Unique Demands of the Femoral Anatomy and Pathology and the Need for Unique Interventions

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

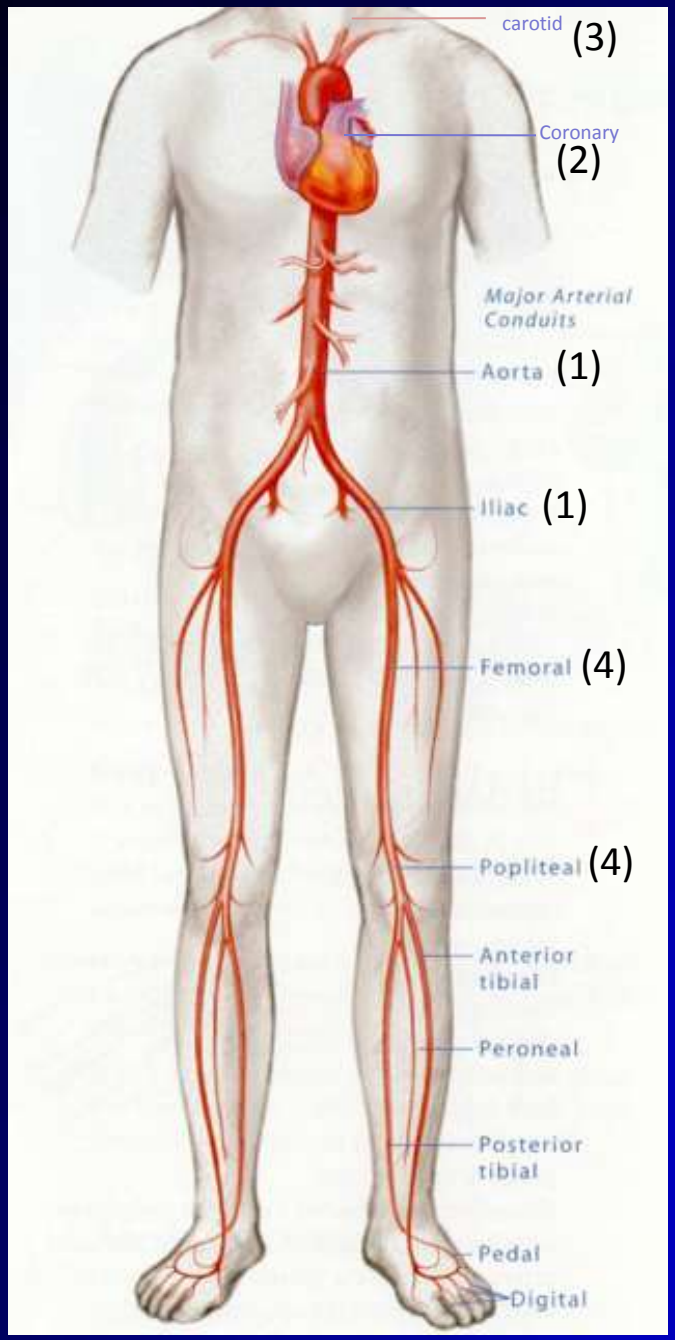
Honorarium: 480 Biomedical, Abbott Vascular, Boston Scientific, Cordis J&J, Lutonix, Medtronic, Merck, Terumo Corporation, and W.L. Gore.

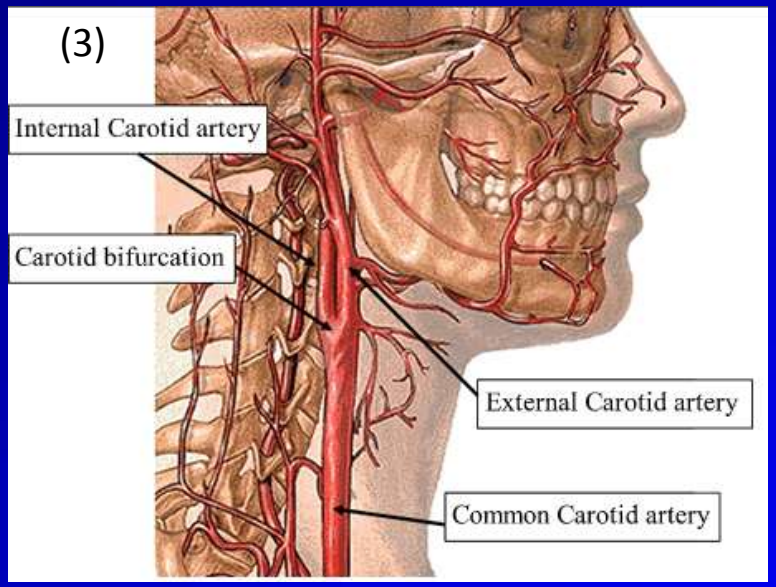
Institutional grant/research support: 480 Biomedical, Abbott Vascular, Atrium, BioSensors International, Biotronik, Boston Scientific, Cordis J&J, GSK, Kona, Medtronic, MicroPort Medical, CeloNova, OrbusNeich Medical, ReCore, SINO Medical Technology, Terumo Corporation, and W.L. Gore.

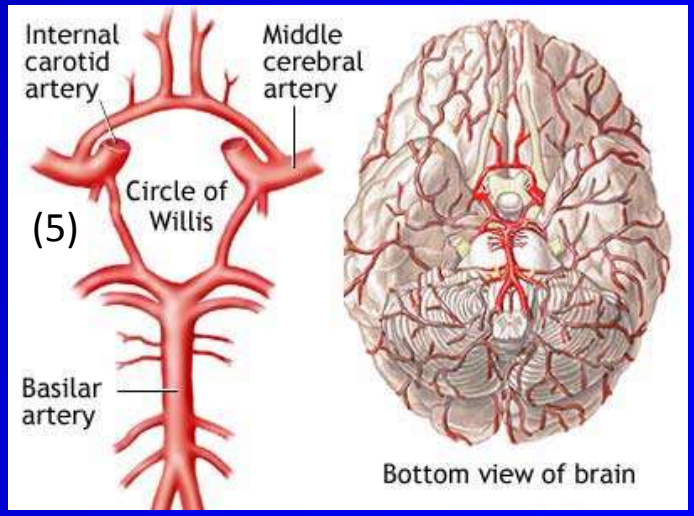
Owner of a healthcare company: No

Stockholder of a healthcare company: No

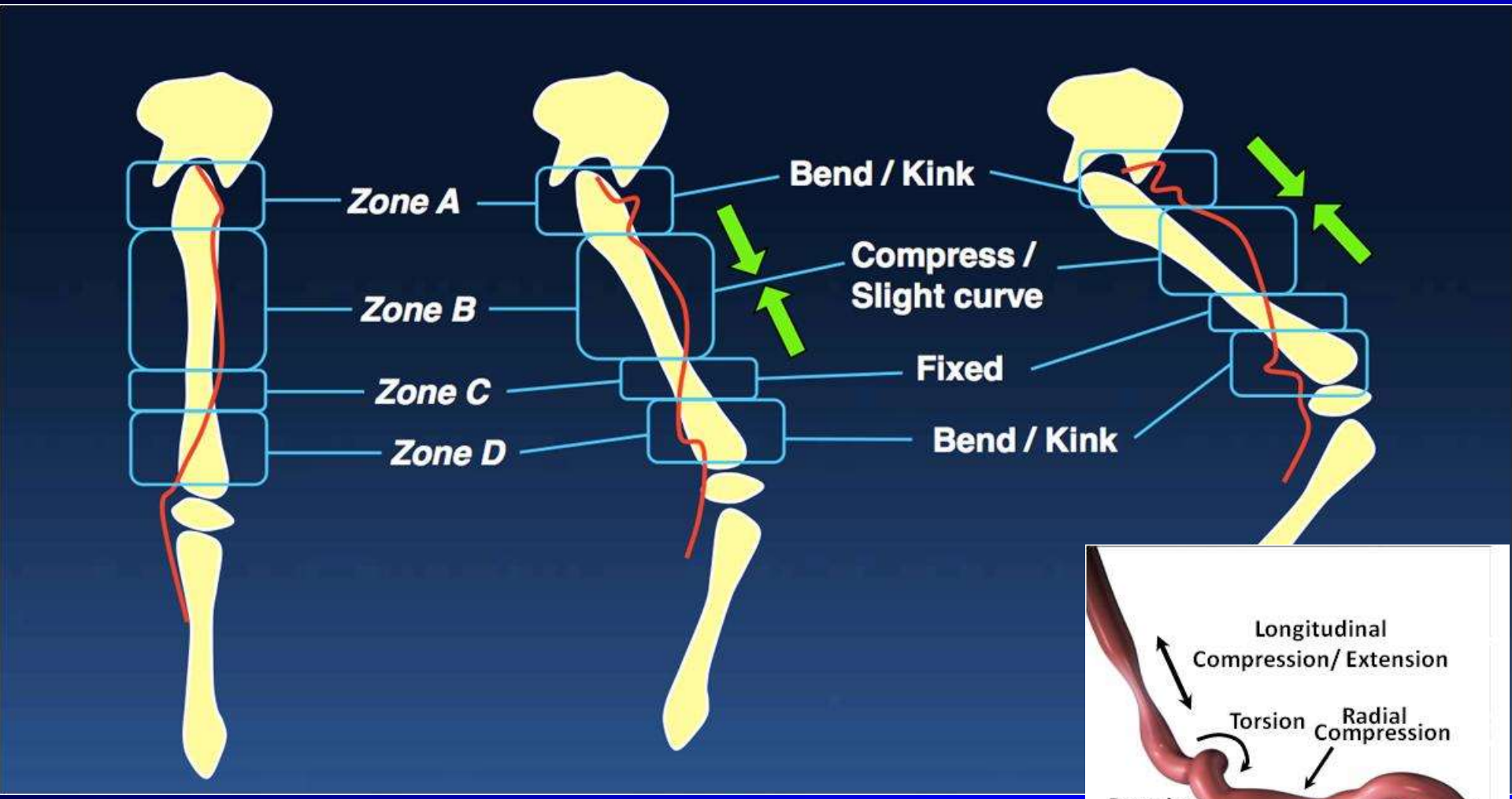
Sites of Severe Atherosclerosis
In order of Frequency







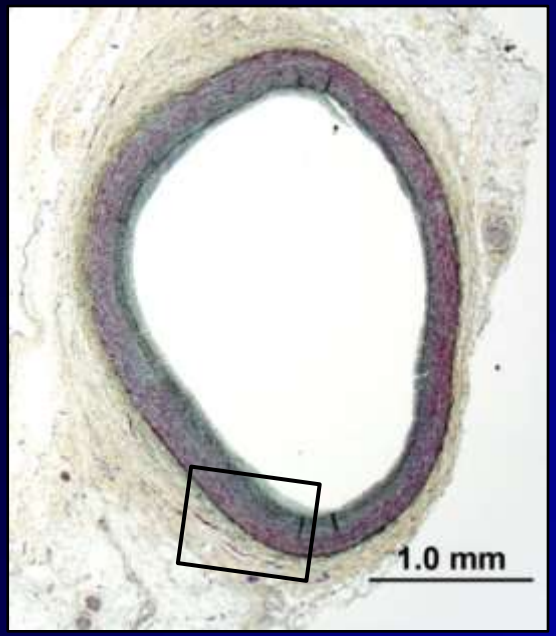
Femoro-Popliteal Artery Biomechanics

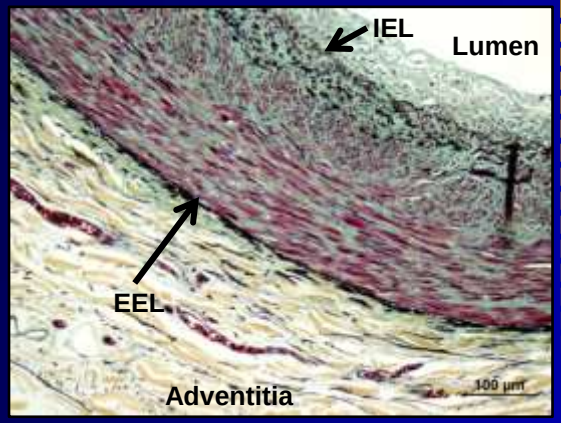


Lansky A. Angiographic Analysis of Strut Fracture in the SIROCCO Trial. TCT2004

Blood Vessel Anatomy: Coronary vs. Peripheral Artery

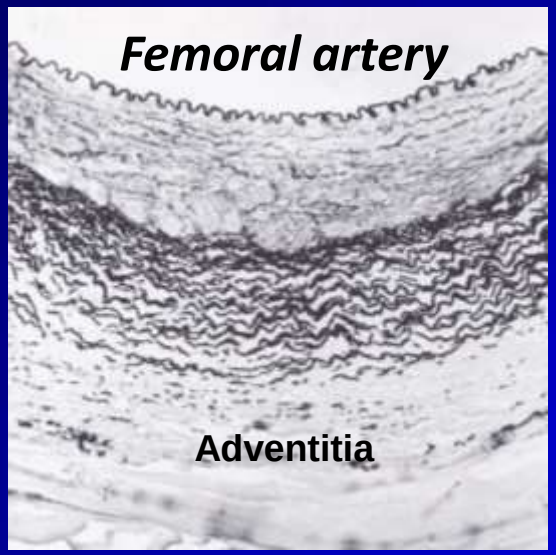
Coronary artery

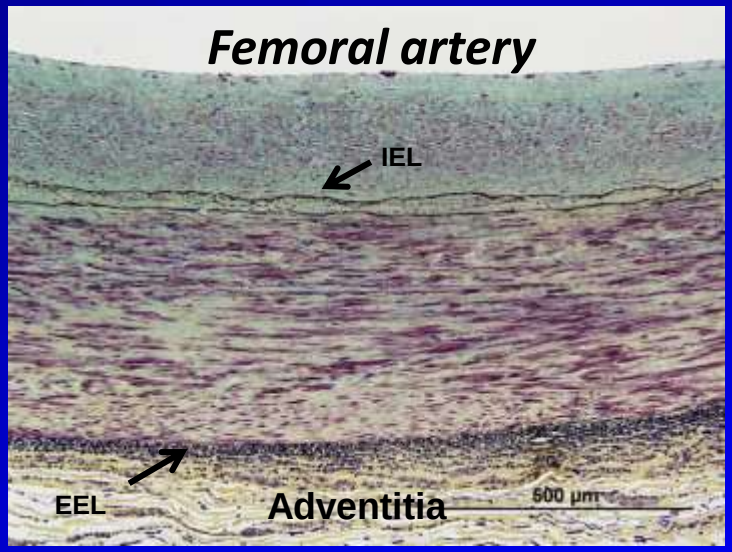


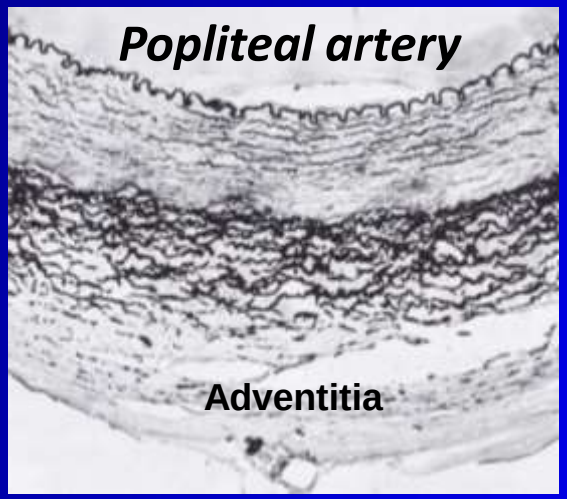


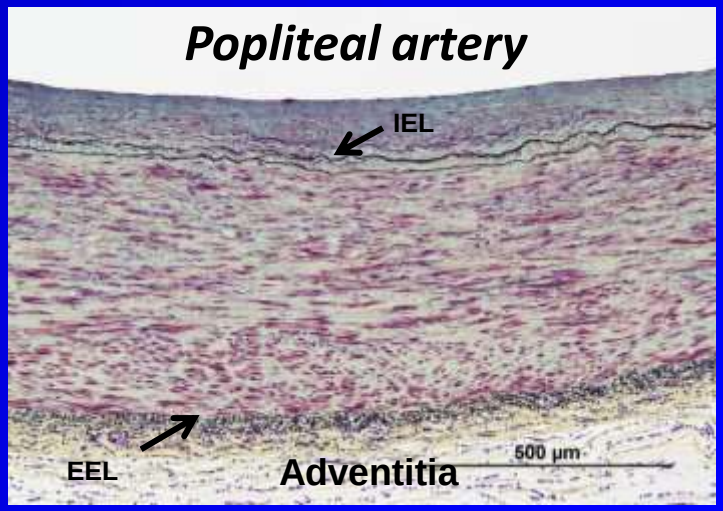
Otsuka F, et al. Mt Sinai J Med 2012;79:641-653.

Peripheral artery



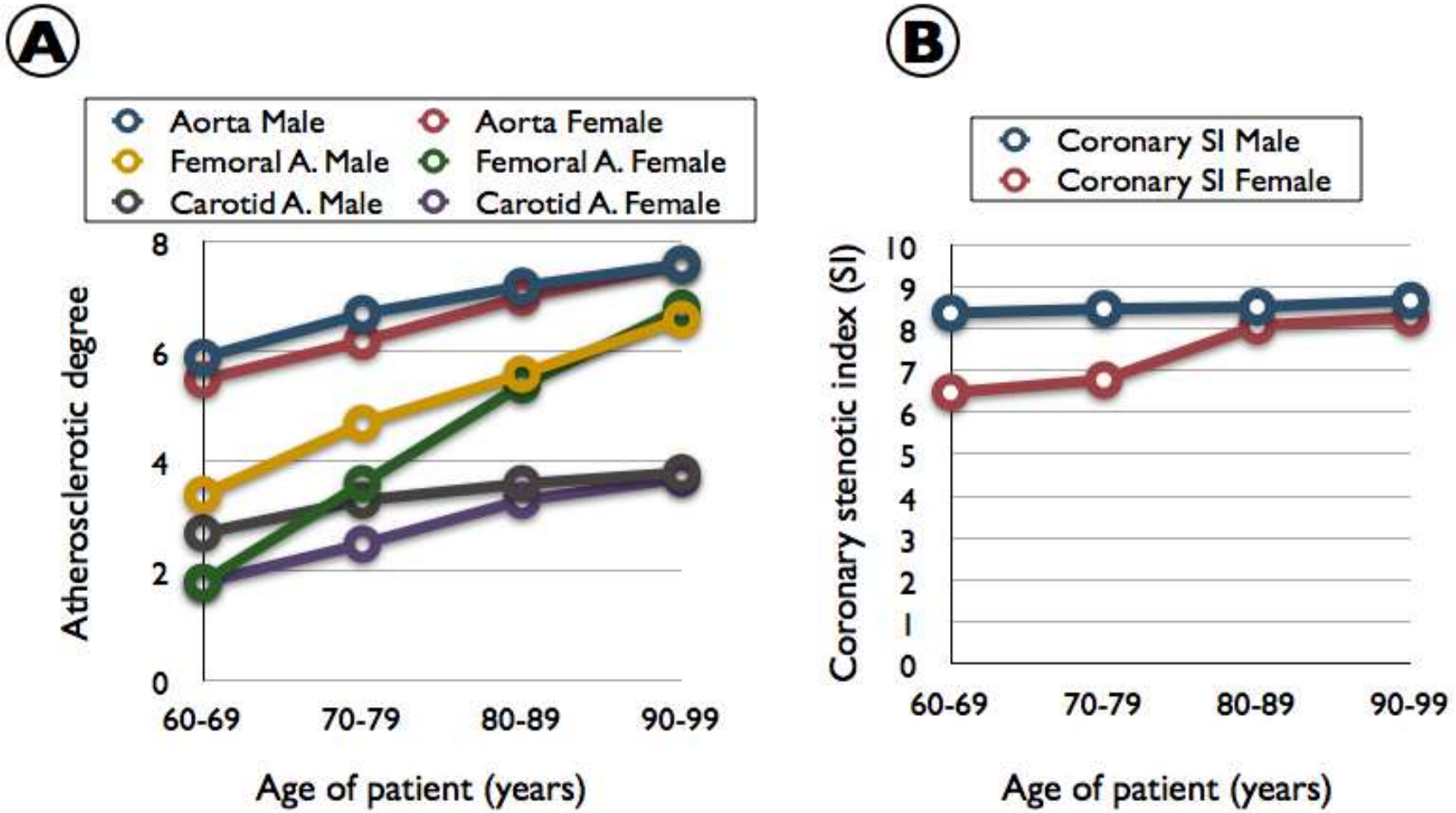






Donald F.M. Bunce, II, D.O., Ph.D. ATLAS OF ARTERIAL HISTOLOGY . 1974 by WARREN H. GREEN, Inc., St. Louis, Missouri, USA.

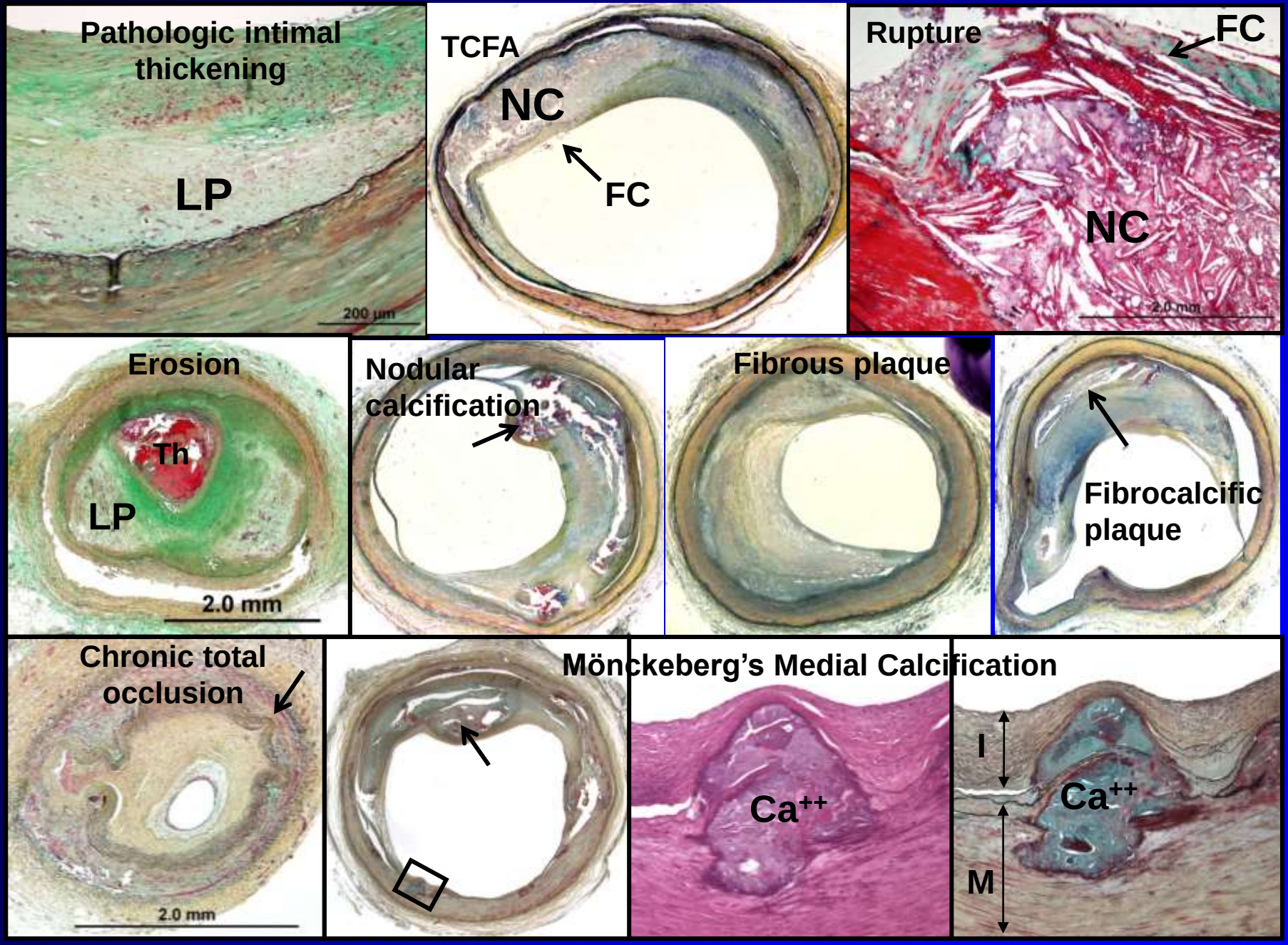
Gender-specific age-related changes of the degree of atherosclerosis in various vascular beds



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

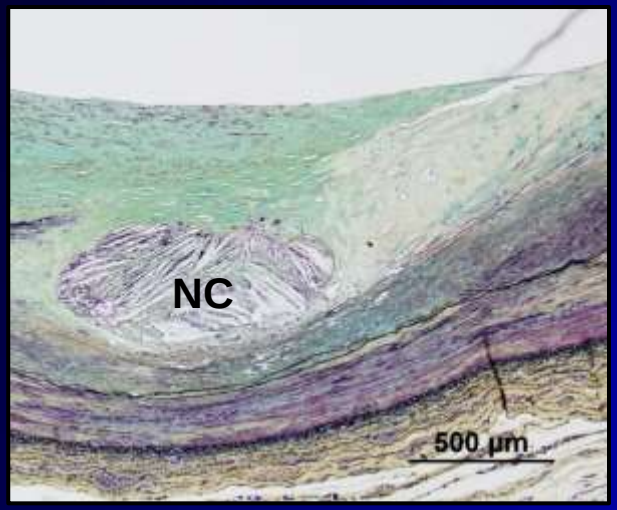
Atherosclerotic Lesions from Human Femoral Arteries



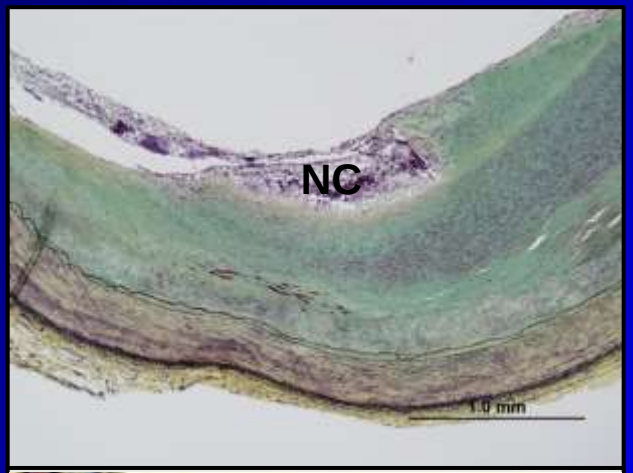
Otsuka F, et al. Mt Sinai J Med 2012;79:641-653.

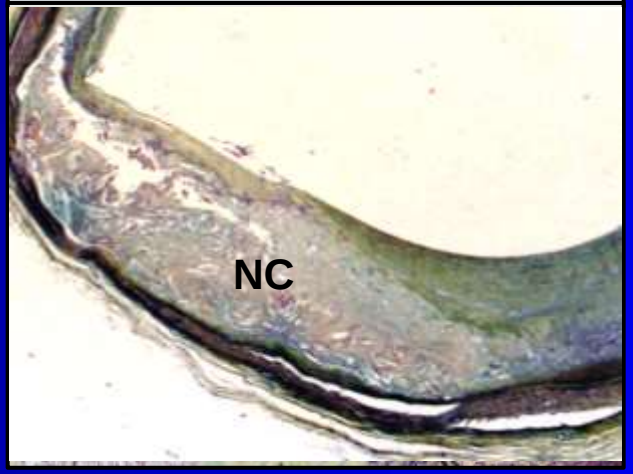
Atherosclerotic Lesions from Human Femoral Arteries

Fibroathroma

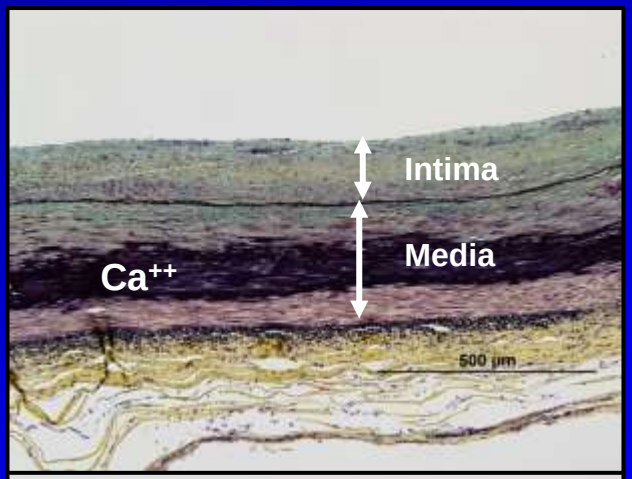


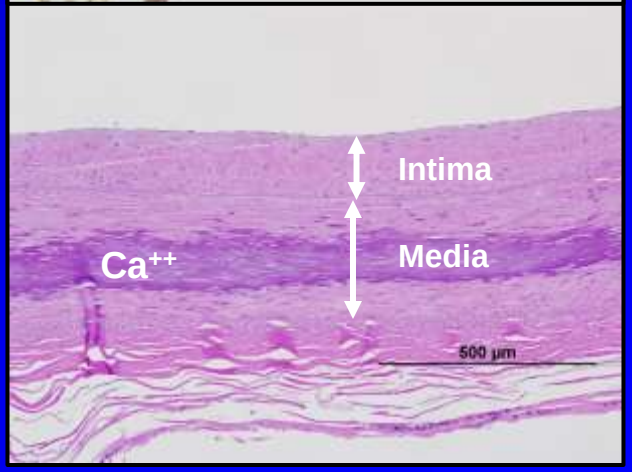
TCFA



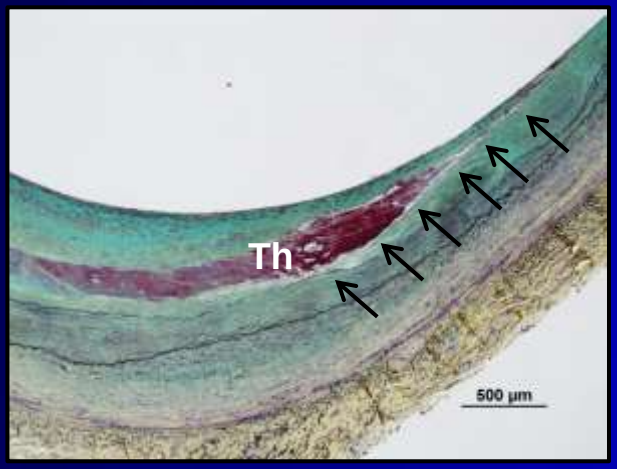


Mönckeberg's
Medial Calcification



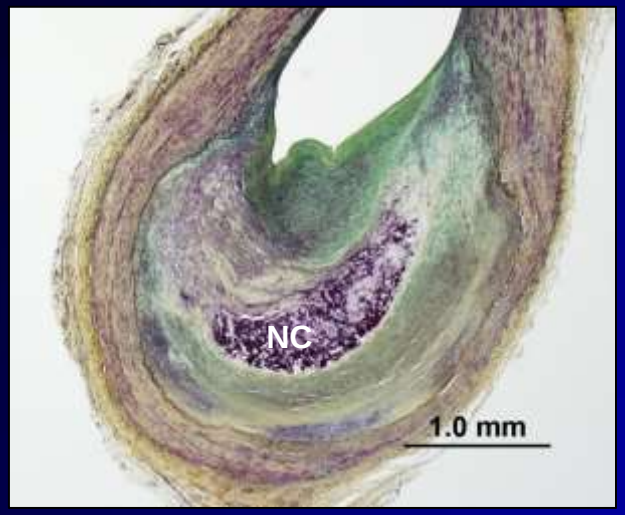


Plaque fissure



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

Fibroathroma



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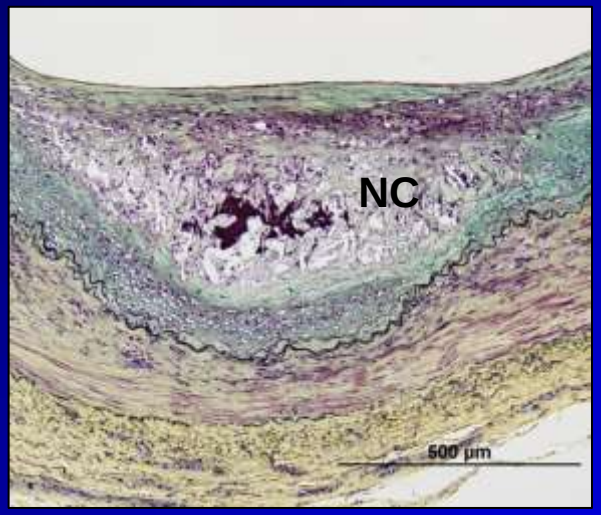
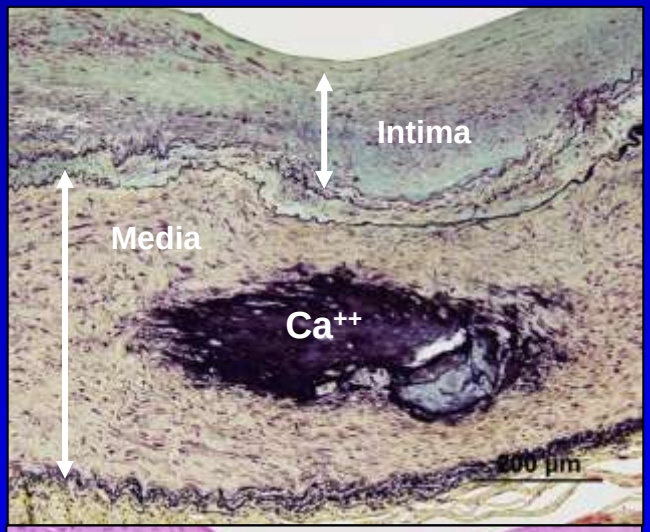
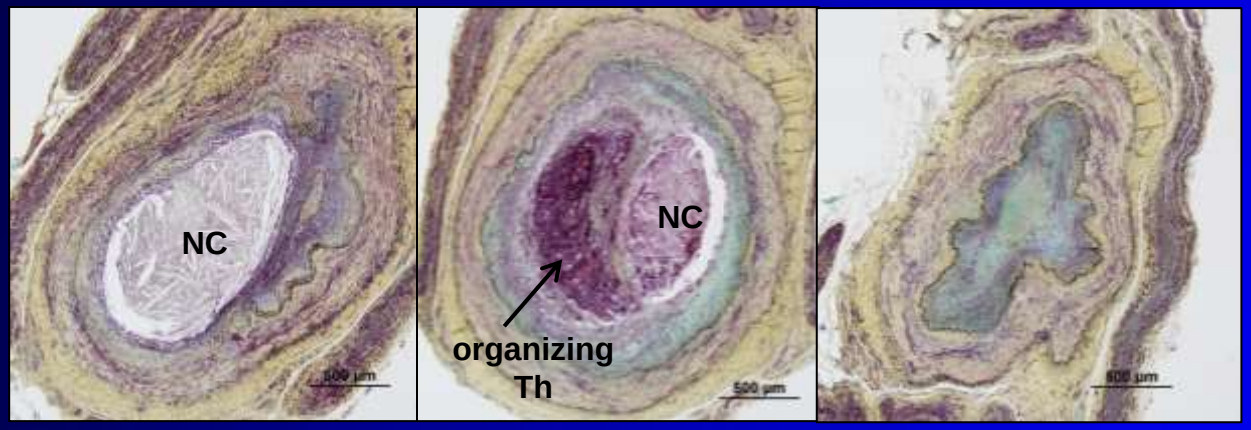
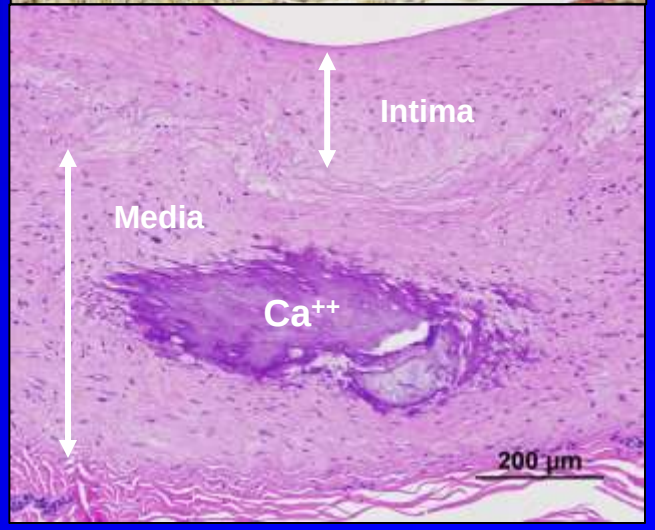


Mönckeberg's Medial Calcification

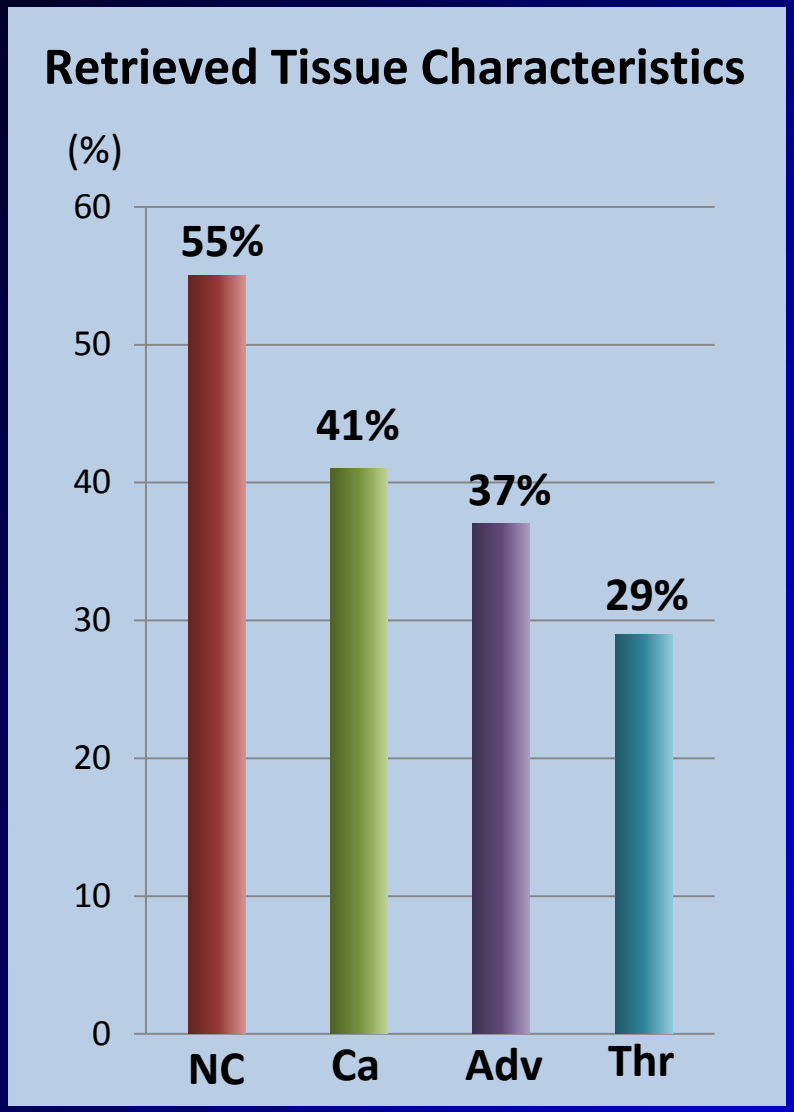


Total occlusion

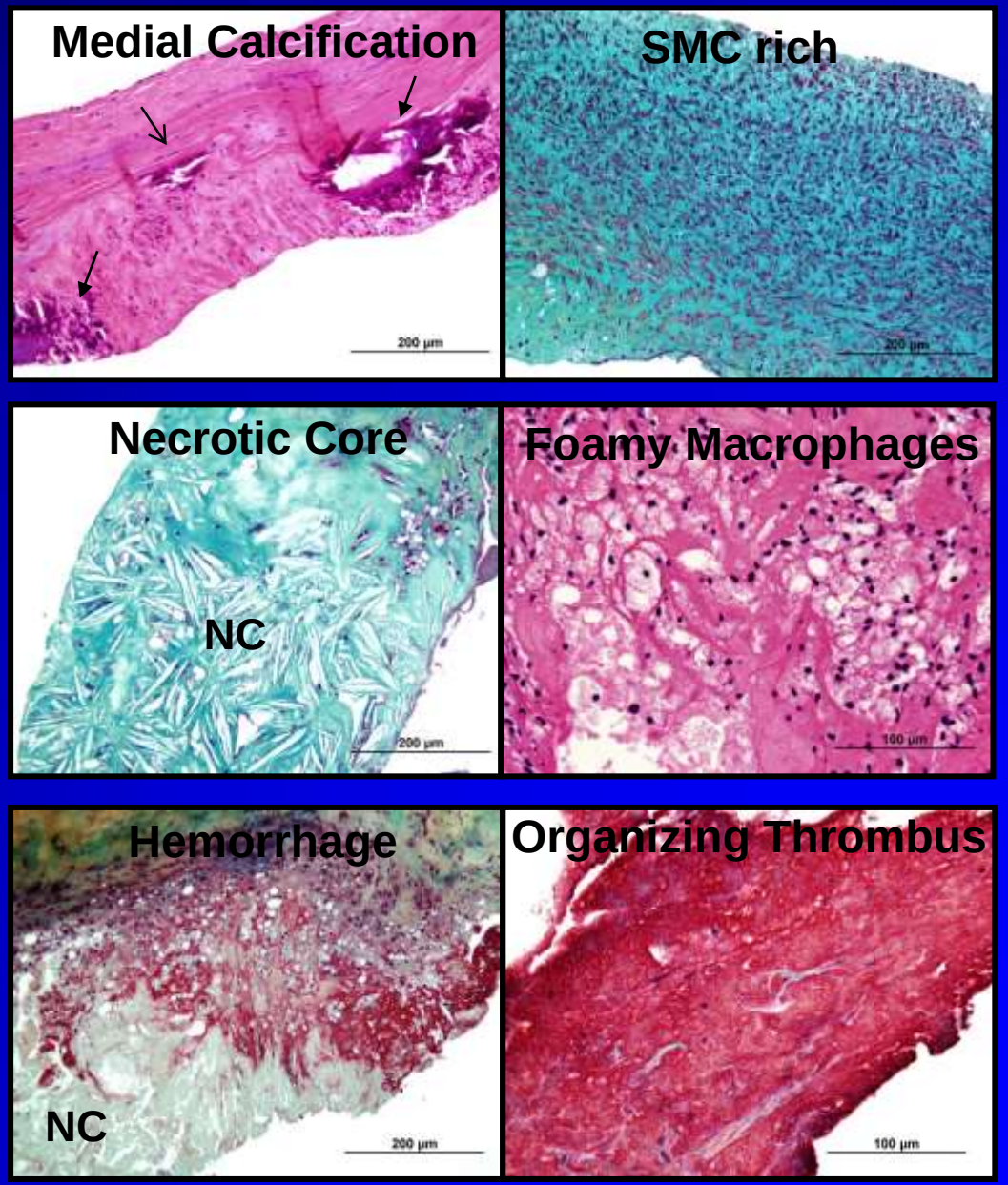




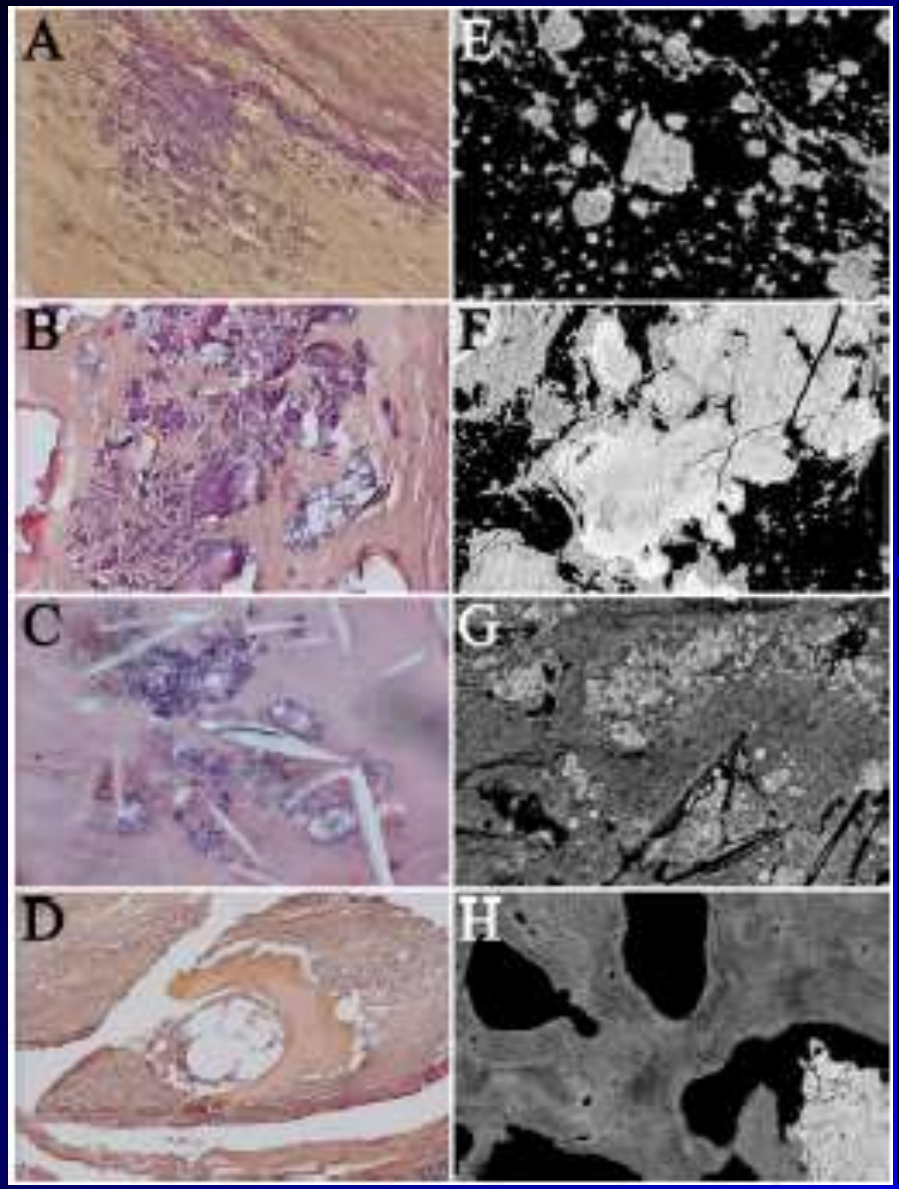
Features of Femoropopliteal and Tibial Plaques from Patients with Claudication Retrieved by SilverHawk

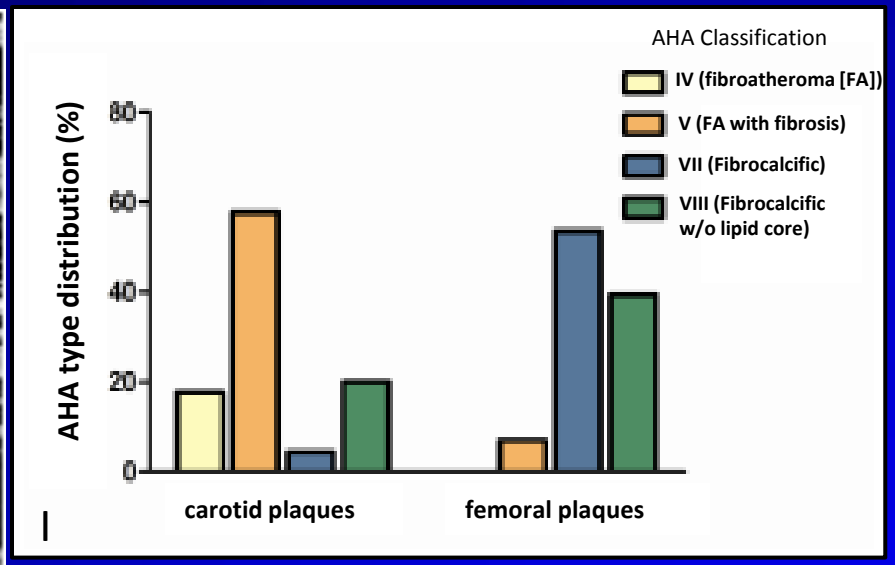


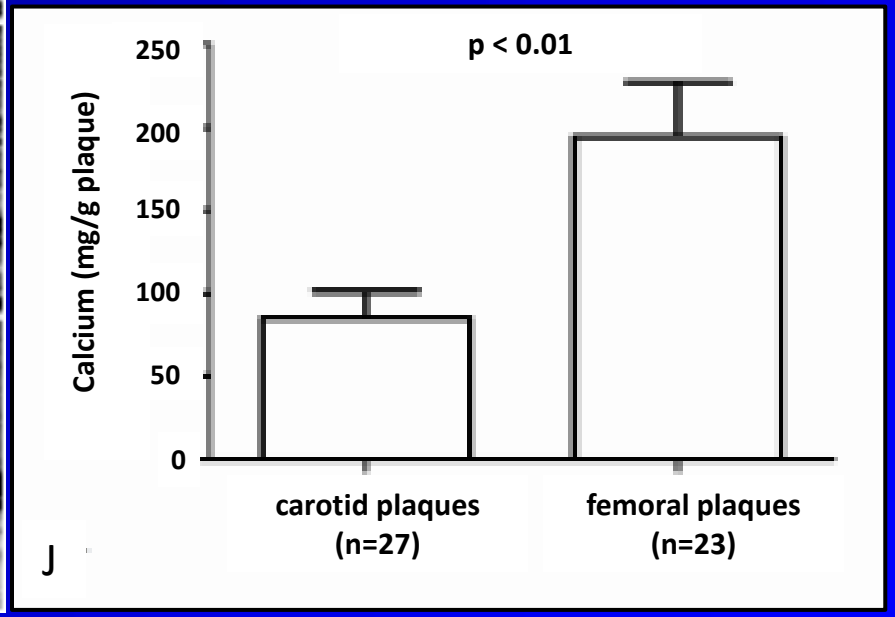
NC=necrotic core ; Ca=calcification; Adv=adventitia; Thr=thrombus



Differences Between Carotid and Femoral plaques







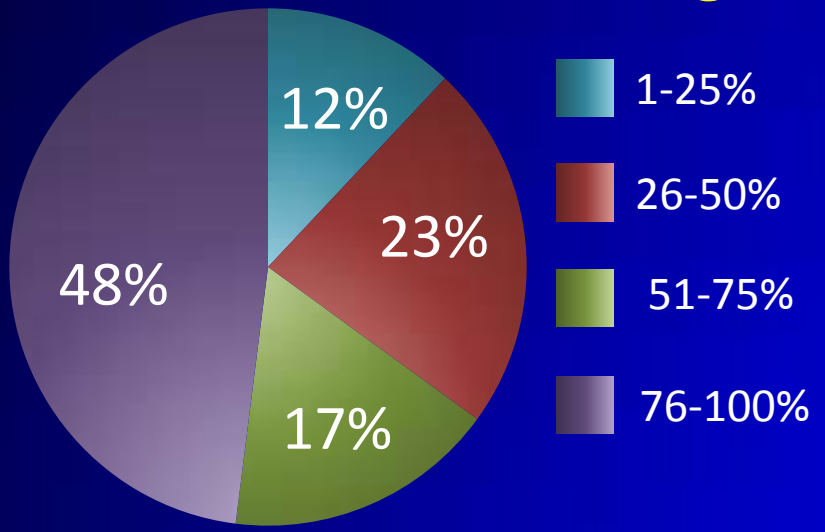
A = micronodular diffuse calcification; B = numerous stratified sheets of calcification with multinodular edges; C = clear center calcification consisting of calcici rim sorrounding some clear content; D = osteoid metaplasia.

Herisson F et al. Atherosclerosis 2011;216:348-54

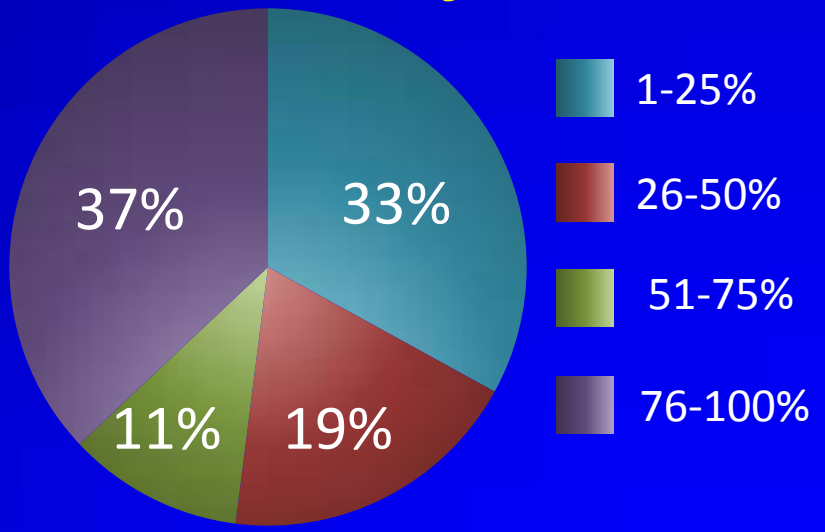
Peripheral vascular disease: who gets it and why?

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



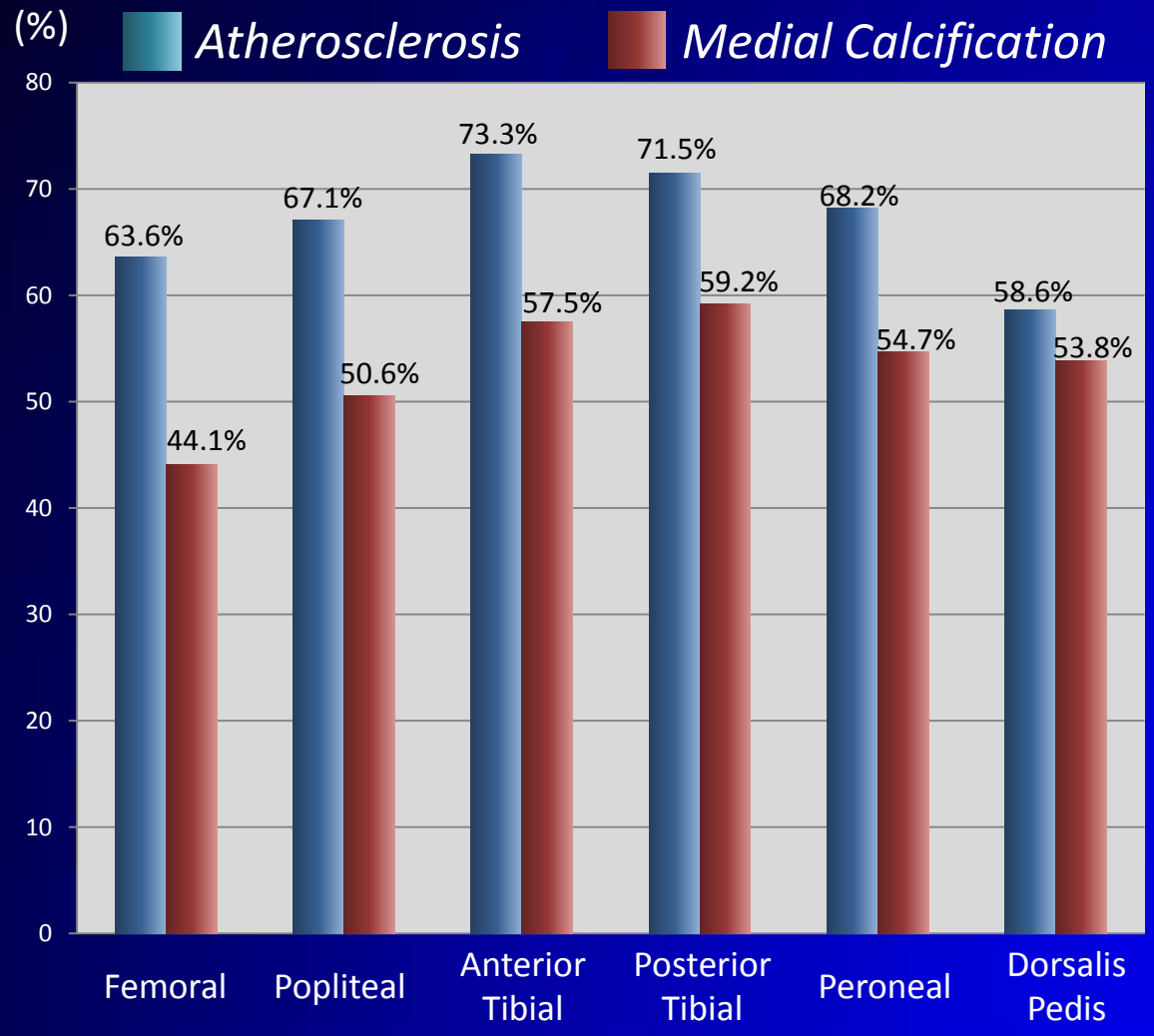
Medial Calcification



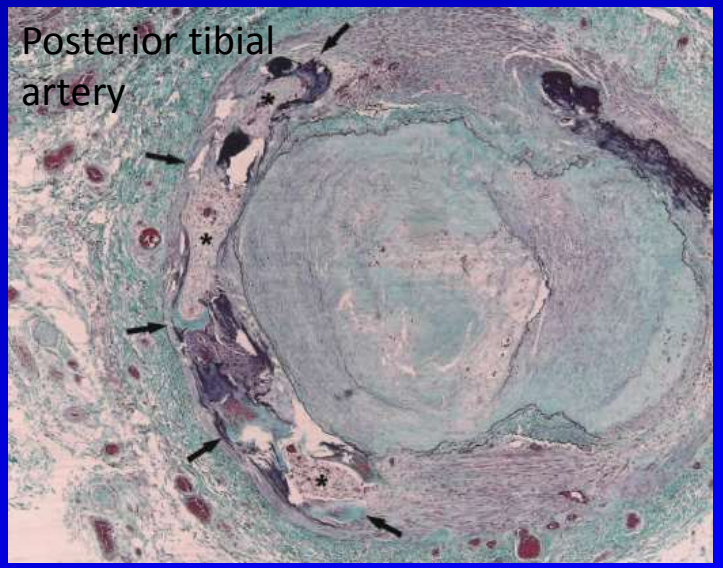
The presence of medial calcification and concomitant atherosclerosis was observed in 168 (77%) of the 218 arterial segments with atherosclerotic plaques. However, the extent of atherosclerosis did not correlate with the extent of medial calcification.

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

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



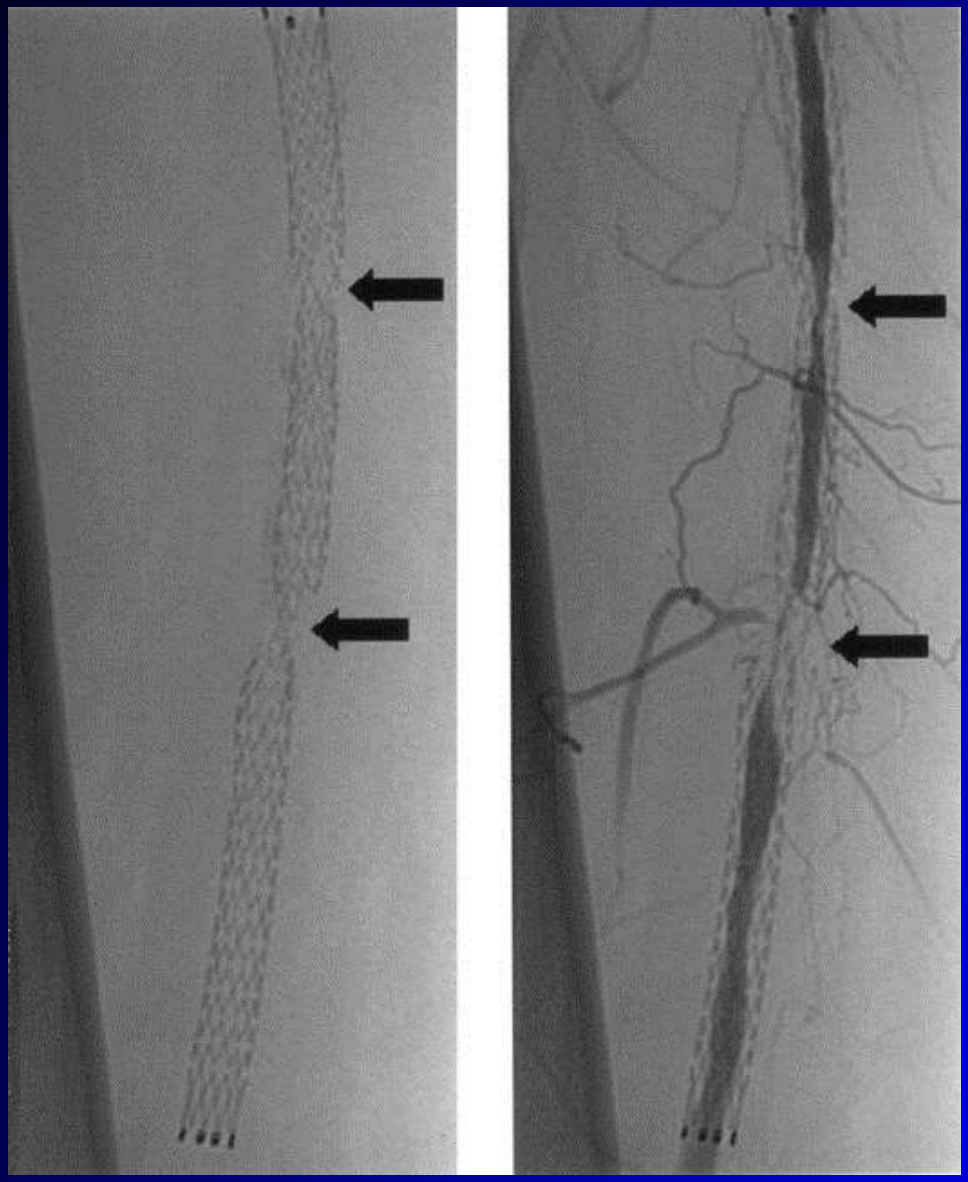
Ossification

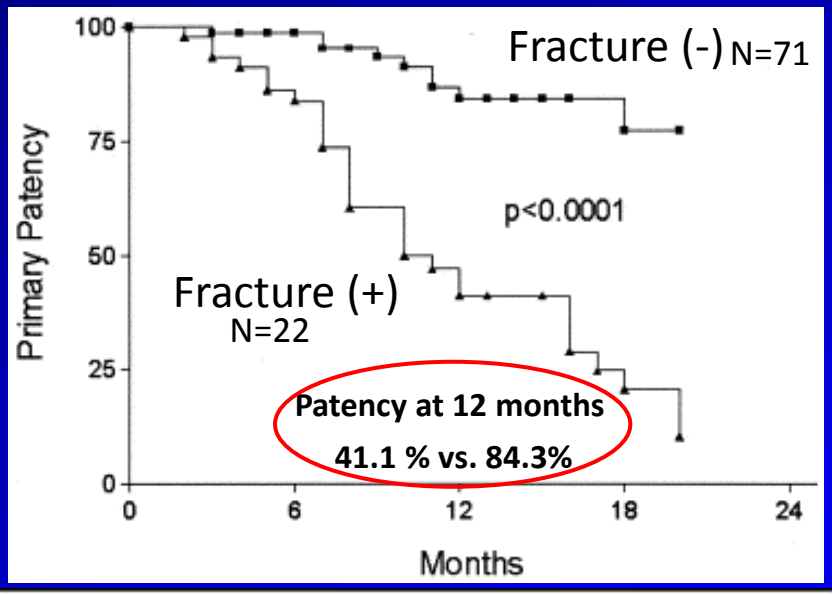


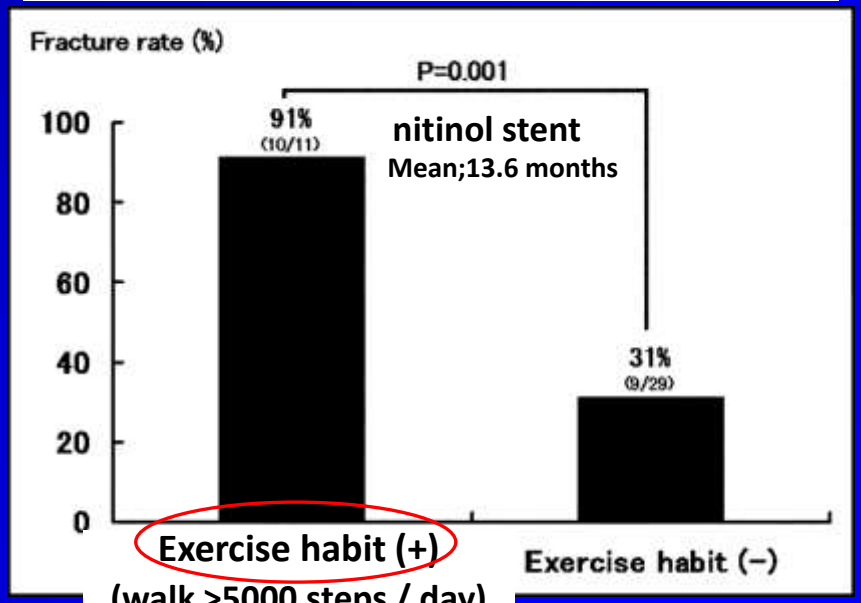
Ossification was found in 19% of the arteries.

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

Stent fracture and Restenosis in SFA and popliteal arteries



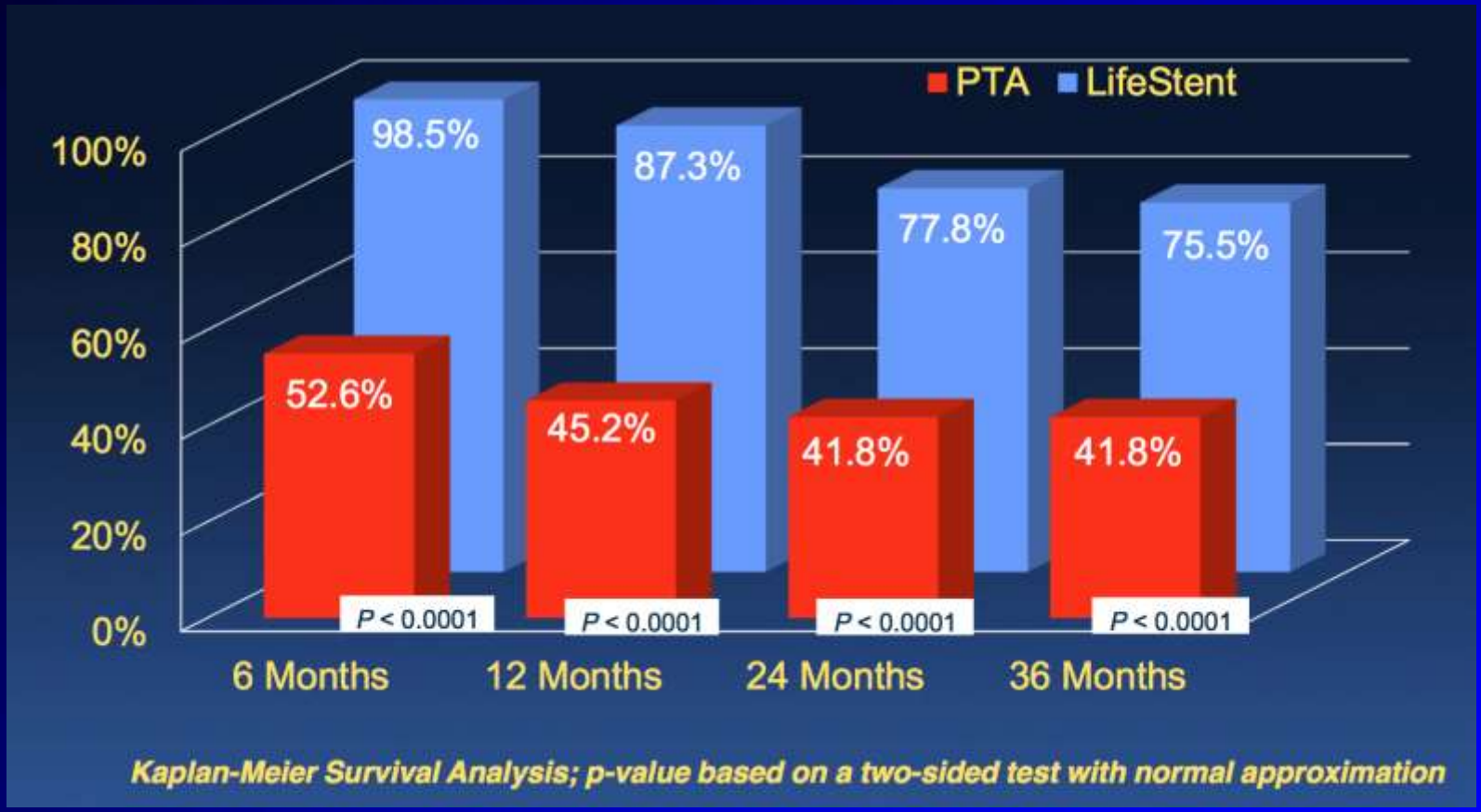


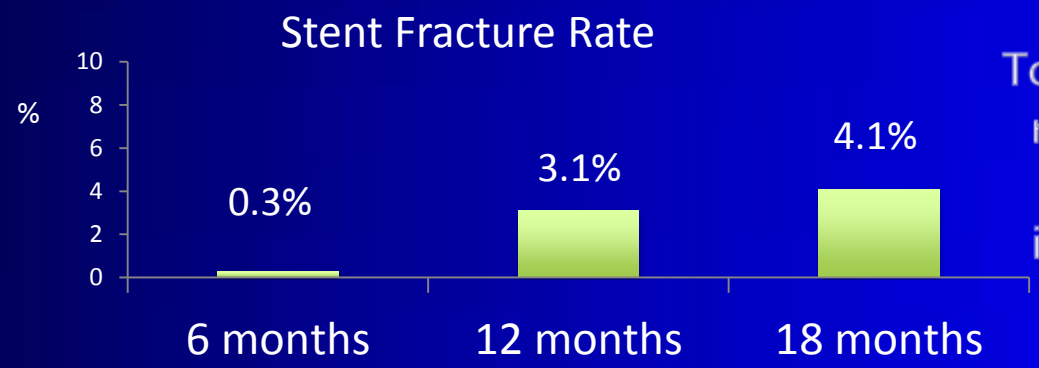


Scheinert, D et al, JACC 2005

Iida, O et al, AJC 2006

RESILIENT Randomized Trial: Freedom from TLR





Barry T. Katzen, MD. TCT 2012

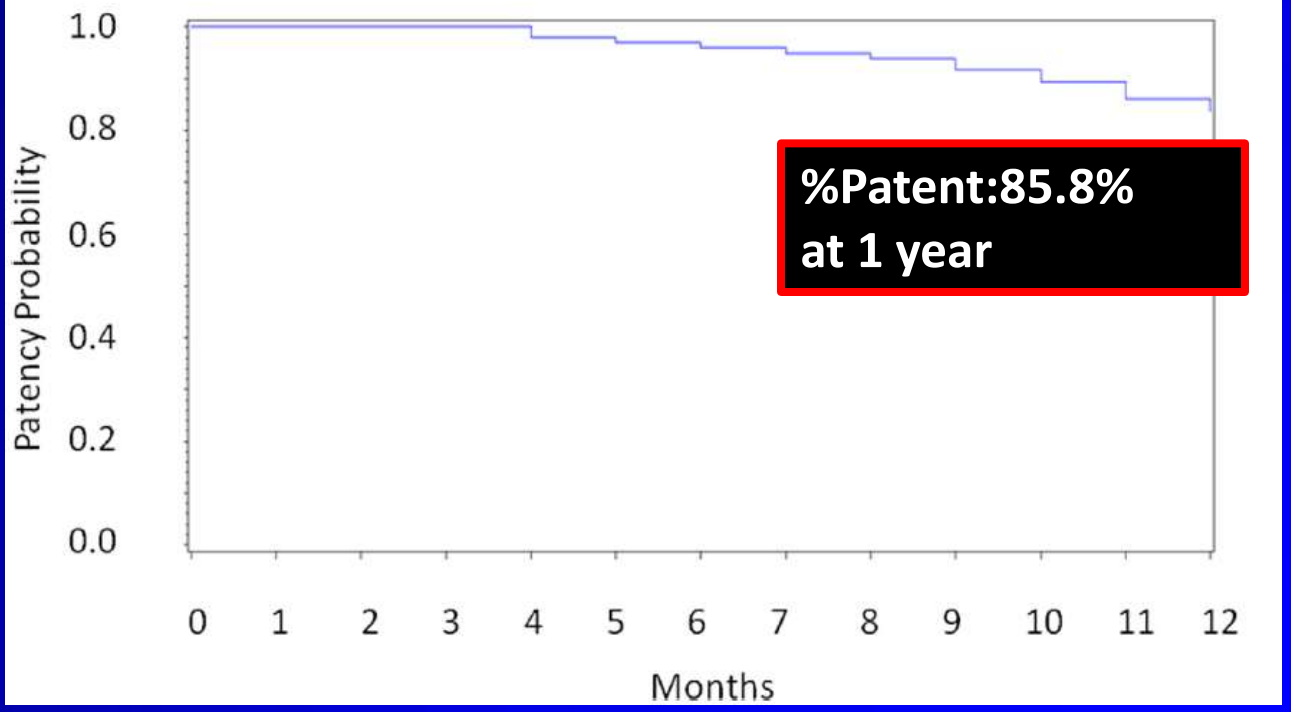
Total lesion length 60.7±37.6 mm, reference diameter 4.8±0.9 mm, Nitinol stent (Medtronic) implanted in SFA and Popliteal

John R. Laird J Endovasc ther 2012; 19:1-9

Freedom from loss of patency in Supera Stent (SAKE Study)

No stent fracture
In the 16 cases who required reintervention

Month	0-3 months	3-6 months	6-9 months	9-12 months	12-months
N at Risk	98	98	95	86	71
# Lost Patency	0	3	3	7	2
# Censored	0	0	6	8	69
% Patent	100%	100%	96.94%	93.8	85.8%
Standard Error	0	0	0.017	0.025	0.037



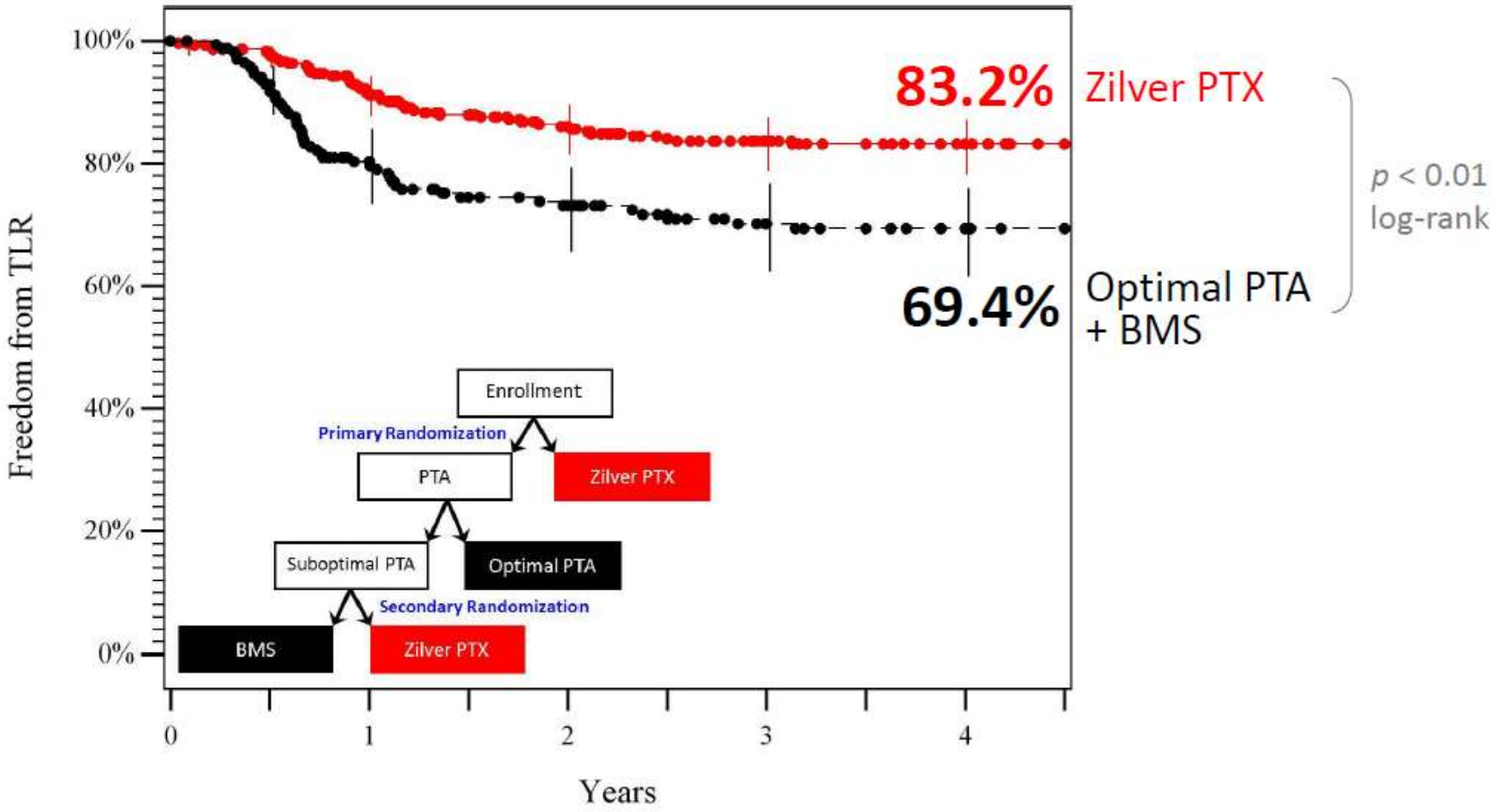
%Patent:85.8%
at 1 year

George J, et al. J Vasc Interv Radiol 2014;25:954-961

Options for Improving Outcomes for Patients with Peripheral Artery Disease

- Drug coated Stents (Zilver PTX)
- Drug Coated Balloons
- Bioabsorable Scaffold ??

4-Year Freedom from TLR
Zilver PTX vs. Standard Care – Drug Effect



45% reduction in reintervention rate due to the drug

Michael D. Dake, MD. TCT 2013

Drug Eluting Balloon Technologies

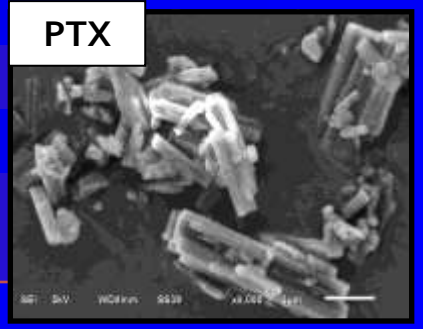
Name of company	Name of device	Status
Aachen Resonance GmbH	Elutax	Available in Europe
Abbott Vascular	Undisclosed	In development
B Braun	SeQuent Please	Available in Europe
Bayer	Paccocath	Available in Europe
Cook Group, Inc.	Advance® 18PTX®	Trials – for peripheral use
Spectronectics	Stellarex	Available in Europe
DSM Biomedical	undisclosed	In development
EuroCor	DIOR®	Available in Europe
Invatec Roncadelle	IN.PACT™ Amphirion/Admiral/Pacific	Available in Europe and U.S.A – peripheral use
Invatec Roncadelle	IN.PACT™ Falcon	Available in Europe– coronary use only
Lutonix,	Lutonix 035™	Available in Europe and U.S.A
Kaneka Corp	Undisclosed	In development
Medrad/Possis Medical	Cotavance™	In development for peripheral use

In.Pact Amphirion

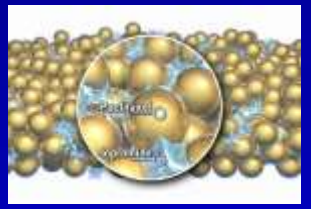
ELUTAX

Sequent Please

Lutonix



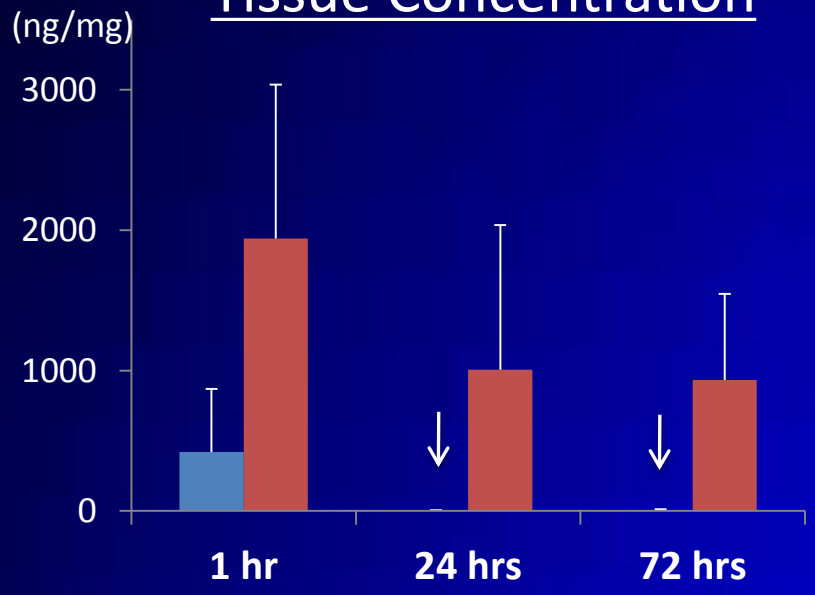
Drug deliver of DEB



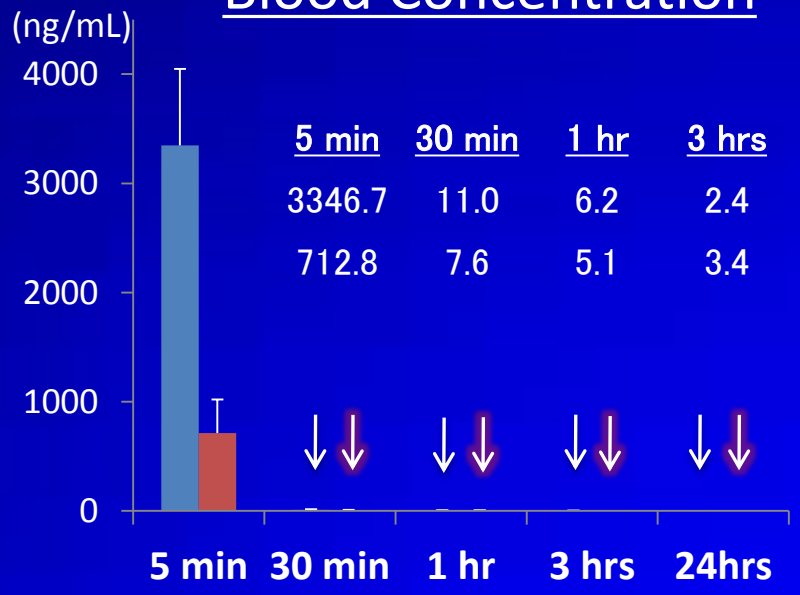
PTX only

PTX + Iopromide (SeQuent)

Tissue Concentration



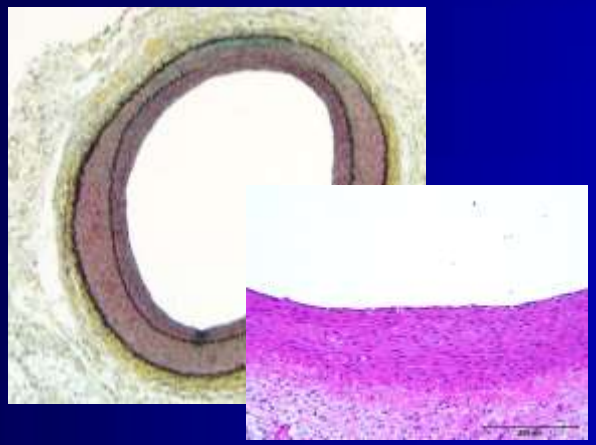
Blood Concentration



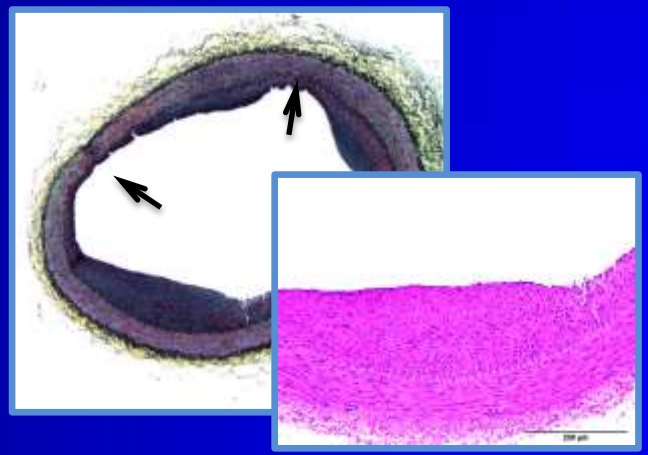
5 min	30 min	1 hr	3 hrs	24 hrs
3346.7	11.0	6.2	2.4	0.4
712.8	7.6	5.1	3.4	1.8

Non-atherosclerotic Rabbit Iliac Model – 28 days

POBA



PTX only



PTX+Iopromide

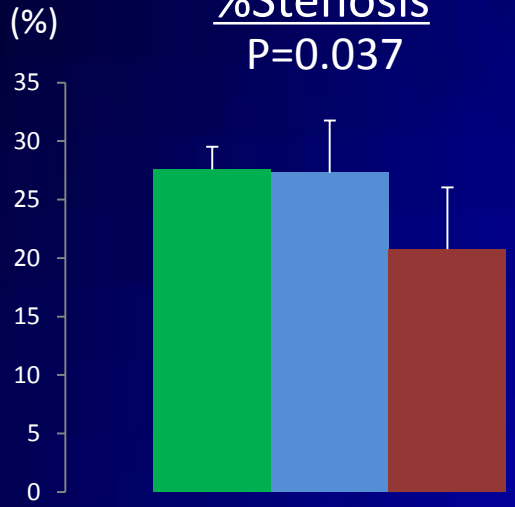
Vascular Response to DEB

At 28-days following treatment in Rabbit Iliac model

POBA PTX only PTX + Iopromide (SeQuent)

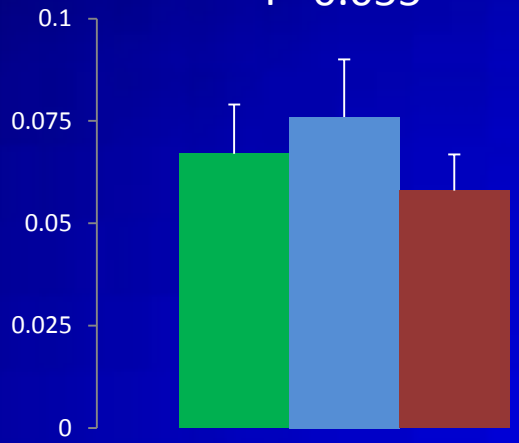
%Stenosis

P=0.037



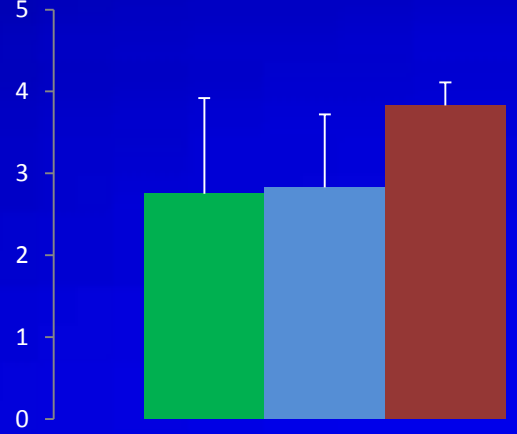
Neoint THK

P=0.055



Media SMC Loss

P=0.044



Fibrin/Platelets

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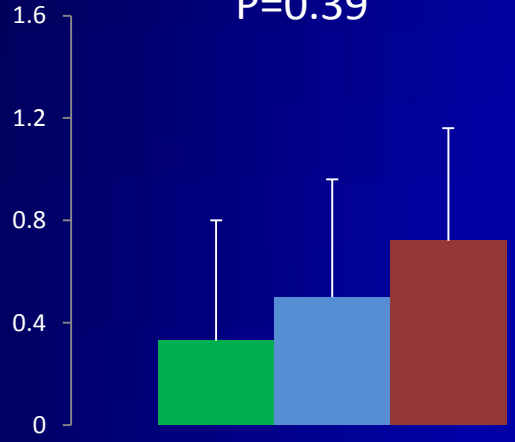

Intima-Media Inf

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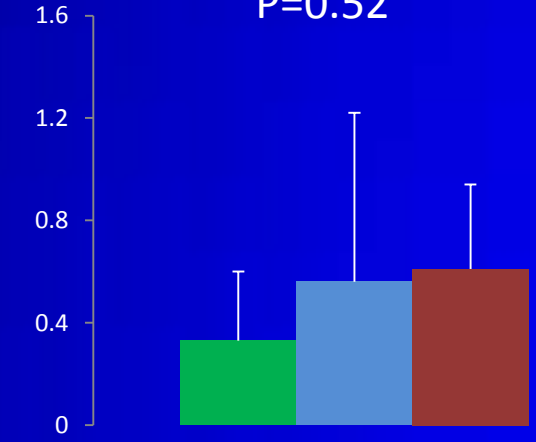

Endothelial Loss

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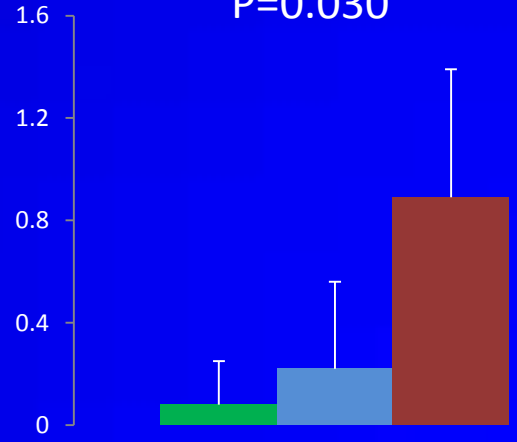
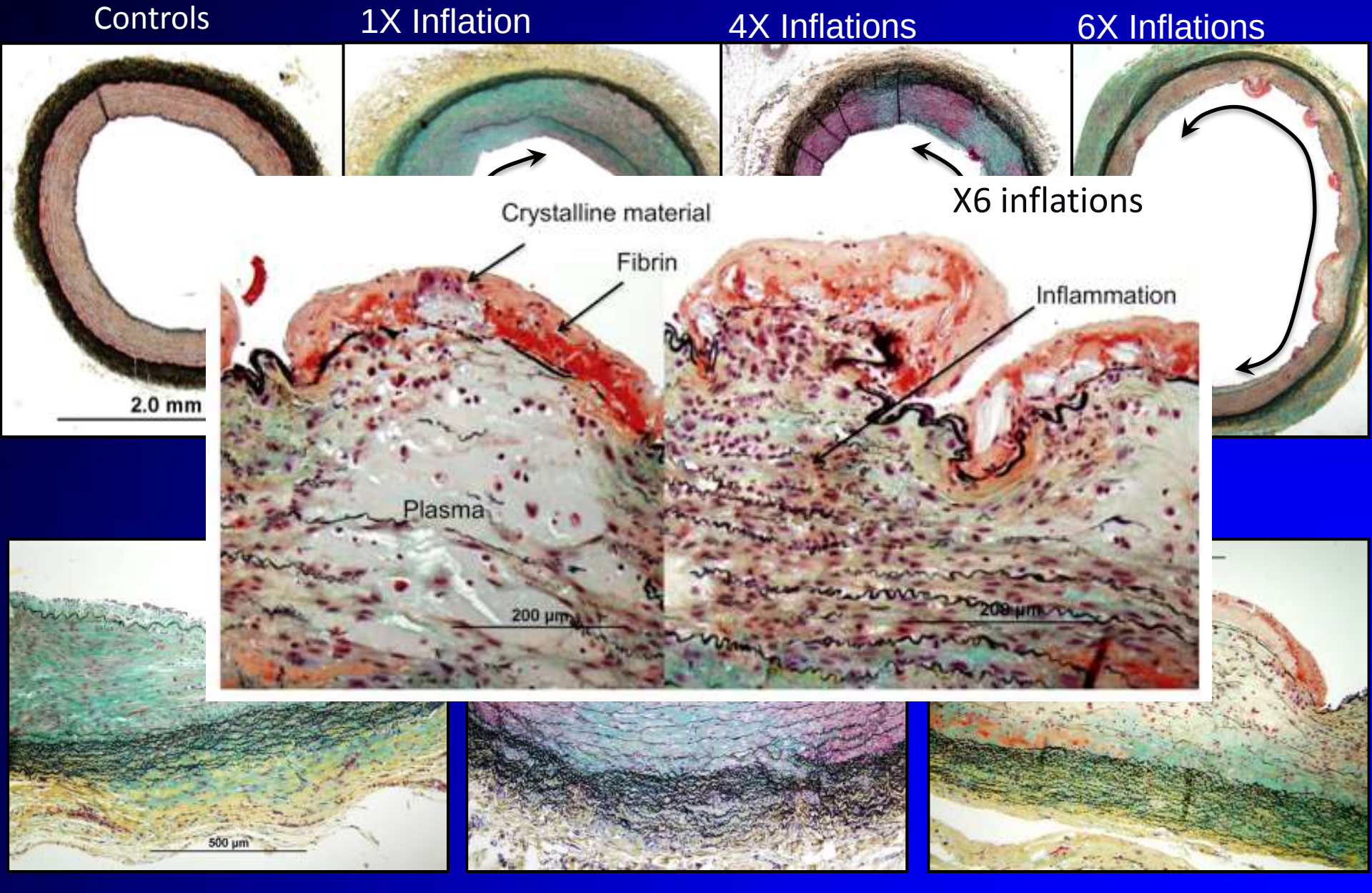
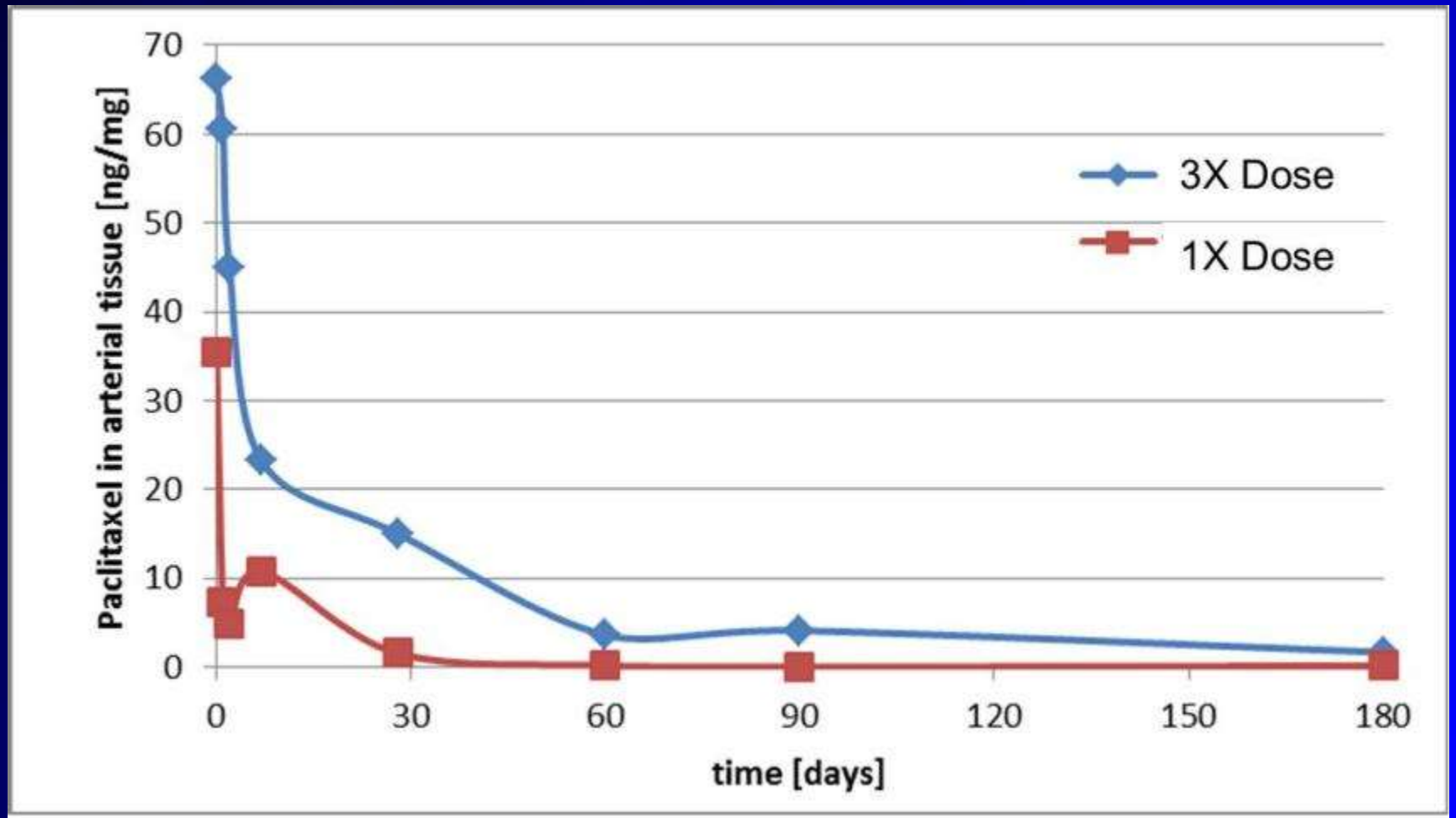


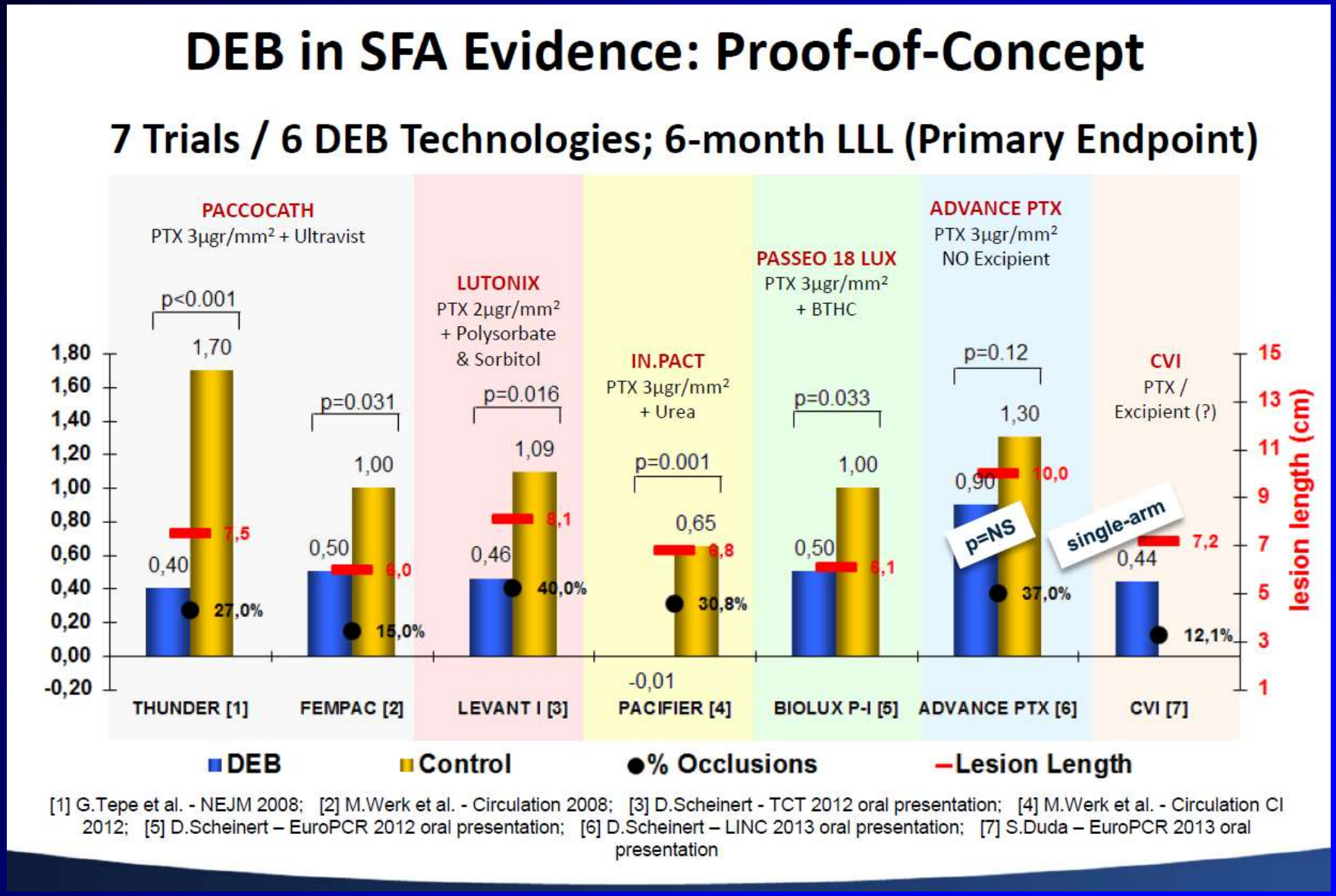
Dose-dependent Changes in Iliofemoral Arteries Following SeQuent DEB treatment at 14 days



IN.PACT™ Pharmacokinetics
Porcine Ilio-Femoral DEB PK: Arterial Tissue



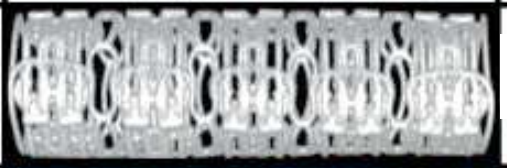
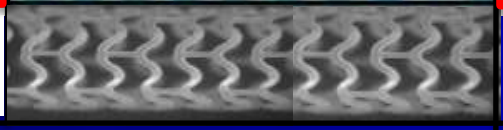
DCB in SFA – Clinical trials



[1] G.Tepe et al. - NEJM 2008; [2] M.Werk et al. - Circulation 2008; [3] D.Scheinert - TCT 2012 oral presentation; [4] M.Werk et al. - Circulation CI 2012; [5] D.Scheinert – EuroPCR 2012 oral presentation; [6] D.Scheinert – LINC 2013 oral presentation; [7] S.Duda – EuroPCR 2013 oral presentation

Late lumen loss at 6 months

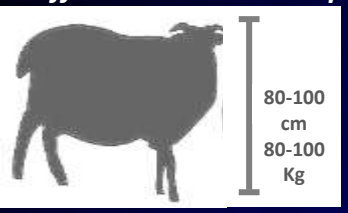
Thomas Zeller MD. TCT 2014

Igaki-Tamai (Kyoto Medical)		DESolve (Elixir Medical)	
AMS 1.0 (Biotronik)		BTI (Xenogenics Corp.)	
AMS 3.0 (Dreams 1st generation)		IDEAL (BTI 2nd generation)	
AMS 4.0 (Dreams 2nd generation)		ART (Arterial Remodeling Technology)	
REVA (REVA Medical)		ART18Z (ART 2nd generation)	
ReZolve (REVA 2nd generation)		Amaranth (Amaranth Medical)	
BVS 1.0 (Abbott Vascular)		Xinsorb (Huaan Biotechnology)	
Absorb BVS (BVS 1.1)		Stanza (480 Biomedical)	
BRS (Micropost)		ReMes (Meril Life Sciences)	

Bioresorbable Scaffold Status Update

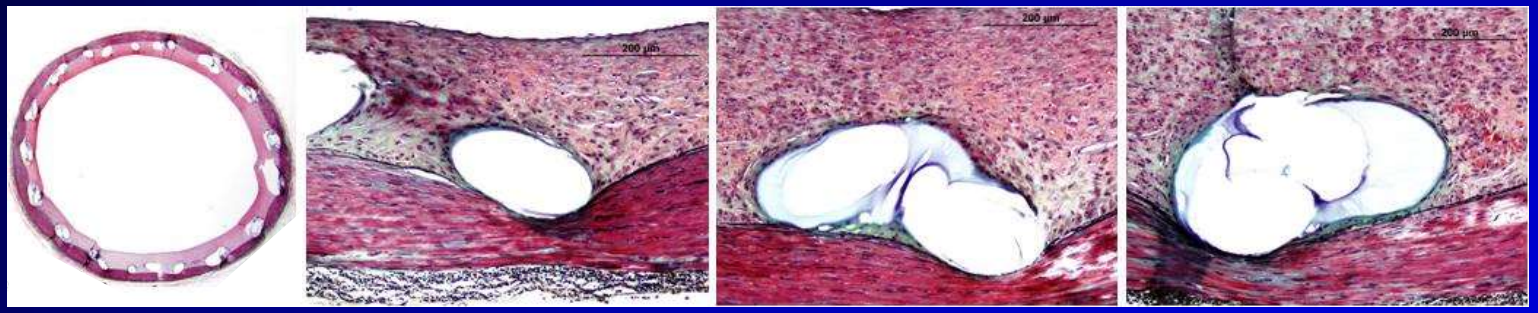
Bioresorbable scaffold, Manufacture	Target Vessel	Strut Material	Drug Coating Material	Drug	Radiopacity	Strut Thickness (µm)	Duration of radial support	Time to Resorption	Current status
Igaki-Tamai (Kyoto Medical)	SFA/Coronary	PLLA	None	None	Gold markers	170	6 mo	2-3 yrs	CE approved (PAD)
STANZA v1.0 (480 Biomedical)	SFA	PLGA	None	None	Platinum markers	150	3 mo	12-15 mo	FIM Initiated (STANCE)
STANZA v1.1 (480 Biomedical)	SFA	PLGA	None	None	Platinum markers	175	6 mo	12- 15 mo	FIM Initiated (STANCE)
STANZA DRS (480 Biomedical)	SFA	PLGA	PCL	Paclitaxel	Platinum markers	175	6 mo	12-15 mo	FIM Initiated (SPRINT)
Esprit (Abbott Vascular)	SFA	PLLA	PDLLA	Everolimus	Platinum markers	157?	6 mo?	2-3 yrs	FIM Initiated
BVS 1.0 (Abbott Vascular)	Coronary	PLLA	PDLLA	Everolimus	Platinum markers	157	Weeks	2-3 yrs	FIM completed
Absorb BVS 1.1 (Abbott Vascular)	Coronary/SFA	PLLA	PDLLA	Everolimus	Platinum markers	157	6 mos	2-3 yrs	CE approved
AMS-1.0 (Biotronik)	Coronary	Mg	None	None	None	165	Days or weeks	<4 mo	FIM completed
AMS-3.0 (Biotronik)	Coronary	Mg	None	Paclitaxel	None	125	Weeks	>4 mo	FIM (BIOSOLVE-1 completed)
AMS-4.0 (Biotronik)	Coronary	Mg	PLLA	Sirolimus	Metalic markers	N/A	N/A	N/A	Used in BIOSOLVE-1
REVA (Reva Medical)	Coronary	Poly-tyrosine-polycarbonate polymer	None	None	Scaffold itself	200	3-6 mo	>4 yrs	FIM completed
ReZolve (Reva Medical)	Coronary	Poly-tyrosine-polycarbonate polymer	None	Sirolimus	Scaffold itself	114-228	4-6 mo	>4 yrs	FIM planned in 2013
DESolve (Elixir Medical)	Coronary	PLLA	PLLA	Mvolimus	Metalic markers	150	N/A	<2 yrs	FIM completed
Ideal BioStent (Xenongenics)	Coronary	Polymer salicylate+linker	Salicylate	Sirolimus	None	175	3 mo	>12 mo	FIM completed
ART 18Z (Arterial Remodeling Technologies	Coronary	PDLLA	None	None	None	170	3-6 mo	18 mo	FIM Initiated
Xinsorb (Huaan Biotechnology)	Coronary	PLLA+PCL+PLGA	None	Sirolimus	Metalic markers	160	N/A	N/A	Preclinical underway

Suffolk Cross-bred sheep

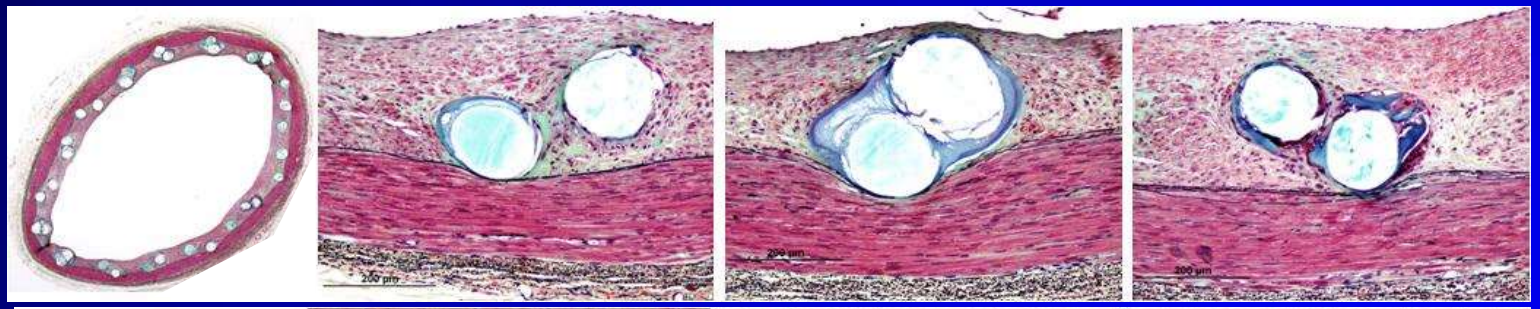


Chronic Performance and Biocompatibility of STANZA

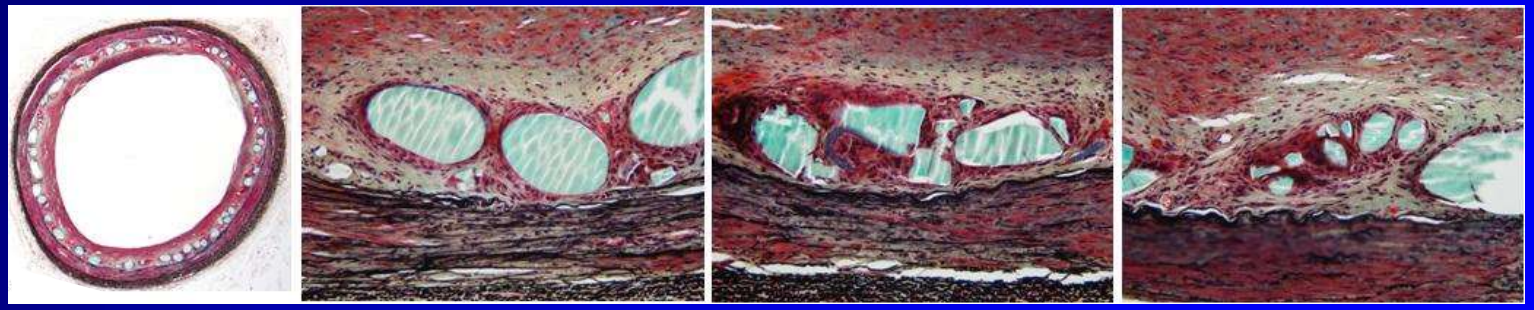
3 mo



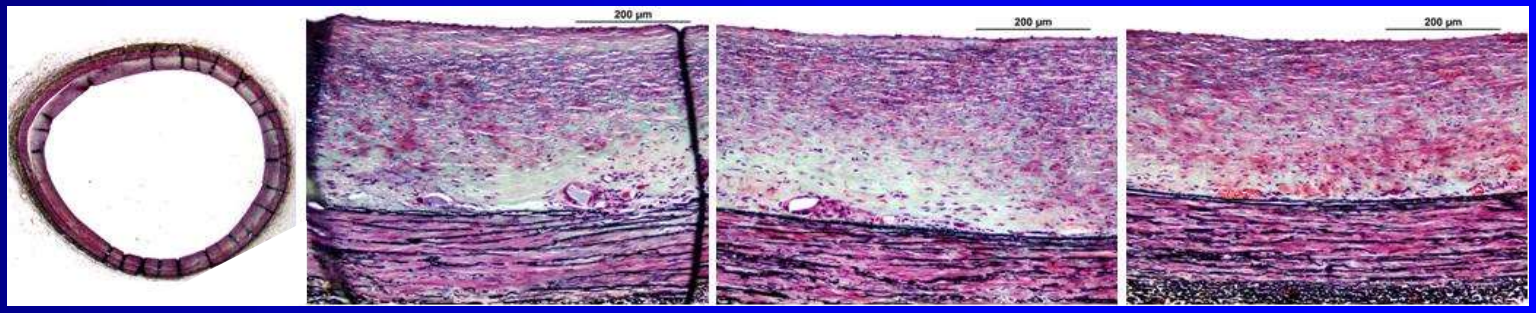
6 mo



12 mo



18 mo



Advantages of Biodegradable Scaffold

- It should be possible to restore natural vessel structure and function after the scaffold breaks down and resorbs?
- What late events might be avoided?
  - Neoatherosclerosis?
  - Late catch up in DES?
  - Late strut malapposition?
  - Chronic inflammatory reaction?
  - Fractures?

TLR and Restenosis in Igaki-Tamai Stent (The GAIA Study)

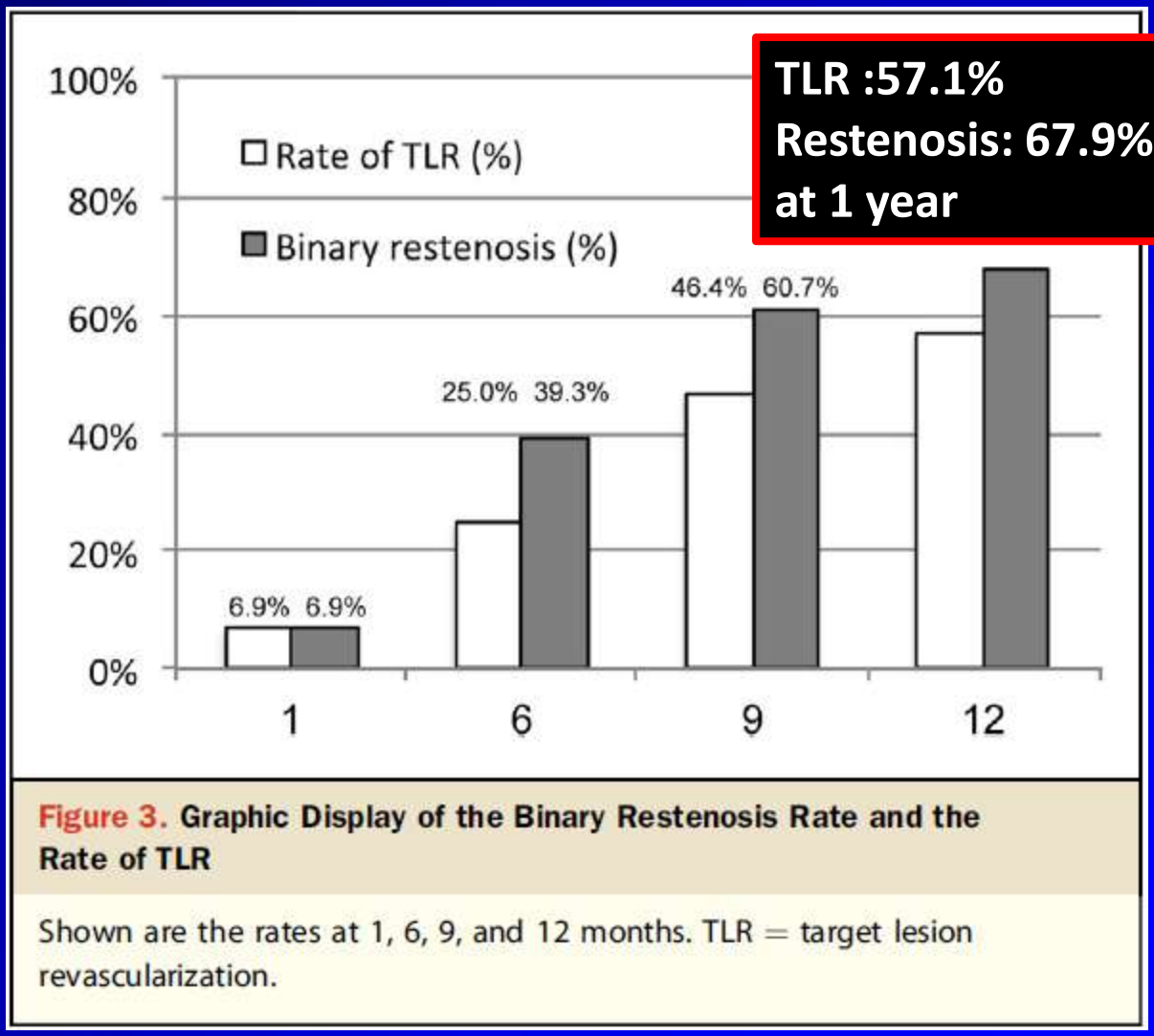


Figure 3. Graphic Display of the Binary Restenosis Rate and the Rate of TLR

Shown are the rates at 1, 6, 9, and 12 months. TLR = target lesion revascularization.

Werner M, et al. JACC:Cardiovascular interventions, Vol.7, No.3, 2014

Unique Demands of the Femoral Artery will require Unique Interventions!

Conclusions:

- Because of unique demands of the femoral /popliteal artery i.e., must have the ability to withstand flexion, extension, compression and torsion, long lesion stenting of arteries is an unlikely solution.
- Thus far DES have only shown only partial success
- May be the future is likely more bright with DCB, but prolapse and dissections is a problem (spot stenting).
- Bioresorbable technology although attractive may not be feasible for the femoral/popliteal disease

Acknowledgments

Funding

CVPath Institute Inc.

CVPath Institute

Hiroyoshi Mori, MD
Kazuyuki Yahagi, MD
Oscar D. Sanchez, MD
Tobias R. Koppara, MD
Erica Pacheco, MS
Robert Kutz, MS
Russ Jones
Ed Acampado, DVM
Youhui Liang, MD
Abebe Atiso, HT
Jinky Beyer
Lila Adams, HT
Elena Ladich, MD
Frank D Kolodgie, PhD
Michael Joner, MD