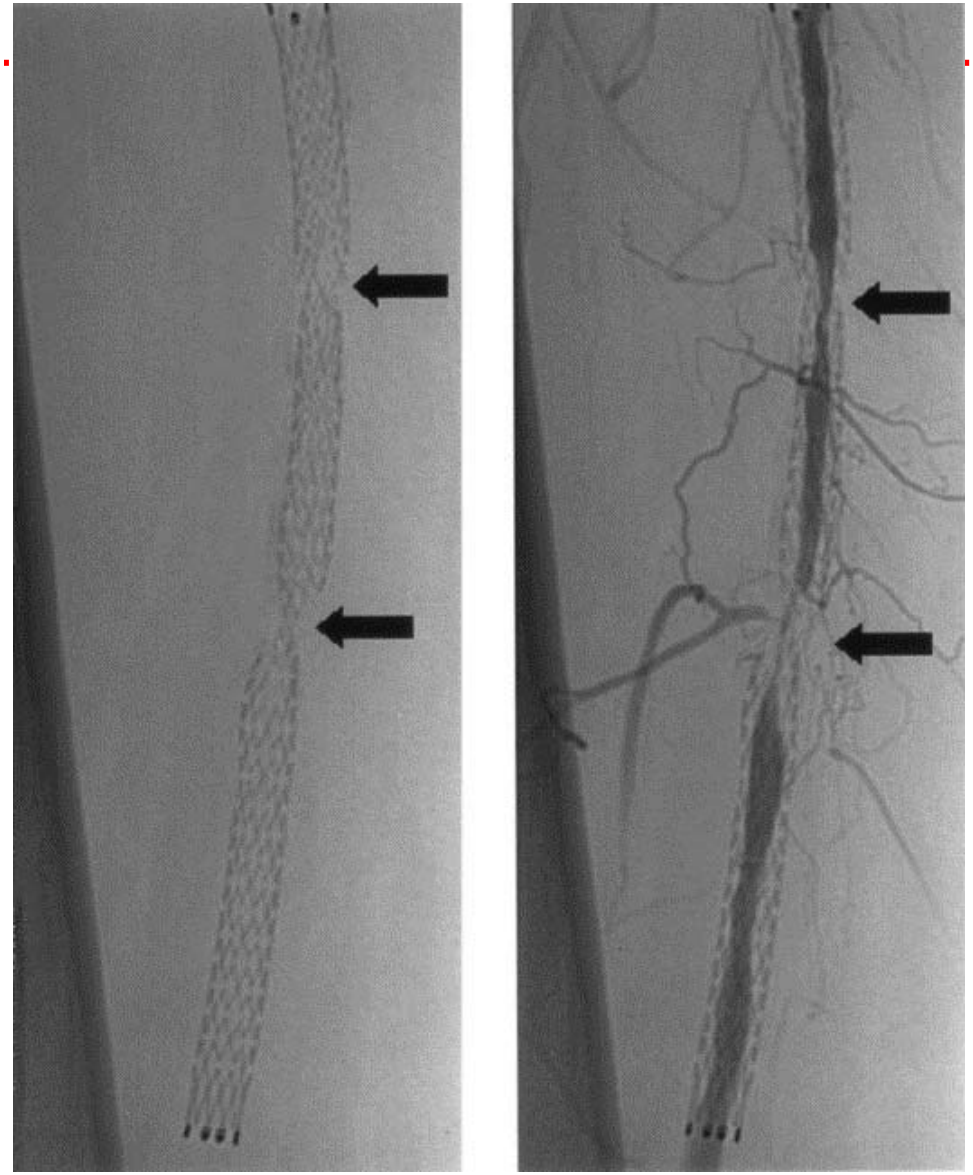
	Mid- SFA	Distal SFA	Popliteal	Popliteal Bending Radius/Angle
70/20 (Shortening)	5%	14%	9%	
90/90 (Shortening)	10%	23%	14%	13 mm 63°

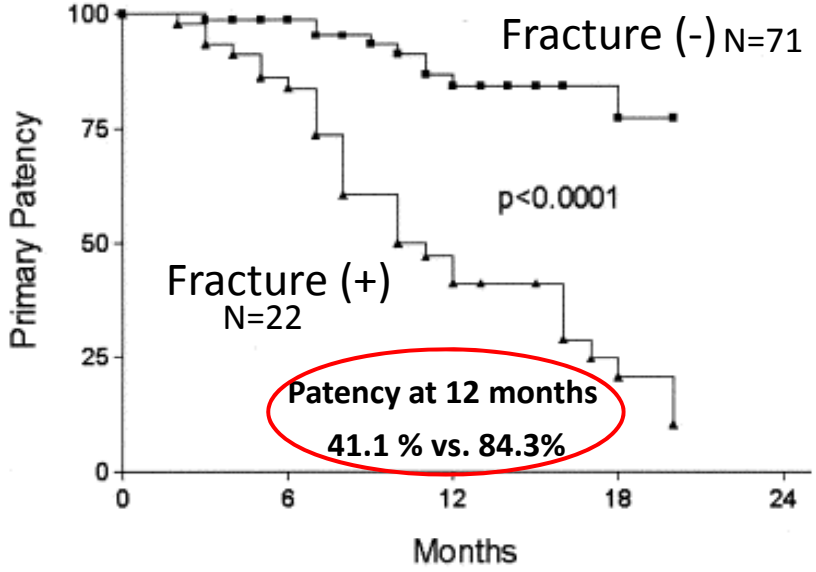
Average values based on seven cadaver, 14 limb study

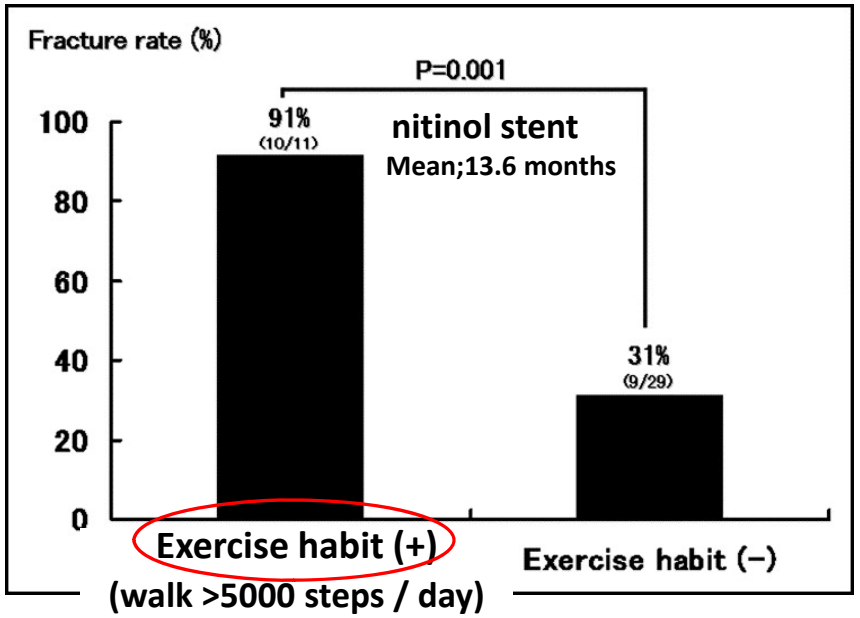


Smouse, HB. et al Endovascular Today, June 2005

Stent fracture and Restenosis in SFA and popliteal arteries





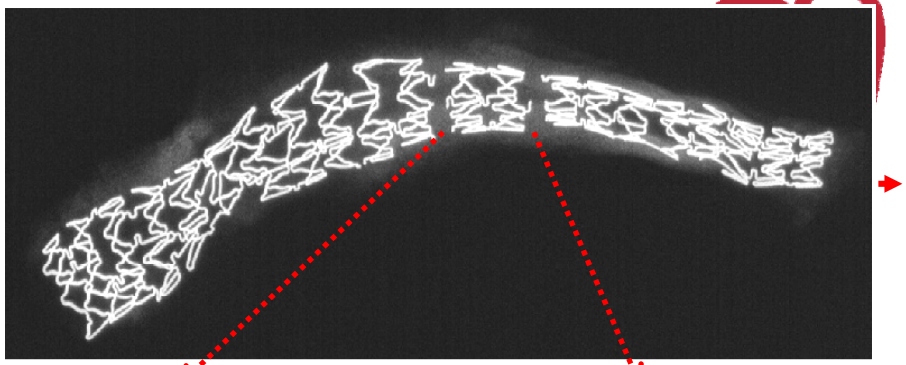


Scheinert, D et al, JACC 2005

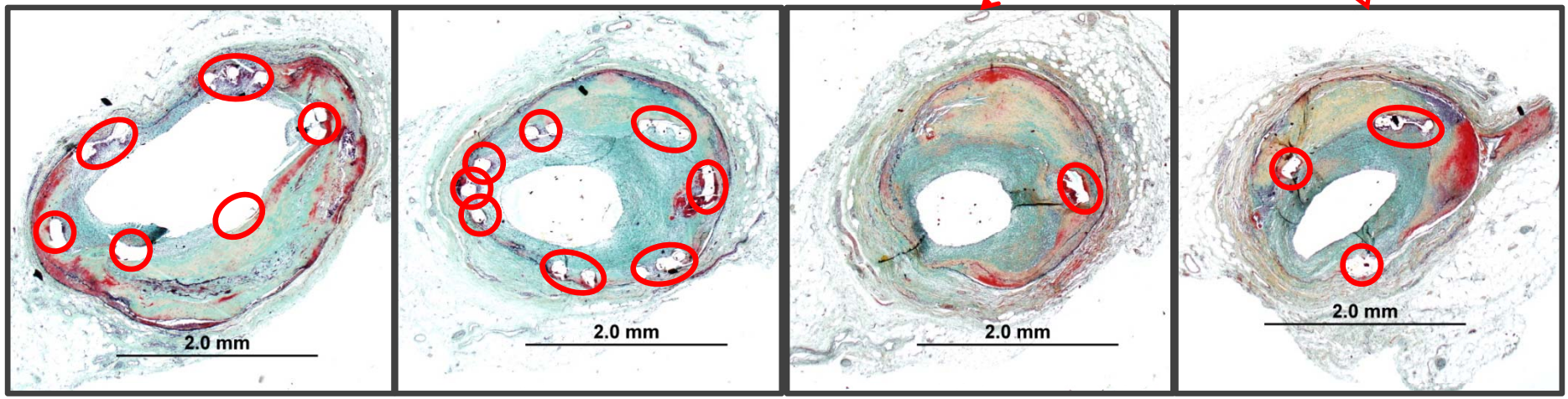
Iida, O et al, AJC 2006

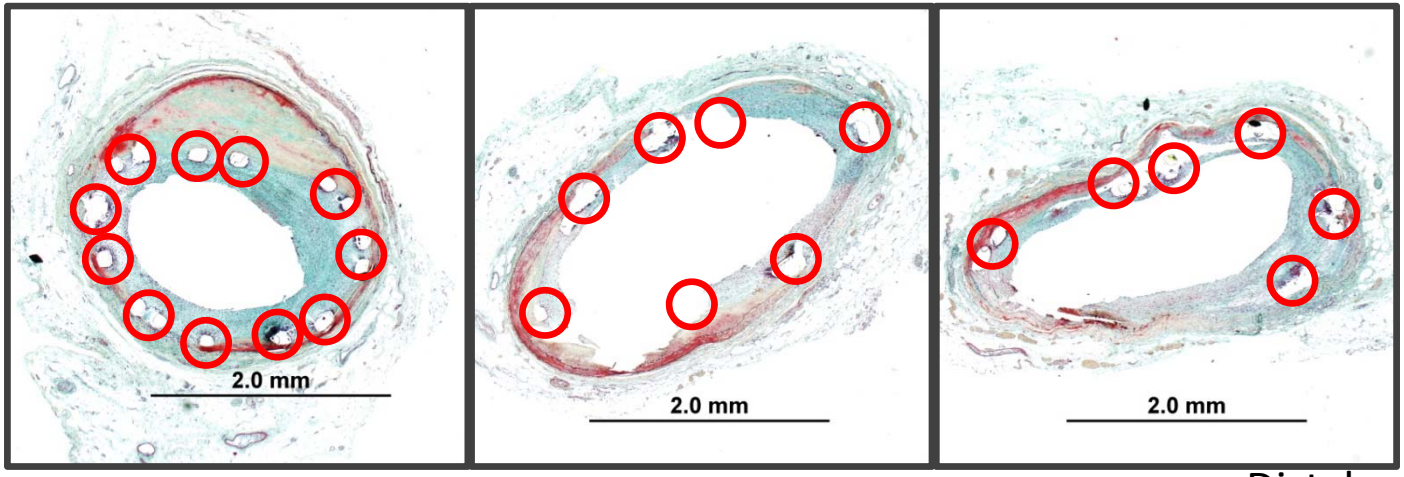
DES Restenosis Associated with Stent Fracture (Coronary)

EES implanted in LOM, 6 months



Proximal





Distal

51 year old male, complained of shortness of breath then became unresponsive.

New Strategies for the Treatment of Atherosclerosis

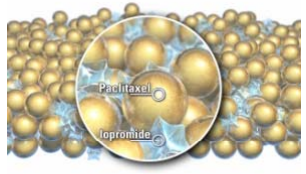
- **Drug Eluting Balloon**
  - has no metal struts that may cause continuous stimulation to the vessel and lead to sustained inflammation.
  - has potential ability to evenly deliver the drug to the vessel wall. However, the best pharmacokinetics and the best formulation of DEB remain unknown.
  - acute or subacute recoil may occur and dampen its efficacy especially in highly calcified arteries.

- **Self-expanding DES**
  - causes less injury and less inflammation on the vessel at the time of deployment.
  - is flexible, and has a lasting resistance to the fracture that is associated with stent failure.
  - maintains the radial force and prevents the occurrence of recoil in long-term.
  - However, the advantage above will be dampened in the presence of heavy calcification as frequently observed in peripheral arteries.

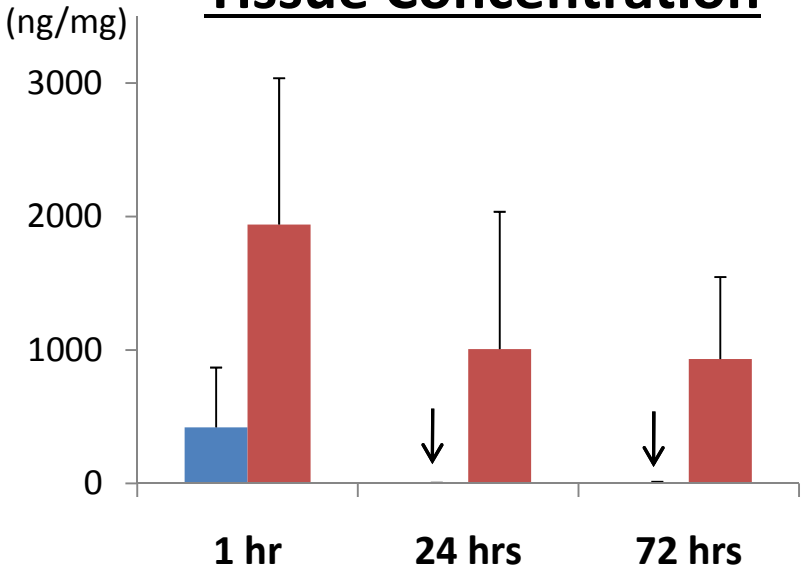
Drug deliver of DEB

PTX only

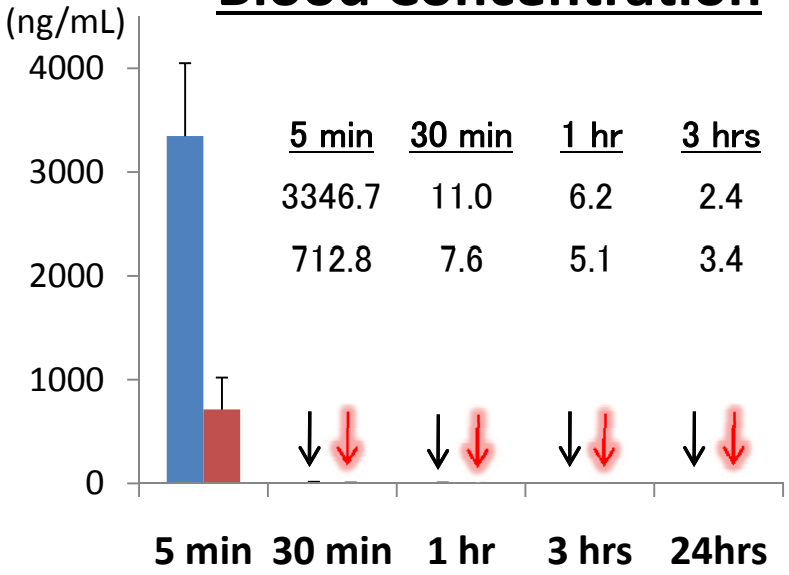
PTX + Iopromide (SeQuent)



Tissue Concentration



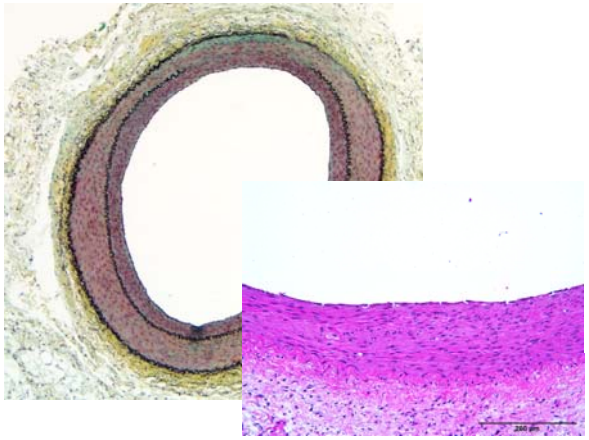
Blood Concentration



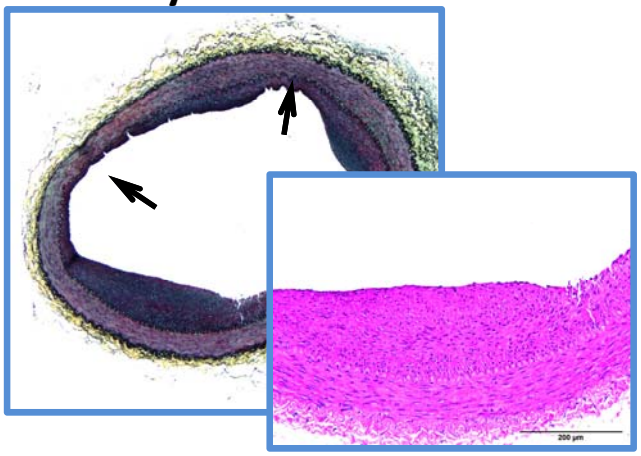
5 min	30 min	1 hr	3 hrs	24 hrs
3346.7	11.0	6.2	2.4	0.4
712.8	7.6	5.1	3.4	1.8

Non-atherosclerotic Rabbit Iliac Model – 28 days

POBA

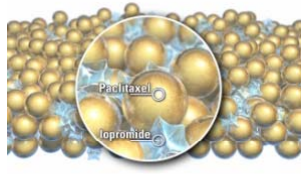


PTX only



PTX+Iopromide

Vascular Response to DEB

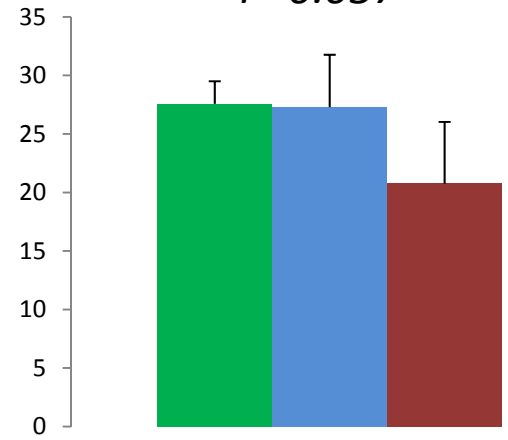


At 28-days following treatment in Rabbit Iliac model

POBA **PTX only** **PTX + Iopromide (SeQuent)**

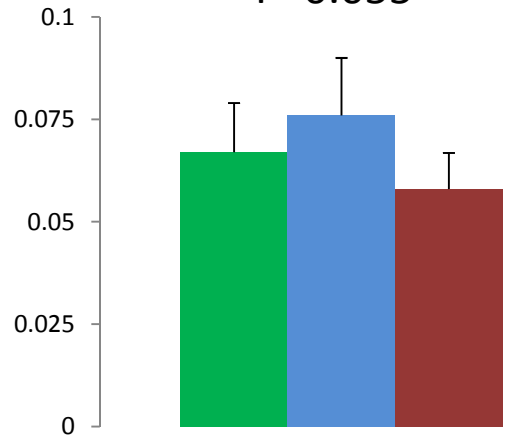
%Stenosis

P=0.037



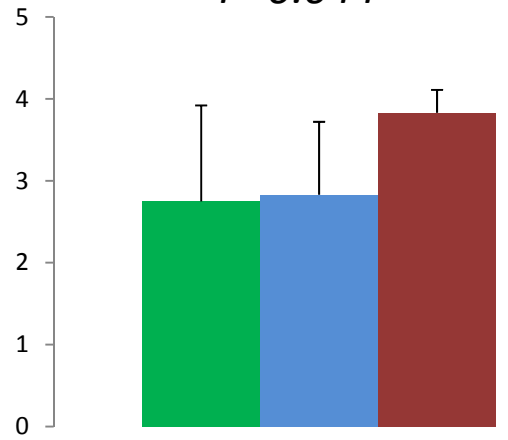
Neoint THK

P=0.055



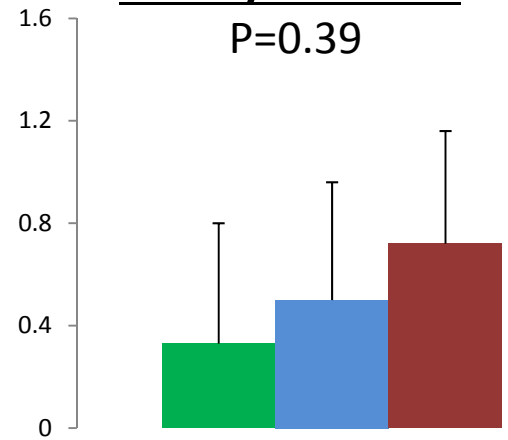
Media SMC Loss

P=0.044



Fibrin/Platelets

P=0.39



Intima-Media Inf

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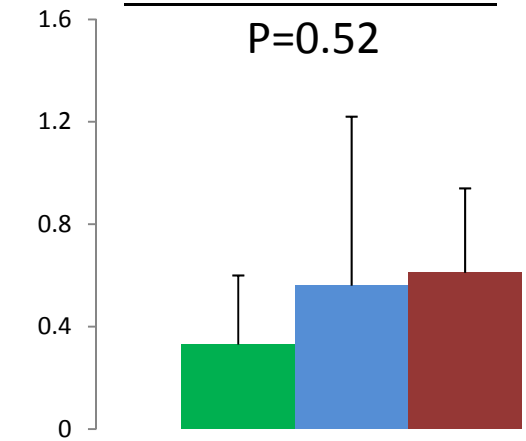
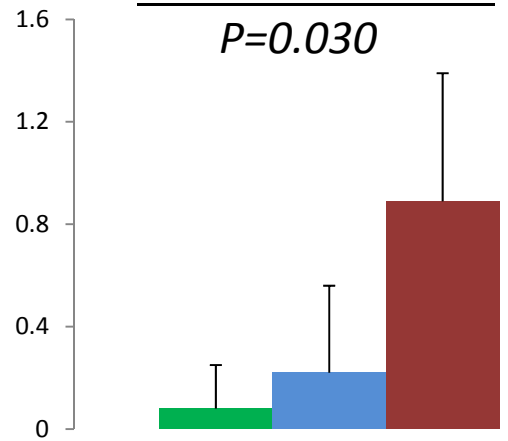
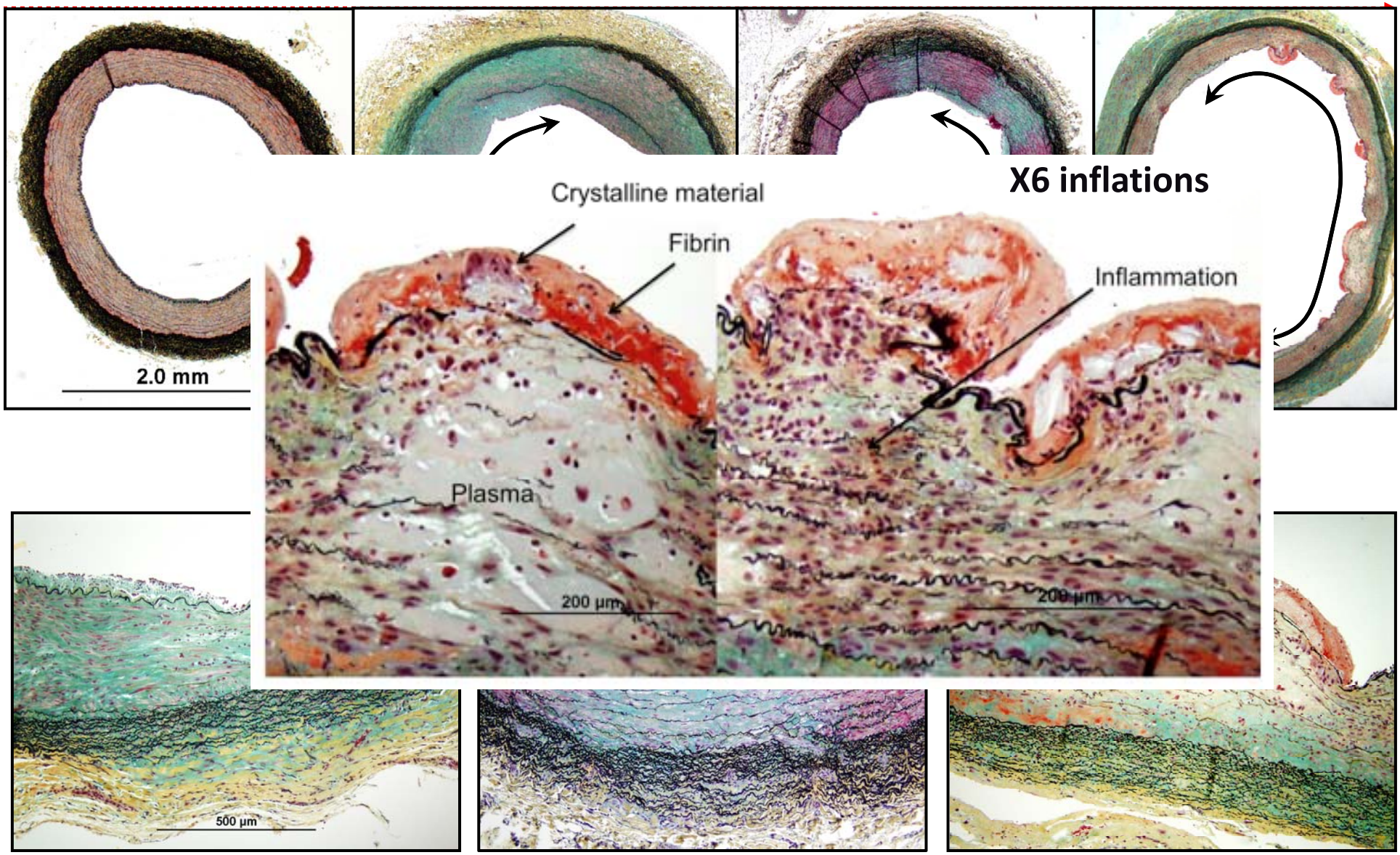


Endothelial Loss

P=0.030



Dose-dependent Changes in Iliofemoral Arteries Following SeQuent DEB treatment at 14 days



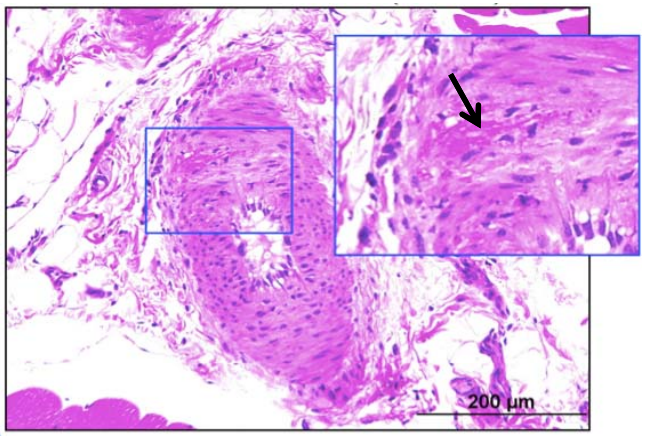
Downstream vascular change following DEB treatment

At 7-days

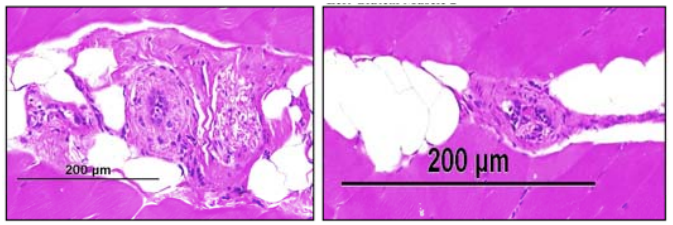
Vascular Changes in the Coronary Band of the Hoof

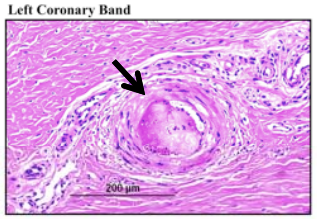
REPEAT TREATMENT

Fibrinoid Necrosis

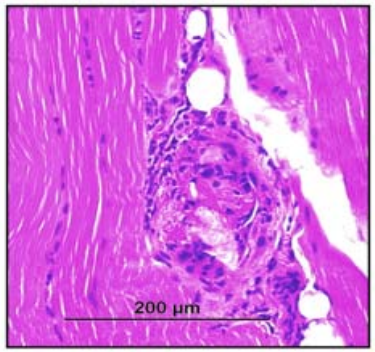


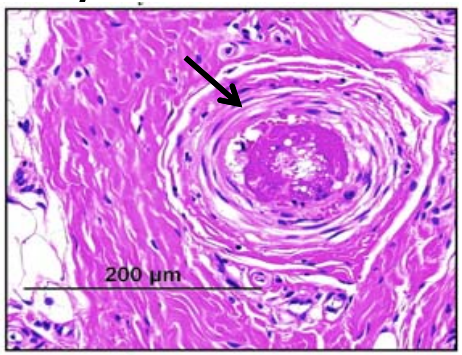
Platelet emboli





Fibrin Thrombus with Crystalline material

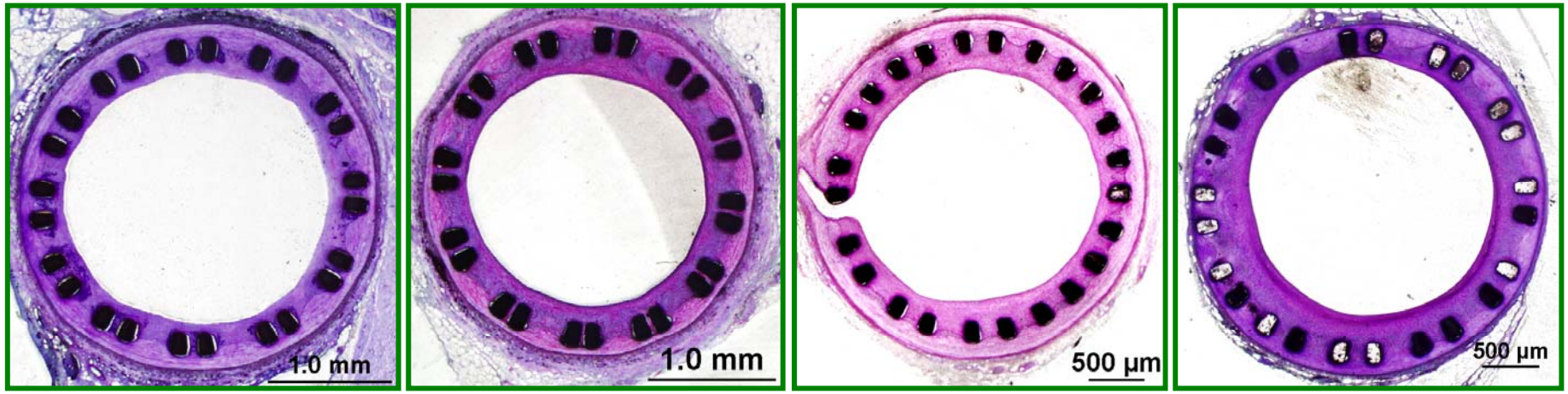




Stable Neointima formation in Access BA9 (Devax) and late catch up of Neointimal Formation in Cypher stents

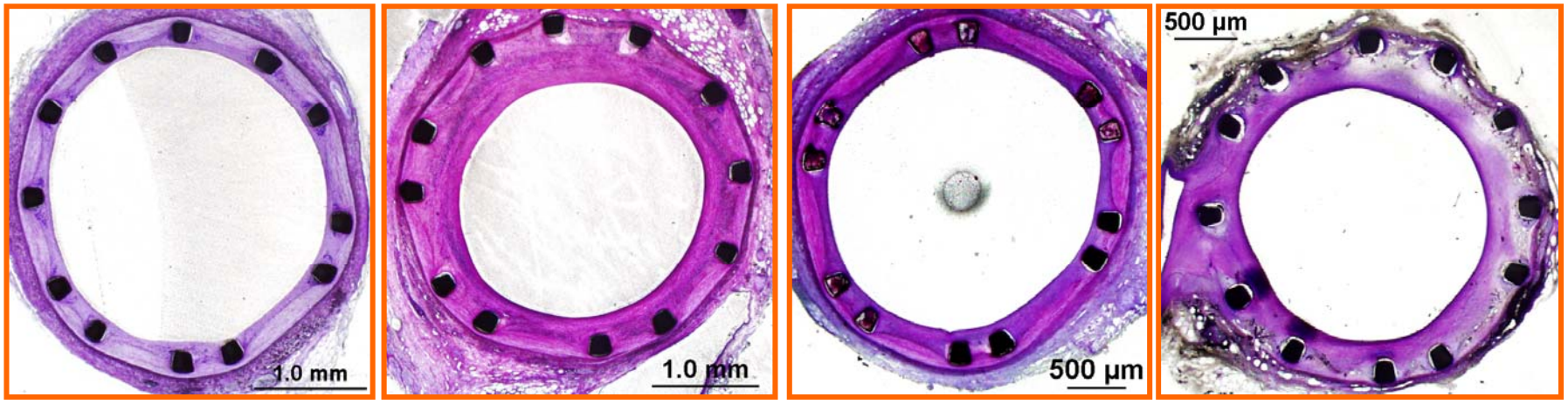
Axxess BA9

30 Days | 90 Days | 180 Days | 365 Days

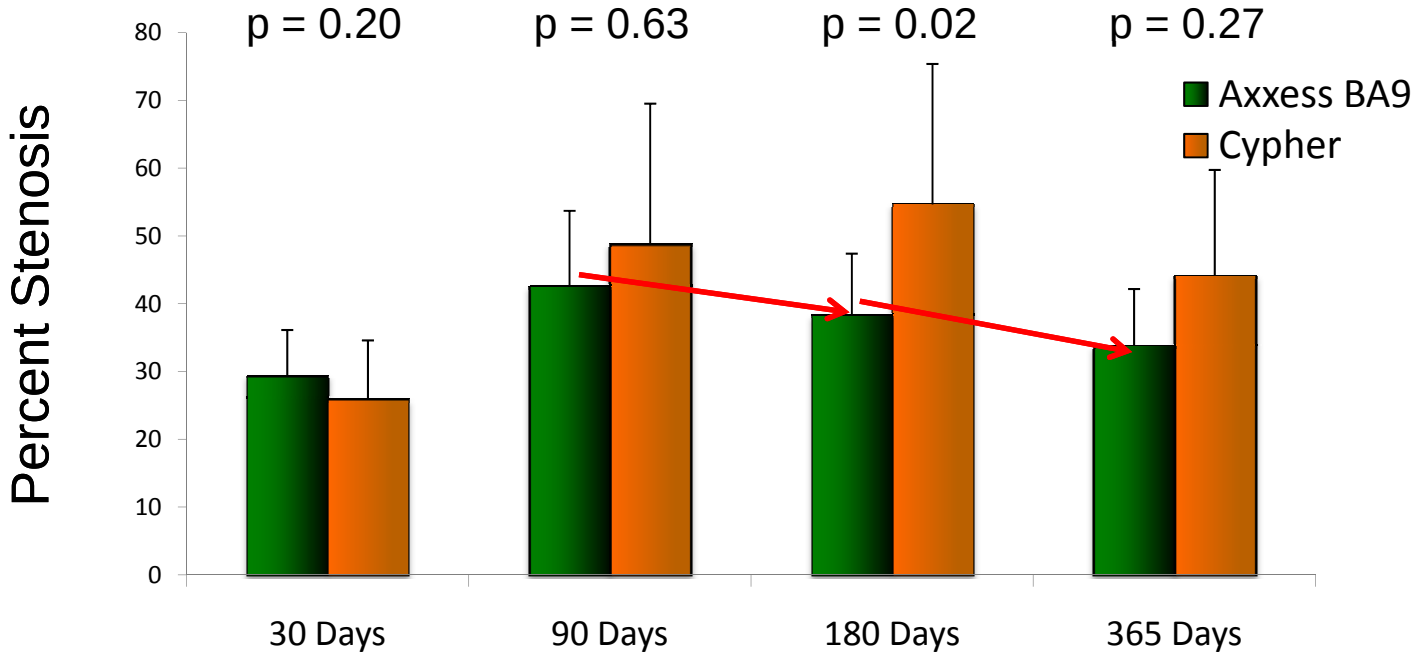


Cypher

30 Days | 90 Days | 180 Days | 365 Days



Percent Stenosis and Injury in Axxess BA9 Self-Expanding Stent v. Cypher



Injury score

	30 days	90 days	180 days	365 days
Axxess BA9	0.039±0.029	0.60±0.68	0.080±0.097	0.31±0.43
Cypher	0.44±0.35	1.53±0.94	1.68±1.10	1.59±0.84
	p= 0.007	p= 0.003	p= 0.005	p= 0.006

Speculative Differences Between DEB and Self-expanding DES vs. balloon expandable DES

	Balloon expandable DES	Drug-eluting Balloon	Self-expanding DES
Injury & acute inflammation at PCI	3 to 4+	3 to 4+	1 to 2+ (w/o post dilatation)
Drug deliverability	3 to 4+	1 to 3+ (depend on solvent)	3 to 4+ (even distribution)
Resistance to Recoil	3 to 4+	0	>5+
Reaction to polymer	2 to 3+	0	2 to 3+
Metal struts stimuli	2 to 3+	0	3 to 4+
Neointimal Growth	1 to 2+	2 to 3+ (incomplete drug distribution)	1 to 2+
Late luminal narrowing (restenosis)	2 to 3+ (fracture / late catch-up)	3 to 4+ (acute - late recoil and late catch-up)	1 to 2+ (continuous expansion)
Uncovered strut	2 to 3+	0	1 to 2+ (w/o post dilation)
Endothelial recovery	Delayed (> 1 year)	Faster (6 to 9 months)	Delayed (> 1year)
Risk of Late thrombosis	2 to 3+	0 to 1+	1 to 2+ (larger luminal area)

Summary

- New technologies such as drug-eluting balloon (DEB) and self-expanding DES has potential advantages that will complement the limitation of current DES technology.
- However, the improvement of DEB is still required to achieve better drug distribution and to prevent distal emboli.
- The sustained radial force of self-expanding DES overcomes the “late-catch-up” phenomenon of balloon expandable DES, however, the superiority will be diminished in the presence of heavy calcification.
- The innovation of biomaterial is further needed.

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