

Not all DCBs Are Created Equal: **Side by Side Pre-clinical Safety Evaluation of Leading DCBs**

Renu Virmani, MD
CVPath Institute Inc.
Gaithersburg, MD.
USA



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.

Consultant: 480 Biomedical, Abbott Vascular, Medtronic, and W.L. Gore.

Employment in industry: No

Honorarium: 480 Biomedical, Abbott Vascular, Boston Scientific, Cordis J&J, Lutonix, Medtronic, Merck, Terumo Corporation, and W.L. Gore.

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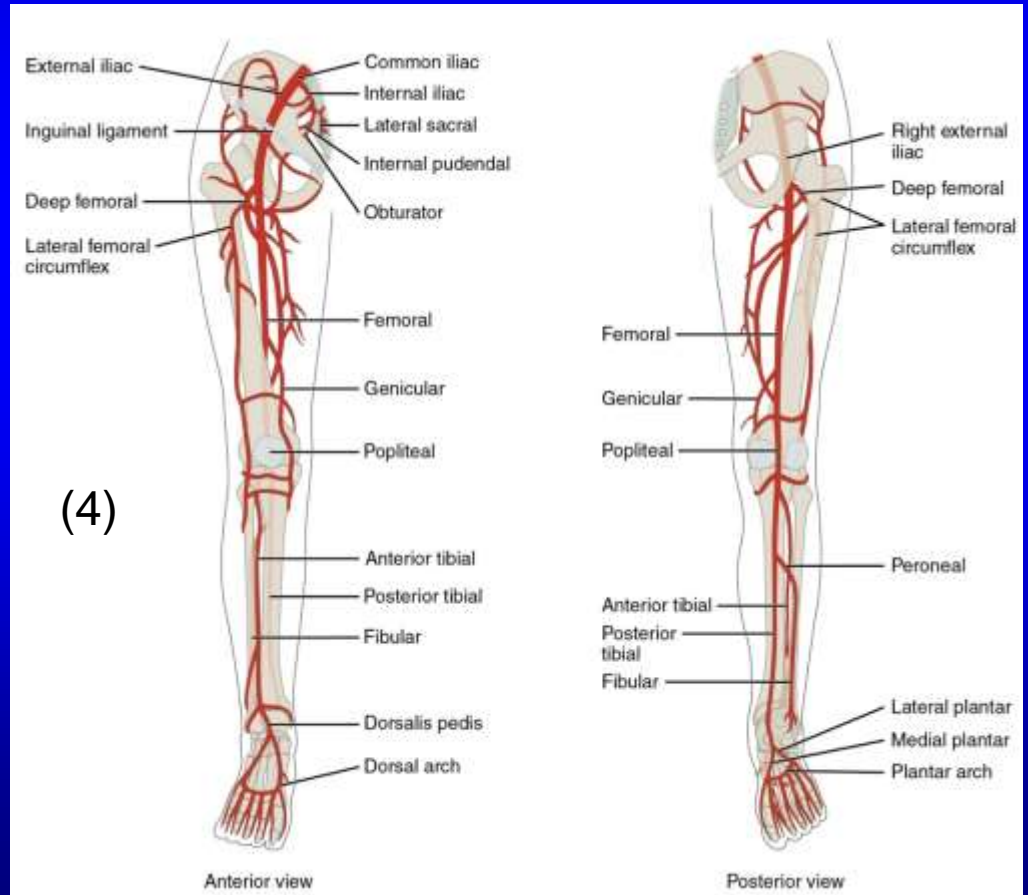
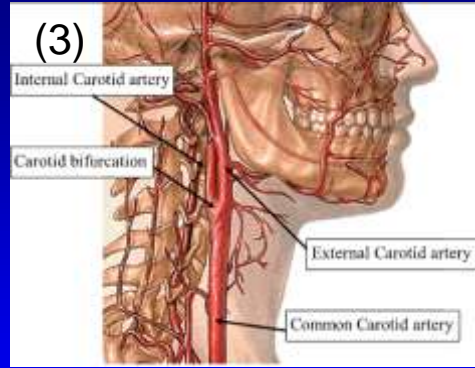
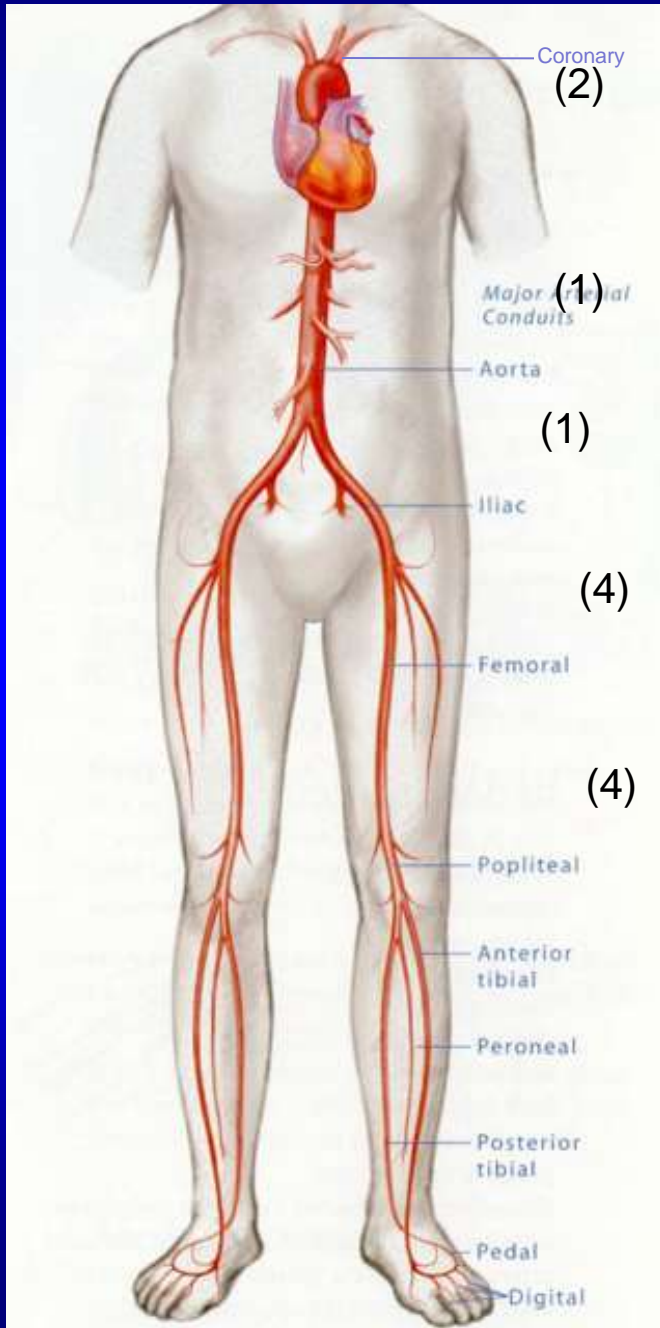
Owner of a healthcare company: No

Stockholder of a healthcare company: No

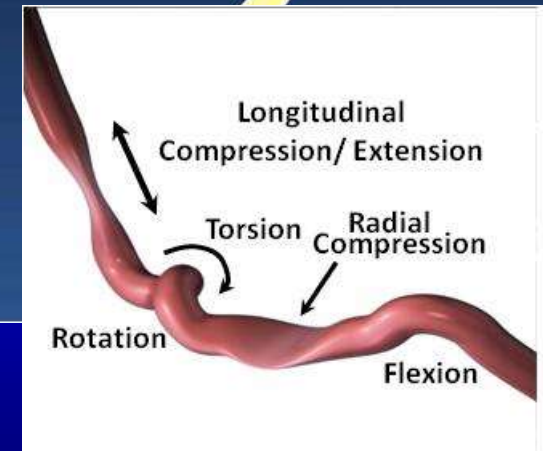
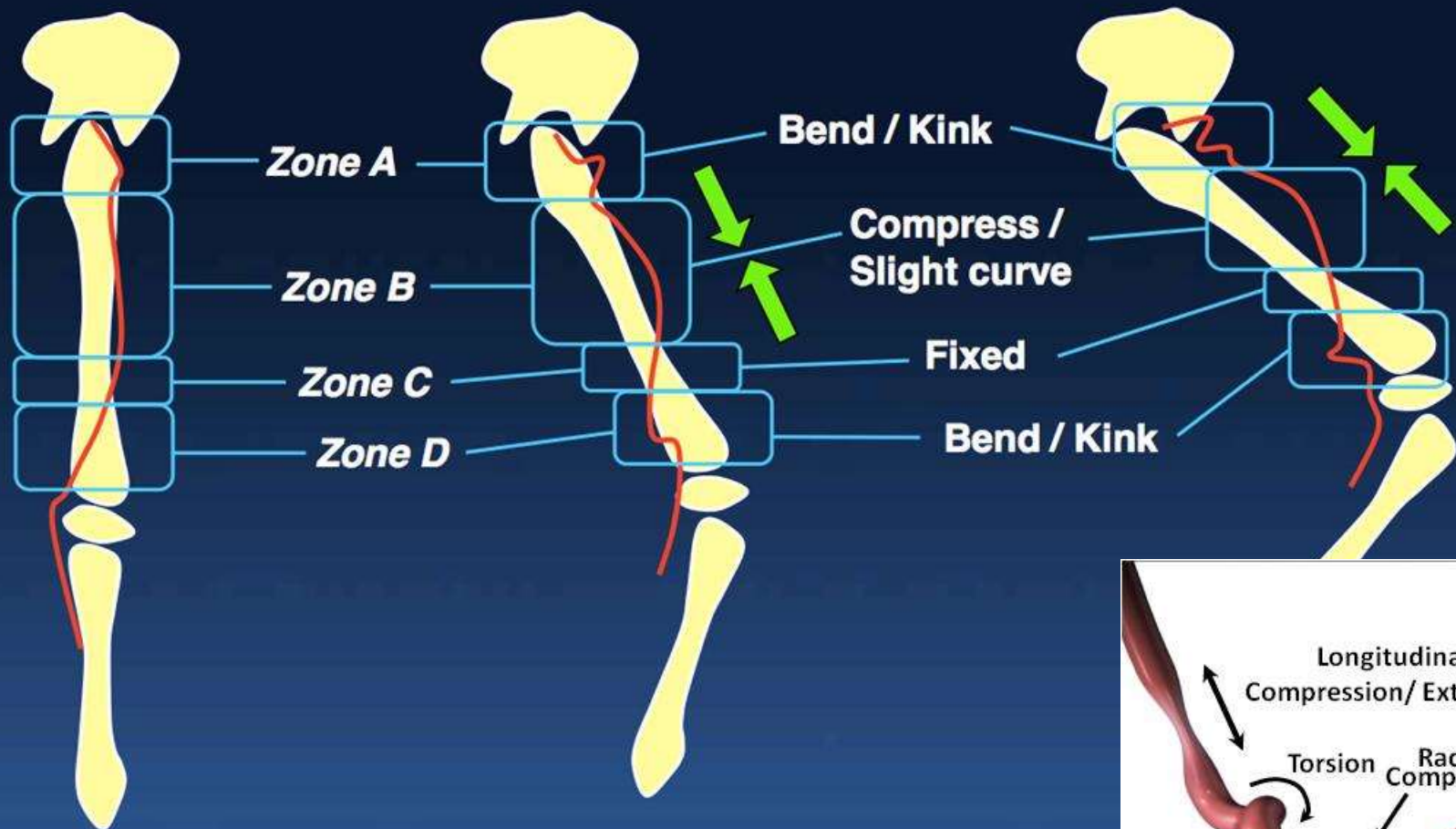
Disclaimer

- The physician has been compensated by C.R. Bard, Inc. to participate in this presentation. The presenter is a consultant of Lutonix, Inc. and Bard Peripheral Vascular, Inc.
- The opinions and data presented herein are for information purposes only, for the sole purpose of engaging in legitimate, scientific exchange regarding the LUTONIX® Drug Coated Balloon Catheter.
- Preclinical data are on file at CV Path and Lutonix, Inc.; results may vary depending on a variety of experimental parameters and may not necessarily be indicative of clinical performance
- Devices discussed are classified as Investigational in the United States, and are limited by Federal law to Investigational Use only.

Sites of Severe Atherosclerosis In order of Frequency

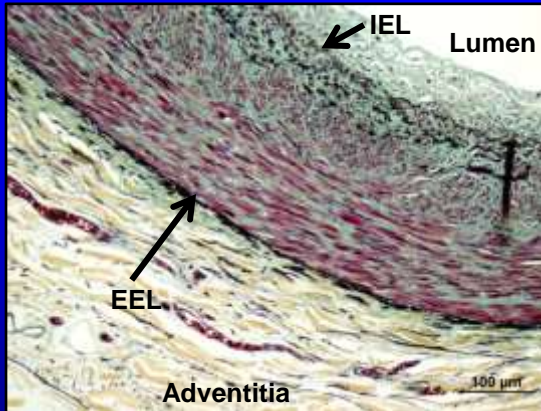
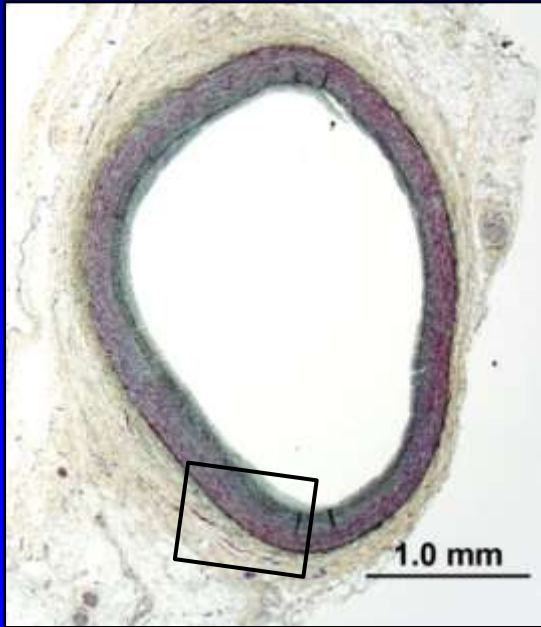


Femoro-Popliteal Artery Biomechanics

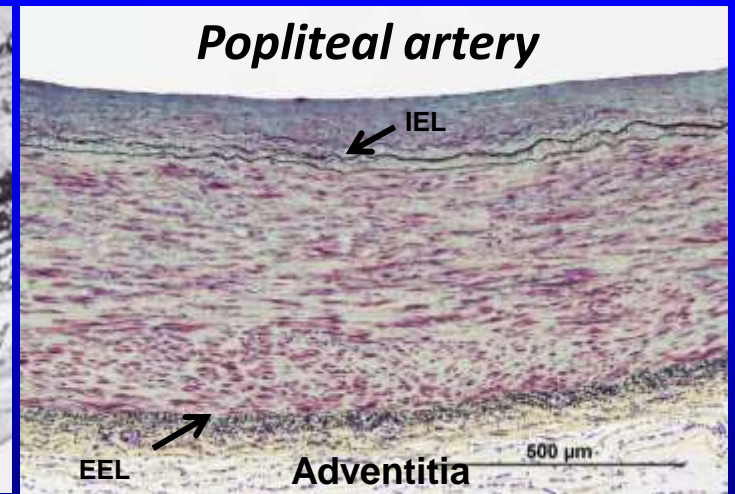
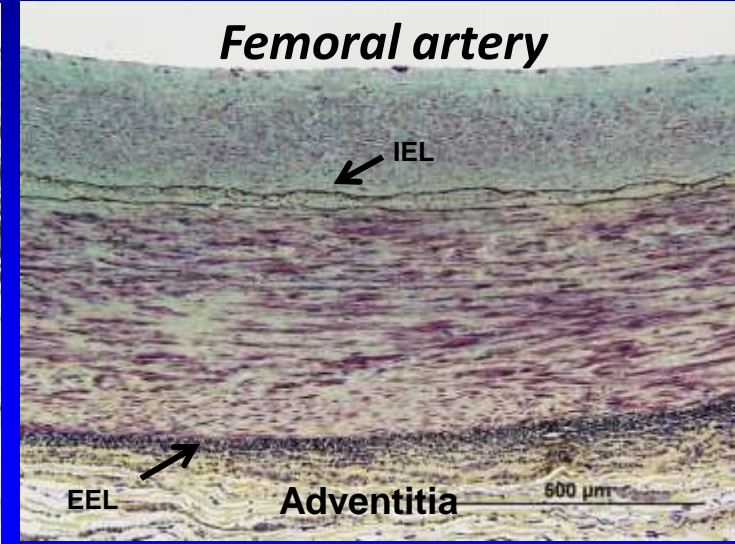
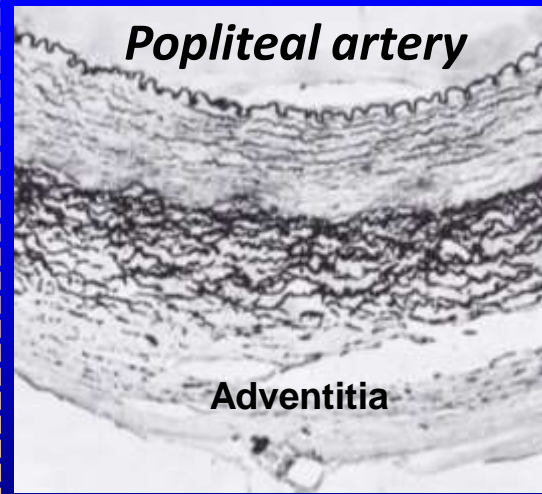
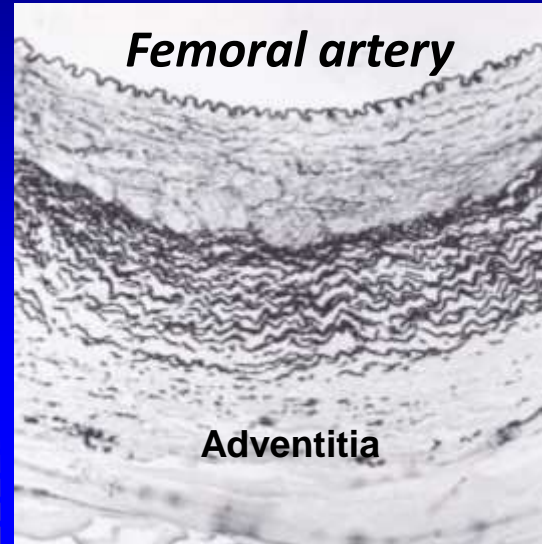


Blood Vessel Anatomy: Coronary vs. Peripheral Artery

Coronary artery



Peripheral artery



Otsuka F, et al. Mt Sinai J Med
2012;79:641-653.

Donald F.M. Bunce, II, D.O., Ph.D. ATLAS OF
ARTERIAL HISTOLOGY. 1974 by WARREN H.
GREEN, Inc., St. Louis, Missouri, USA.

Degree of Atherosclerosis and Score

Atherosclerosis in the large arteries was semi-quantitatively scored on a scale of 0–8

1

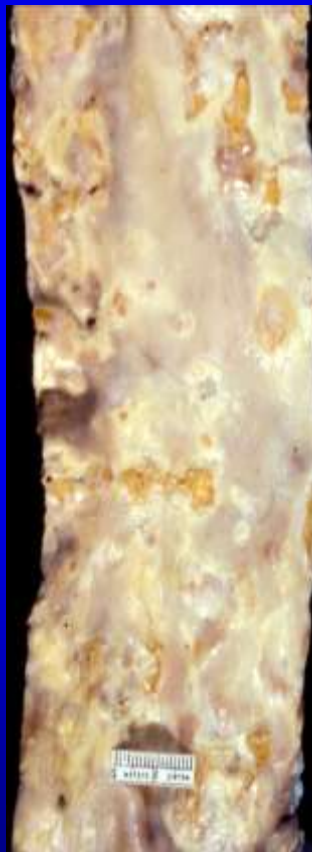
2

3

5

6

8



None

Minimal

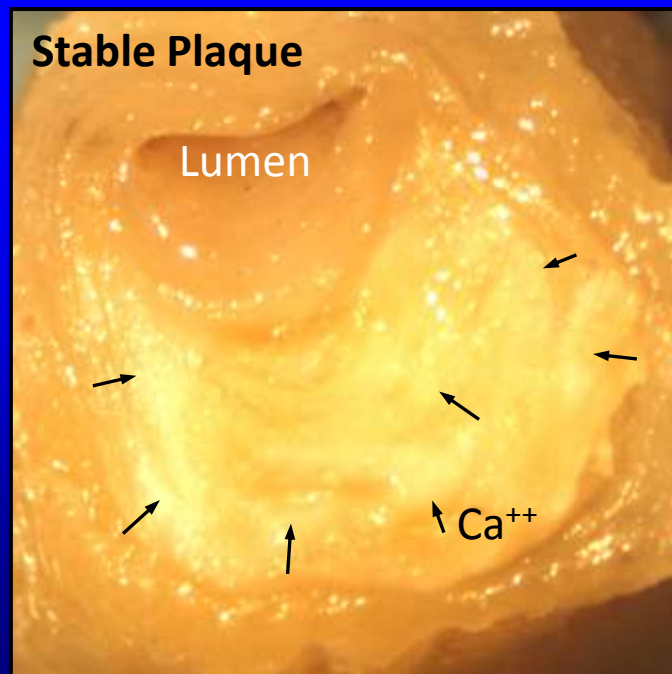
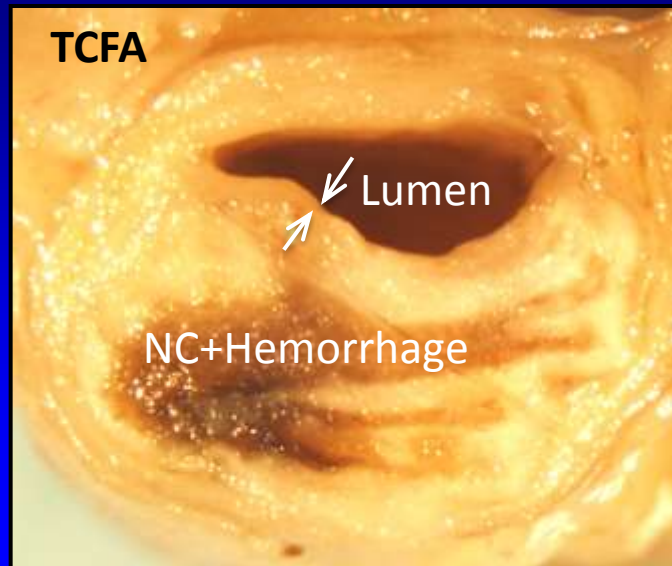
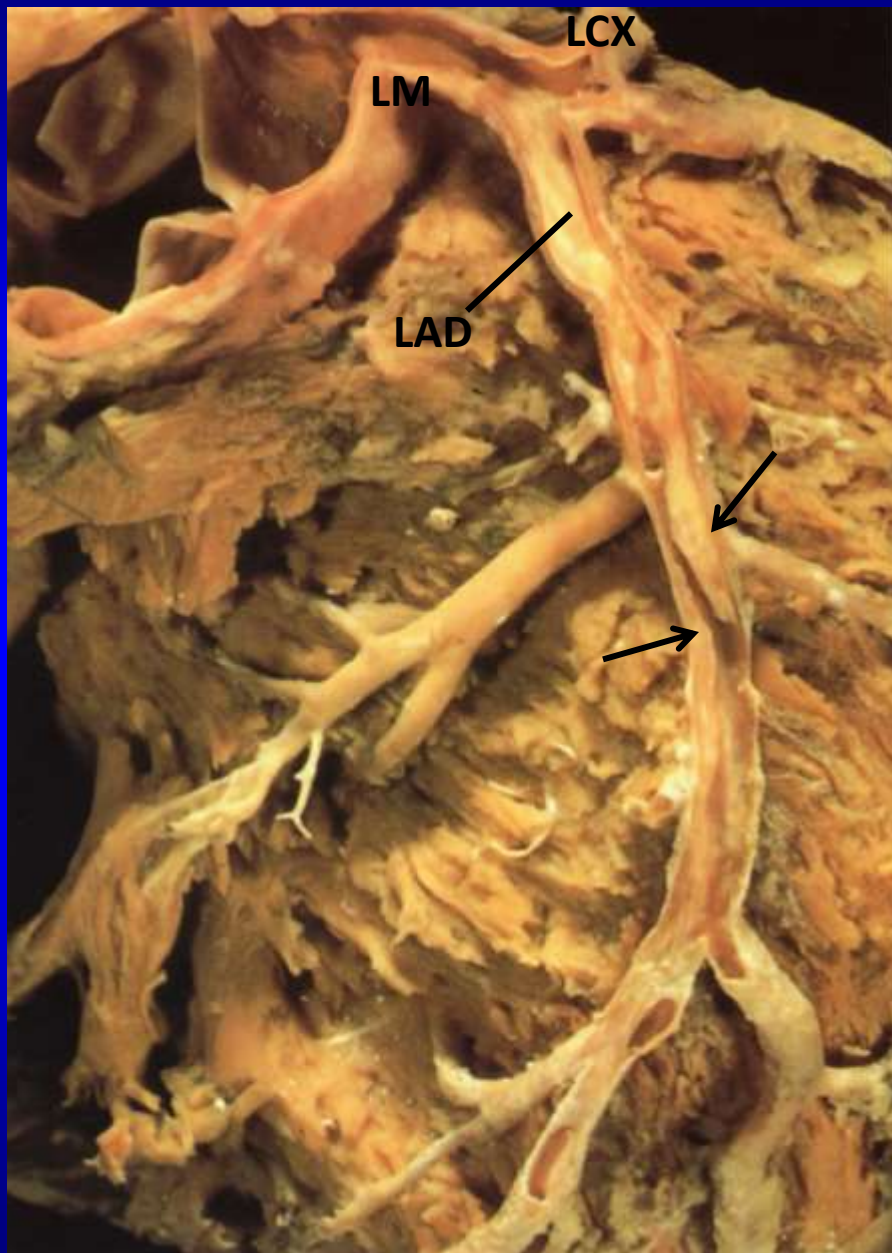
Mild

Moderate

Moderate/
Severe

Aneurysm/
Severe

Gross Pictures of Coronary Atherosclerosis



Gross Assessment of Extent of Coronary Artery Narrowing used to determine Coronary Stenosis Index

Score 0 to 5:

0 no sclerosis

1 with slight sclerosis

2 with 25% stenosis

3 with 50% stenosis

4 with 75% stenosis

5 with total occlusion

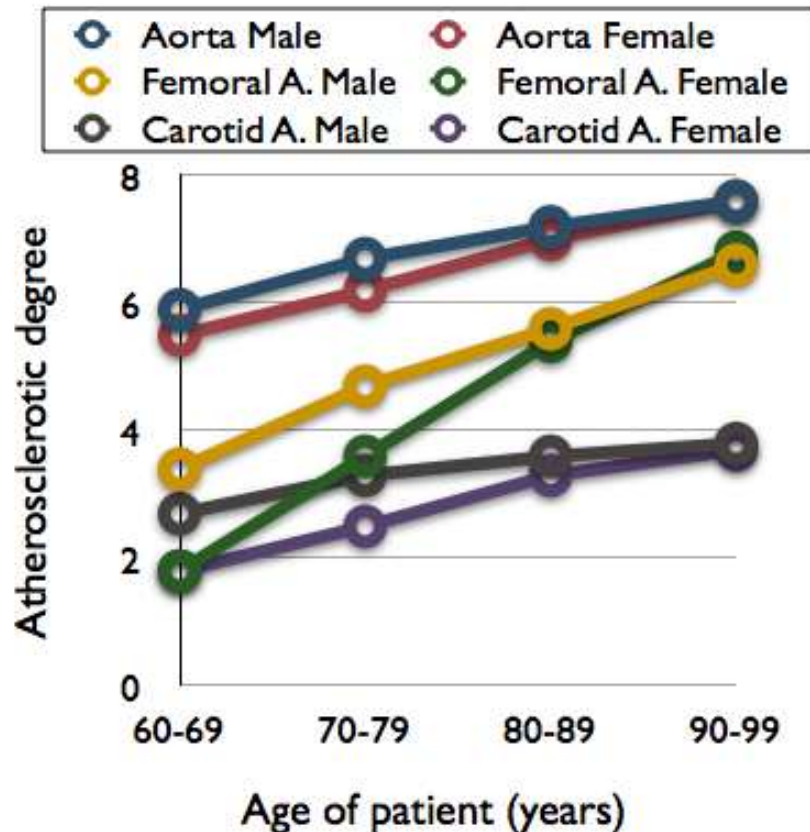
Coronary Stenotic Index (CSI)

was determined as the sum of the 3 major coronary arteries, and ranged from 0 to 15.

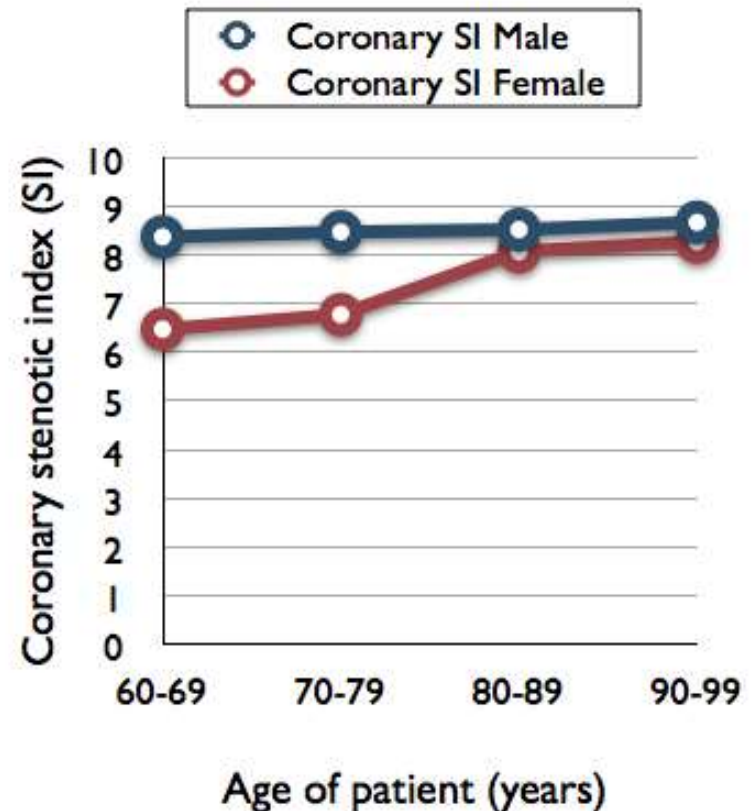


Gender-Specific Age-Related Changes of the Degree of Atherosclerosis in Various Vascular Beds

A



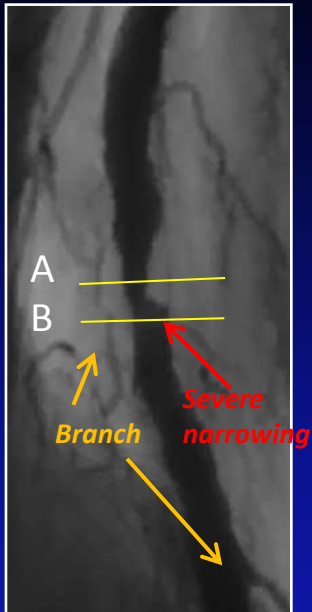
B



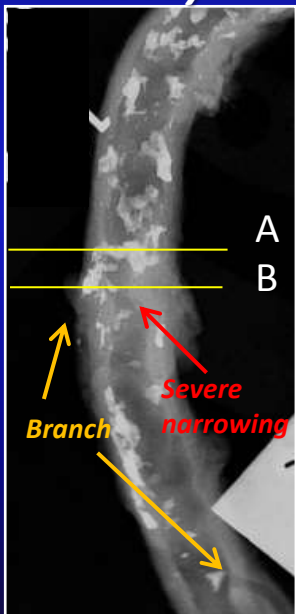
Atherosclerosis in the large arteries was semi-quantitatively scored on a scale of 0–8 according to the ratio of the atheroma-occupied area to the entire surface area: negligible (0 point, ratio = 0–1/20), minimal (2 points, 1/20–1/6), mild (4 points, 1/6–1/3), moderate (6 points, 1/3–2/3), and severe (8 points, 2/3–1) where as for coronary arteries it was based on stenosis. 1074 autopsy cases.

Intimal Calcification in Popliteal artery

Angiography



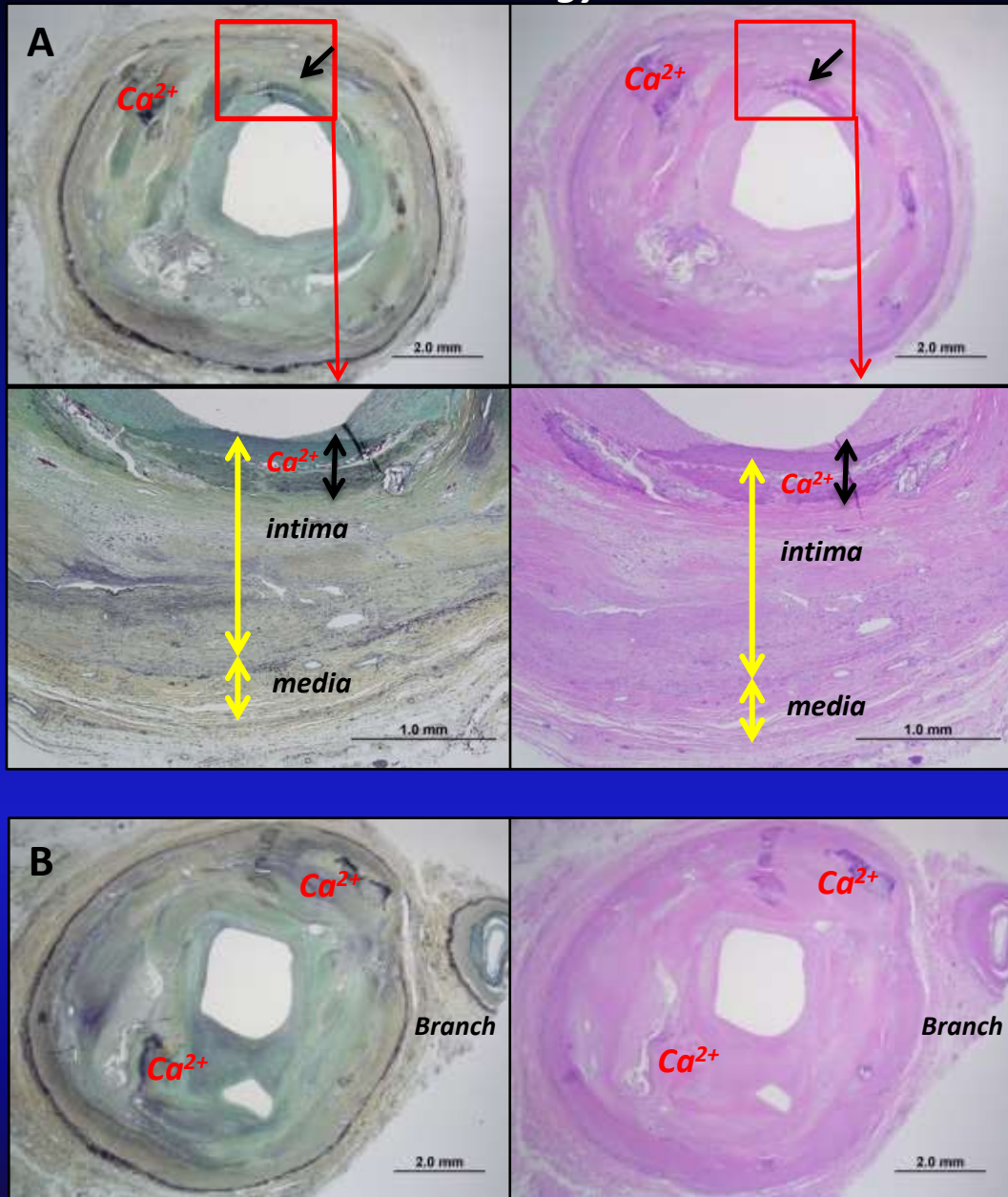
X-ray



CT



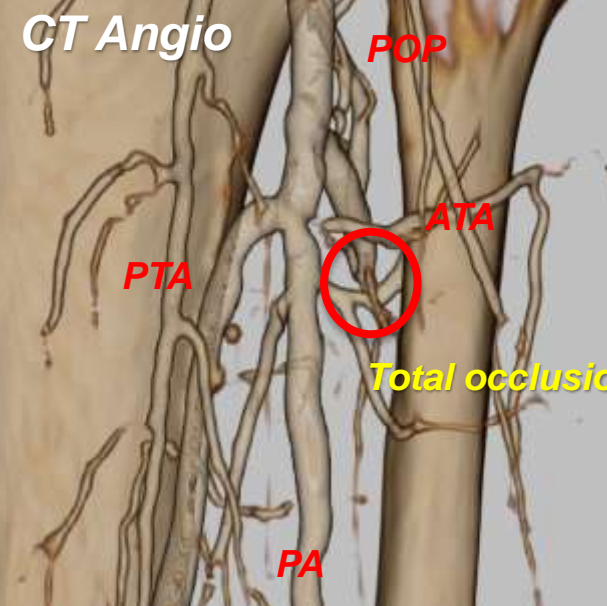
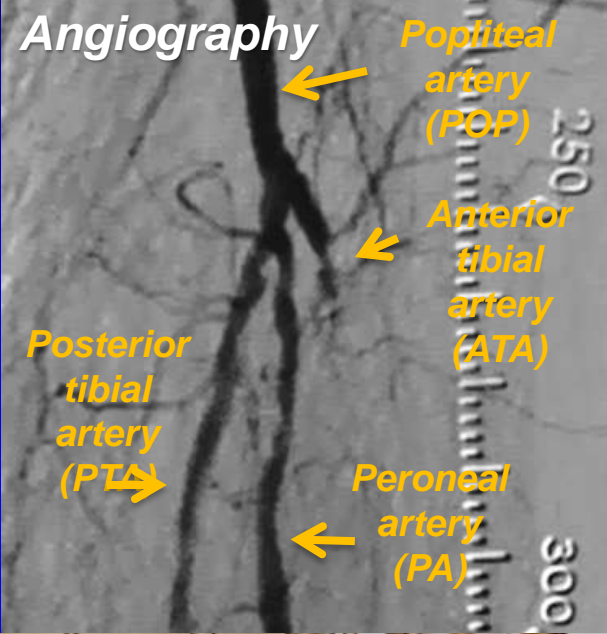
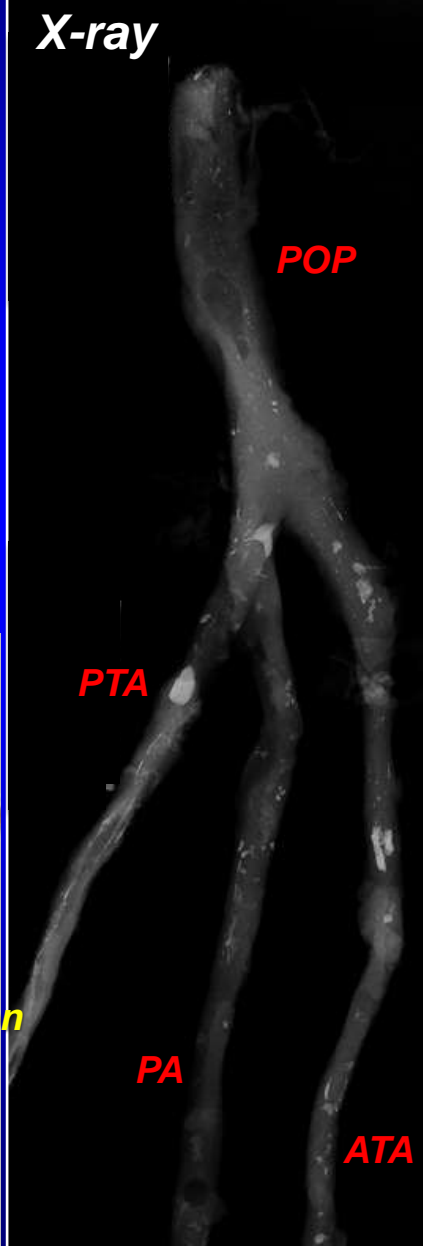
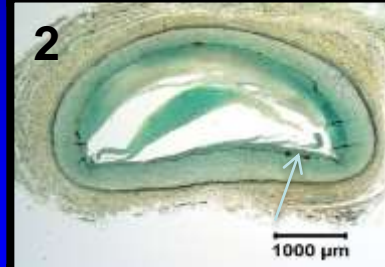
Histology



Peripheral artery disease (Below the knee)

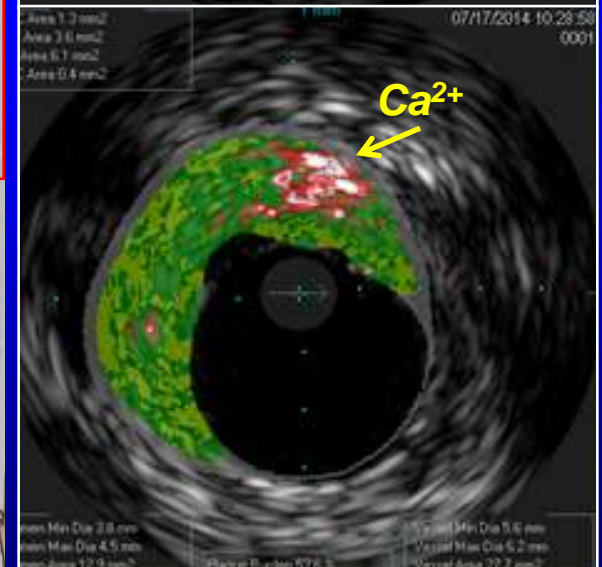
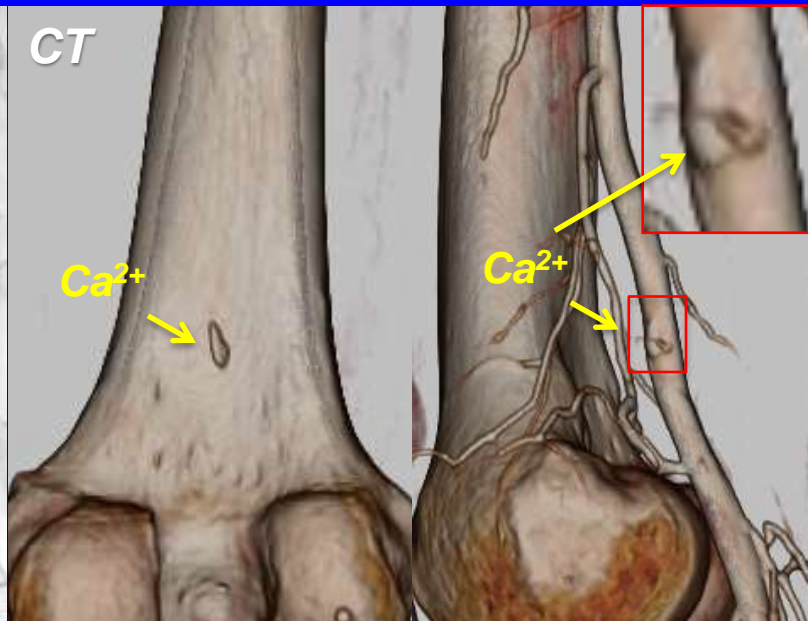
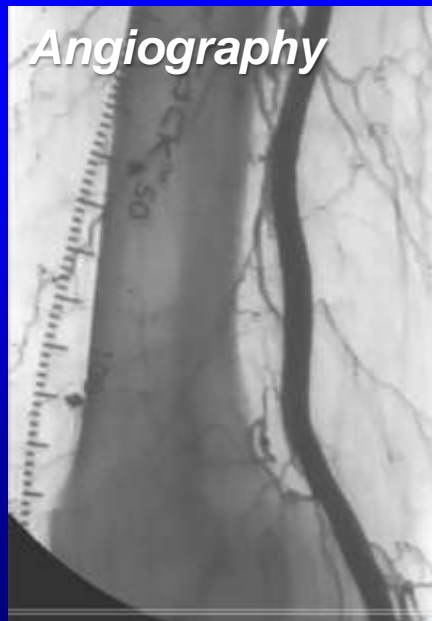
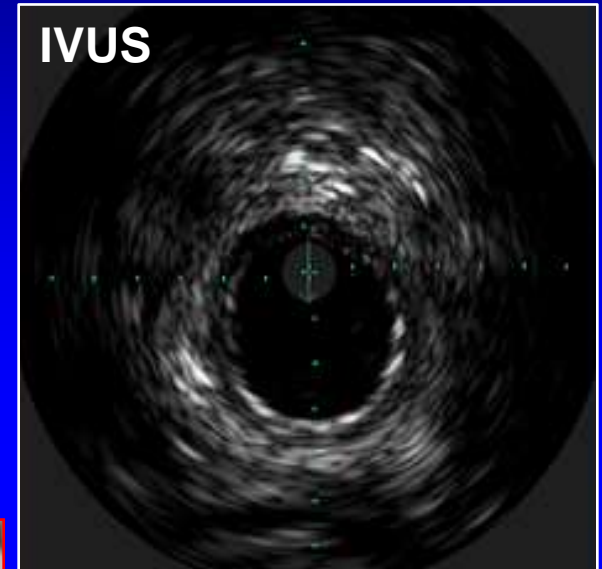
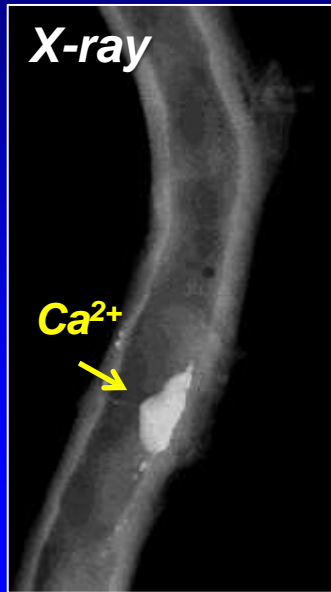
Anterior tibial

Proximal



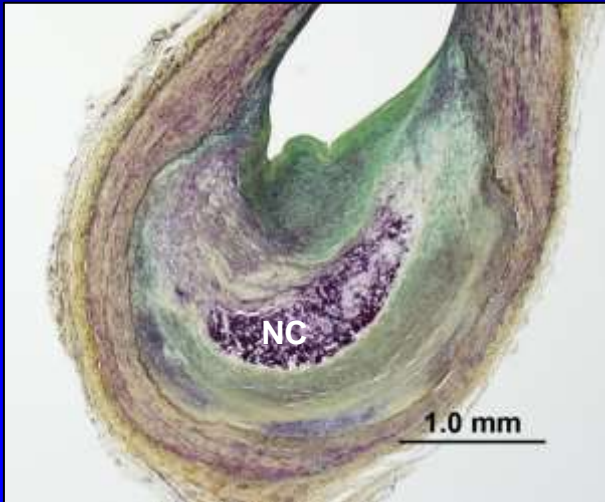
Distal

Intimal Calcification in Popliteal artery

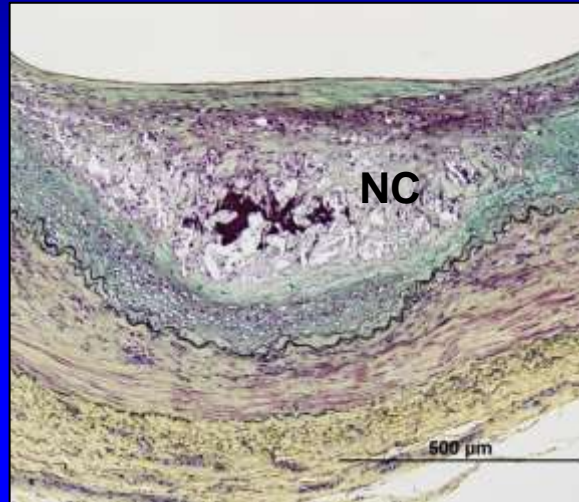


Atherosclerotic Lesions from Human Peripheral Arteries (Below the knee: Posterior tibial artery)

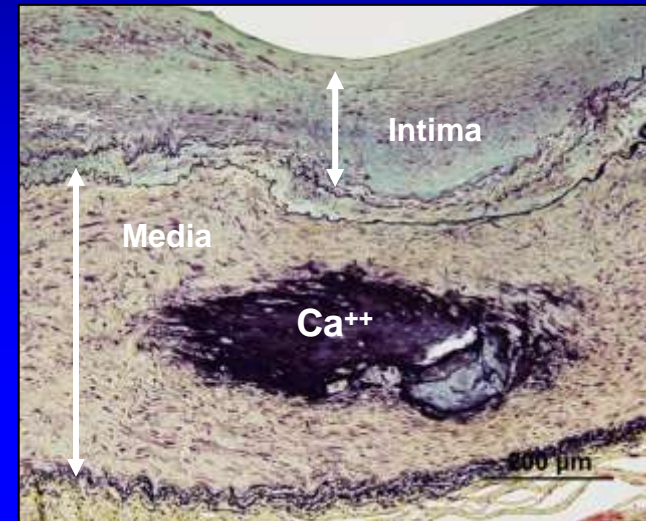
Fibroathroma



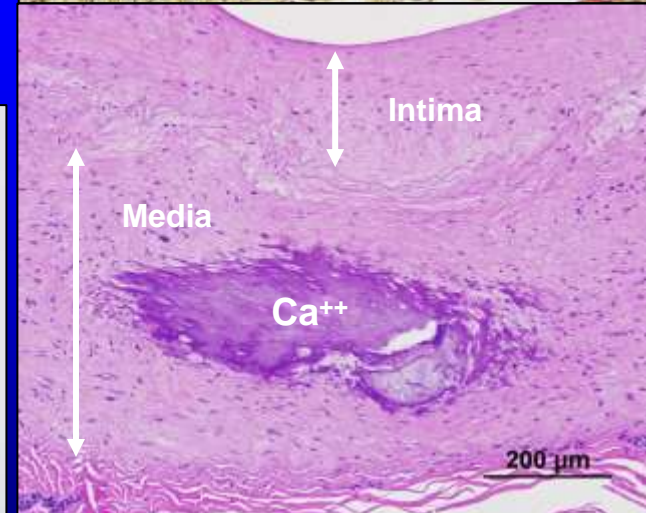
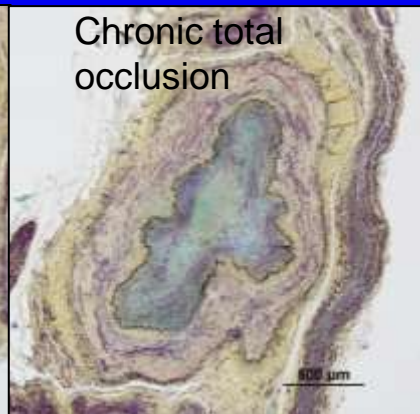
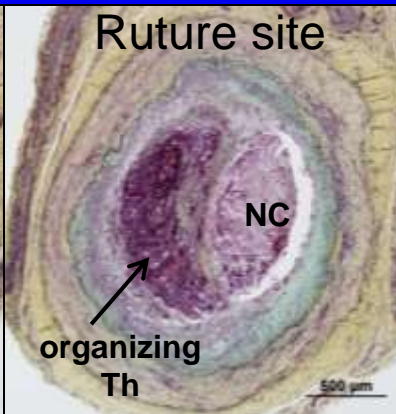
TCFA



Mönckeberg's
Medial Calcification

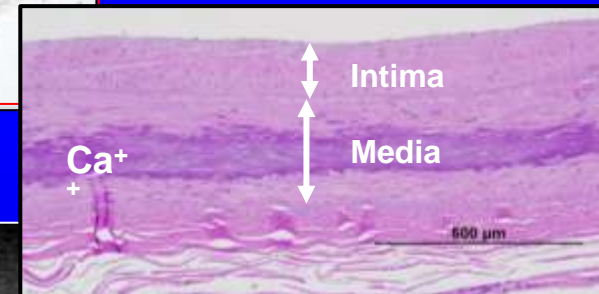
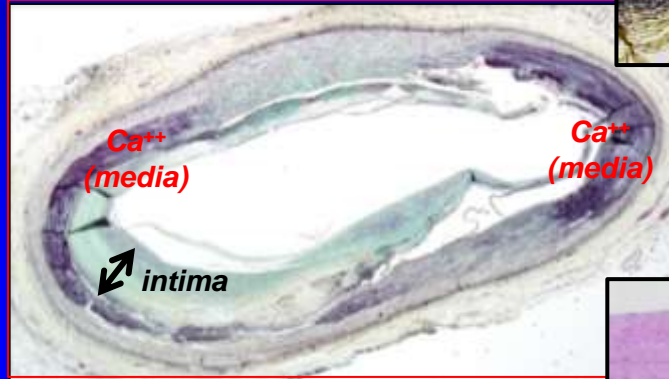
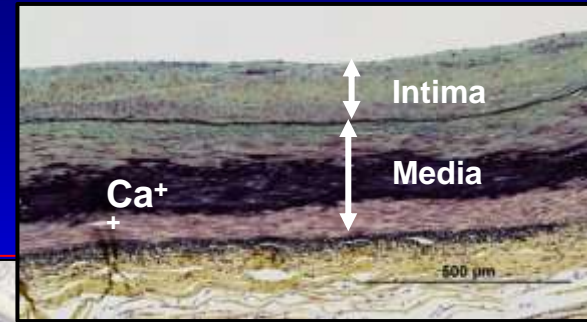
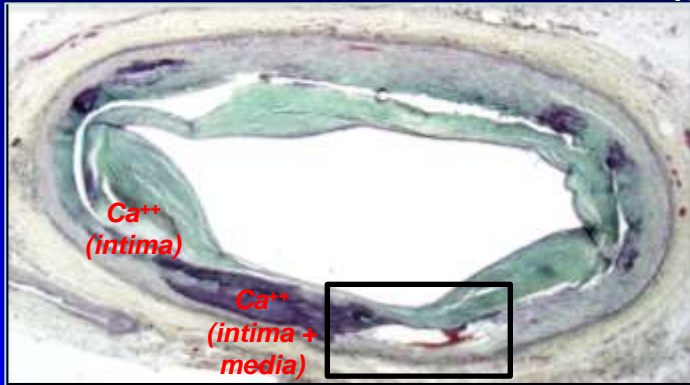


Total occlusion Posterior tibial

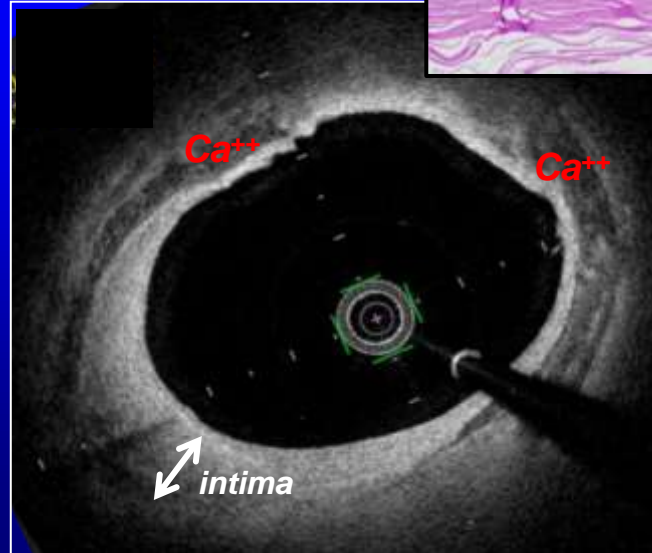
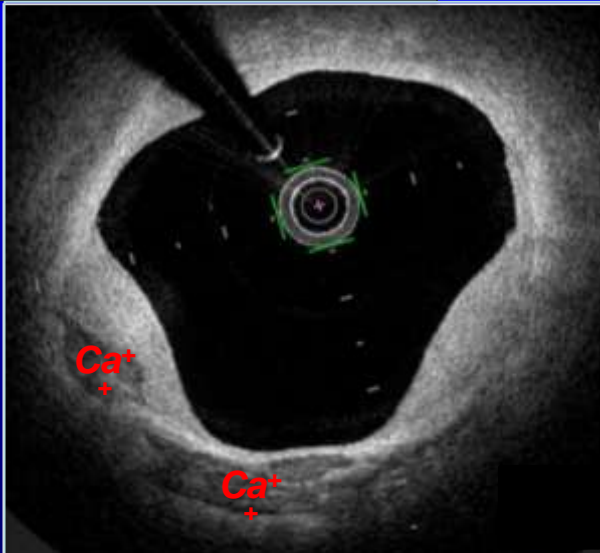


Superficial femoral artery

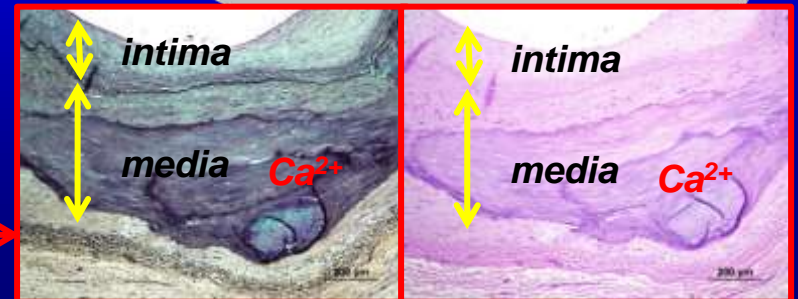
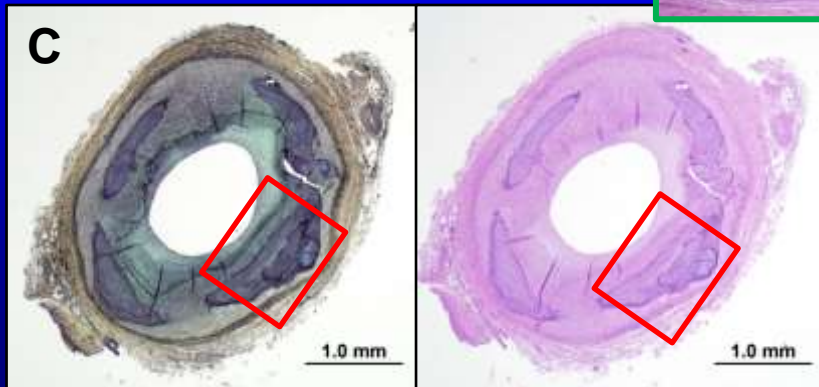
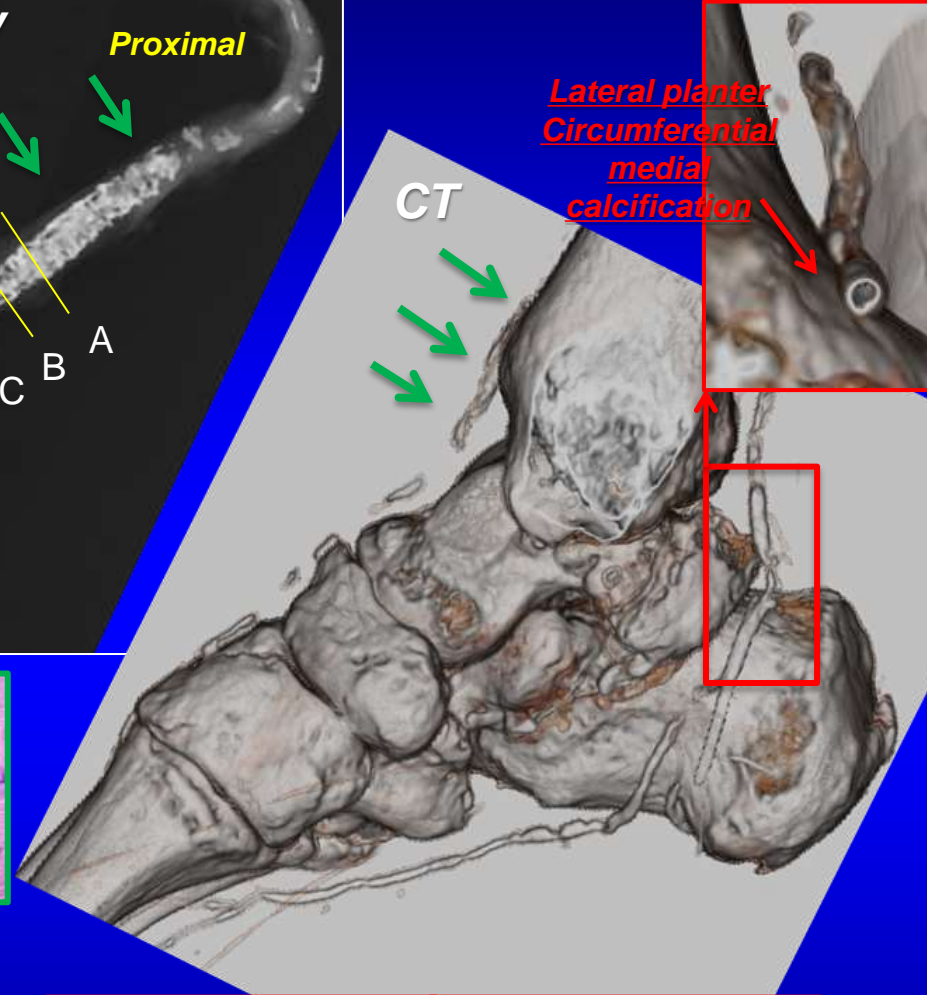
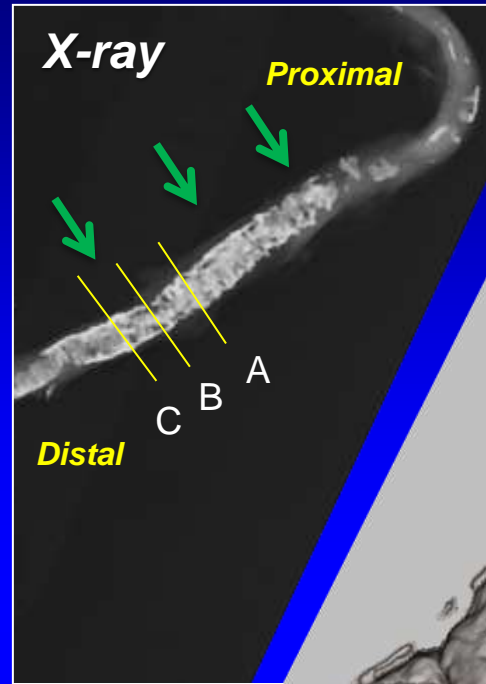
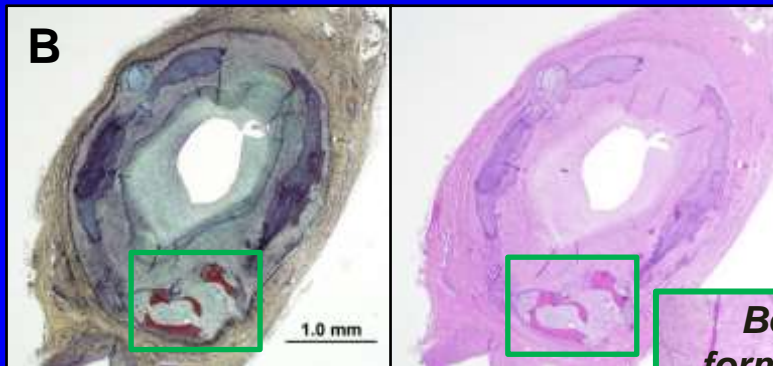
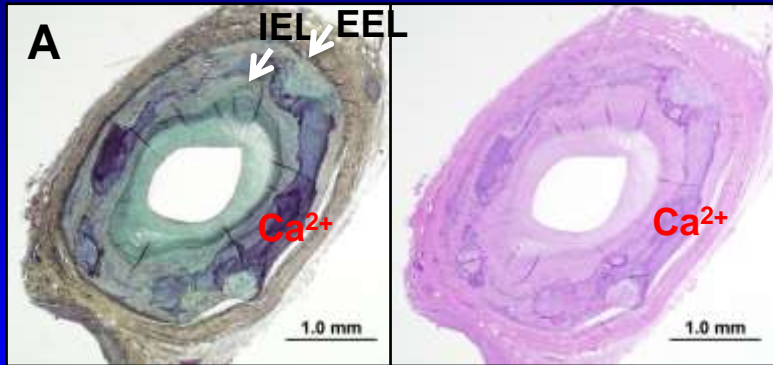
Monckeberg's Medial Calcification



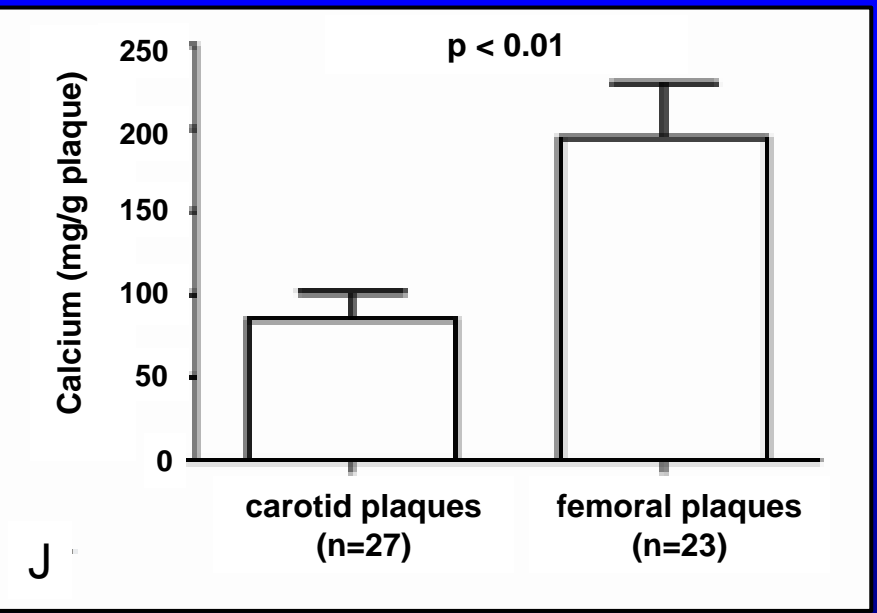
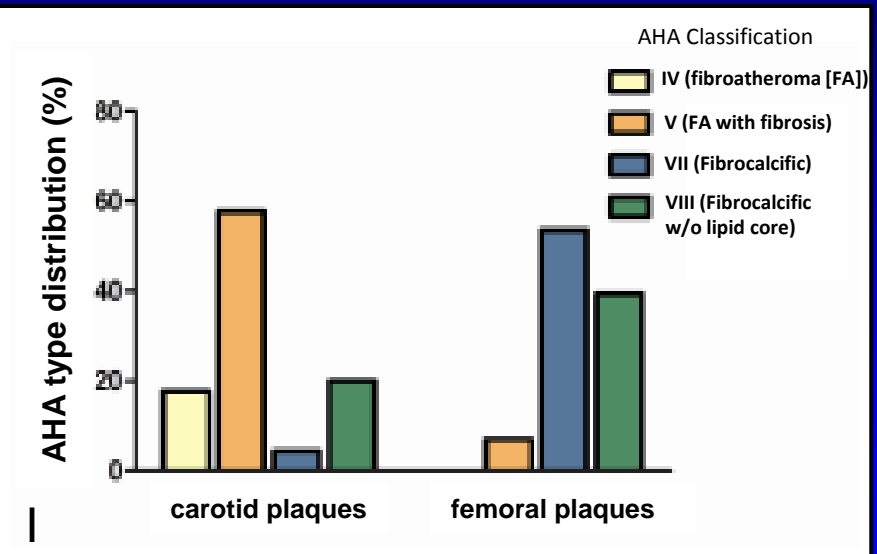
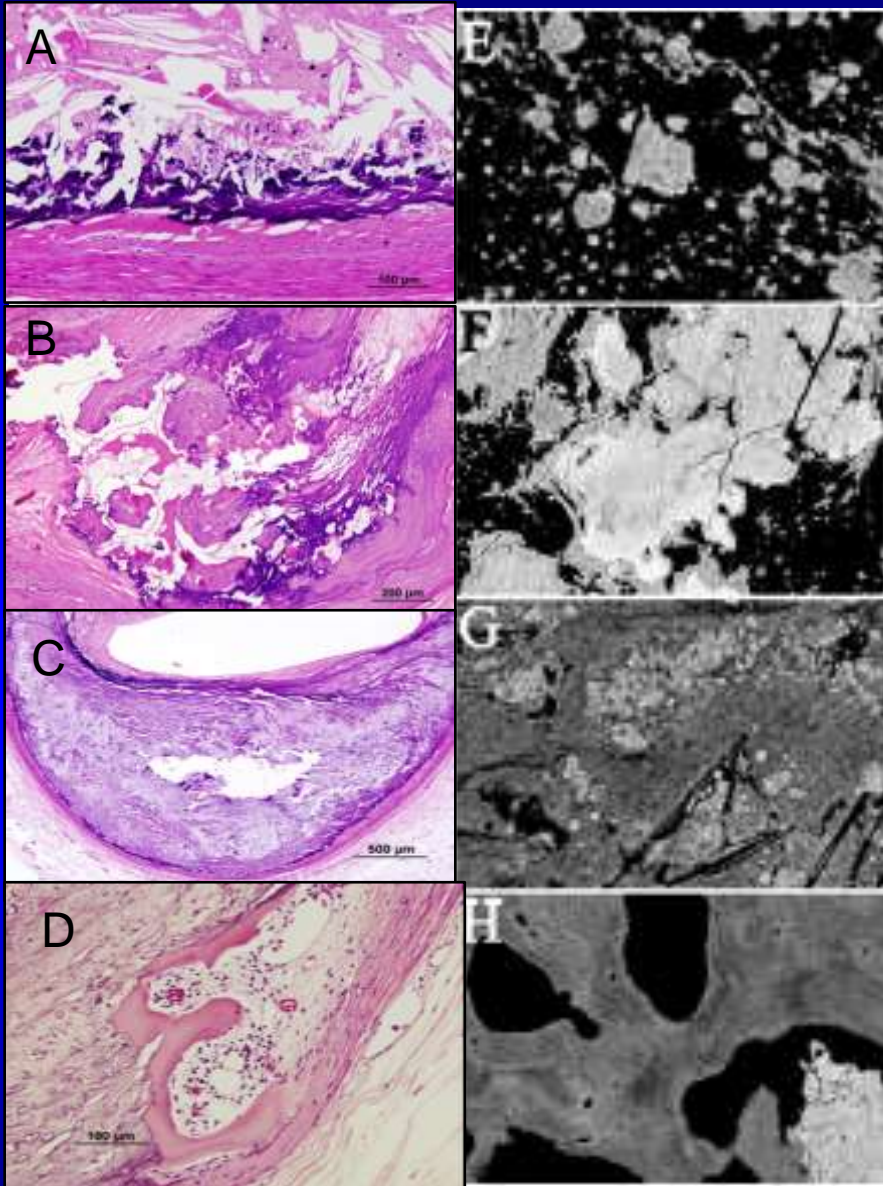
OFDI



Medial Calcification (Mönckeberg's) in Dorsalis pedis artery



Differences Between Carotid and Femoral plaques

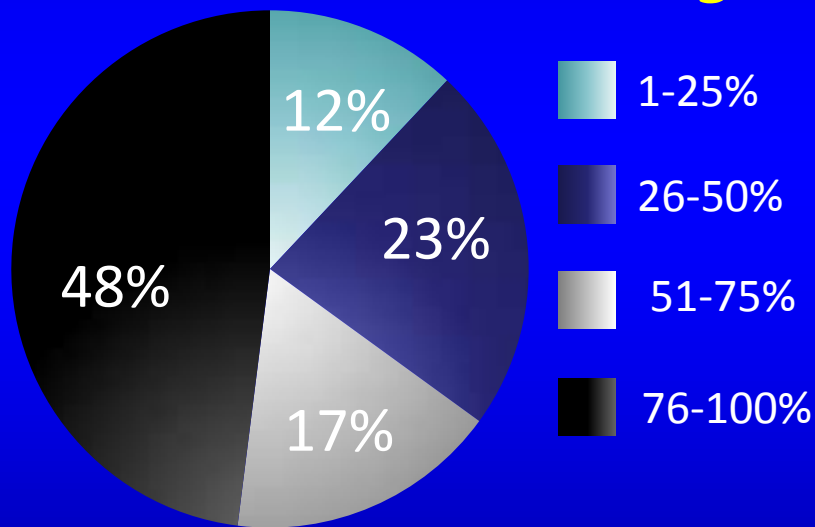


A = micronodular diffuse calcification; B = numerous stratified sheets of calcification with multinodular edges; C = clear center calcification consisting of calcific rim surrounding some clear content; D = osteoid metaplasia.

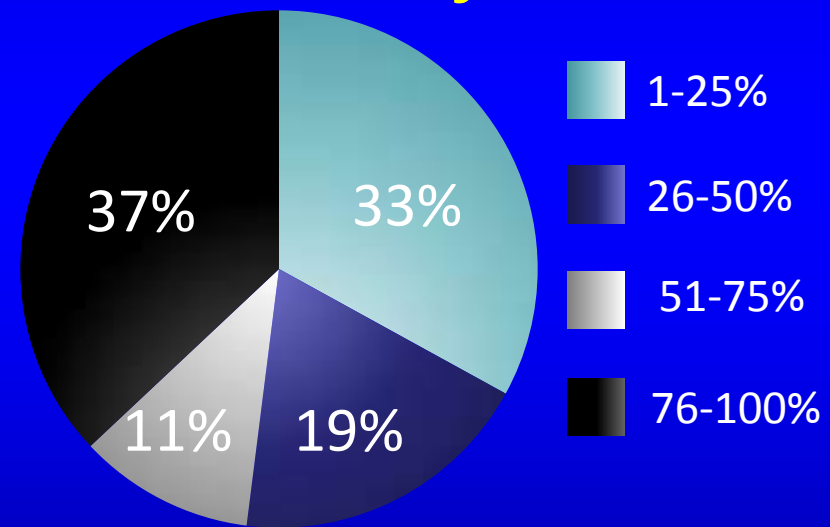
Peripheral vascular disease: who gets it and why?

58 patients (33 men [57%] and 25 females [43%]), age 43 to 95 years (mean 68.7 ± 12.5 years), who underwent a lower extremity amputation (33 [57%] below knee and the rest 25 [43%] above knee) over a 2 year period (Jan 2002 to Dec 2003). 50% had extensive non-healing ulcers and 71% had gangrene, which was more frequent in diabetics (n=34) versus non-diabetics (n=8, p=0.0032).

Luminal Narrowing

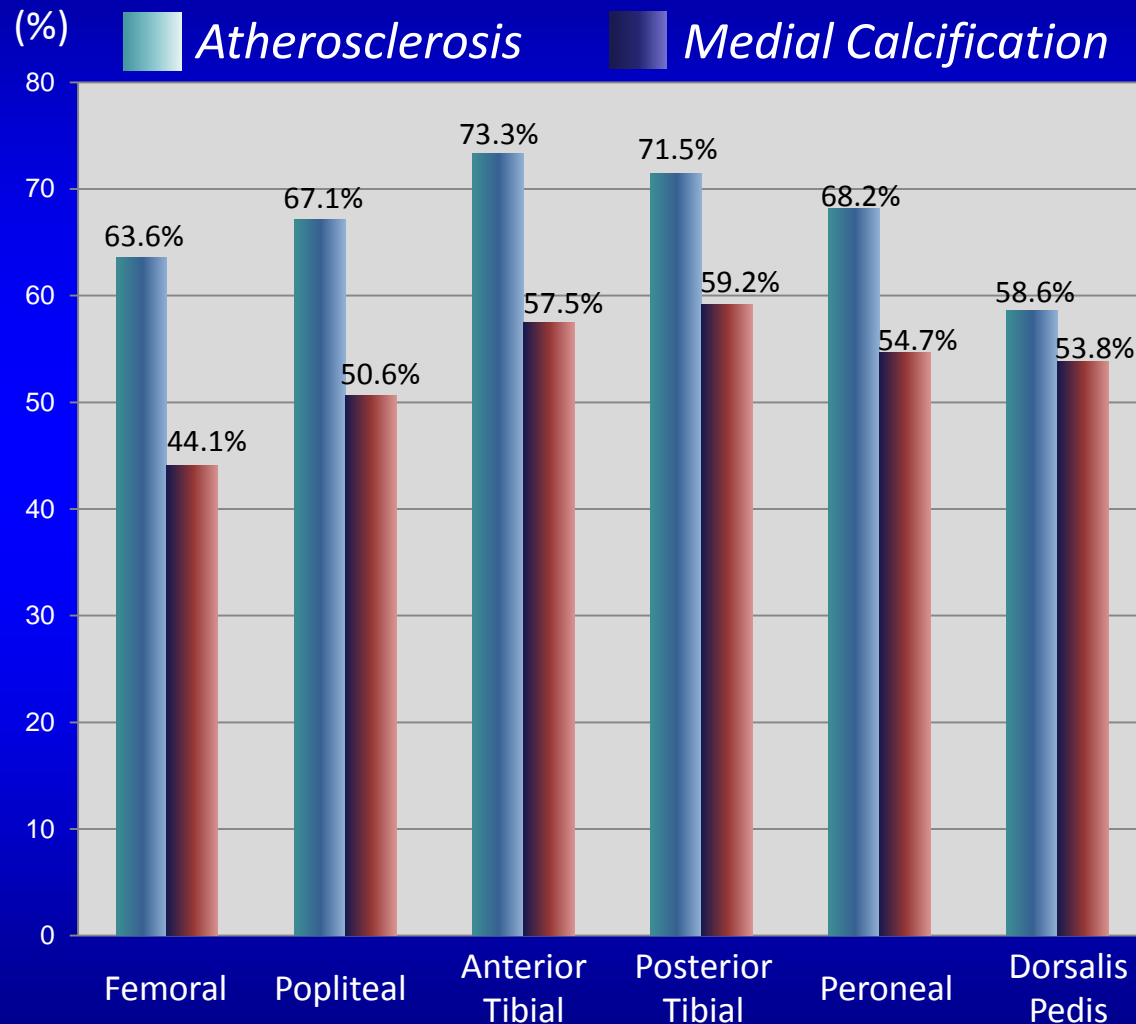


Medial Calcification

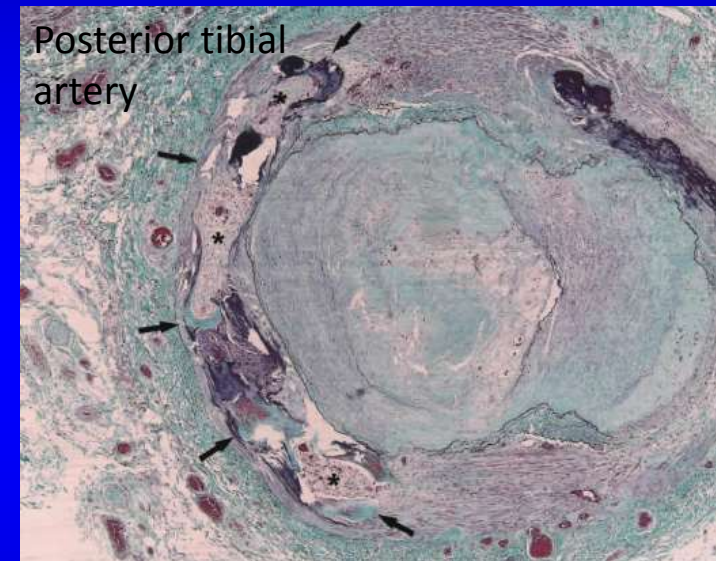


The presence of medial calcification and concomitant atherosclerosis was observed in 168 (77%) of the 218 arterial segments with atherosclerotic plaques. However, the extent of atherosclerosis did not correlate with the extent of medial calcification.

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



Ossification



Ossification was found in 19% of the arteries.

Requirements For DCB

- Must deliver large quantities of the drug within seconds
- Distribute within the media in the first few days
- Therapeutic drug levels must be maintained for at least several weeks
- Must allow rapid healing as compared to DES
- No need for long-term anticoagulation
- Biologic effects at 28-days at least

Drug coated balloon devices (*Peripheral artery*)

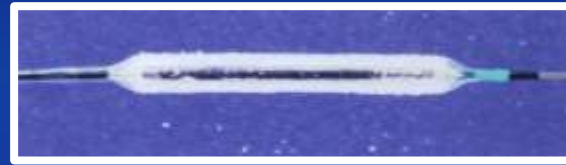
Device	Company	Coating	Drug dose ($\mu\text{g}/\text{mm}^2$)	CE mark*
Advance 18 PTX™	Cook Medical, Bloomington, IN, USA	Paclitaxel	3.0	Yes
Cotavance®	Bayer Schering Pharma AG, Berlin, Germany	Paclitaxel–iopromide	3.0	Yes
Freeway™	Eurocor, Bonn, Germany	Paclitaxel–shellac	3.0	Yes
IN.PACT™ Admiral, Amphirion, Pacific	Medtronic Vascular, Santa Clara, CA, USA	Paclitaxel–urea	3.0	Yes
Lutonix DCB® (Moxy)	BARD, Murray Hill, NJ, USA	Paclitaxel–polysorbate/sorbitol	2.0	Yes
Legflow®	Cardionovum, Warsaw, Poland	Paclitaxel–shellac	3.0	Yes
Passeo-18 Lux®	Biotronik, Bülach, Switzerland	Paclitaxel–butyryl-tri-hexyl citrate	3.0	No → Yes
Stellarex®	Covidien, Mansfield, MA, USA	Paclitaxel	2.0	No → Yes

* *Lutonix DCB®* and *IN.PACT™* are currently approved by the FDA for clinical use.

Byrne RA, Joner M. et al. *Nat Rev Cardiol.* 2014;11:13-23



In.Pact



Sequent Please



SurModics



ELUTAX



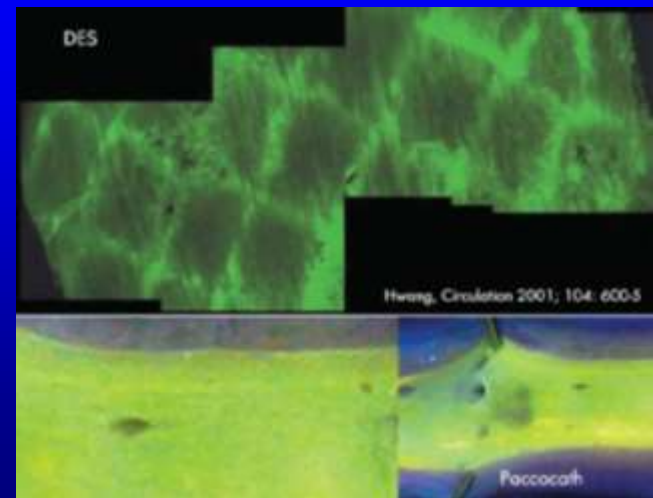
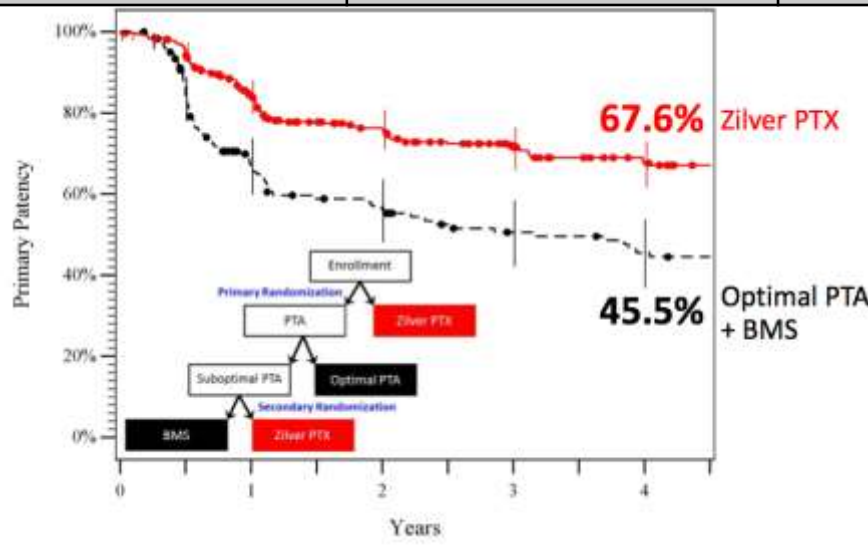
Pantera Lux



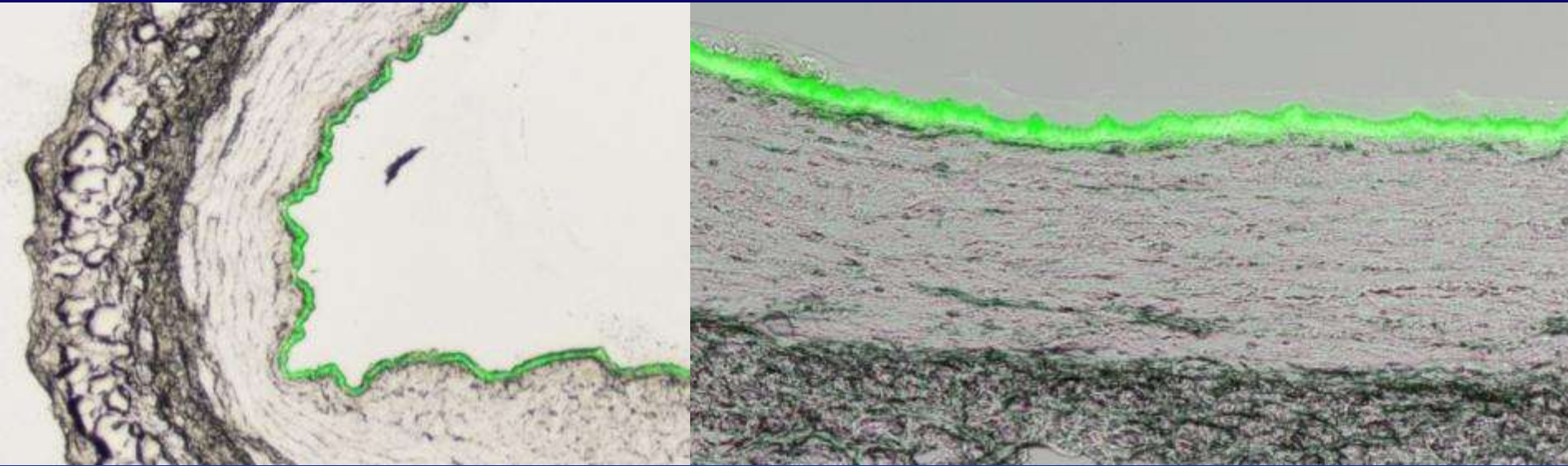
Moxy

HOW IS DCB DIFFERENT FROM DES

Parameters that distinguish DCB from DES	DES (Drug-eluting stent)	DCB (Drug-coating stent)
Drug concentration on the device	Low <100 to 200 µg	Very High 300 to 600µg (typical 20-30 µg/mm)
Drug transfer at the time of deployment	Slow and controlled	Rapid, all at once
Reservoir of drug	Polymer, strut based	No (excipient important)
Drug retention in tissues	Short term	Need a drug which binds to cell membranes and is easily transferable to adjacent cells (crystalline)
Diffusion	Good	Excellent
Lipophilic	yes	Even better
Active ingredient	Not necessary	Should be active immediately



Ex Vivo Administration of Fluorescent-Labeled PTX to Excised Porcine Artery



10% Oregon green labeled paclitaxel incorporated into Lutonix DCB coating

LUTONIX[®] 035 vs. In.Pact[™] Differences

	LUTONIX [®] 035	In.Pact [™]
Paclitaxel Dose	2 $\mu\text{g}/\text{mm}^2$	3.5 $\mu\text{g}/\text{mm}^2$
Carrier	Polysorbate & Sorbitol	Urea
Systemic Downstream Effects	None	Present
SFA/BTK Product Line	SFA= 1 st with FDA Approval/ BTK Ongoing Trial	SFA, FDA Approval/ BTK Product Recall 2014

LUTONIX[®] 035

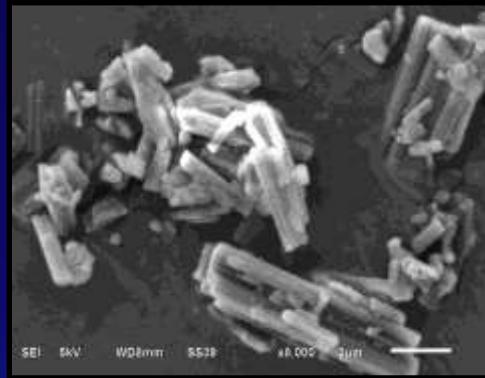


In.Pact[™]
Distal Tip
Medial

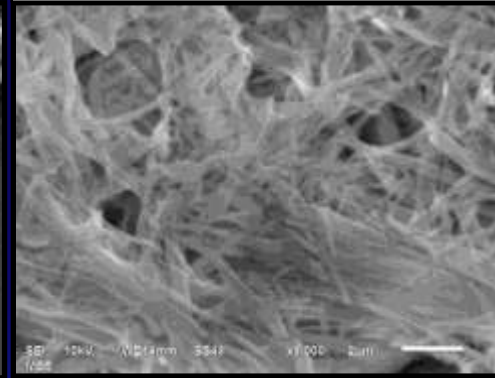


Coating Integrity is Variable

Paclitaxel



Paclitaxel in coating after aqueous exposure



LUTONIX® 035

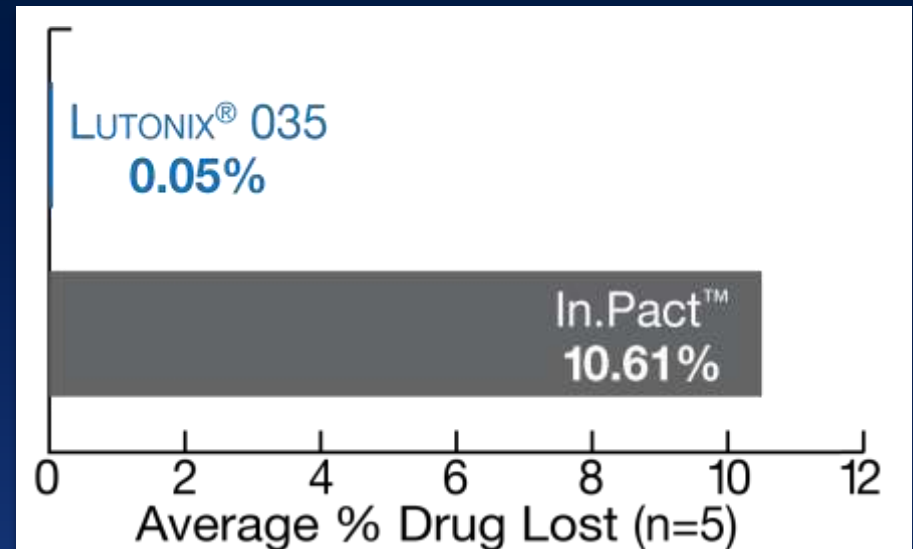


MDT/Invatec (Admiral)

Paclitaxel Adherence to the Balloon Polysorbate & Sorbitol vs. Urea

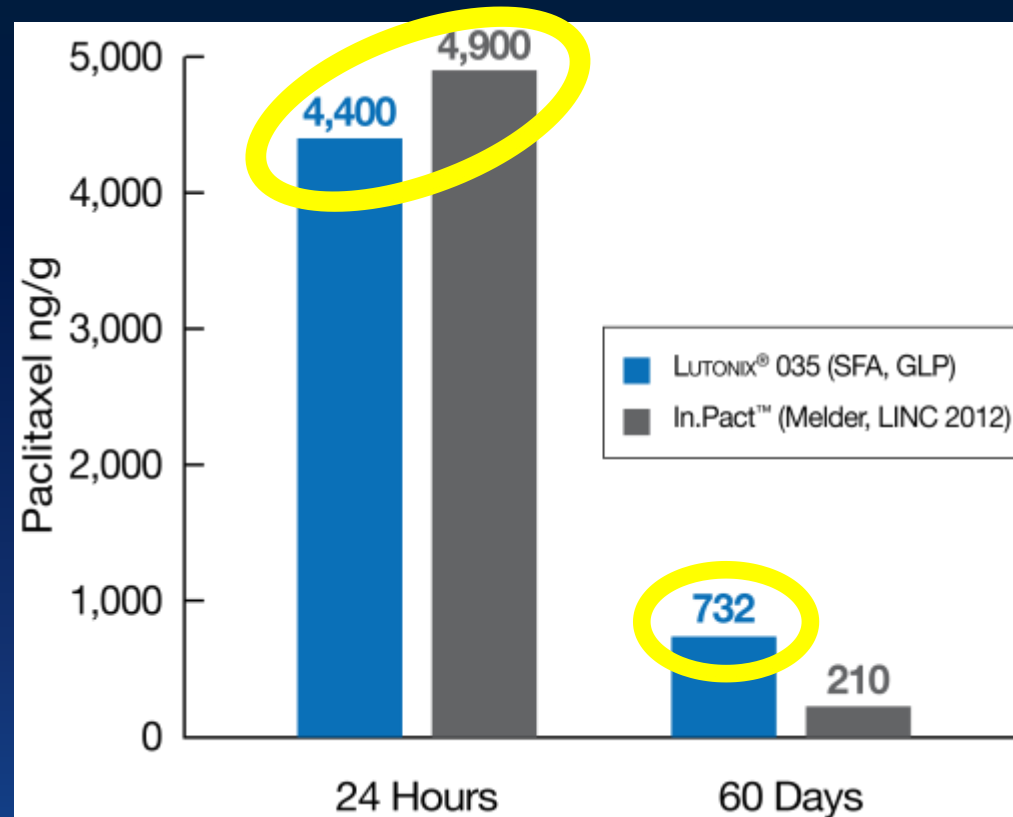
- **Significantly less drug loss than In.Pact™** during simulated shake test
- Balance of 2.0 µg/mm² paclitaxel and carriers polysorbate and sorbitol, **minimizes unwanted drug loss in the lab**

Drug Lost During Shake Test
LUTONIX® 035 vs. In.Pact™



Paclitaxel Uptake in the Arterial Wall

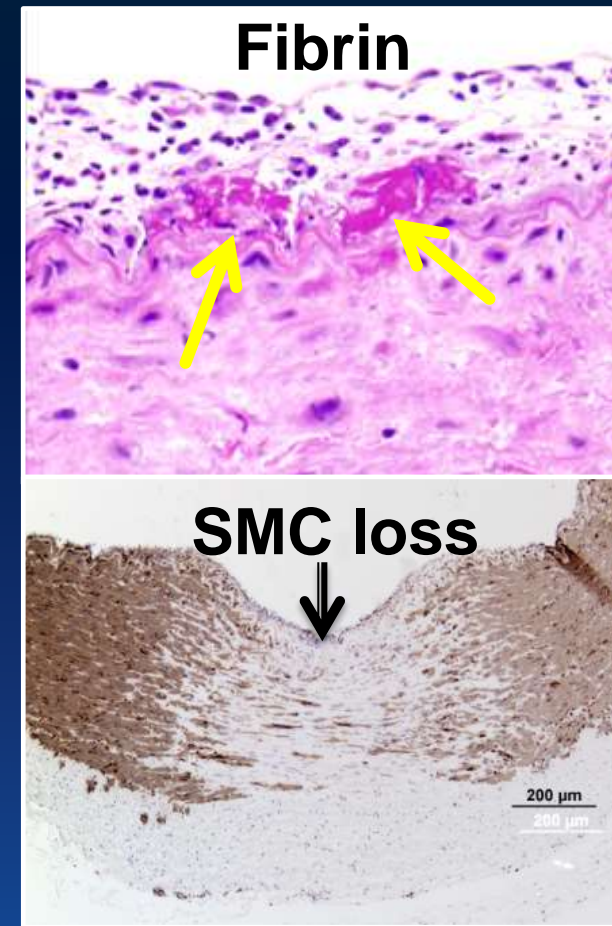
- LUTONIX[®] 035 offers similar paclitaxel arterial tissue concentration levels at 24 hours
- Greater concentration levels at 60 days with 75% less paclitaxel



Similar efficacy concentration levels with significantly less drug

Histologic Parameters for Evaluation of DEB Efficacy

- Key parameters:
 - Endothelial Loss
 - Fibrin/Platelets deposition
 - Inflammation
 - Extent of Injury
 - Medial Smooth Muscle Cell Loss
 - Proteoglycan deposition
 - Fibrosis – intimal, medial and adventitial



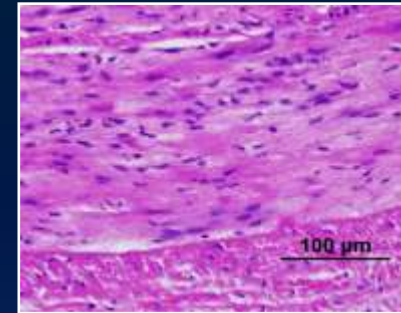
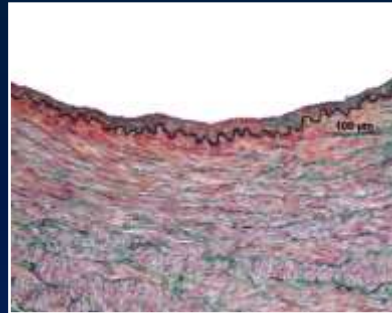
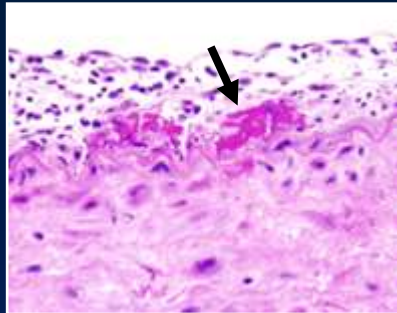
Intimal Scoring Parameters

Fibrin/Platelets

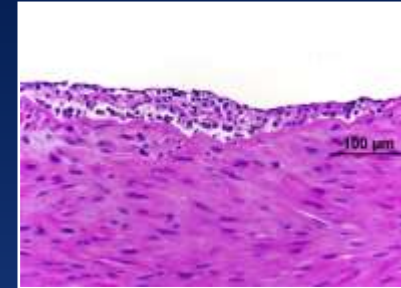
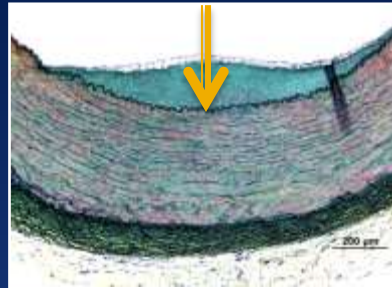
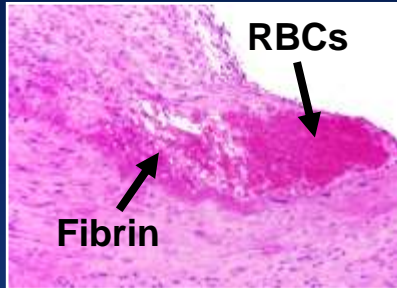
Proteoglycan

Inflammation

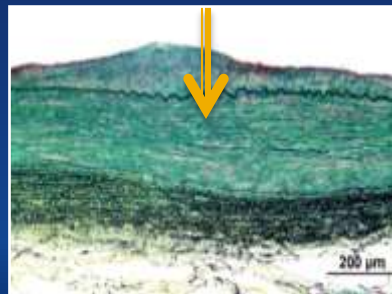
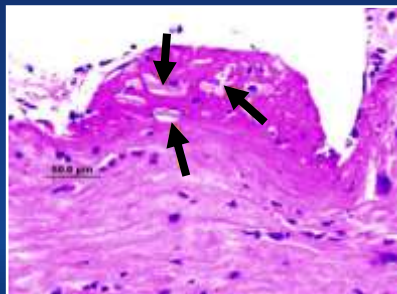
Minimal



Mild



Moderate



RBC = red blood cells.

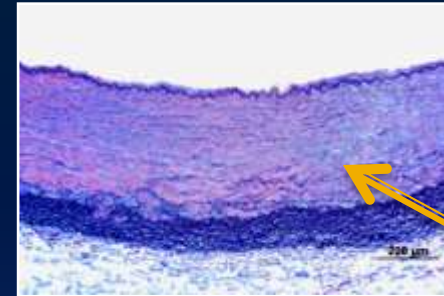
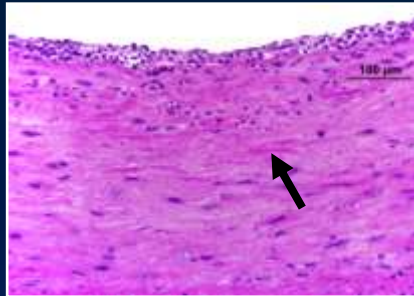
Medial Scoring Parameters

Medial Fibrin
(H&E)

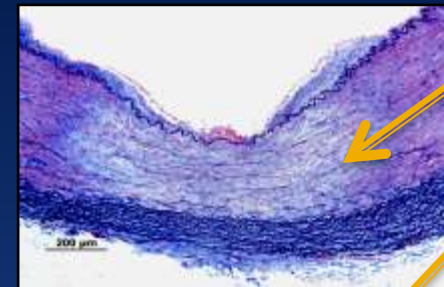
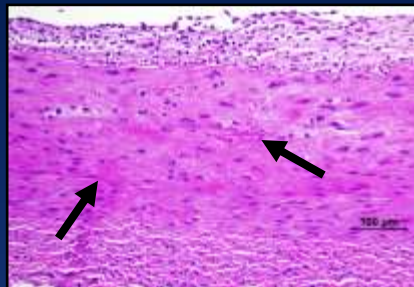
Proteoglycans
(Movat
pentachrome)

Medial SMC loss
(Masson
Trichrome)

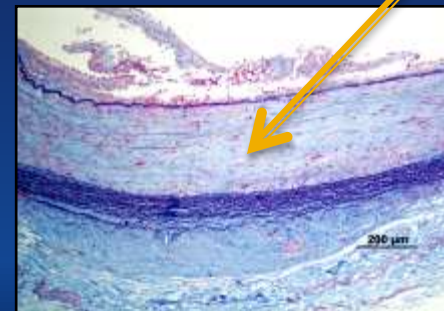
Minimal



Mild



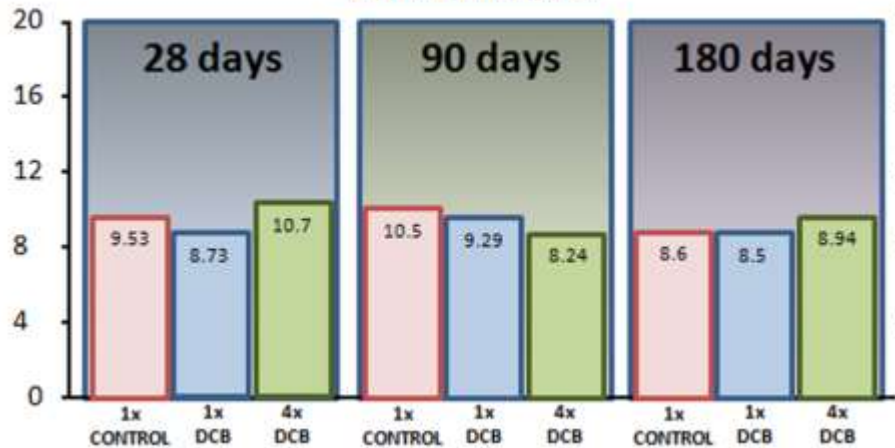
Moderate



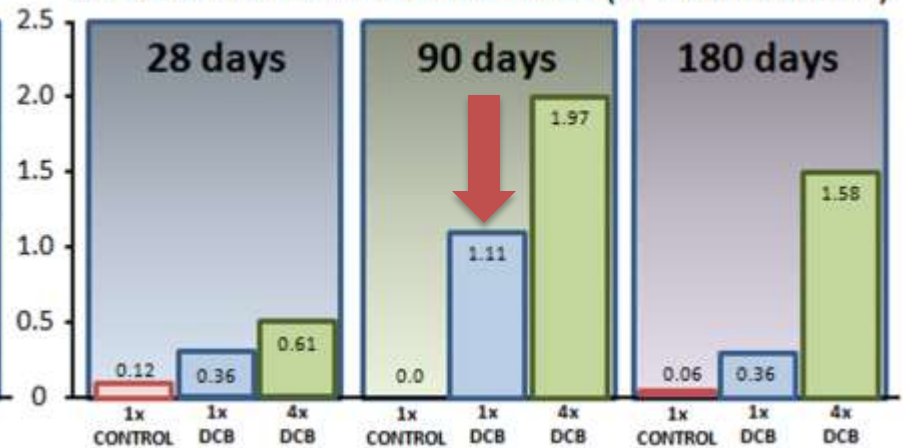
Blue represent
s areas of
scarring

Vascular Pharmacokinetic Responses to Treatment with a Lutonix® 035 in a Swine Femoral Artery

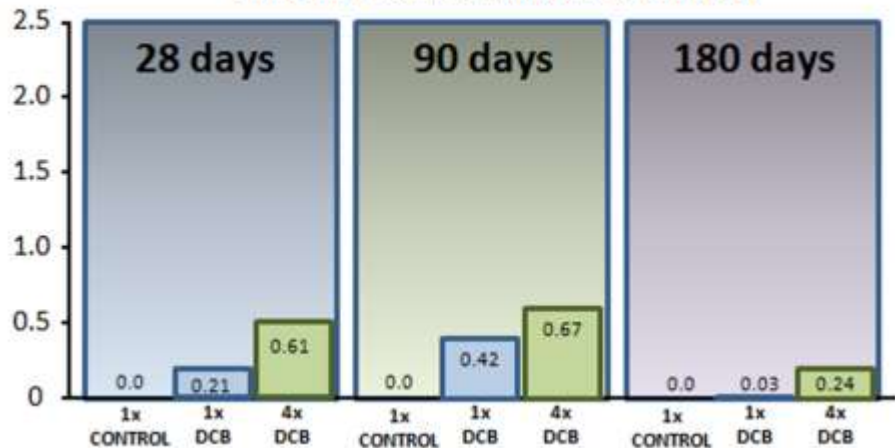
LUMEN AREA



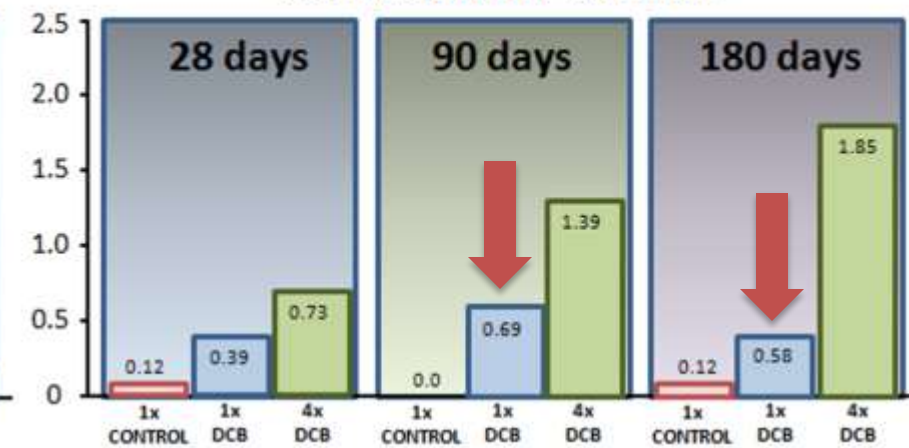
SMOOTH MUSCLE CELL LOSS (TRANSMURAL)



PROTEOGLYCAN DEPOSITION



COLLAGEN DEPOSITION

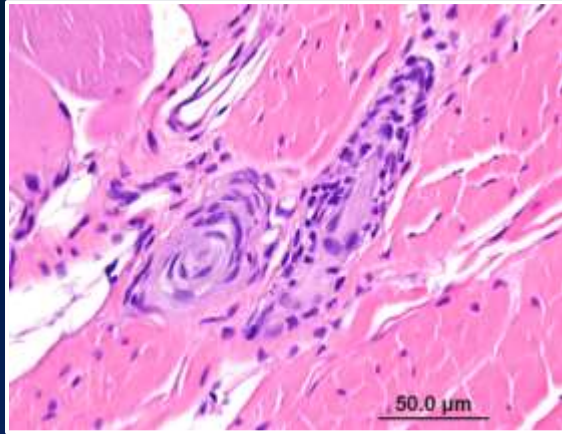


Vascular Changes in Downstream Skeletal Muscle

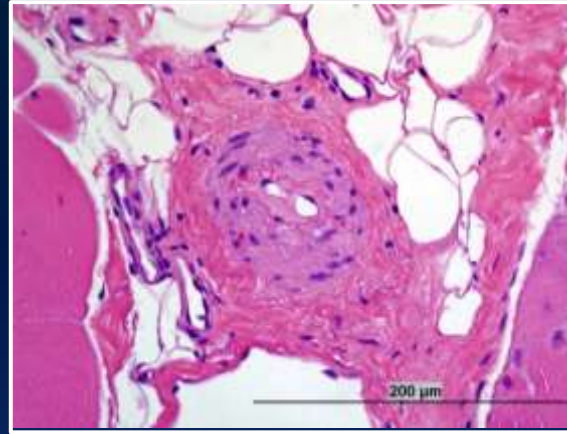
(None of physiological significance observed for LUTONIX[®] at any time)

1x Dose

28 Days



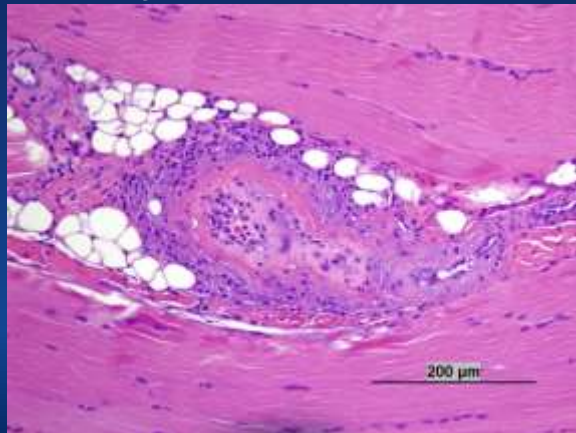
90 Days



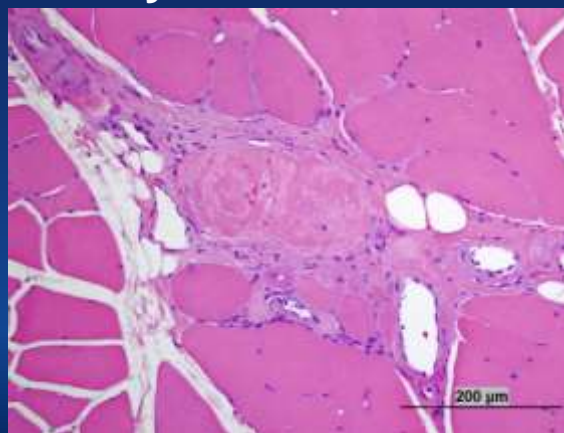
(None observed for 1x dose at 180 days)

4x Dose

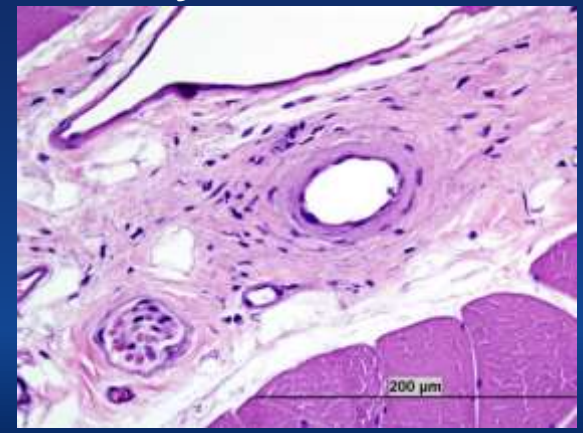
28 Days



90 Days



180 Days

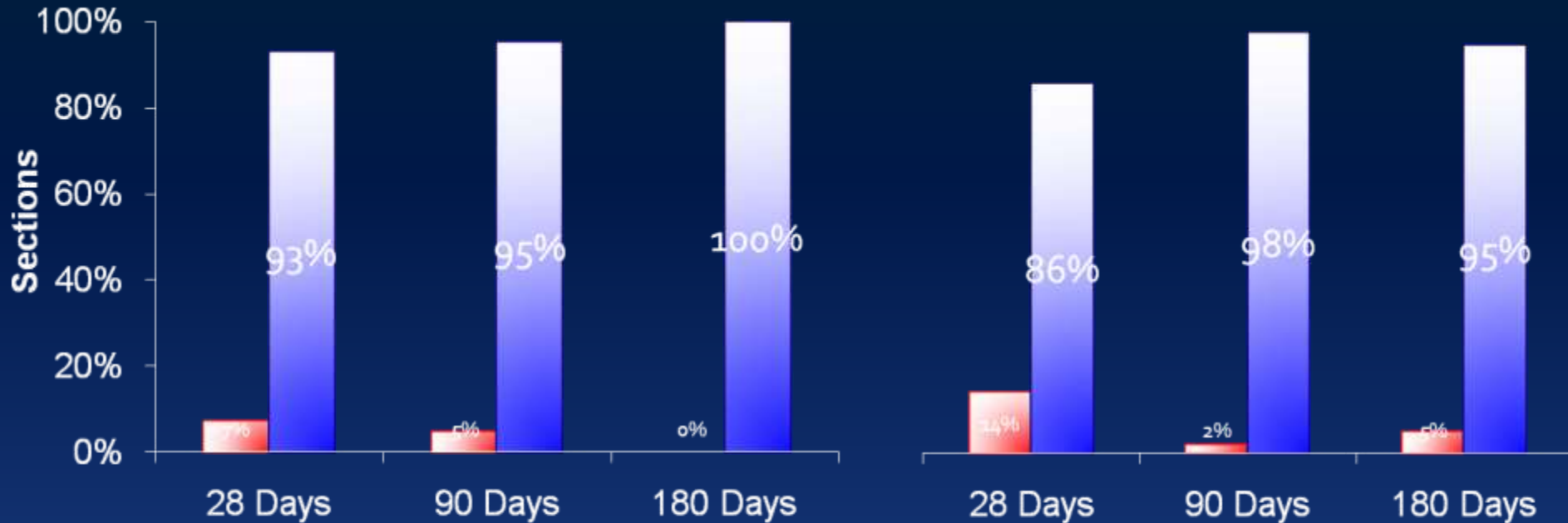


Rare Changes in Downstream Porcine Skeletal Muscle: None of Physiological Significance LUTONIX® DCB Catheter Final Formulation

(1x dose)

(4x dose)

■ Vascular Change Present ■ Vascular Change Absent



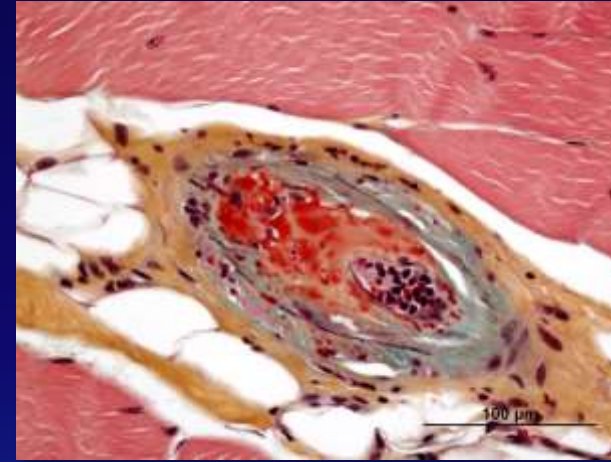
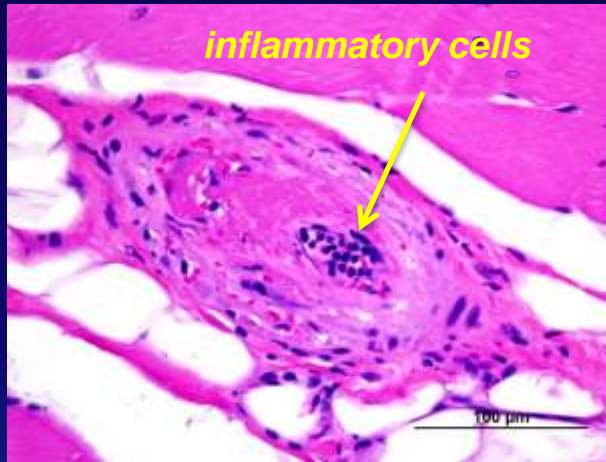
Dose	Time Point	*Total Vessels with changes in Skeletal Muscle/Area (mm ²)
1x	28 Days	0.0035
	90 Days	0.0046

Dose	Time Point	*Total Vessels with changes in Skeletal Muscle/Area (mm ²)
4x	28 Days	0.0057
	90 Days	0.0024
	180 Days	0.0015

*Mean of only sections showing changes

Histological Findings of Emboli/vascular Changes, Skeletal Muscle Arteries

LUTONIX[®] 035 x3 (2 μ g/mm² paclitaxel) at 90-days



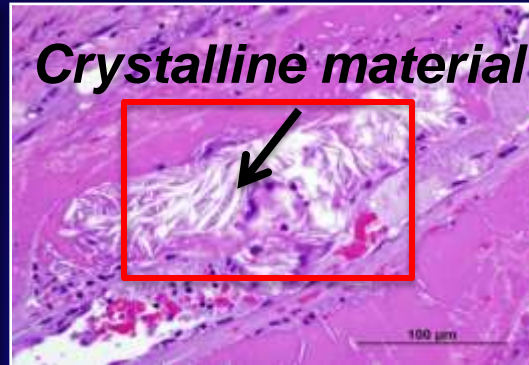
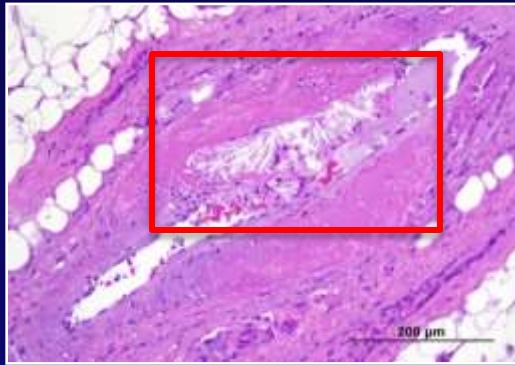
Loss of medial SMCs with replacement by proteoglycan/collagen

No.	No. of sections (Downstream muscle/corony band)	Vascular Changes	Skeletal Muscle Necrosis/Fibrosis	Crystalline material
1	14 (12 / 2)	1	0	0
2	14 (12 / 2)	0	0	0
3	14 (12 / 2)	4	0	0
4	14 (12 / 2)	0	0	0
Total	56	5	0	0

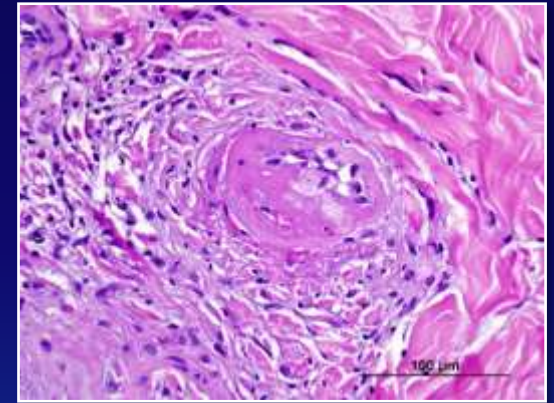
5 /56 (8.9 %) from DCB treatment showed findings of vascular change associated with paclitaxel and/or excipient (drug carrier).

Histological Findings of Emboli/vascular Changes, Skeletal Muscle Arteries

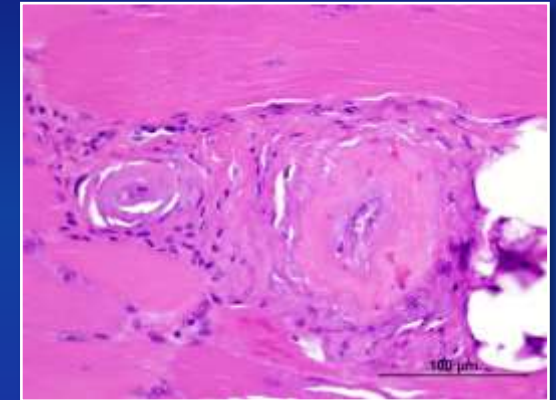
In.Pact™ DCB x3 (3µg/mm² paclitaxel) at 90-days



Fibrinoid Necrosis



Skeletal Muscle



No.	No. of sections (Downstream muscle/coronyary band)	Vascular Changes	Skeletal Muscle Necrosis/Fibrosis	Crystalline material
1	13 (12 / 1)	6	0	0
2	13 (12 / 1)	5	1	0
3	13 (12 / 1)	7	2	1
4	13 (12 / 1)	8	2	1
5	13 (12 / 1)	8	3	1
6	13 (12 / 1)	4	1	1
Total	78	38	9	4

38 /78 (48.7 %) from DCB treatment showed findings of vascular change associated with paclitaxel and/or excipient (drug carrier).

Skeletal Muscle necrosis at 28d

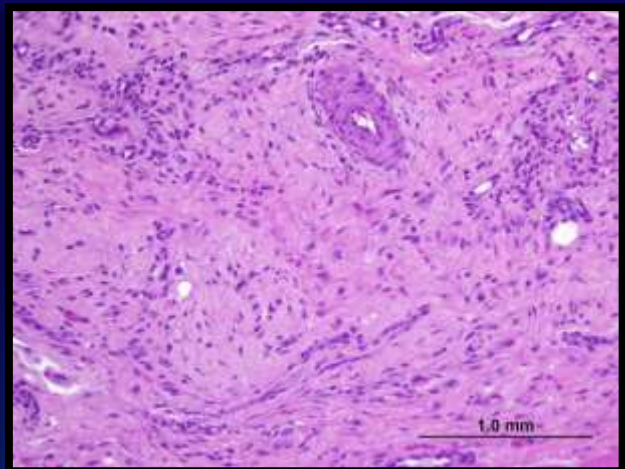
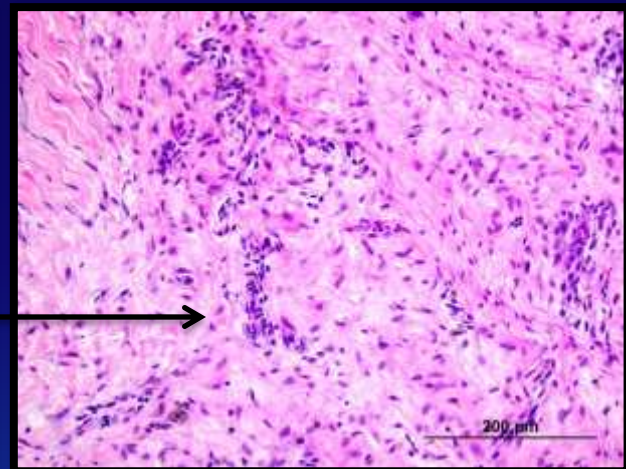
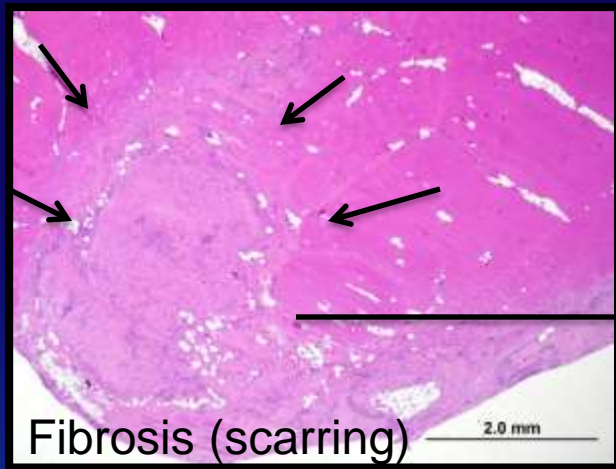
Lt Semit 1

Lt Semit 2

A

a

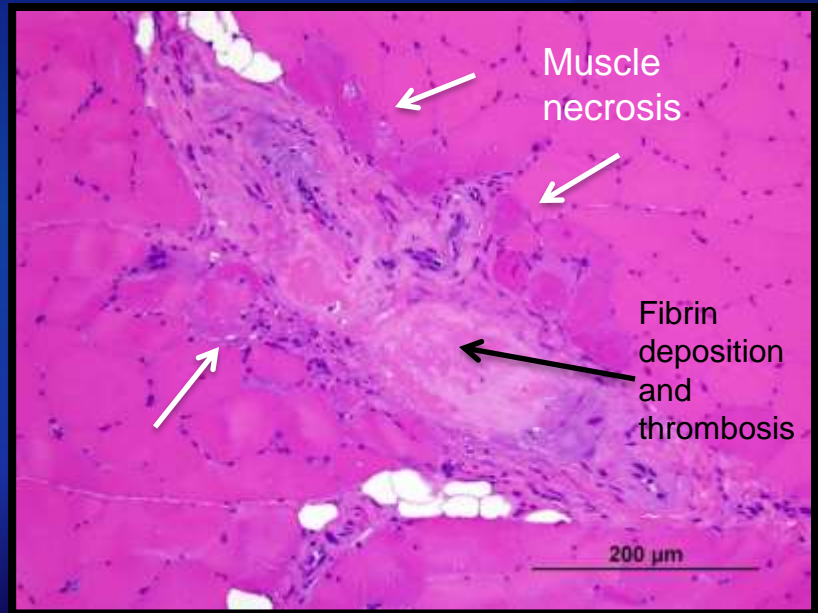
B



C

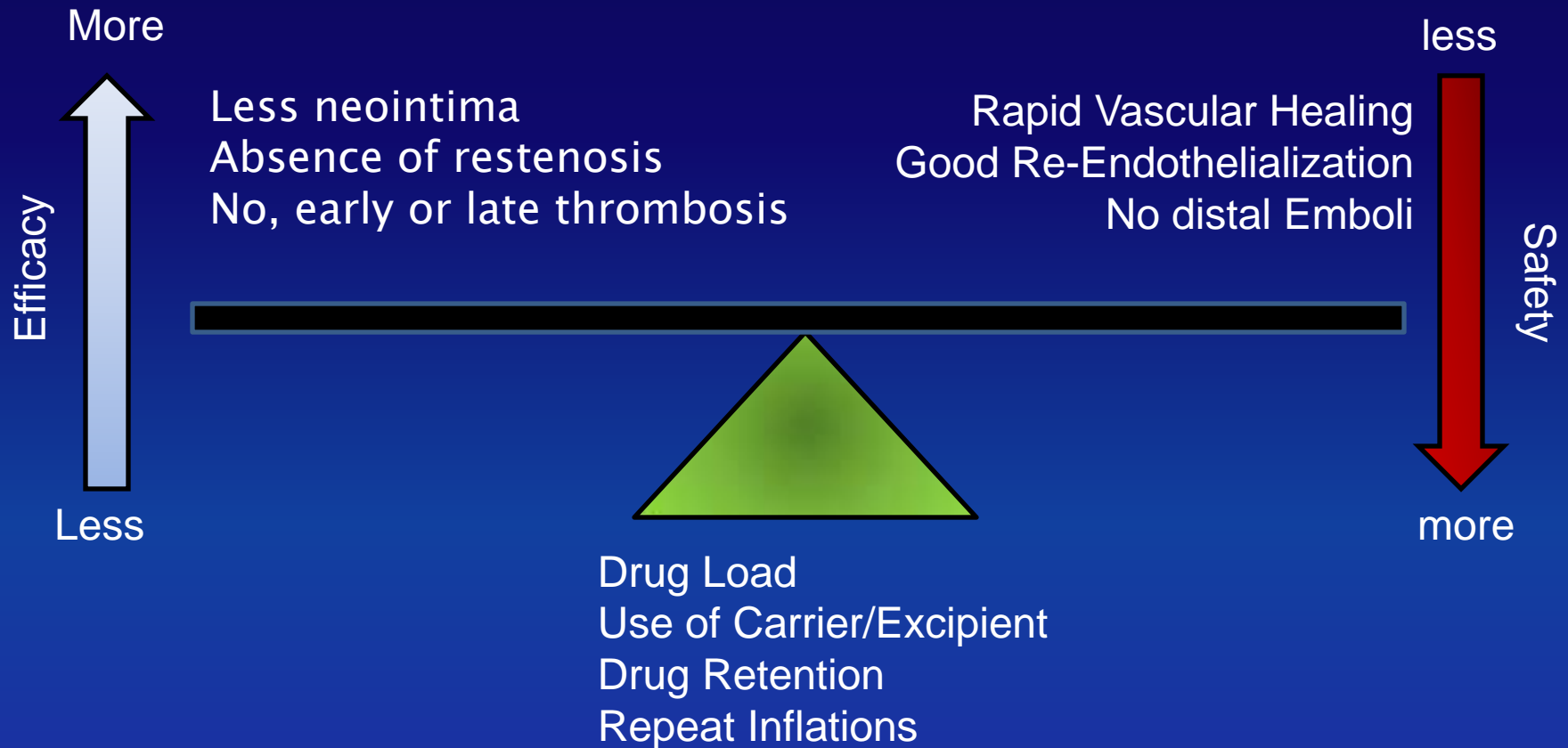
Rt Semit 1

Muscle Necrosis and Vascular Changes



Safety Profile: All about Balancing Safety, Efficacy and Biologic Response

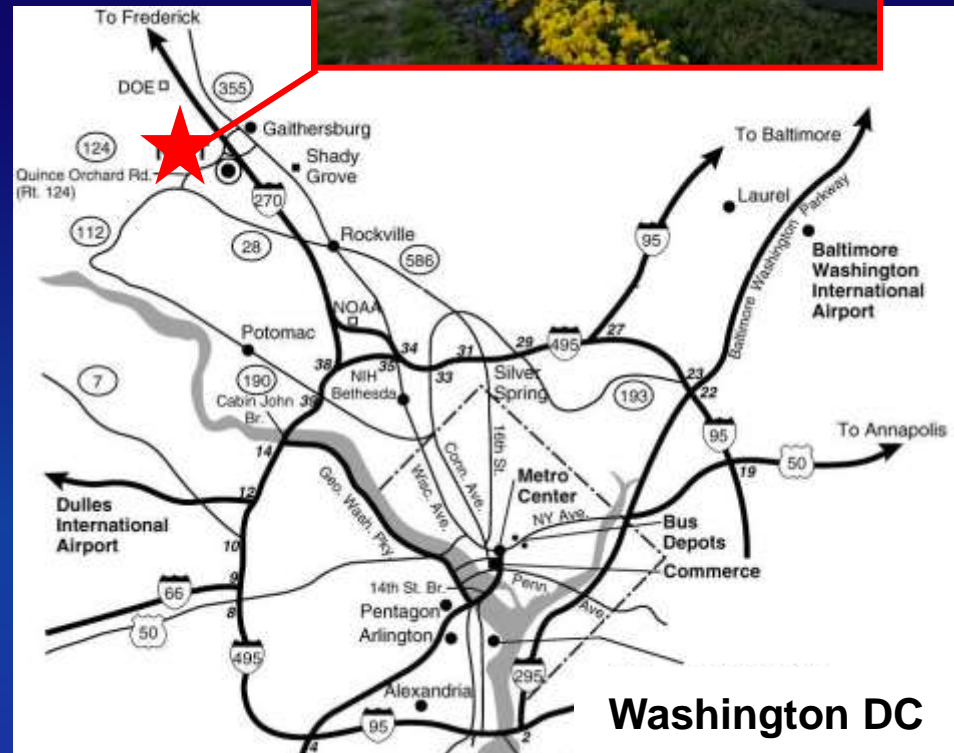
Not all balloons are created equal



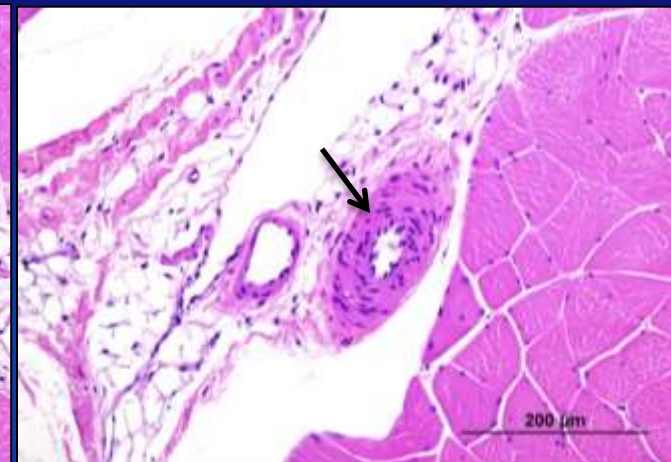
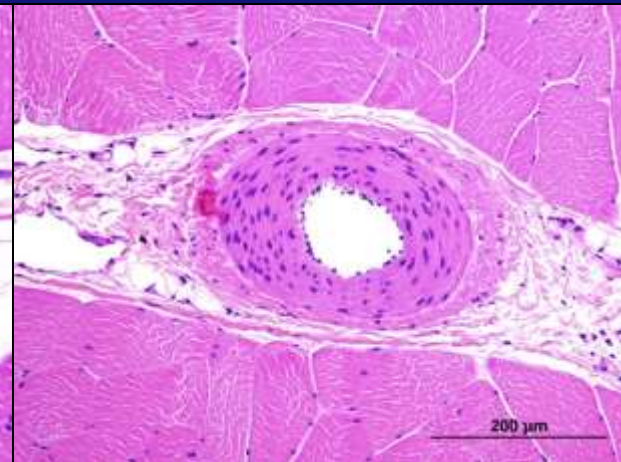
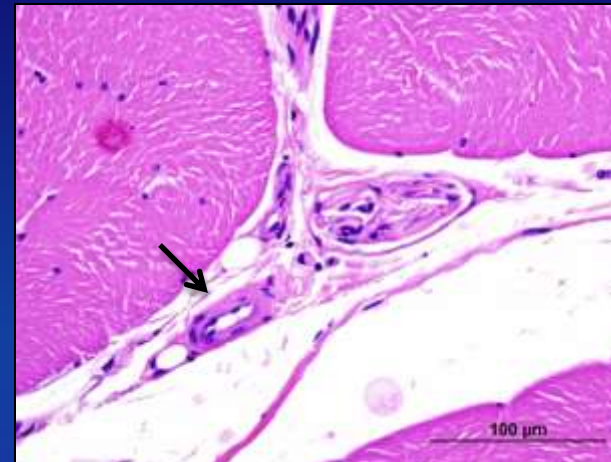
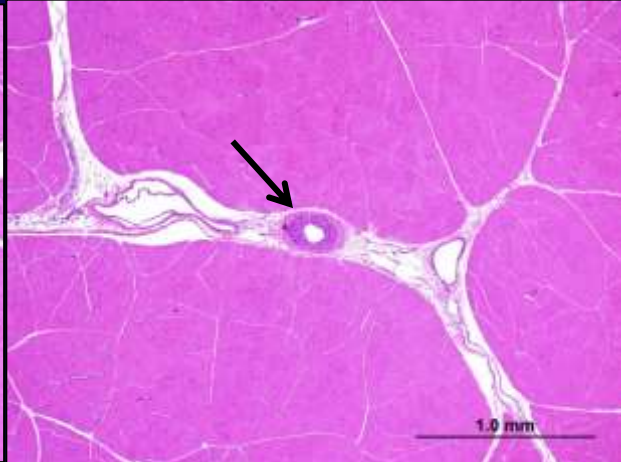
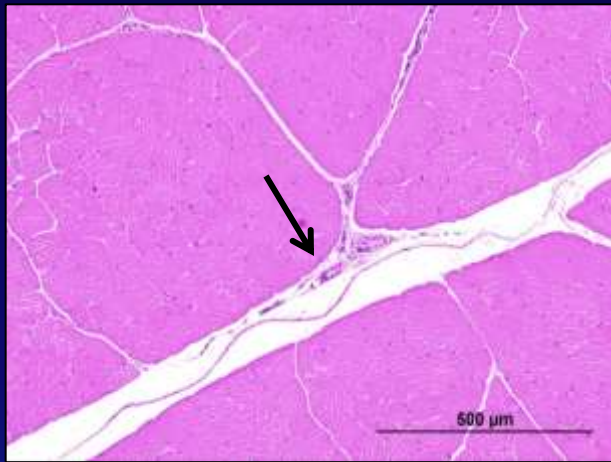
Acknowledgments

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Arteries and Arterioles in Normal Skeletal Muscle



Arteriole

Muscular artery

Muscular artery

Changes in the Arteries and Arterioles within the Skeletal Muscle from Paclitaxel

