

SAD e MAC: guidano la scelta terapeutica?

Disclosure

Roberto Ferraresi, MD

Negli ultimi 2 anni ho avuto rapporti economici con le seguenti ditte medicali:

- Limflow/Inari/Stricker
- Boston Scientific
- Cardiva
- Ivascular

Nessun conflitto di interesse con questa presentazione

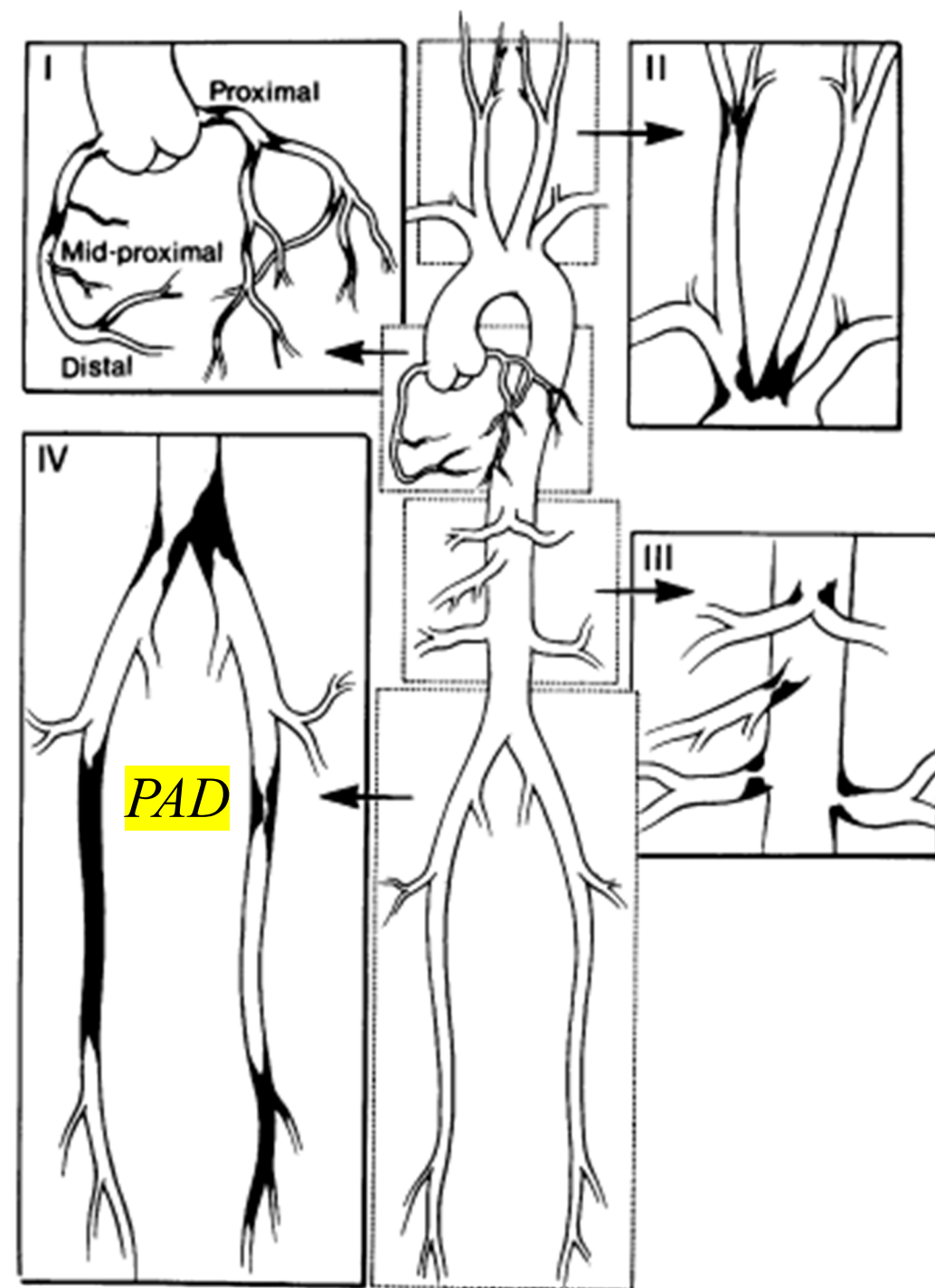
- The BAD-PAD dogma

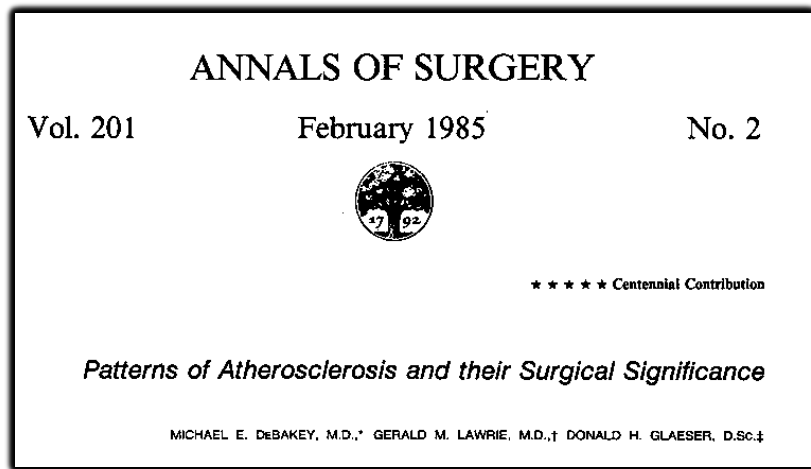
- SAD is the main actor in CLTI
- SAD & MAC are the same disease
- Anatomopathological study



13.827 pts from
1948 to 1983

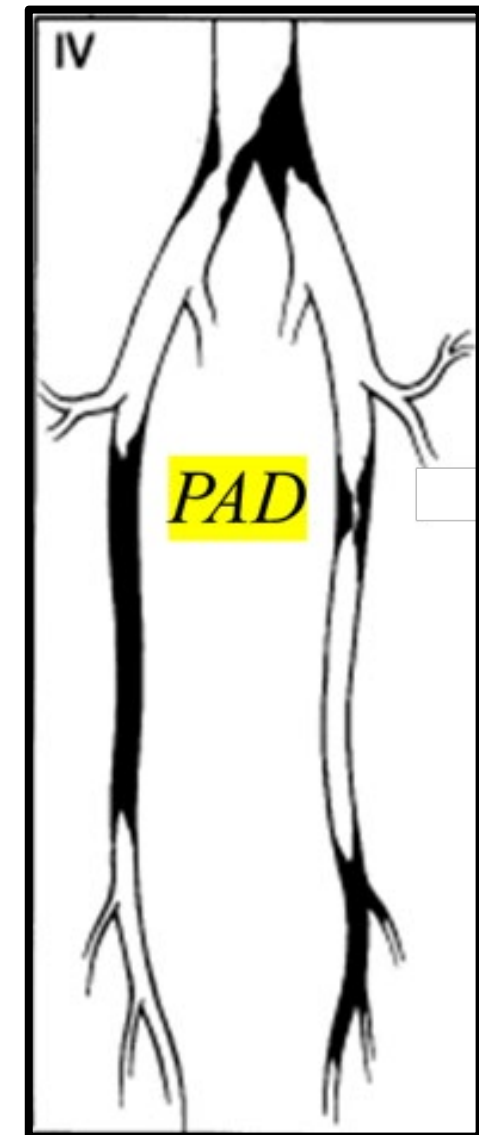
“Particularly important is the fact that atherosclerotic lesions often tend to be **segmental and fairly well localized**, with relatively normal proximal and distal arterial beds. Such atheromas are usually located in the **proximal and/or mid-proximal portions of the arterial bed**”





*13.827 pts from
1948 to 1983*

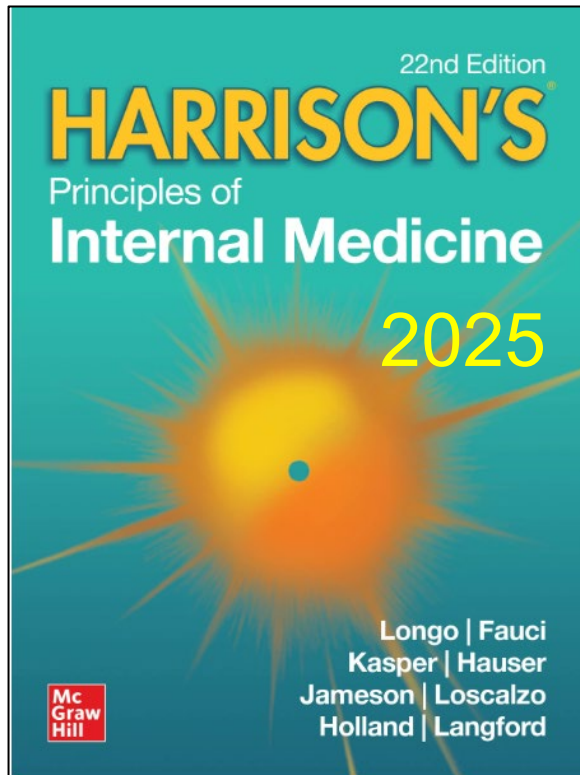
“Particularly important is the fact that atherosclerotic lesions often tend to be segmental and fairly well localized, with relatively normal proximal and distal arterial beds. Such atheromas are usually located in the proximal and/or mid-proximal portions of the arterial bed”



Foot arteries were not considered

1985 → 2025

40-year jump!



Chapter 292: Arterial Diseases of the Extremities - Peripheral Artery Disease

Mark A. Creager; Joseph Loscalzo

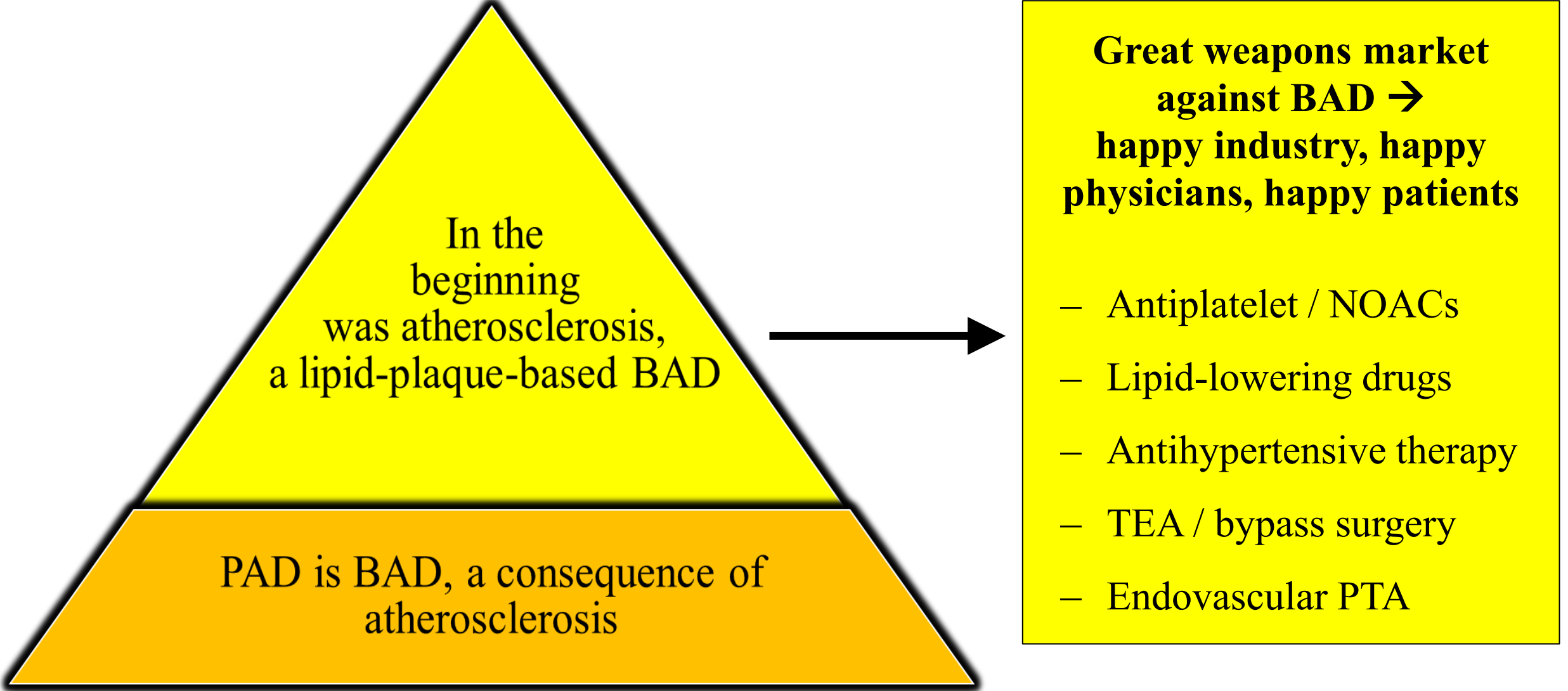
Atherosclerosis is the leading cause of PAD in patients >40 years old. Segmental lesions that cause stenosis or occlusion are usually localized to **large and medium-size vessels**.

The primary sites of involvement are:

- Abdominal aorta and iliac arteries (**30%**)
- Femoral and popliteal arteries (**80–90%**)
- More distal vessels, including the tibial and peroneal arteries (**40–50%**)

Foot arteries are not considered

The PAD dogma



In the beginning
was atherosclerosis,
a lipid-plaque-based BAD

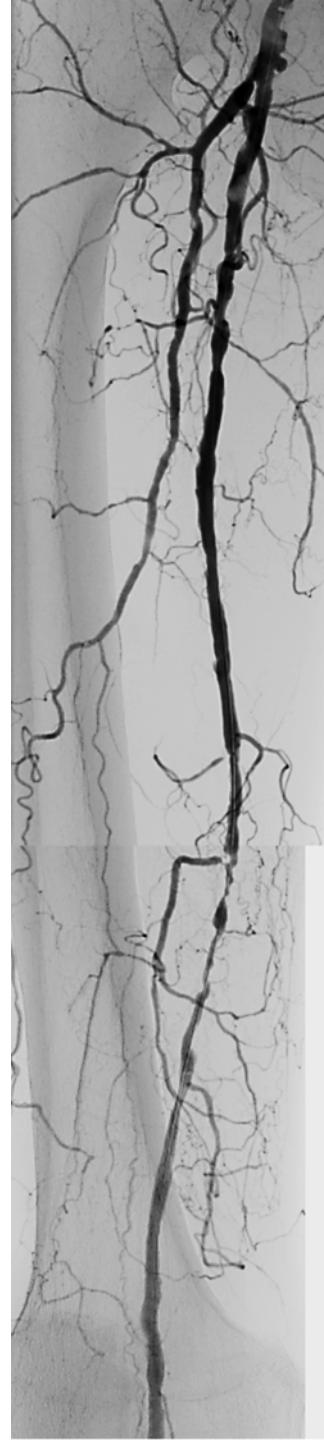
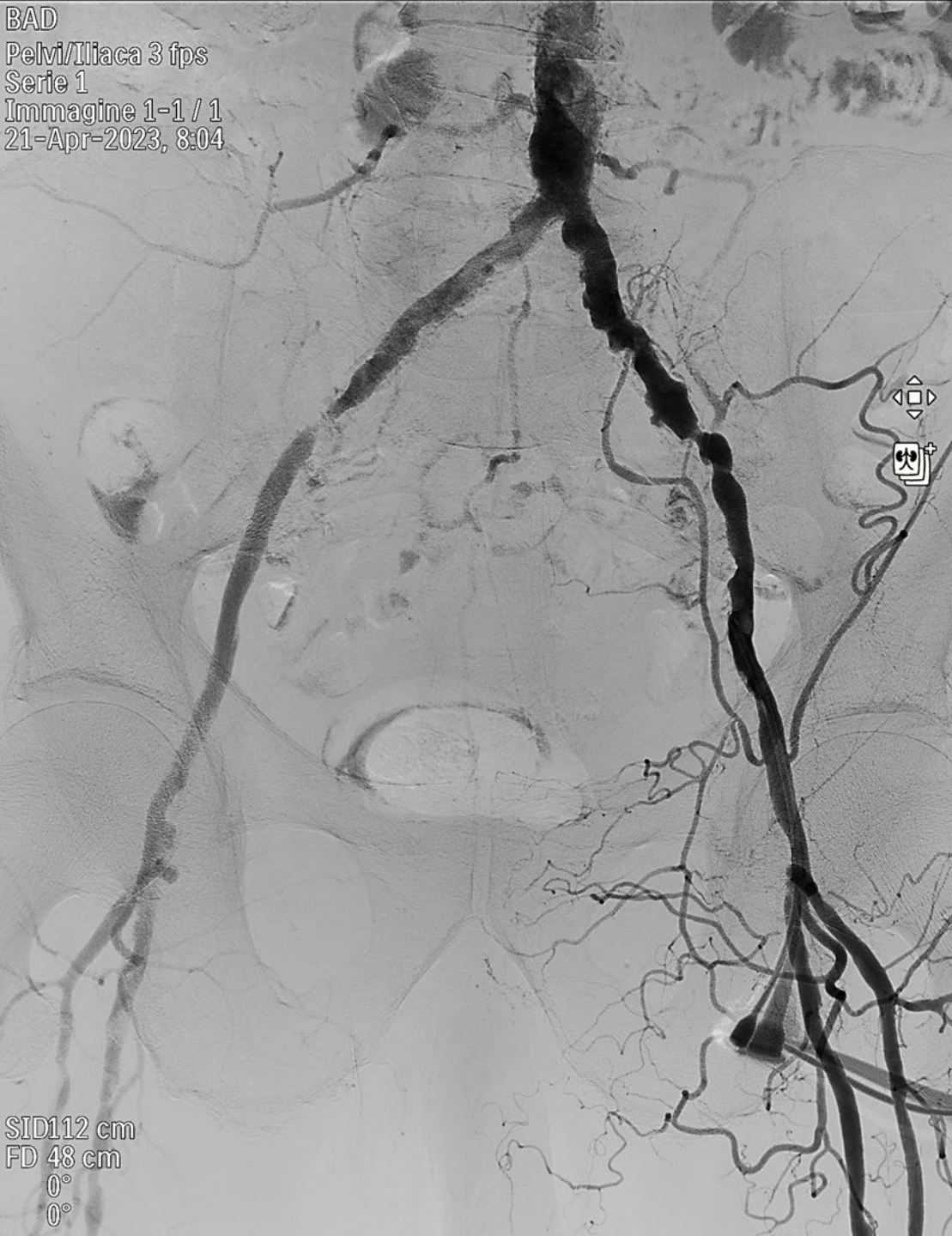
PAD is BAD, a consequence of
atherosclerosis

**Great weapons market
against BAD →
happy industry, happy
physicians, happy patients**

- Antiplatelet / NOACs
- Lipid-lowering drugs
- Antihypertensive therapy
- TEA / bypass surgery
- Endovascular PTA

Patient A:

A pure atherosclerotic BAD pt





TREATMENT



BAD
Mano/piede 3 fps
Serie 19
Immagine 1-1 / 1
19-Apr-2023, 14:56



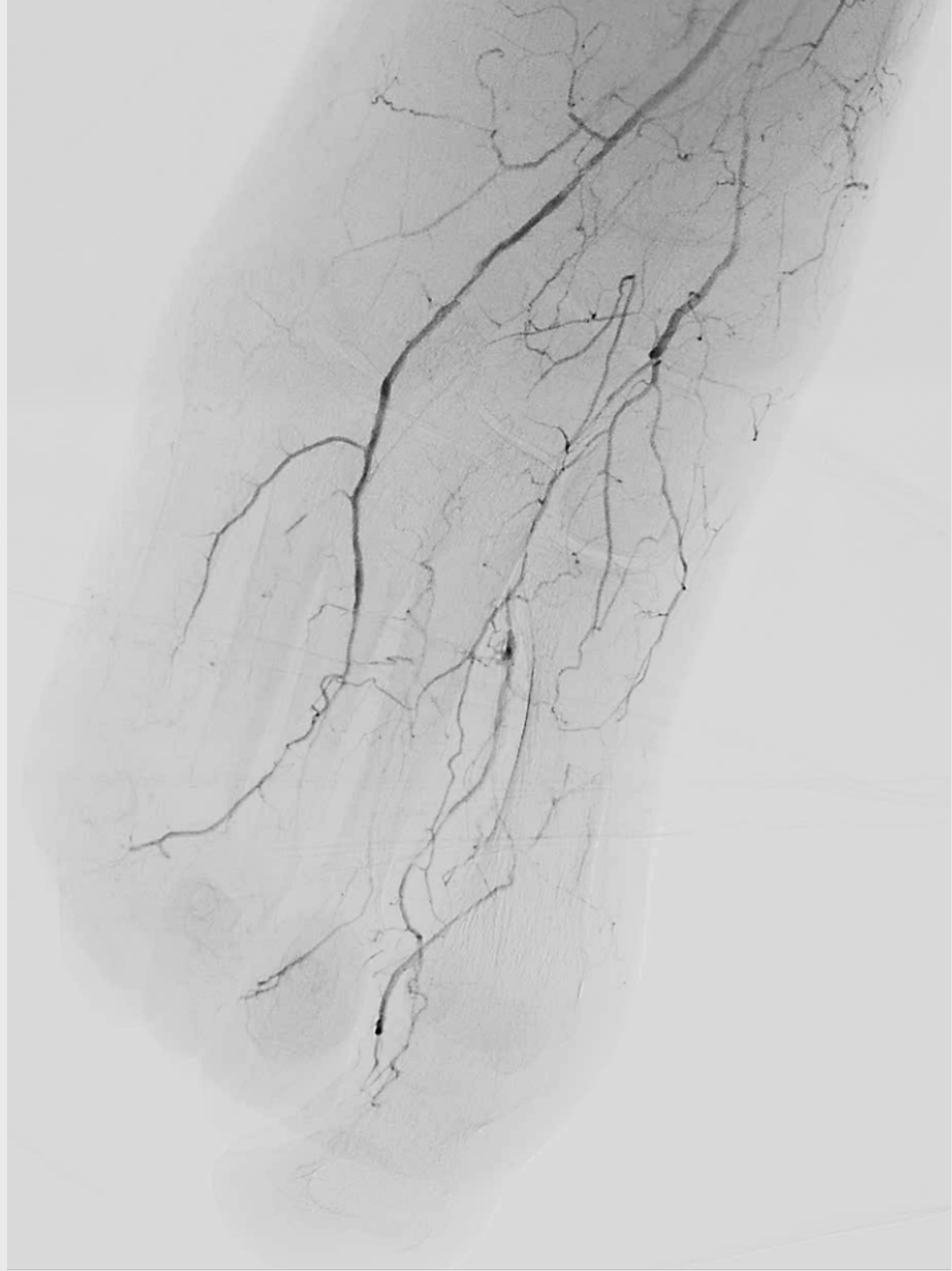
SID112 cm
FD 48 cm
LA035°
CRAN



Patient B:
a BAD & SAD pt







Patient A



Patient B



- The BAD-PAD dogma

- SAD is the main actor in CLTI

- SAD & MAC are the same disease

- Anatomopathological study

Iliacs & CFA
~ 5%

FEM-POP
~ 60%

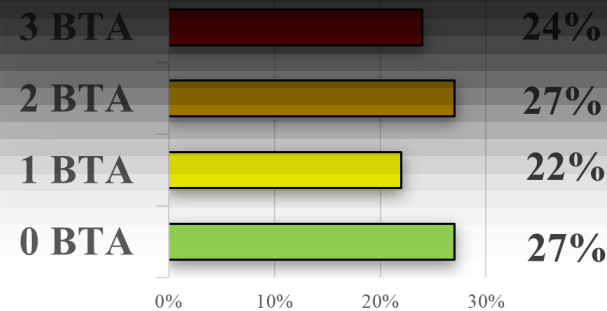
BTK
> 90%

BTA
> 90%

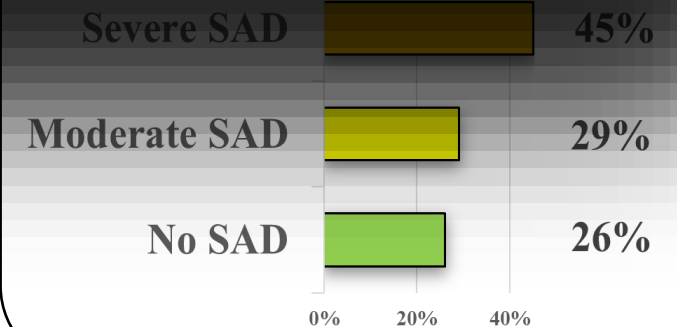
Harrison's Chapter 292: PAD

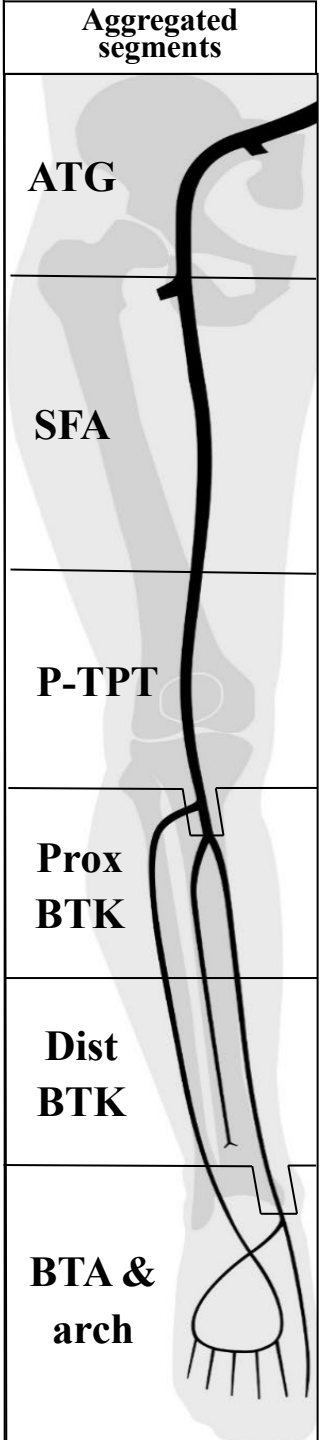
- Abdominal aorta and iliac arteries **30%**
- Femoral and popliteal arteries **80–90%**
- Tibial and peroneal arteries **40–50%**
- ***Foot arteries are not mentioned***

No diseased BTA vessels



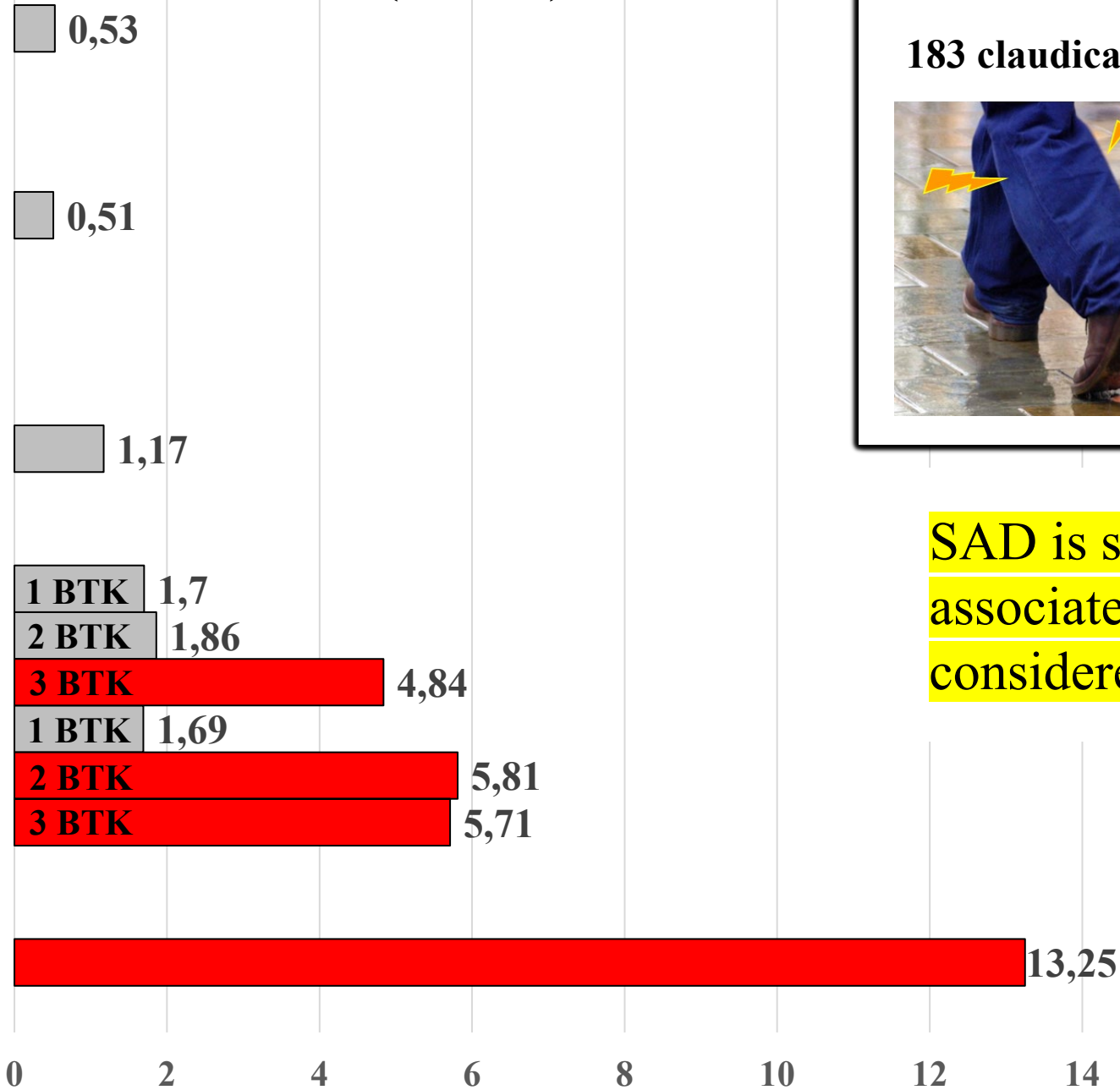
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Risk factors for CLTI

Odds Ratio (95% CI)



1915 pts with symptomatic PAD

183 claudicants

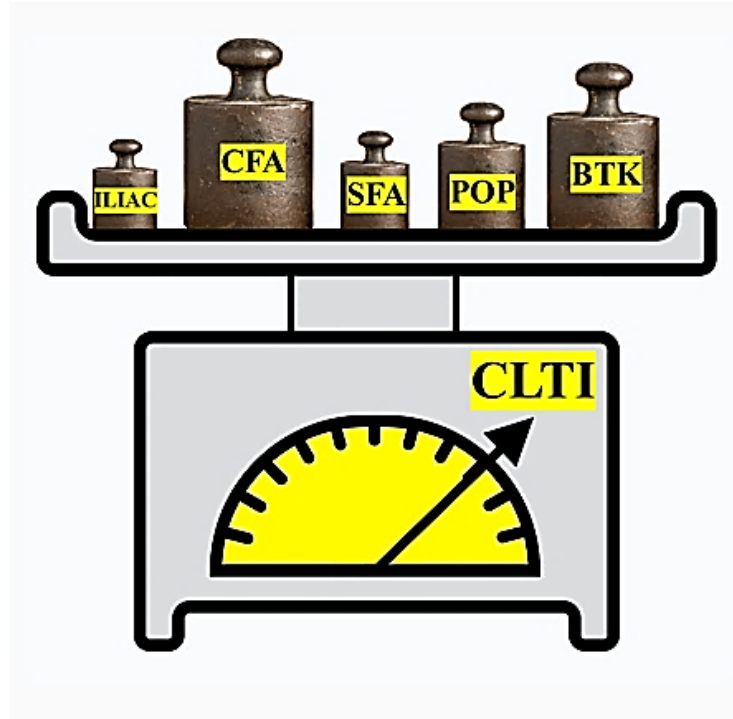
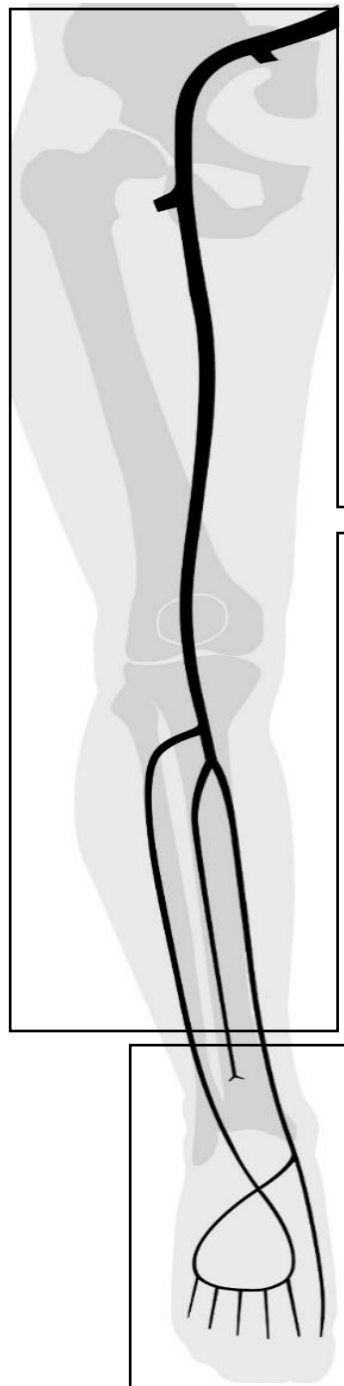


1732 CLI pts

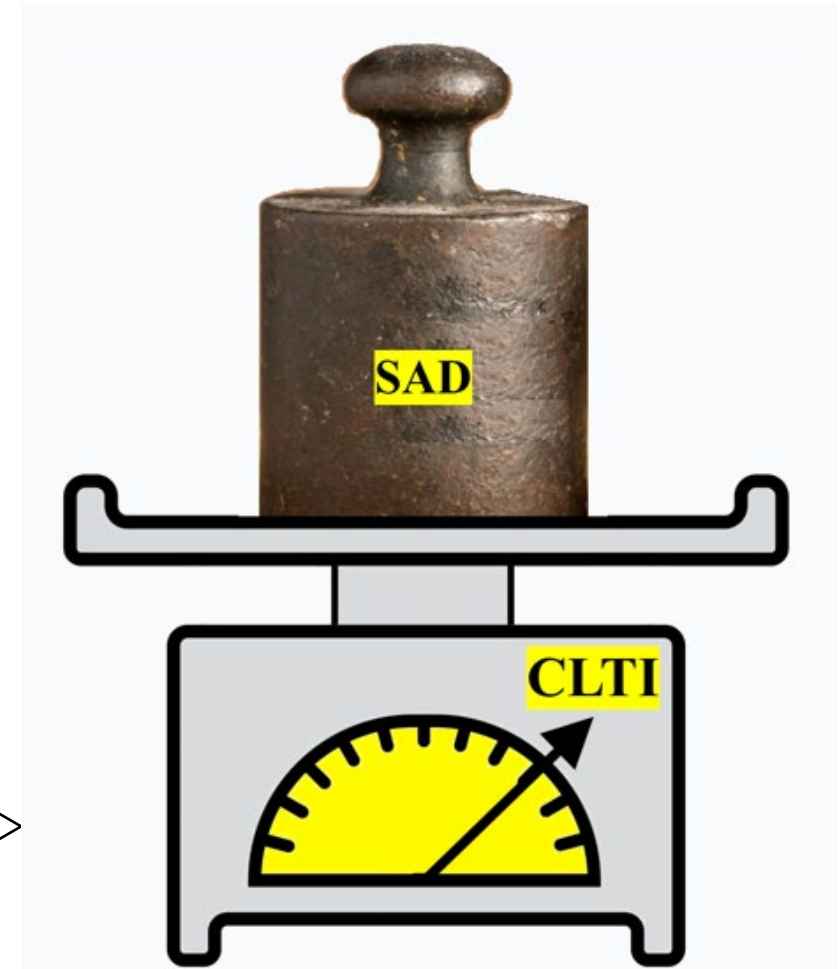


SAD is strongly and independently associated with CLTI and must be considered the main actor in CLTI

BAD → transmission failure

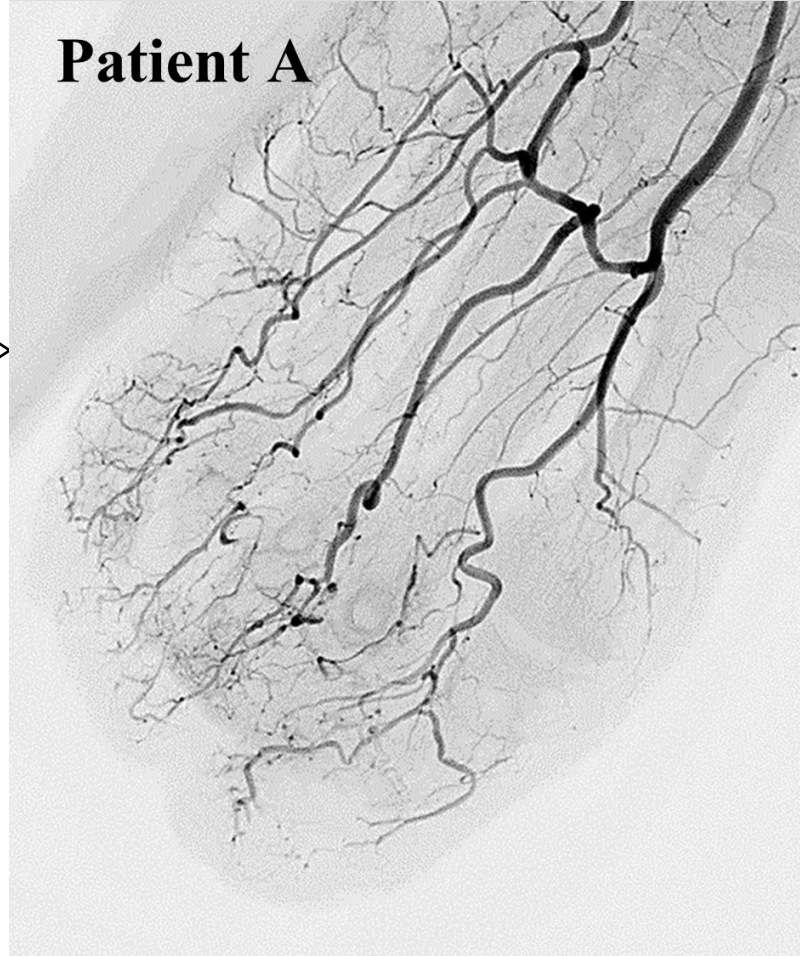


SAD → distribution failure



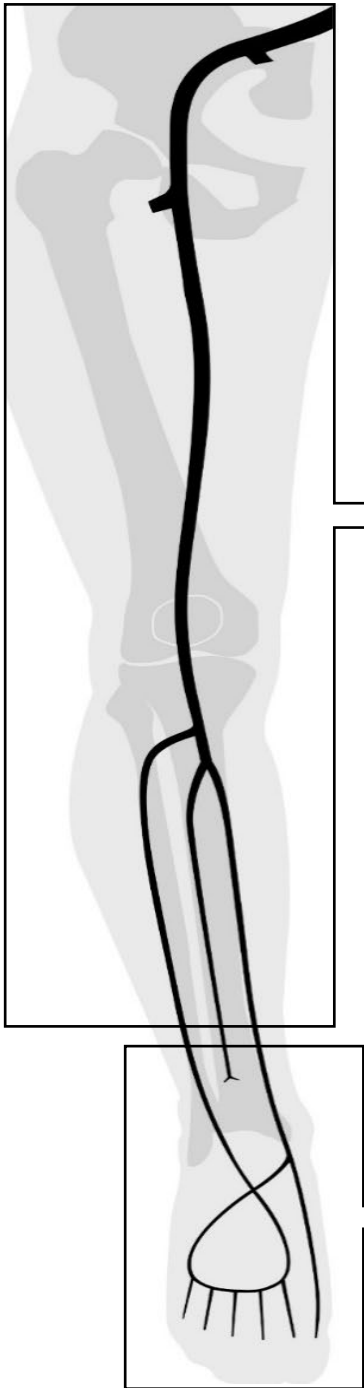
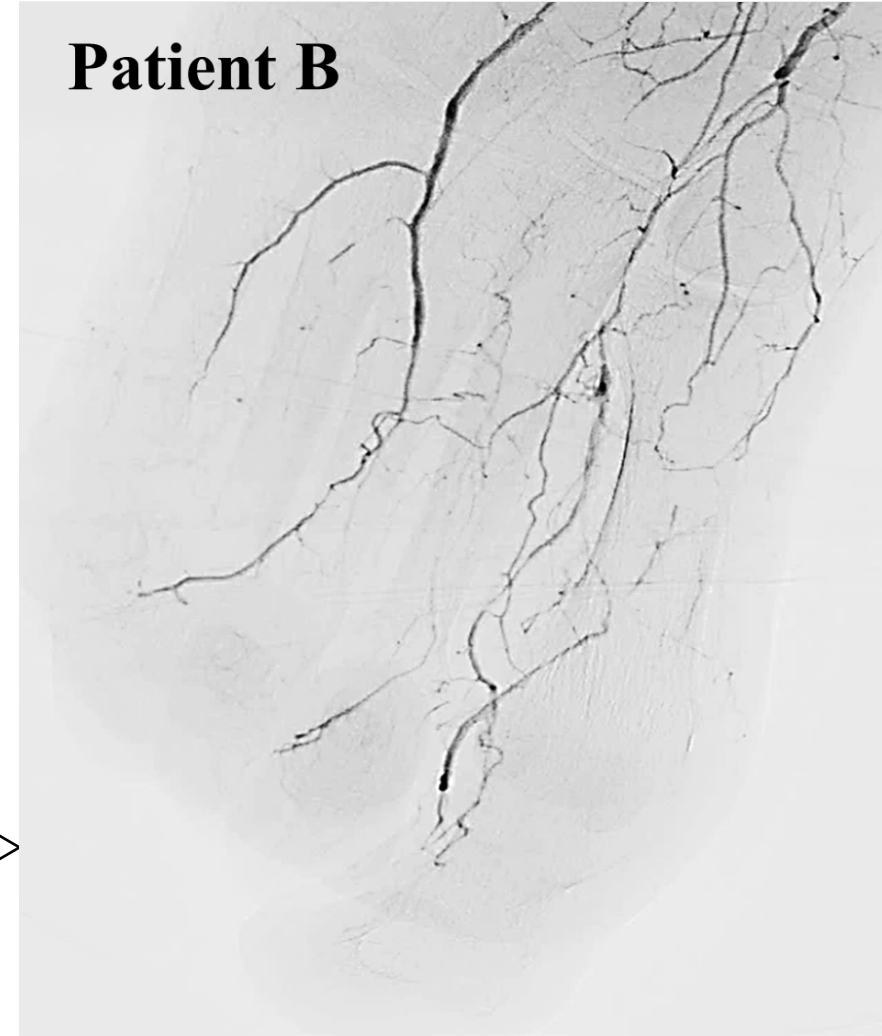
BAD → transmission failure

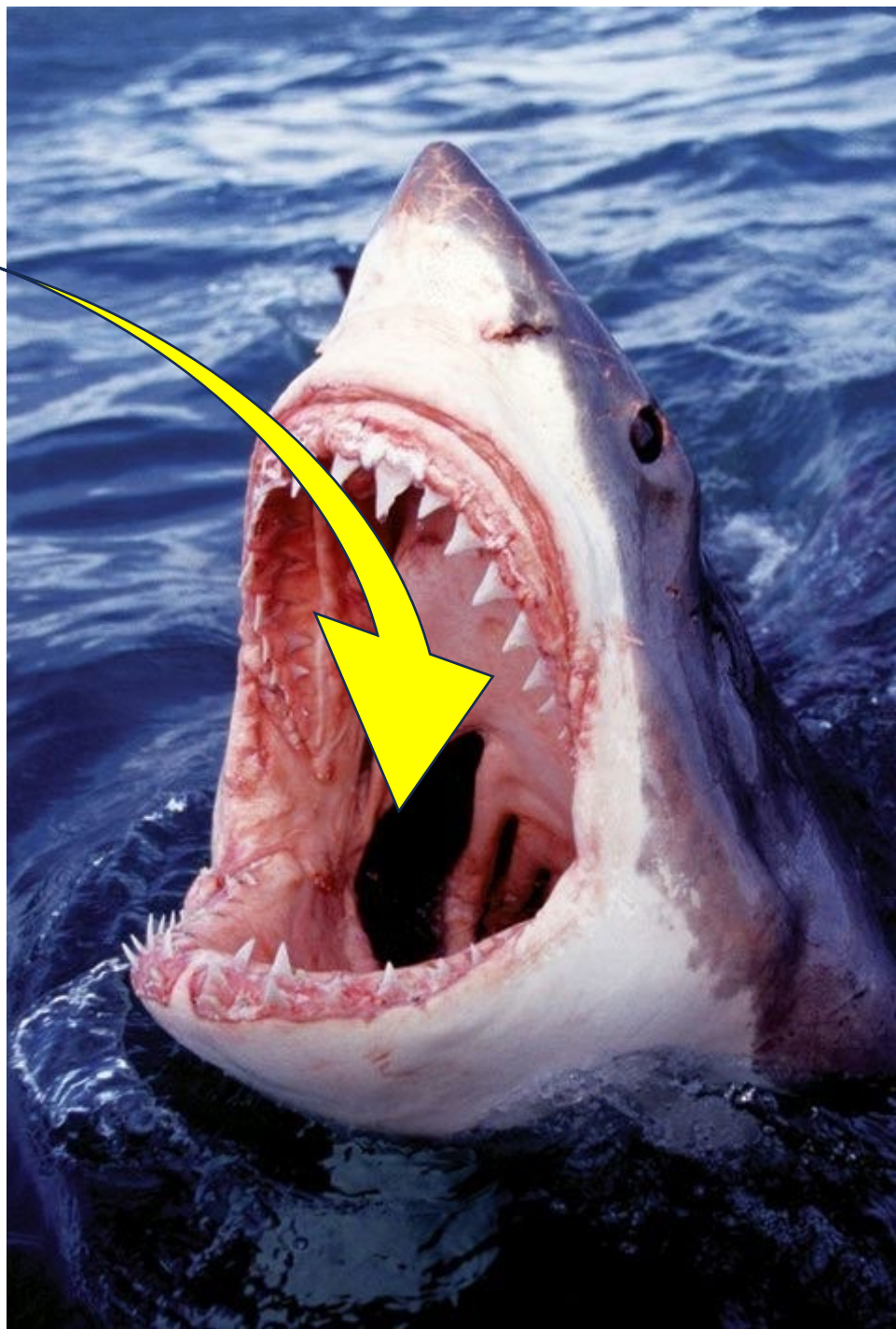
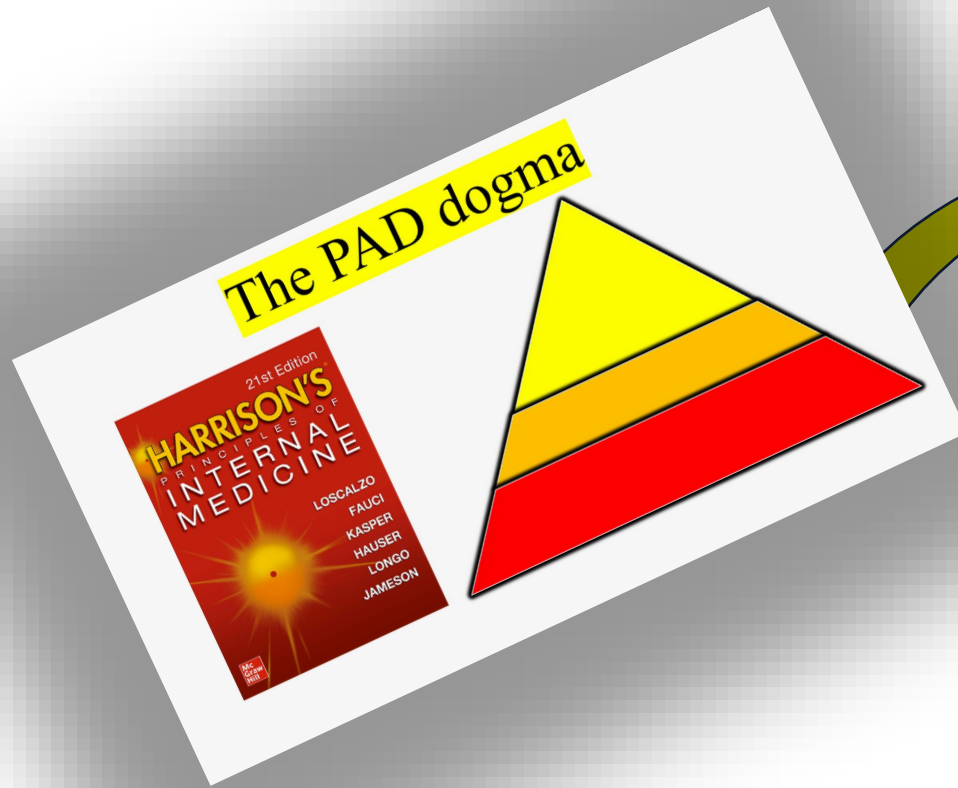
Patient A



SAD → distribution failure

Patient B





**“The death of dogma is
the birth of morality”
Immanuel Kant**

- The BAD-PAD dogma
- SAD is the main actor in CLTI
- SAD & MAC are the same disease
- Anatomopathological study

What is MAC?

VÄI.

**Über die reine Mediaverkalkung der
Extremitätenarterien und ibr Verhalten zur
Arteriosklerose.**

(Aus dem Pathologisch- anatomischen Institut des Allgem. Krankenhauses
Haroburg-Eppendorf.)

Von

Dr. J. G. Monckeberg.

MAC was firstly described
in 1903 by Monckeberg



Medial Arterial Calcification

JACC State-of-the-Art Review

Peter Lanzer, MD,^a Fadil M. Hannan, DPhil,^b Jan D. Lanzer, MD,^{c,d,e} Jan Janzen, MD,^f Paolo Raggi, MD,^g Dominic Furniss, DM, MBBCh,^h Mirjam Schuchardt, PhD,ⁱ Rajesh Thakker, ScD,^j Pak-Wing Fok, PhD,^k Julio Saez-Rodriguez, PhD,^c Angel Millan, PhD,^l Yu Sato, MD,^m Roberto Ferraresi, MD,ⁿ Renu Virmani, MD,^m Cynthia St. Hilaire, PhD^{o,p,q}

J Am Coll Cardiol 2021;78:1145–1165



ESC

European Society
of Cardiology

European Heart Journal (2025) 00, 1–25
<https://doi.org/10.1093/eurheartj/ehaf341>

STATE OF THE ART REVIEW

Vascular biology and medicine

Medial arterial calcification in ageing and disease: current evidence and knowledge gaps

Peter Lanzer ^{1,*}, Leon Schurgers ², Aleksandra Twarda-Clapa³, Roberto Ferraresi⁴, Huang Hui⁵, Alexey Kamenskiy⁶, Yabing Chen^{7,8}, Tomoyo Hamana⁹, Pak-Wing Fok¹⁰, Ángel Millán¹¹, Renu Virmani ⁹, and Cynthia St. Hilaire¹²

VASCULAR
MEDICINE

Original Article

Association of infrapopliteal medial arterial calcification with lower-limb amputations in high-risk patients: A systematic review and meta-analysis

Fabrizio Losurdo^{1,2} , Roberto Ferraresi³, Alessandro Ucci⁴, Anna Zanetti¹, Giacomo Clerici³ and Antonella Zamboni^{1,5}

Vascular Medicine
1–11
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DOI: 10.1177/1358863X20979738
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MAC is a systemic vascular disorder characterized by progressive calcification and petrification of the arterial media accompanied by intimal thickening

MAC can be considered the silent killer of the cardiovascular system because MAC is a strong marker of future cardiovascular events and death

MAC is strongly associated with occlusive PAD, foot ulcer, and amputation

SAD = MAC ?

Patient A



BAD
Mano/piede 3 fps
Serie 19
Immagine 1-1 / 1
19-Apr-2023, 14:56



SID112 cm
FD 48 cm
LA035°
CRAN



Patient B

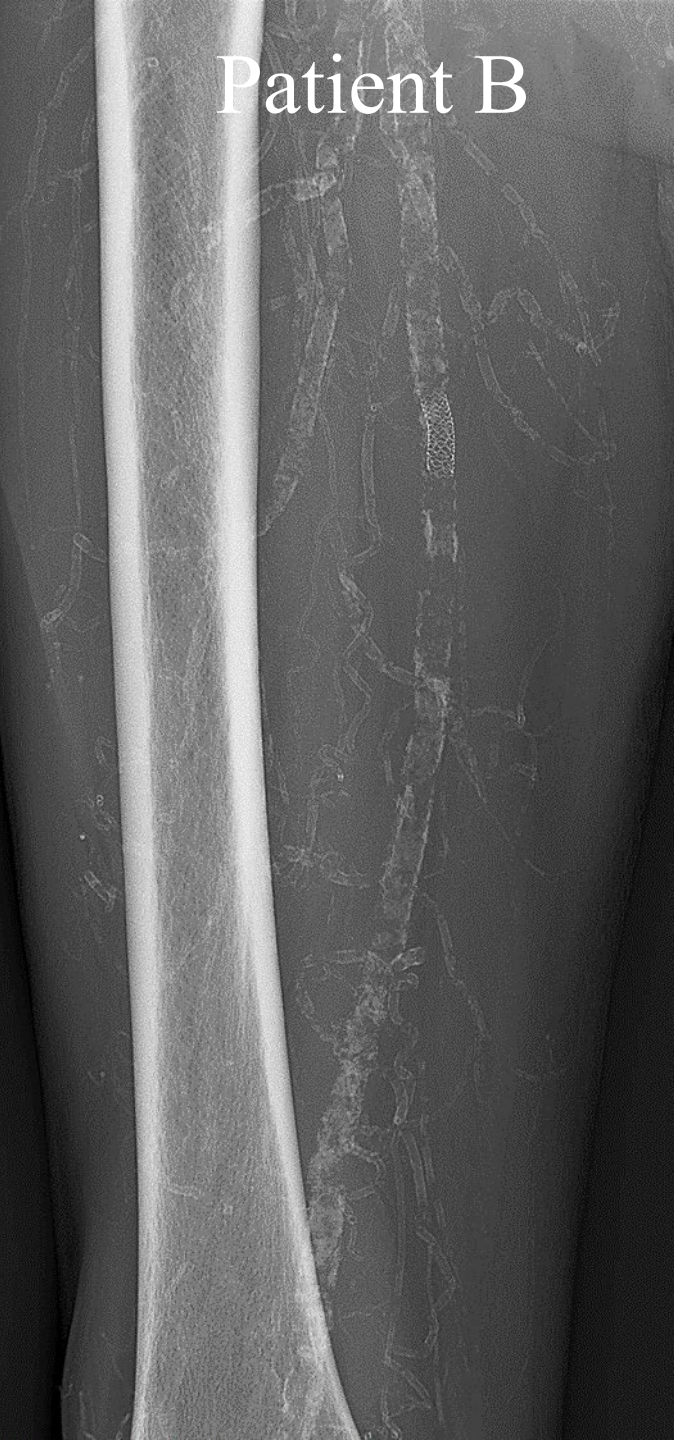


Patient B



Just a foot
problem?

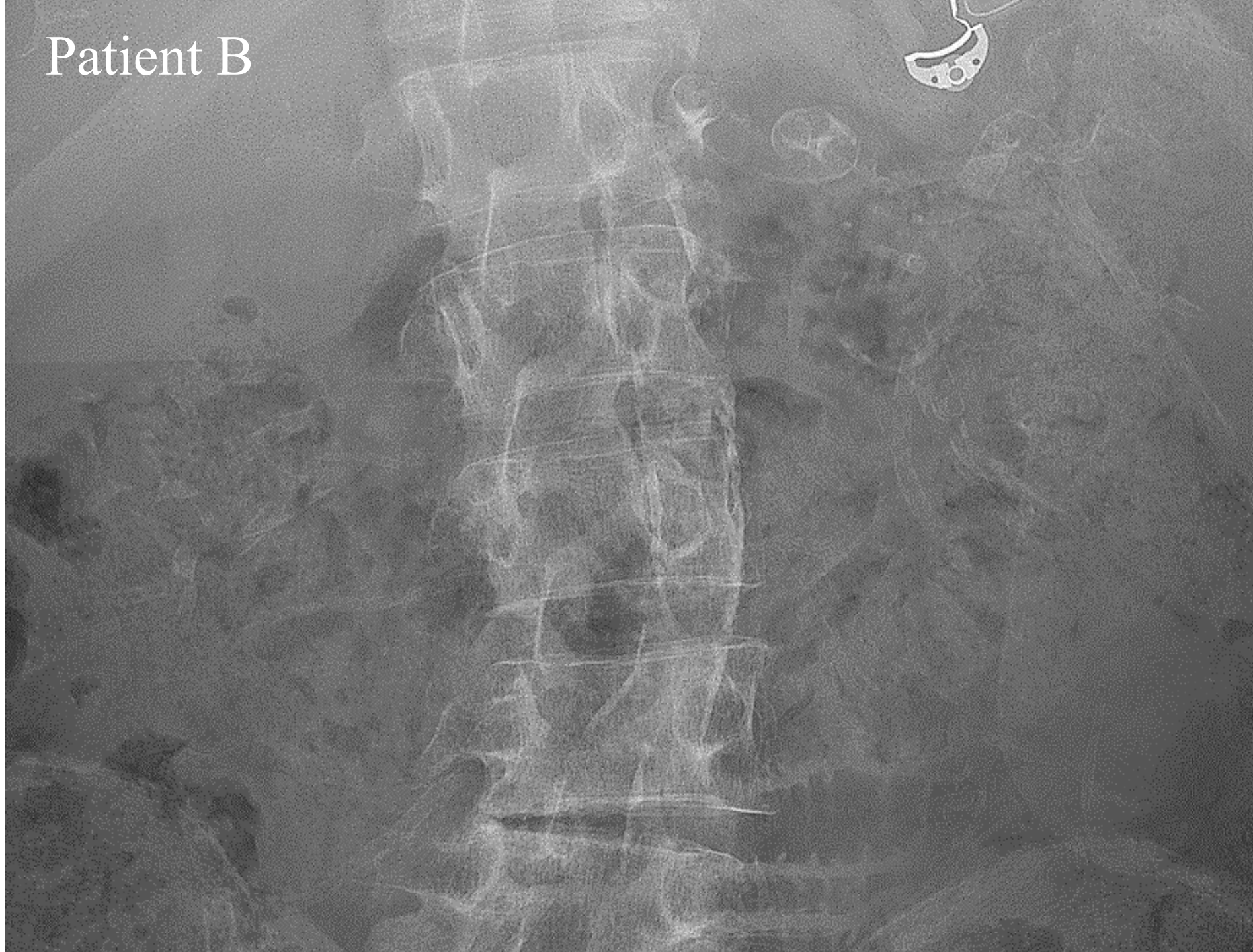
Patient B



Patient B



Patient B



Patient B



At the best of our knowledge, SAD and MAC were never considered directly correlated

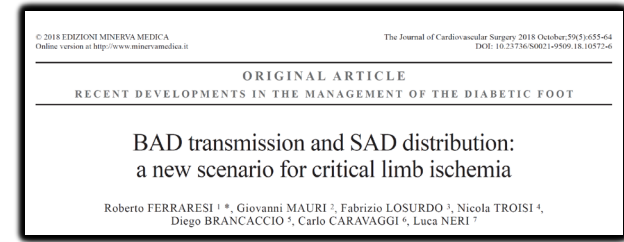
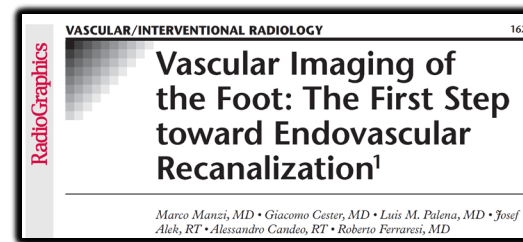
However, in our daily practice in treating CLTI patients, we very often observe their coexistence, raising the question if they could be expression of different pathophysiological conditions or of the same underlying non-atherosclerotic disease, leading to common clinical symptoms

A Novel Scoring System for Small Artery Disease and Medial Arterial Calcification Is Strongly Associated With Major Adverse Limb Events in Patients With Chronic Limb-Threatening Ischemia

Roberto Ferraresi, MD¹, Alessandro Ucci, MD², Alessandra Pizzuto, MD³, Fabrizio Losurdo, MD⁴, Maurizio Caminiti, MD⁴, Daniela Minnella, MD⁴, Andrea Casini, MD⁵, Giacomo Clerici, MD⁴, Miguel Montero-Baker, MD⁶, and Joseph Mills, MD⁶

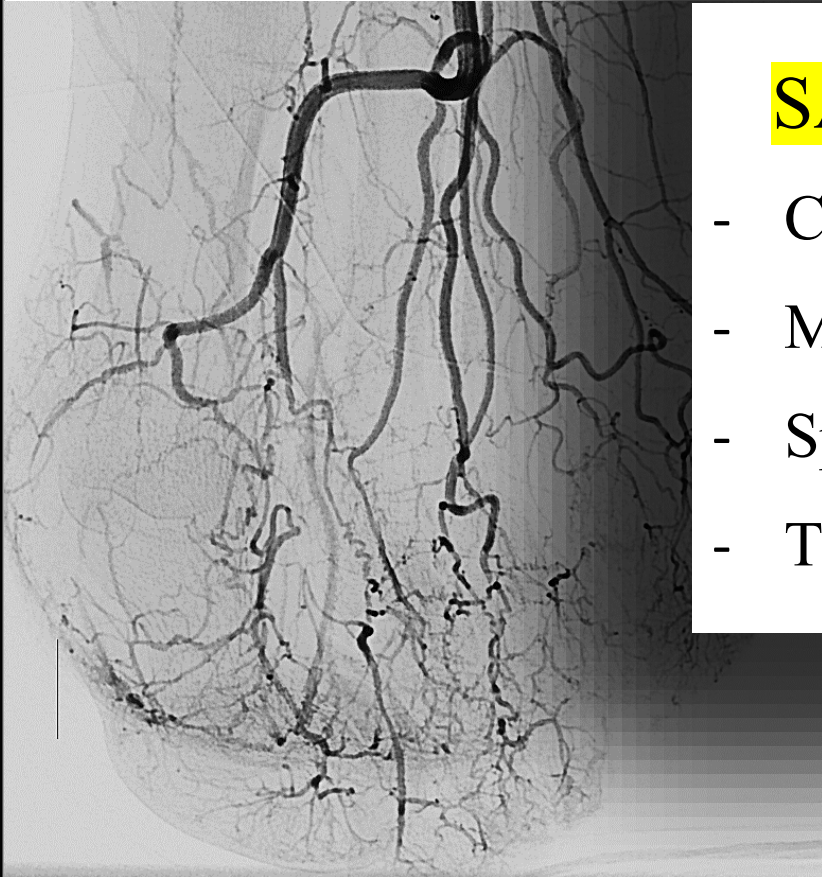
	N	
CLTI pts	221	100%
Mean age	74 yy	
Male	194	76%
DM	191	86%
ESRD-HD	53	24%
Limbs	259	100%
Wifi-WOUND 1	37	14%
Wifi-WOUND 2	198	77%
Wifi-WOUND 3	24	9%
Mean FU	19 months (3-59)	

SAD-score



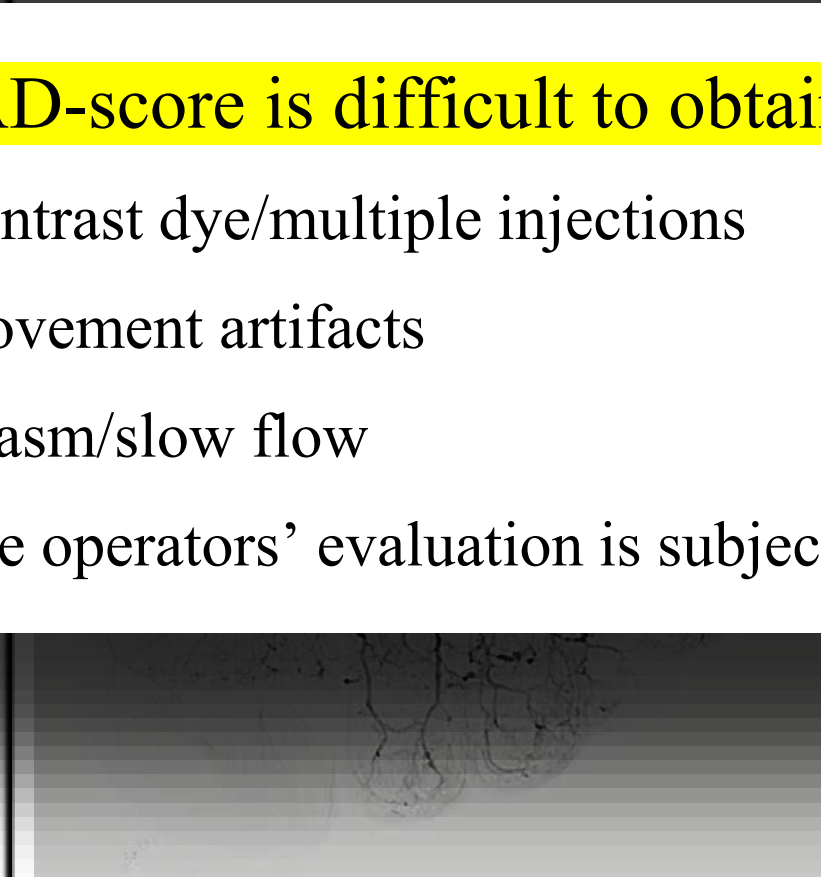
No SAD

Absence of disease or mild disease with a well-represented network of forefoot and calcaneal arteries



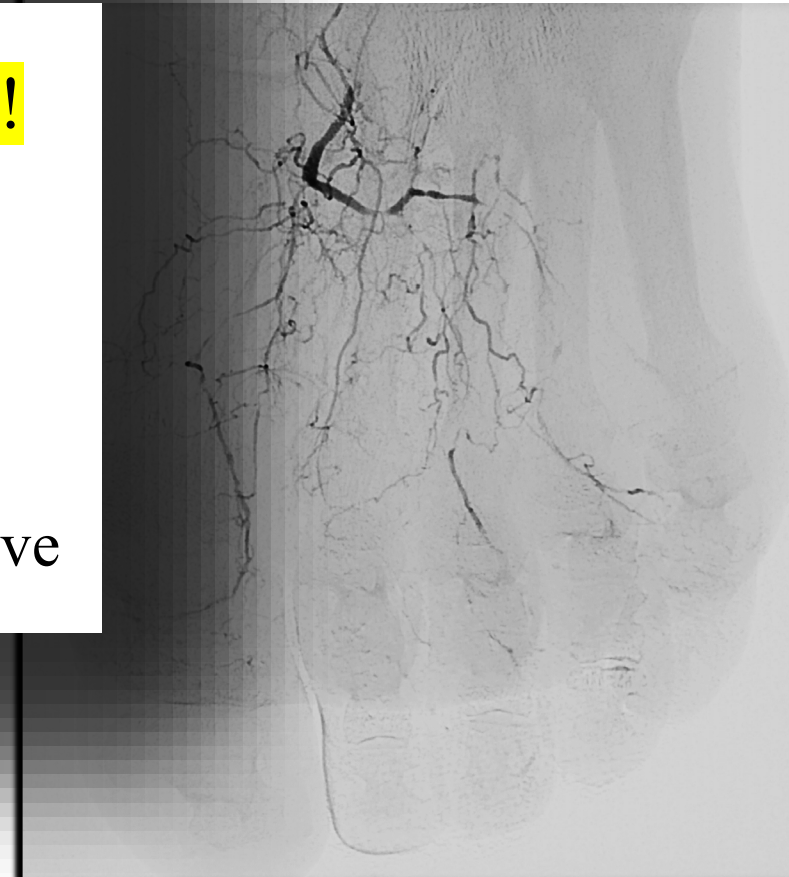
Moderate SAD

Diffuse disease with narrowing and poverty of arch, metatarsal, digital and calcaneal arteries



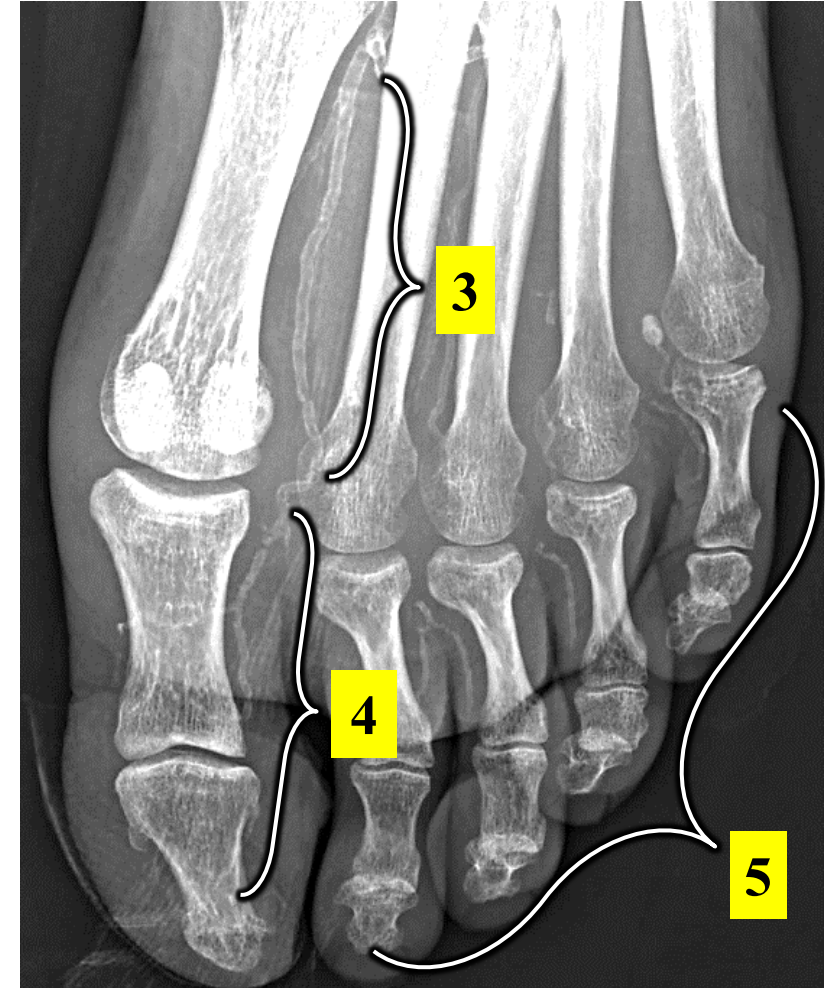
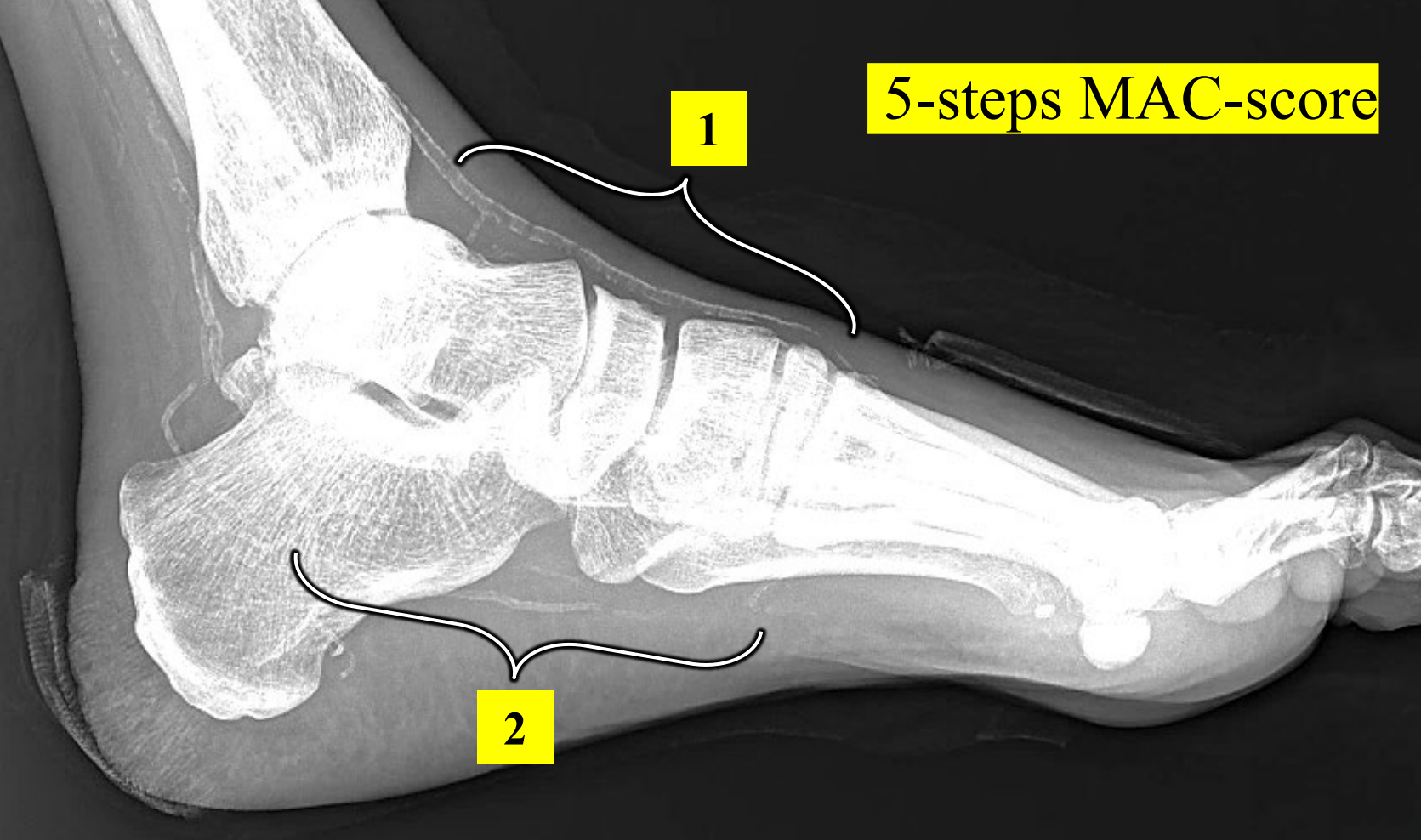
Severe SAD

Occlusion or severe disease with extreme poverty of arch, metatarsal, digital and calcaneal arteries



SAD-score is difficult to obtain!

- Contrast dye/multiple injections
- Movement artifacts
- Spasm/slow flow
- The operators' evaluation is subjective



1	≥ 2 cm?	yes = 1 or no = 0
2		yes = 1 or no = 0
3		yes = 1 or no = 0
4	≥ 1 cm?	yes = 1 or no = 0
5		yes = 1 or no = 0

Sum all
points up



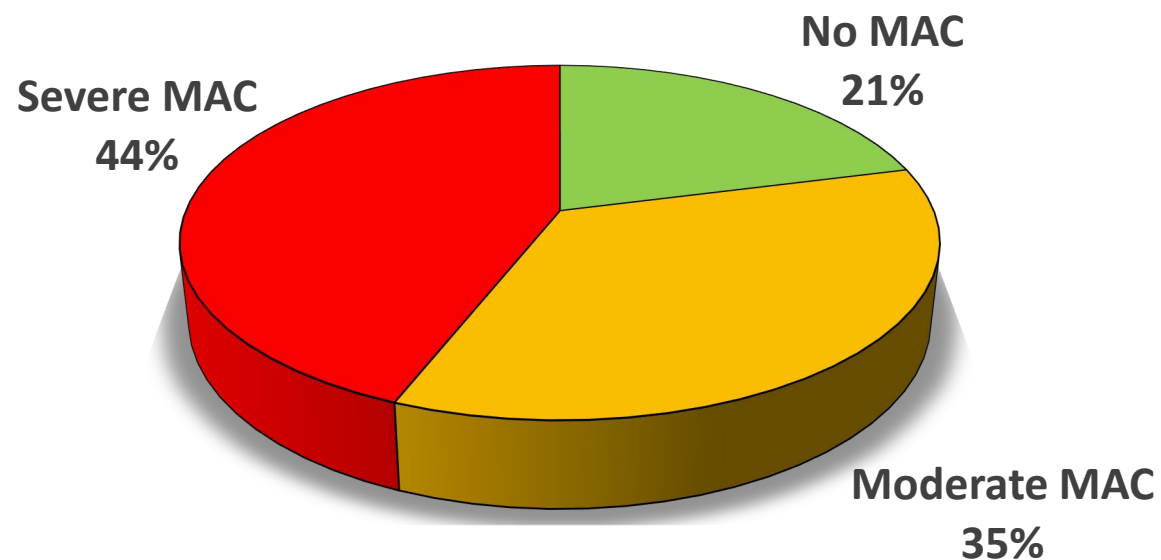
0-1 = no MAC

2-3 = moderate MAC

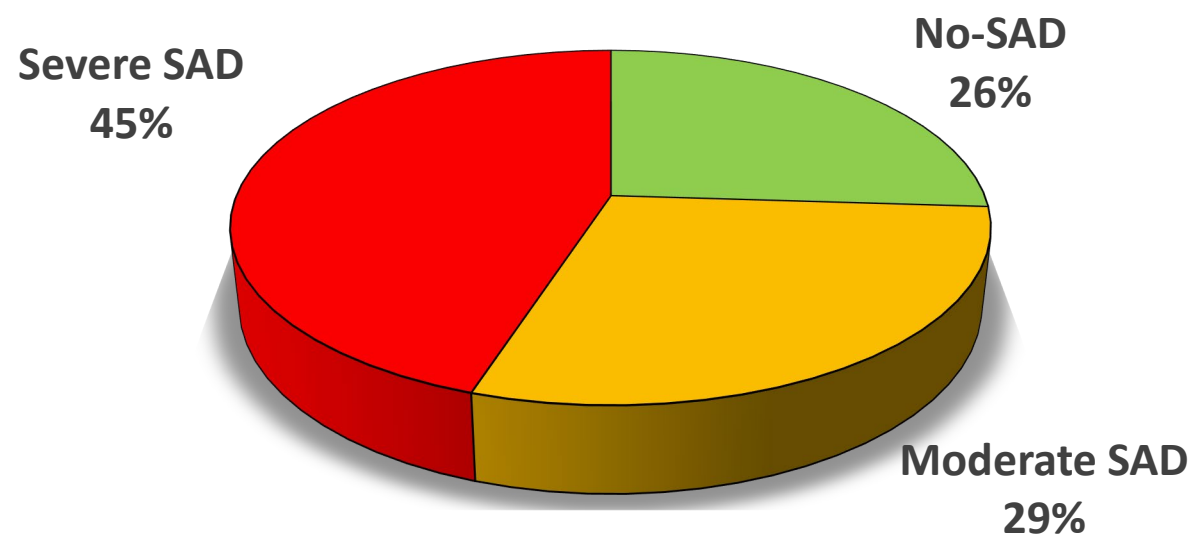
4-5 = severe MAC

Distribution in 259 CLTI-limbs

MAC-score

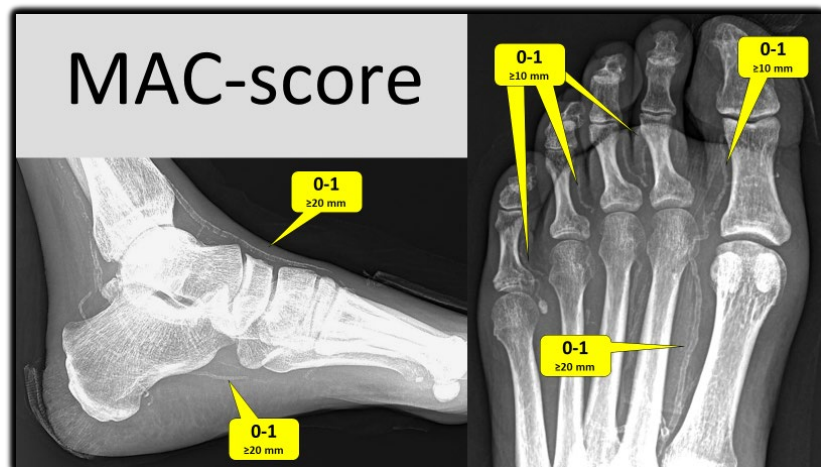


SAD-score

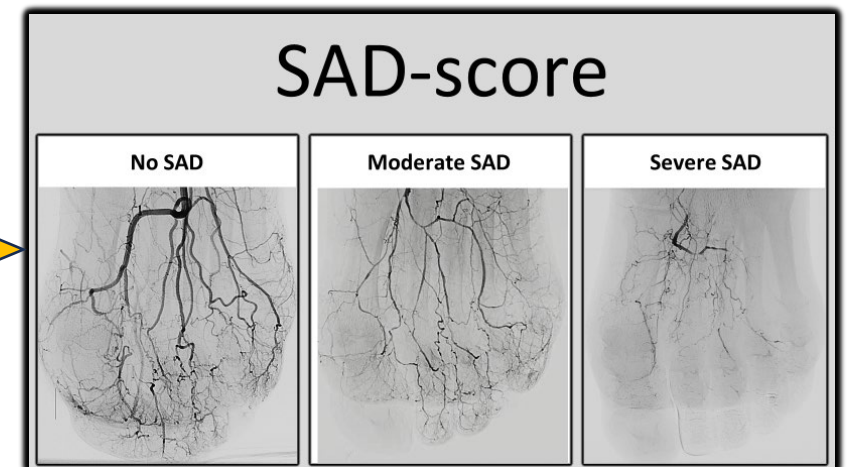


MAC-score versus SAD-score

MAC-score	sensitivity	specificity
no-MAC	100 %	98.1 %
moderate MAC	99.1 %	92.7 %
severe MAC	100 %	98.1 %

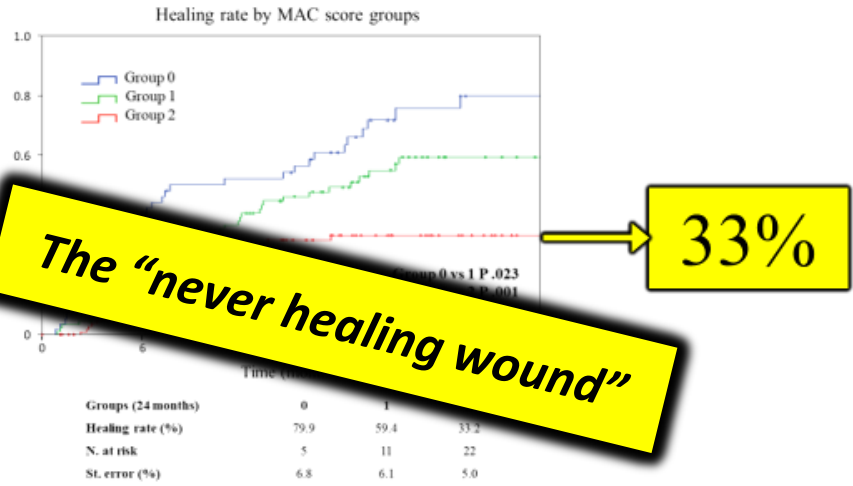


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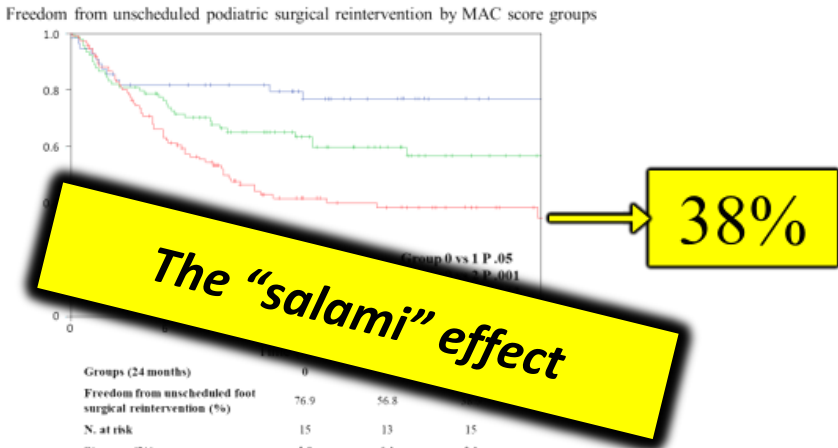


Patient's
outcomes by
MAC-score
groups

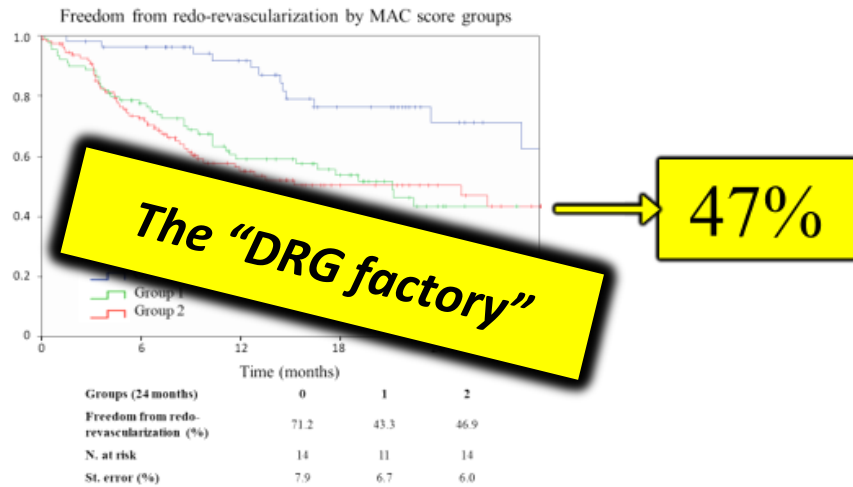
Healing rate



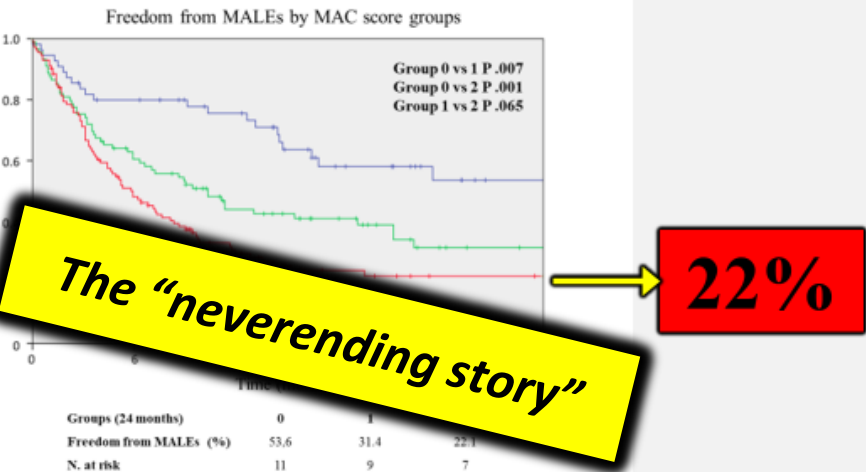
FF surgical
reintervention



FF redo-rev.



FF MALEs



Other authors confirmed the MAC score value

The MAC score reflects systemic vascular disease, and is a simple, practical tool and a strong independent predictor of:

- Impaired wound healing
- Major amputation
- Failure of percutaneous revascularization
- Cardiovascular events and mortality

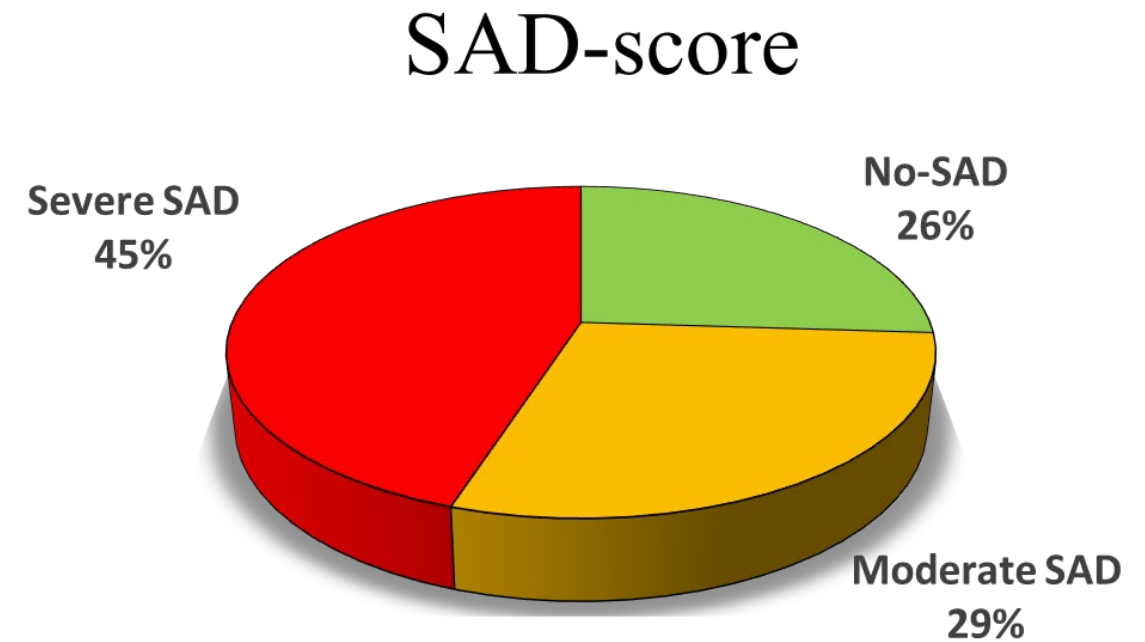
1. Liu IH, Wu B, Krepiy V, et al. Pedal arterial calcification score is associated with the risk of major amputation in chronic limb-threatening ischemia. *J Vasc Surg.* 2022;75(1):270-278.e3. doi:10.1016/j.jvs.2021.07.235
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Kim IT et al. A Review and Proposed Classification System for the No-Option Patient With Chronic Limb-Threatening Ischemia. J Endovasc Ther 2021;28(2):183-193

Up to 20% of CLTI patients are considered no-option because of so-called ‘desert foot’, where no revascularization is feasible.

The main cause of desert foot is SAD-MAC disease.

At 1 year, these patients face about 46% limb loss, severely impaired QoL, and high mortality.

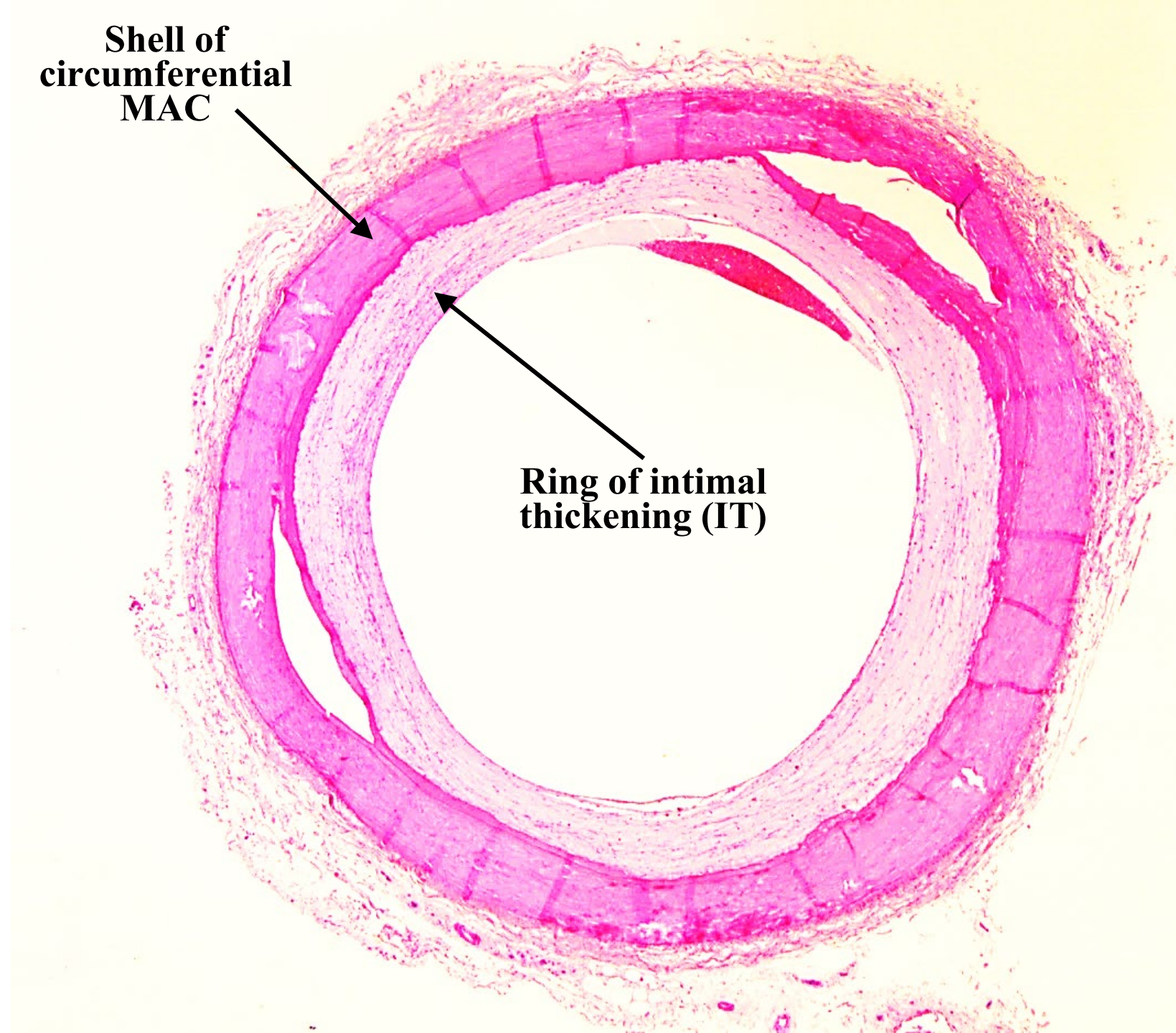


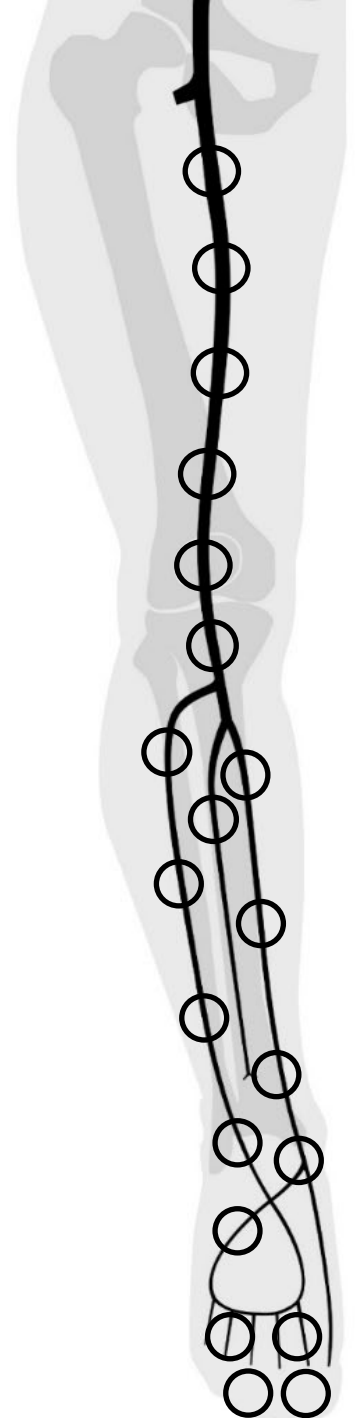
- The BAD-PAD dogma
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- Anatomopathological study

Open question

MAC develops within the medial layer of the arterial wall (outside the lumen) and is not inherently obstructive

How can be MAC correlated to SAD? What is the material obstructing the lumen?



A diagram of a human leg, showing the femur, tibia, and fibula. A series of circles are drawn along the length of the leg, representing sampling sites for arterial analysis. The circles are more densely packed in the lower leg and foot area.

A new detailed histopathological study on 26 CLTI amputated limbs. Extensive arterial sampling evaluating:

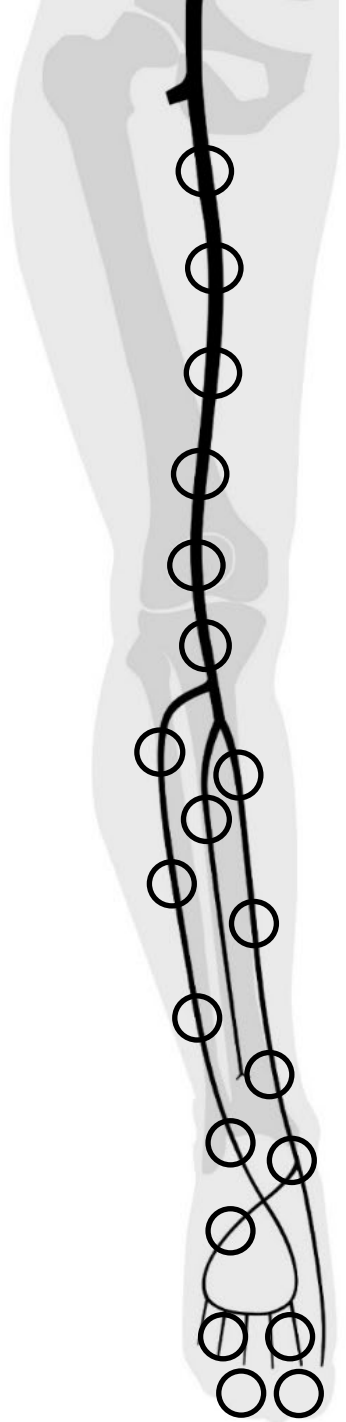
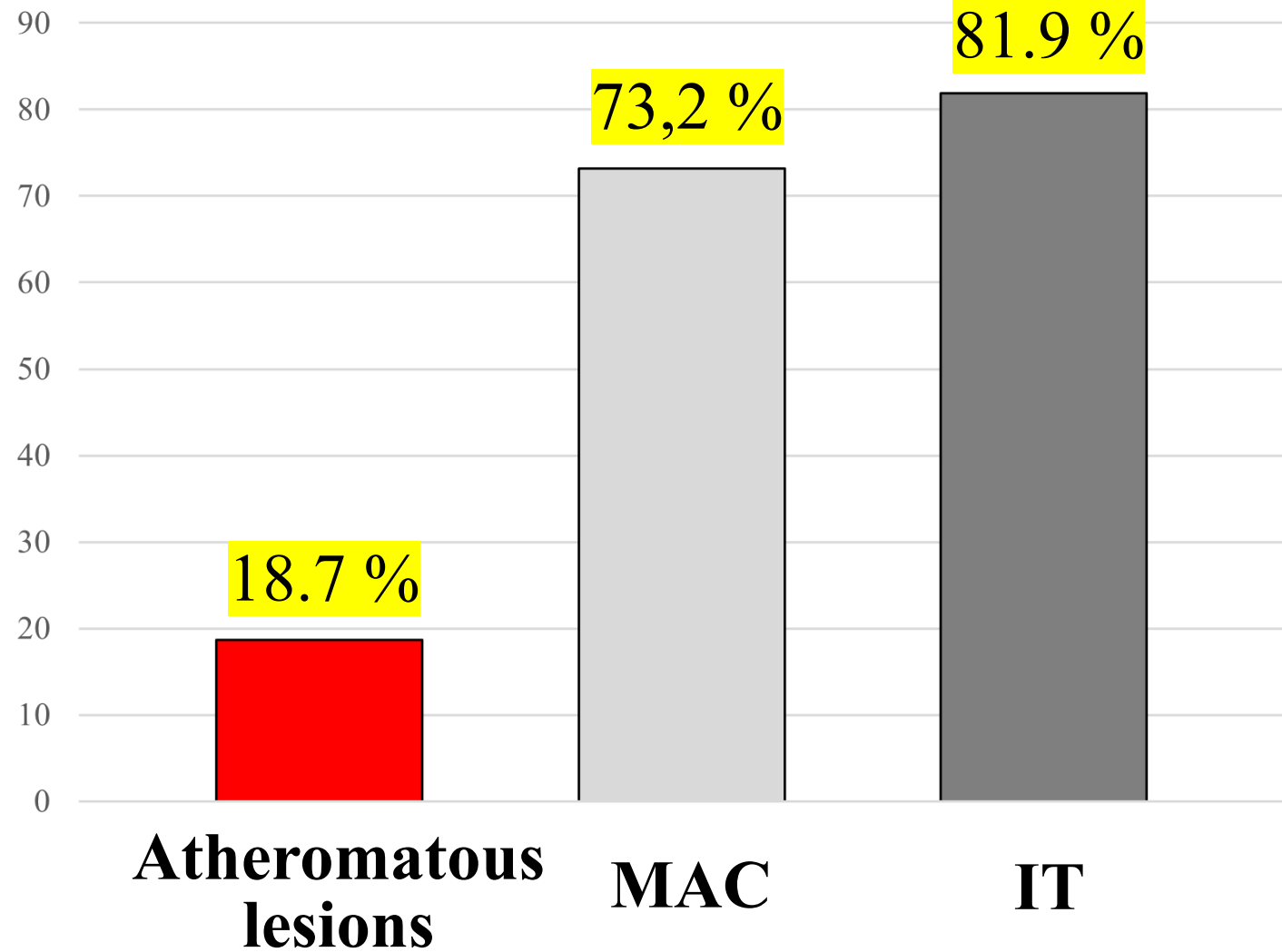
- Atheromatous lesions
- Medial artery calcification (MAC)
- Intimal thickening (IT)

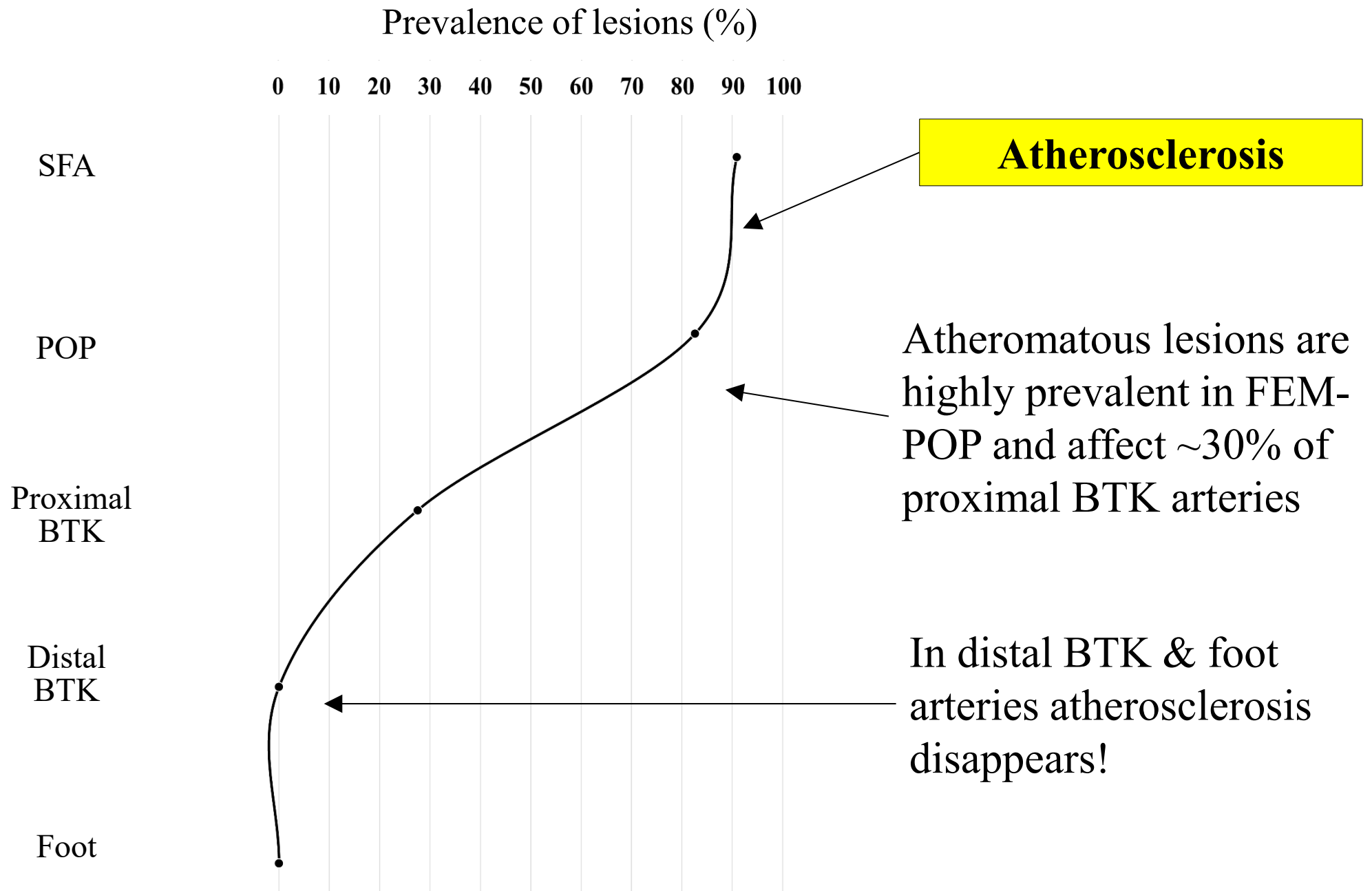
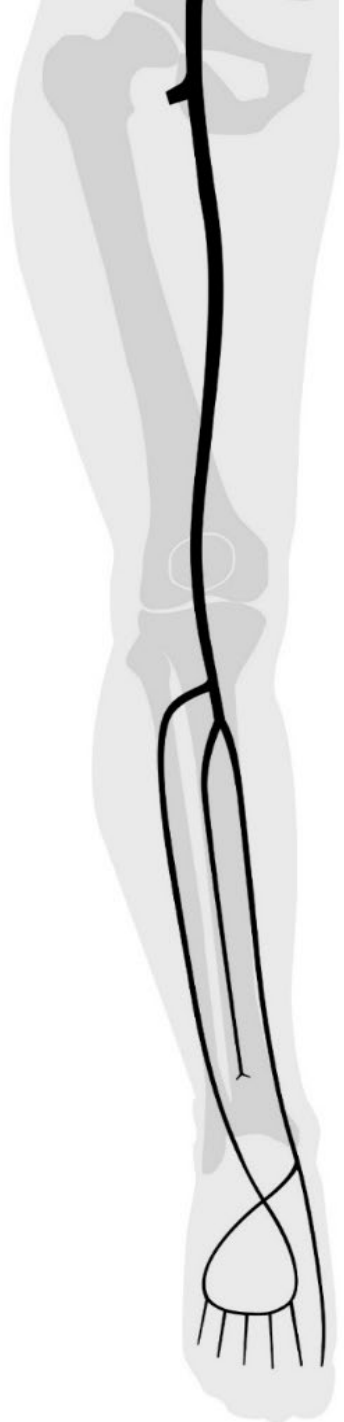
Patterns of Arterial Obstruction in Chronic Limb-Threatening Ischemia: A Comprehensive Histopathological Analysis of Amputated Limbs

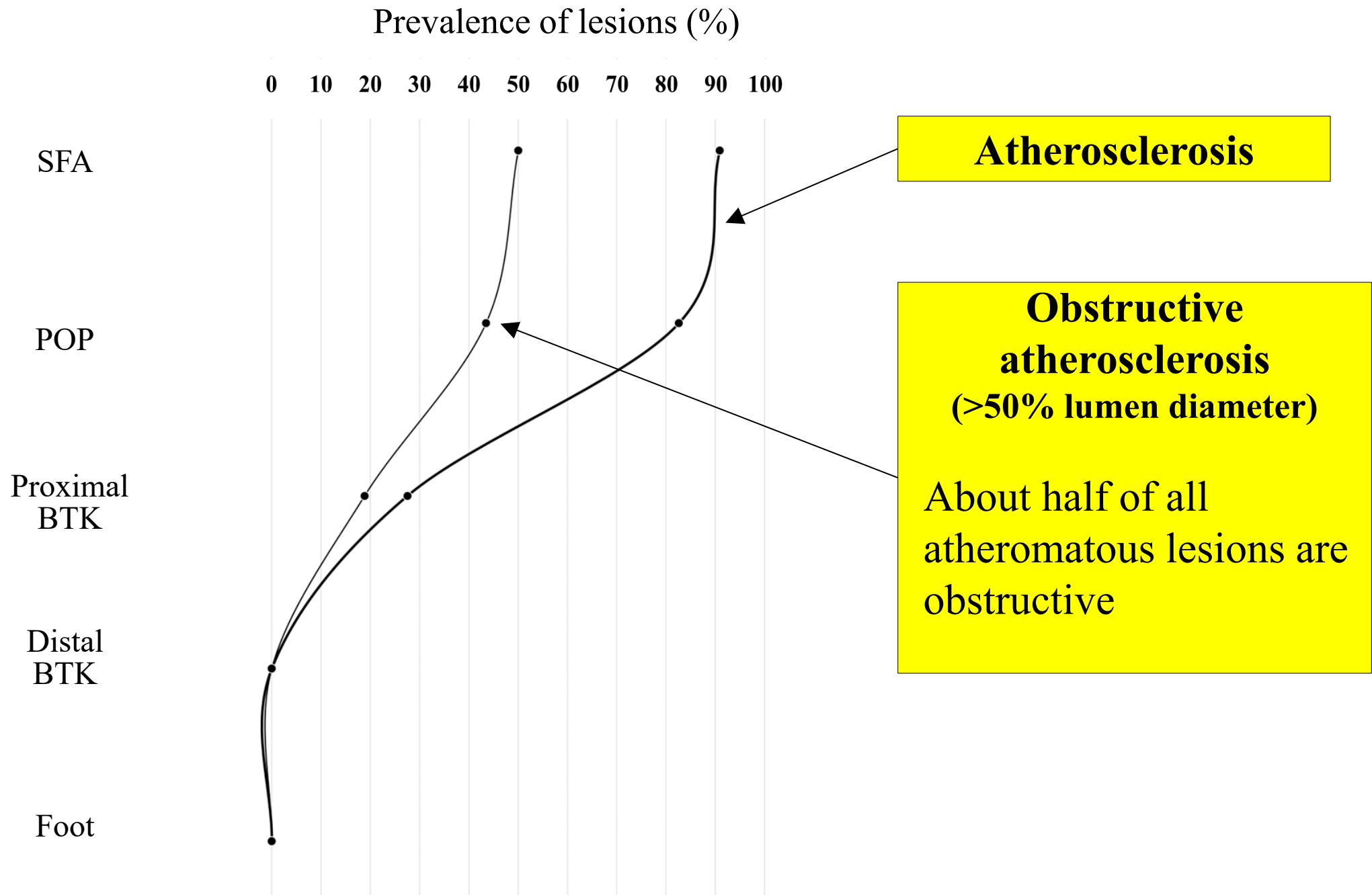
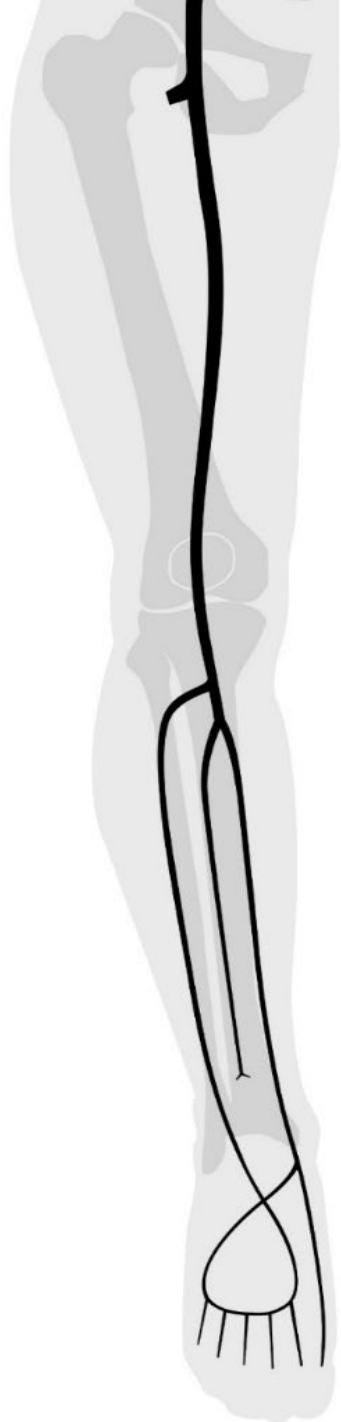
Alessandro Ucci,¹ Claudio Bianchini Massoni,¹ Paolo Perini,¹ Elisa Cabrini,¹ Anna Fornasari,¹ Alessandro Tafuni,² Debora Guareschi,² Antonio Freyrie,¹ Domenico Corradi,² and Roberto Ferraresi,³ Parma and Milan, Italy

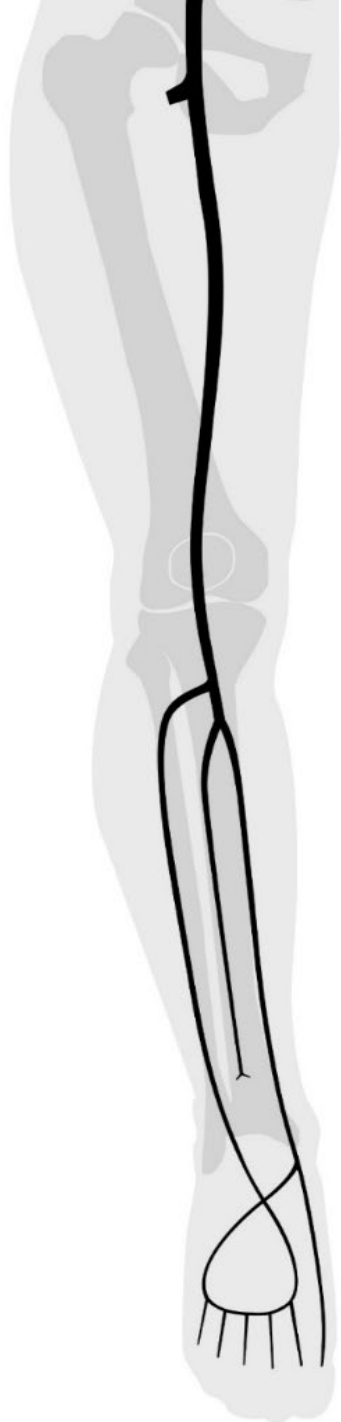
Global prevalence of lesions (%)

%









Prevalence of lesions (%)

0 10 20 30 40 50 60 70 80 90 100

SFA

POP

Proximal
BTK

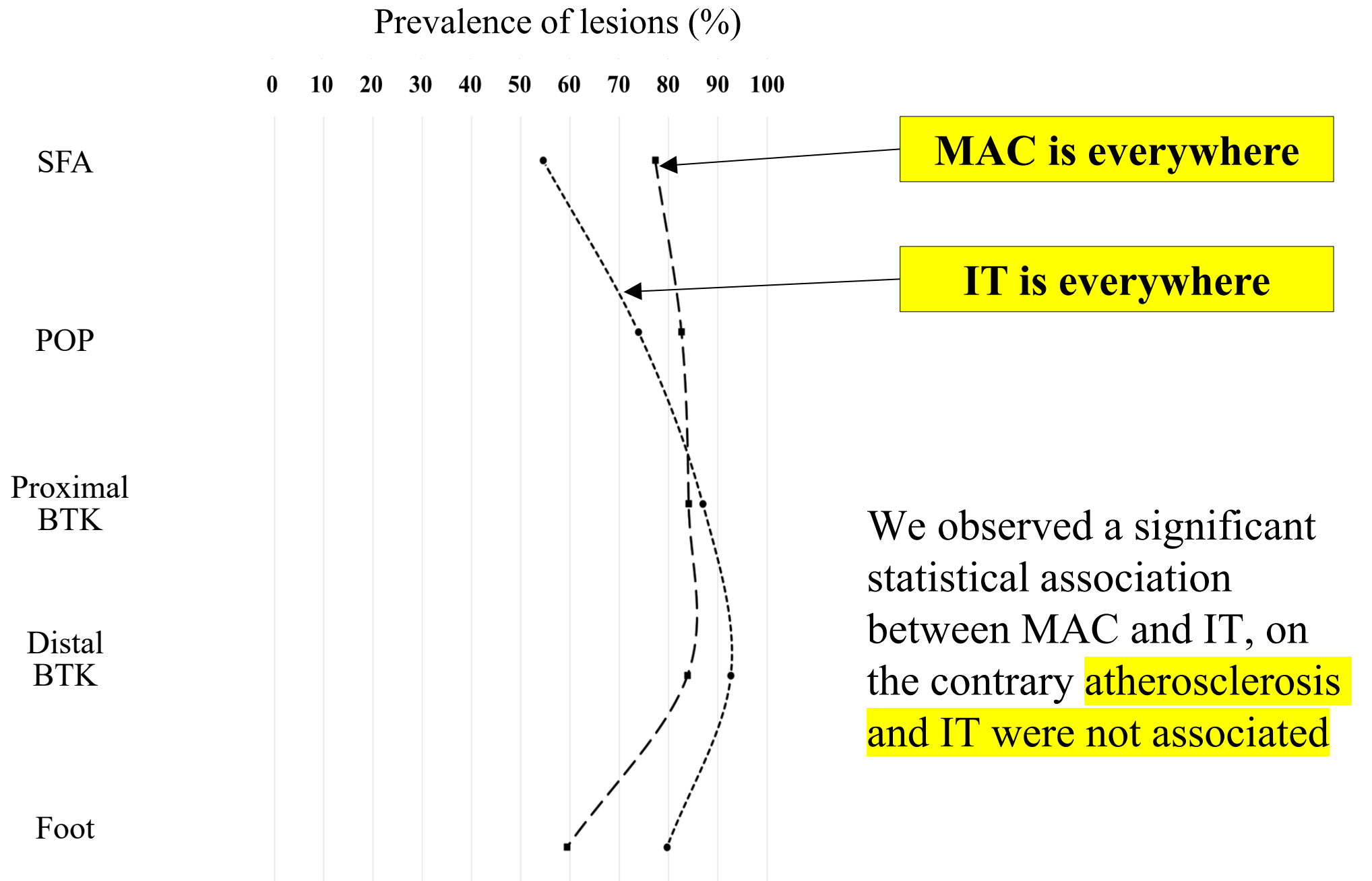
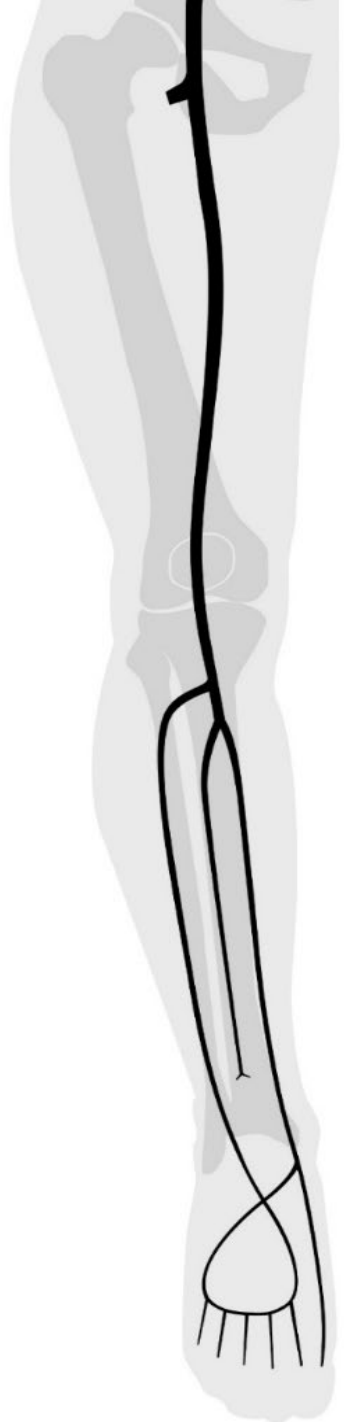
Distal
BTK

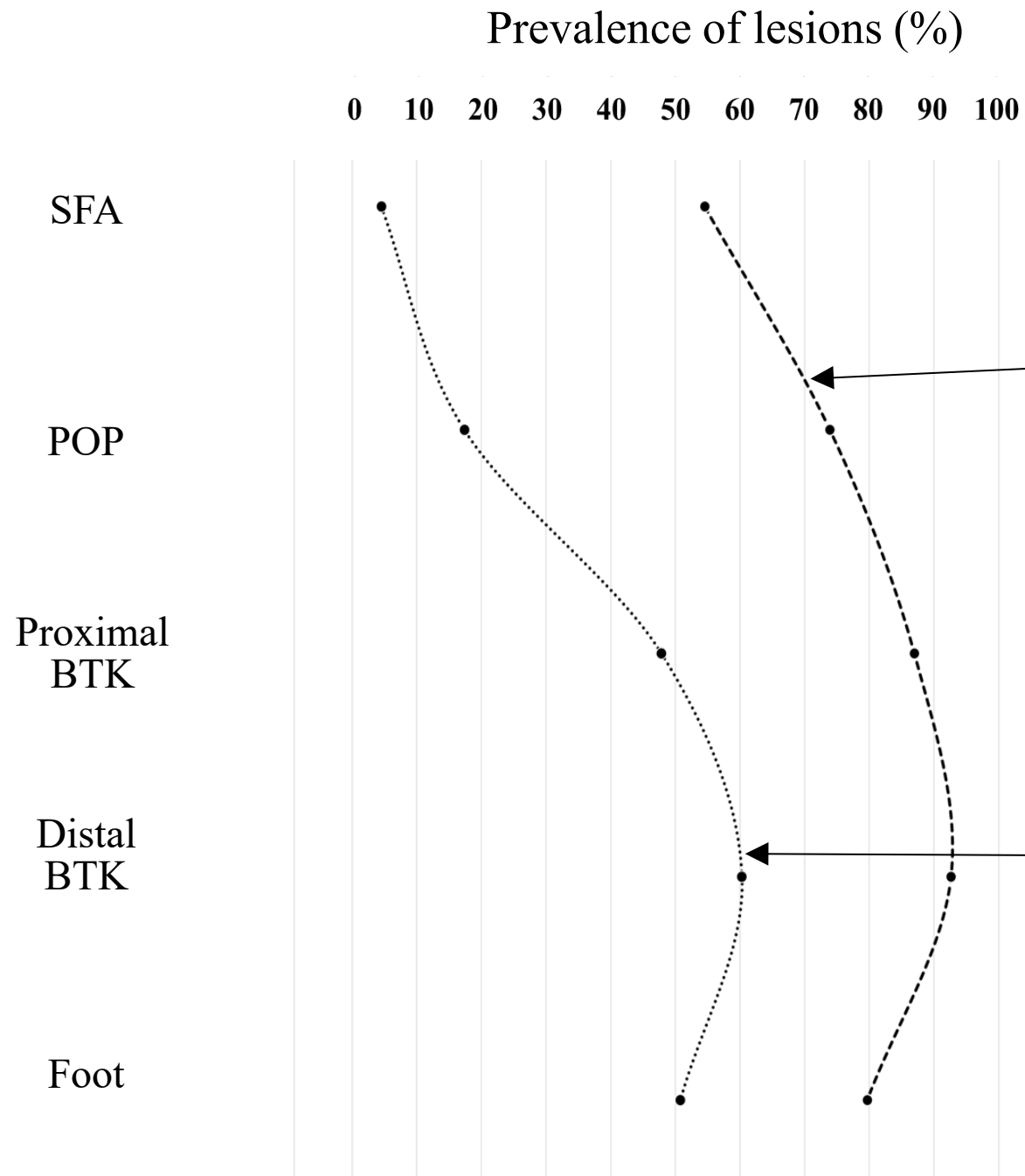
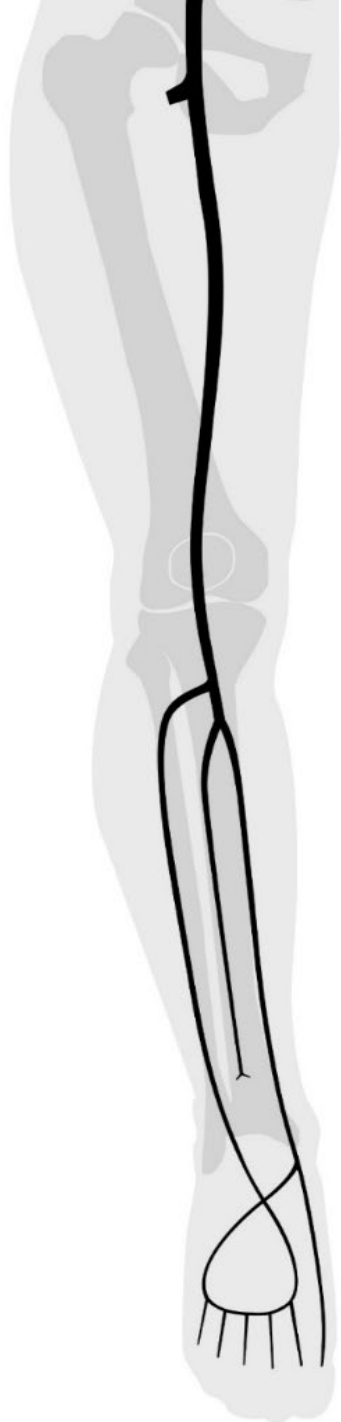
Foot

MAC is everywhere





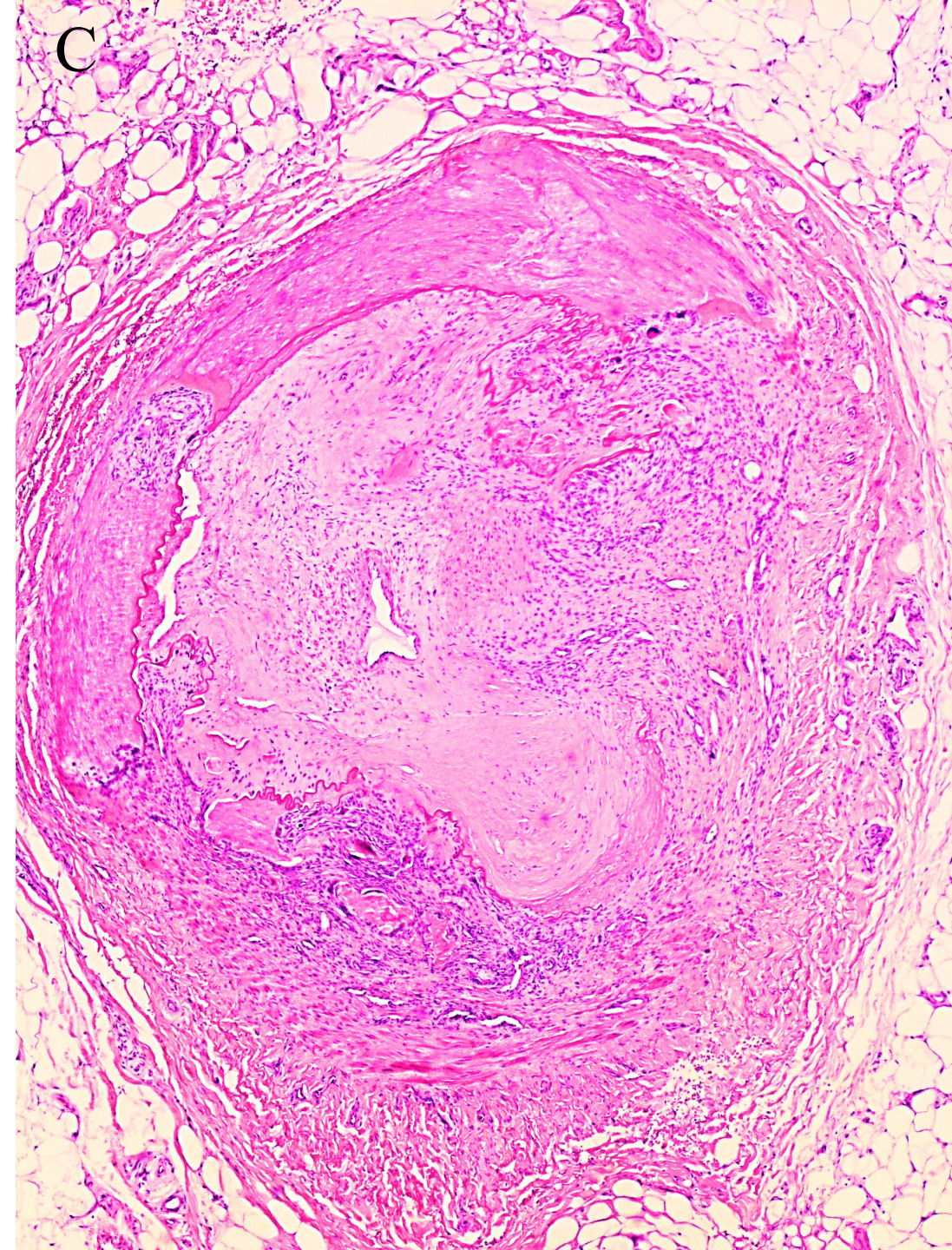
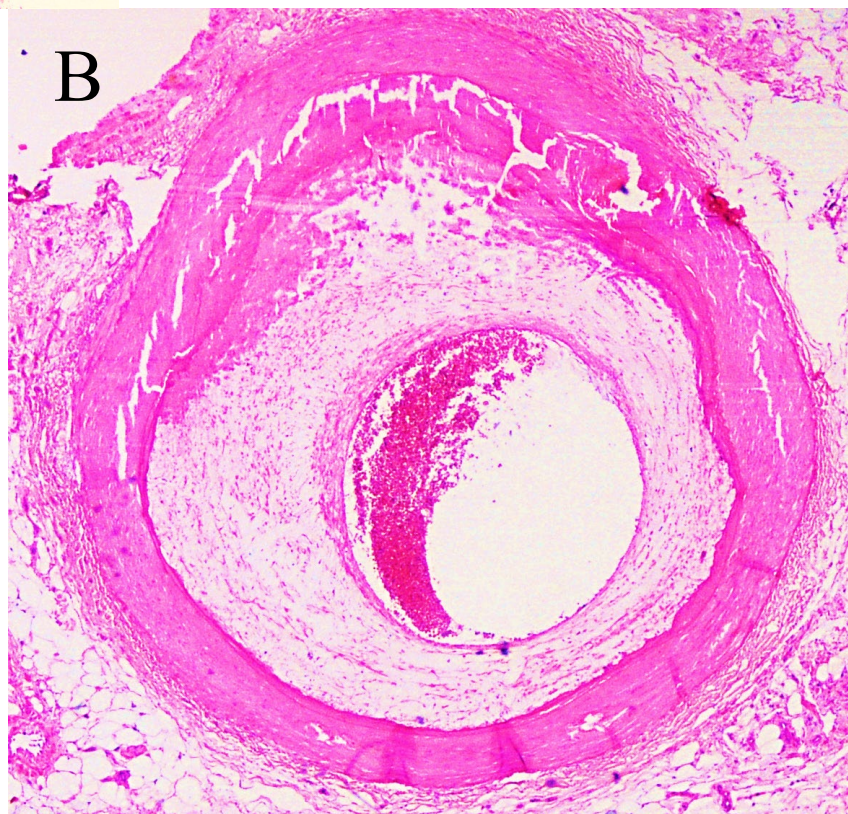
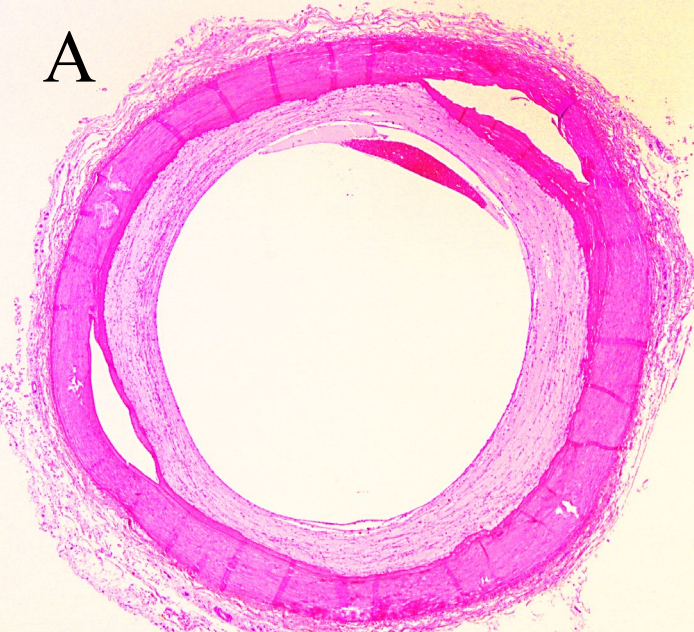


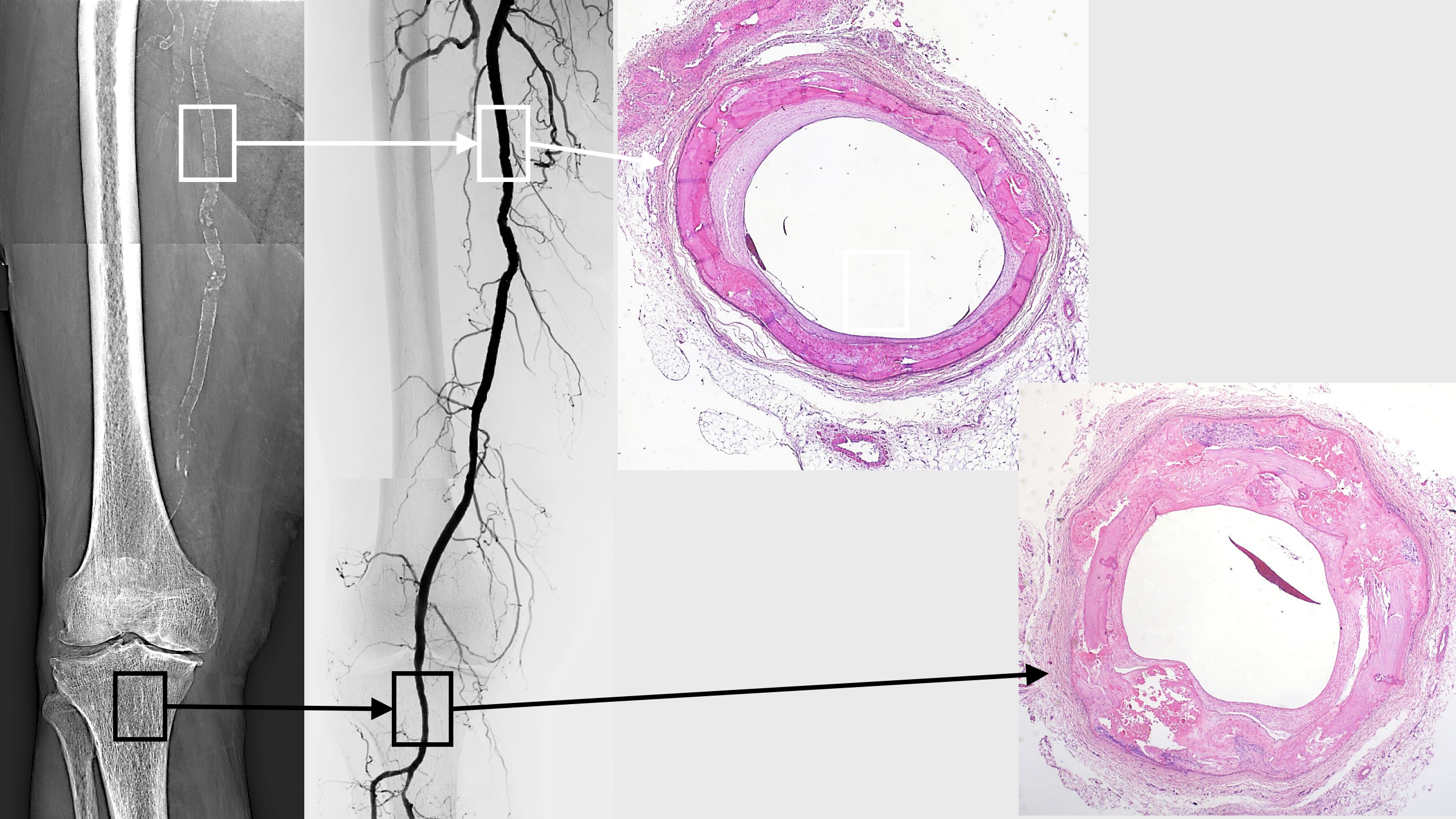


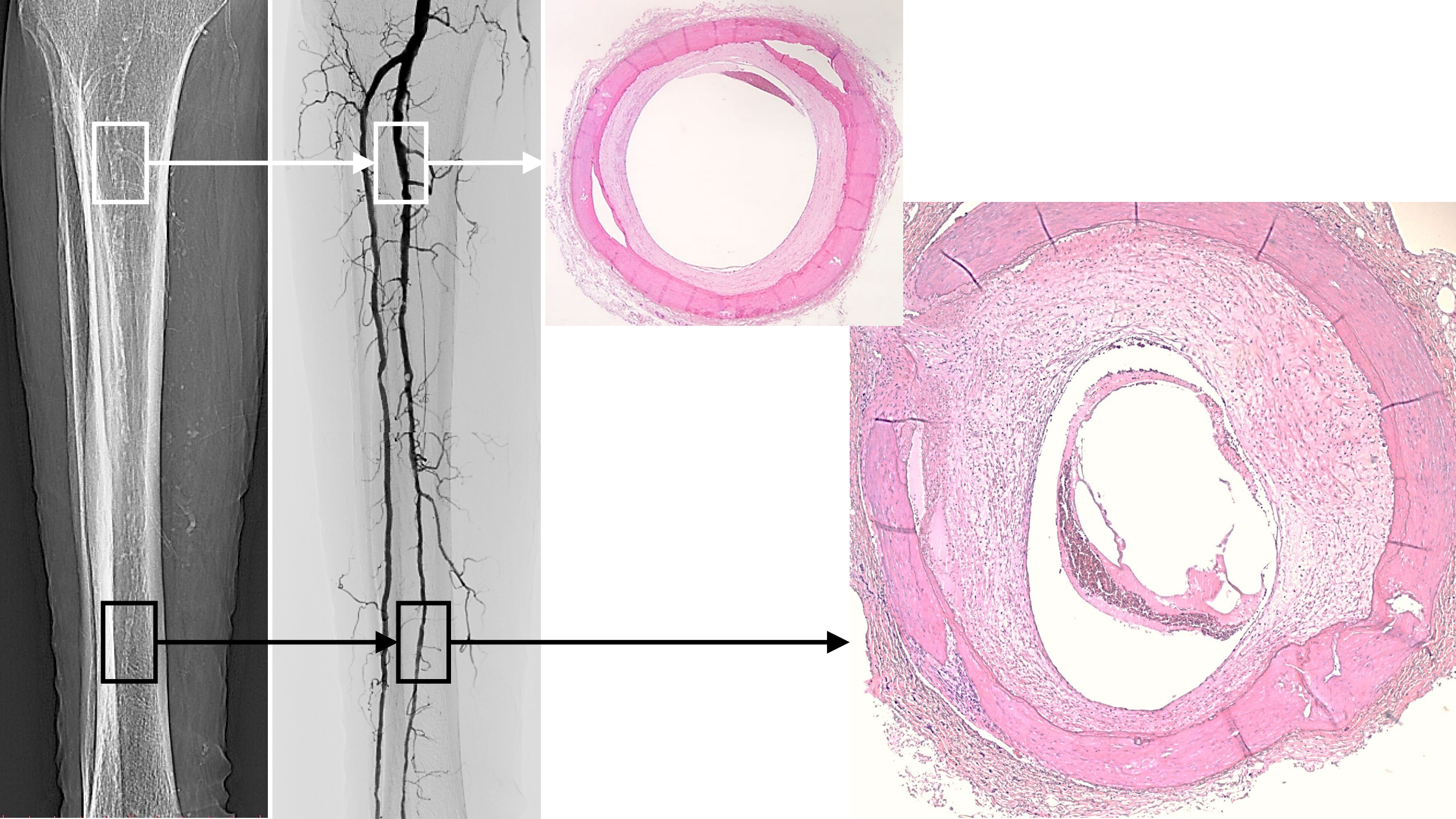
IT is everywhere

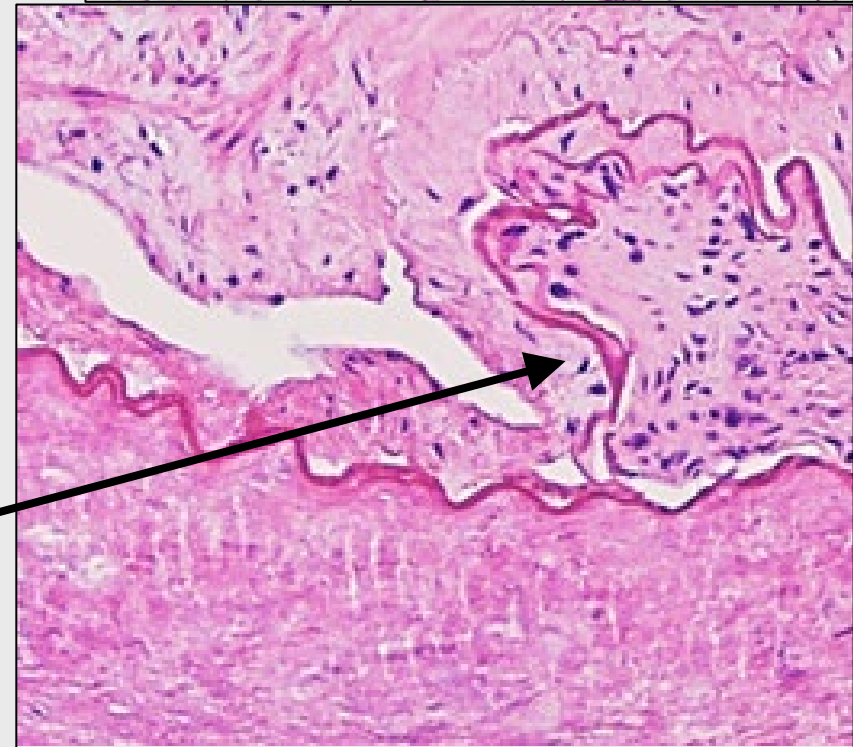
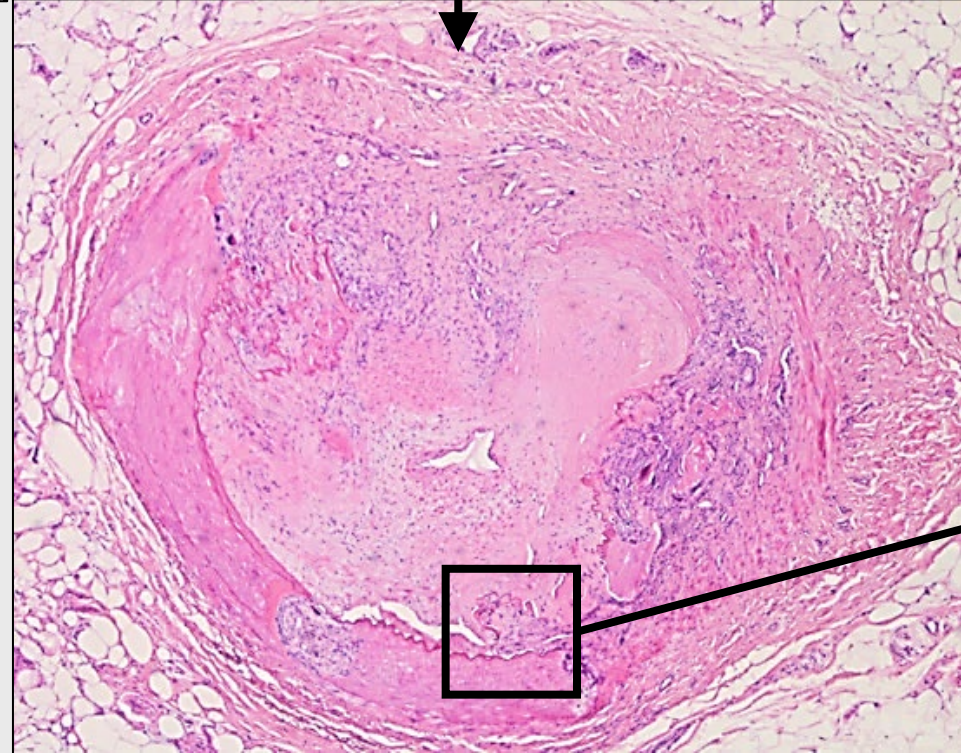
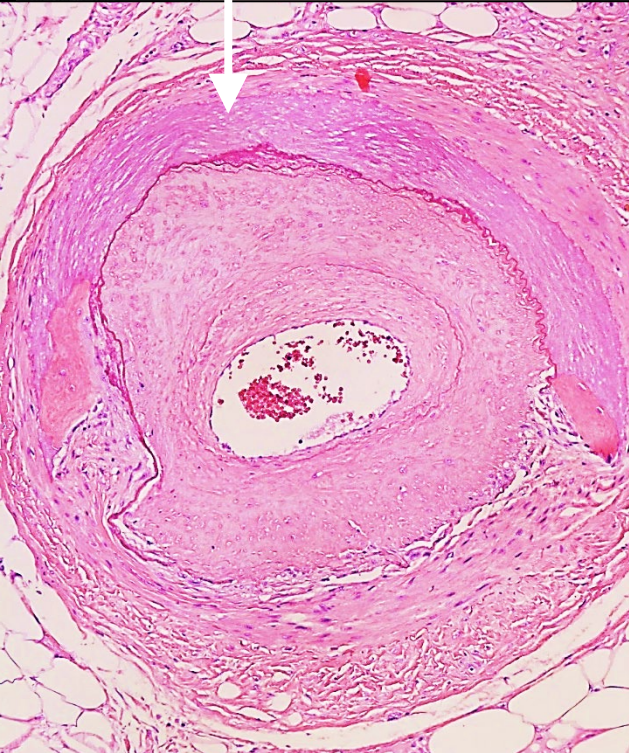
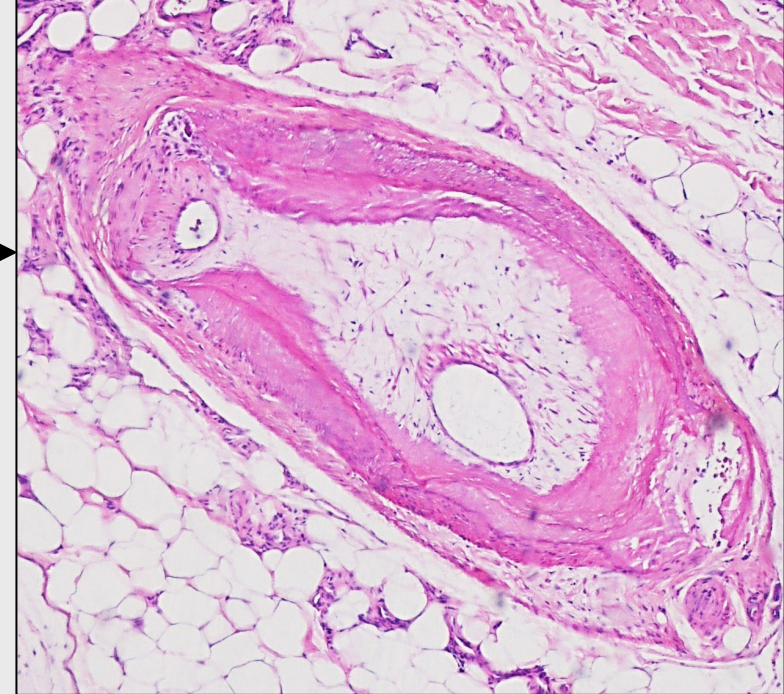
Obstructive IT
(**>50% lumen diameter**)

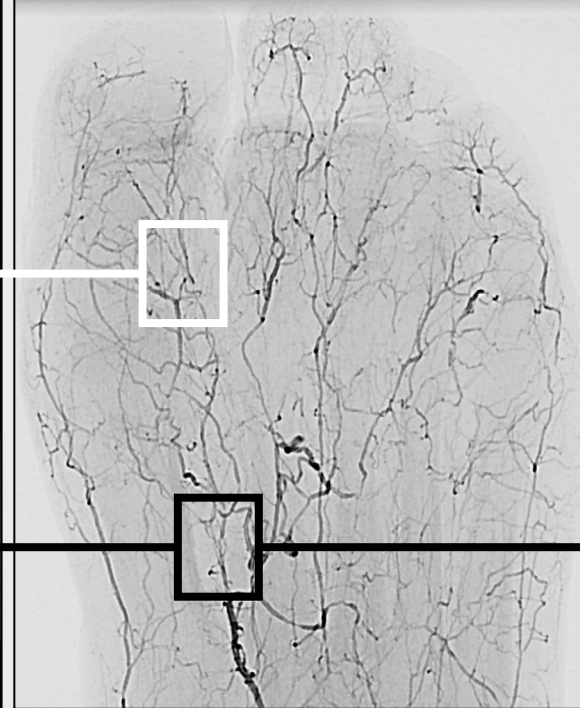
IT is non-obstructive in
SFA-POP, highly
obstructive in BTK &
FOOT arteries



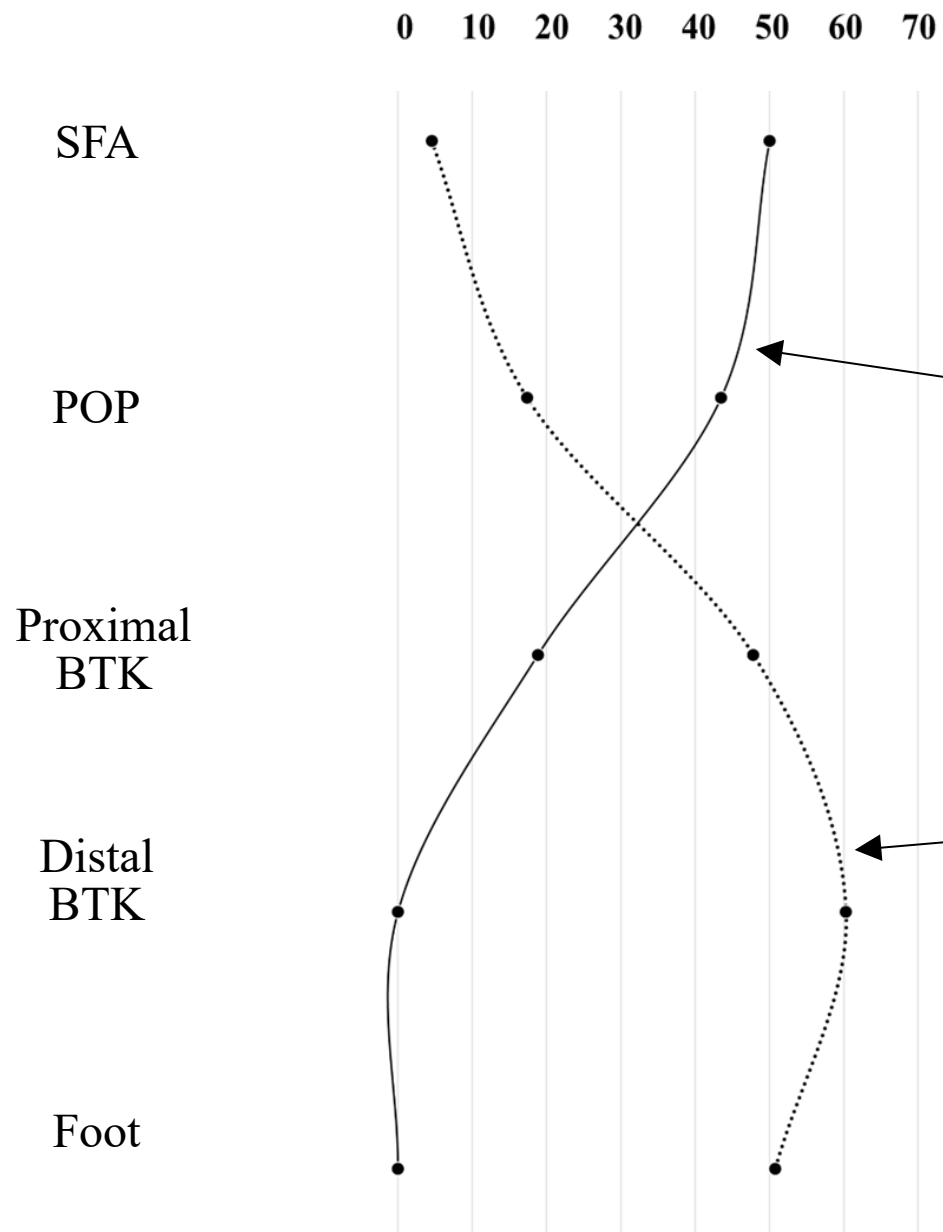








Prevalence of obstructive lesions (%)

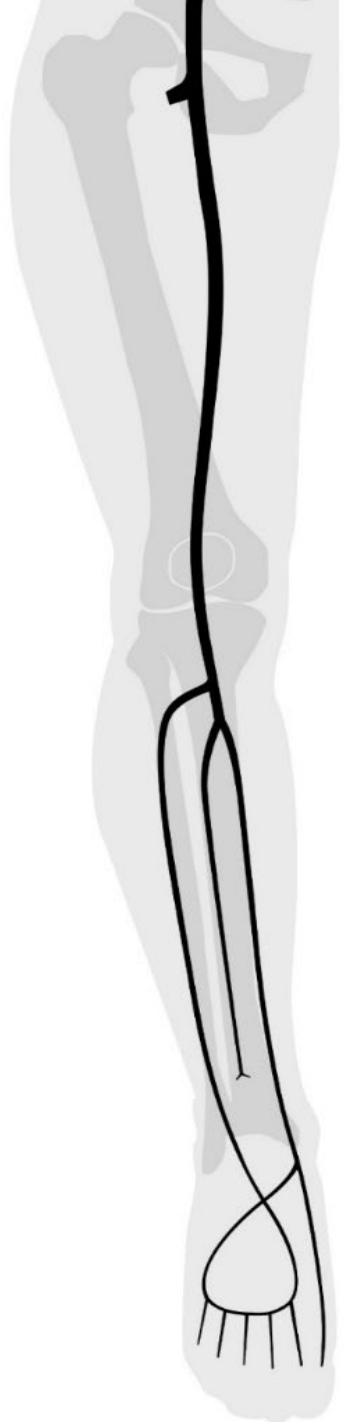


What is the true cause of vessel obstruction in CLTI patients?

Atherosclerosis >50%

IT >50%

Conclusion



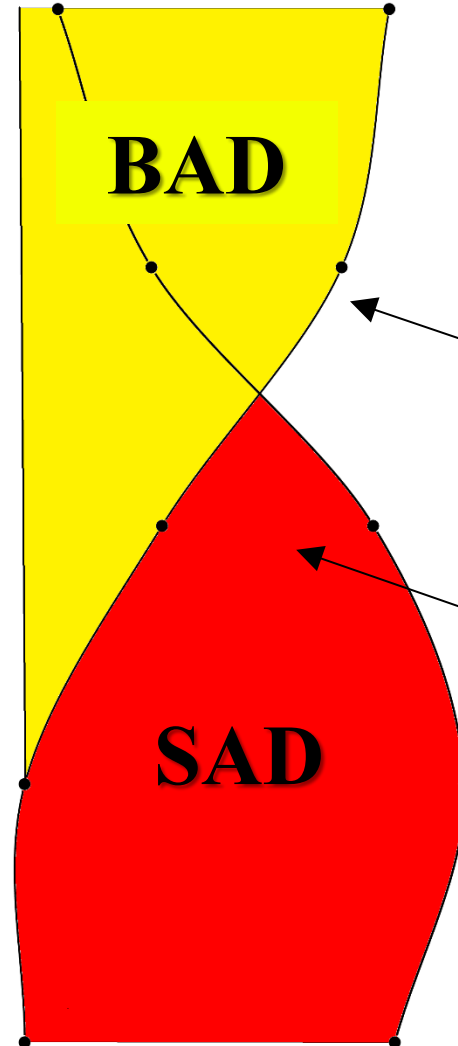
SFA

POP

Proximal
BTK

Distal
BTK

Foot



BAD

SAD

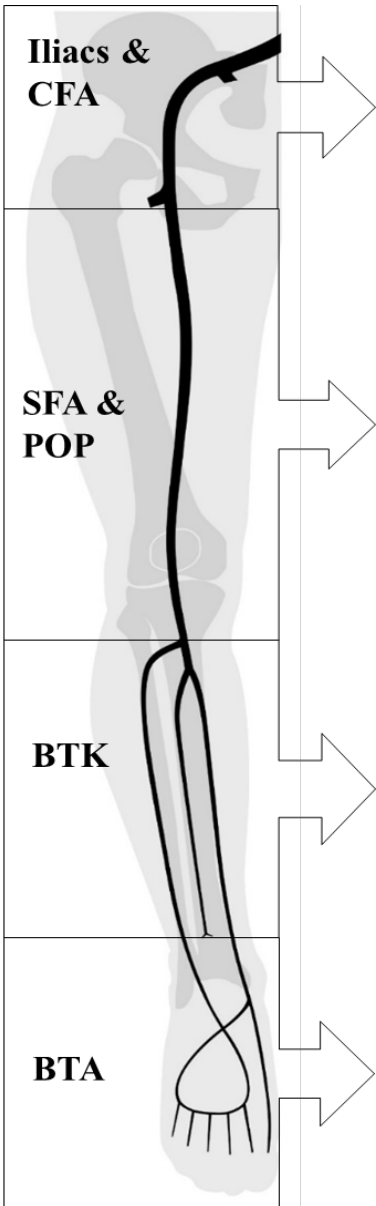
Vascular obstruction in CLTI results from both, atherosclerosis and MAC-IT, however, MAC-IT is highly prevalent

Atherosclerosis is responsible of BAD → transmission failure

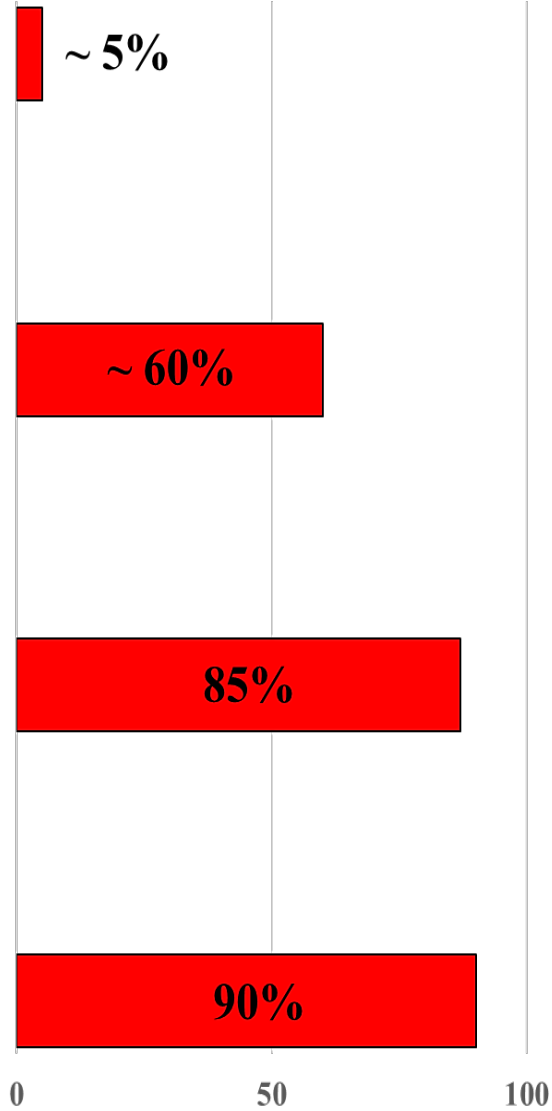
Prox BTK arteries are the overlapping zone between BAD & SAD

IT-MAC is responsible of SAD → distribution failure

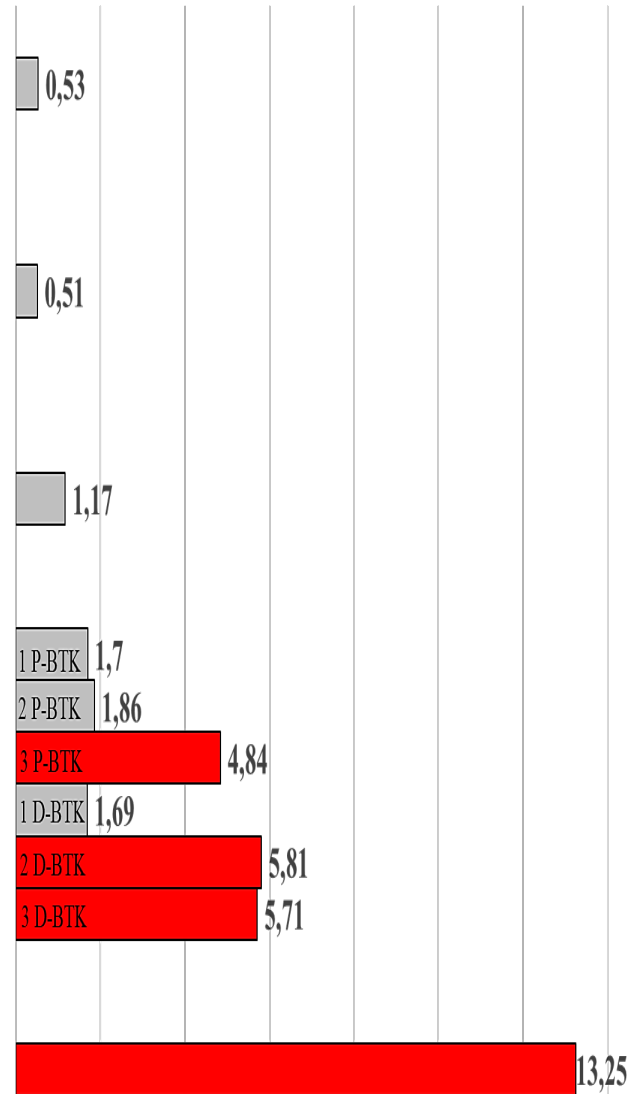
CLTI



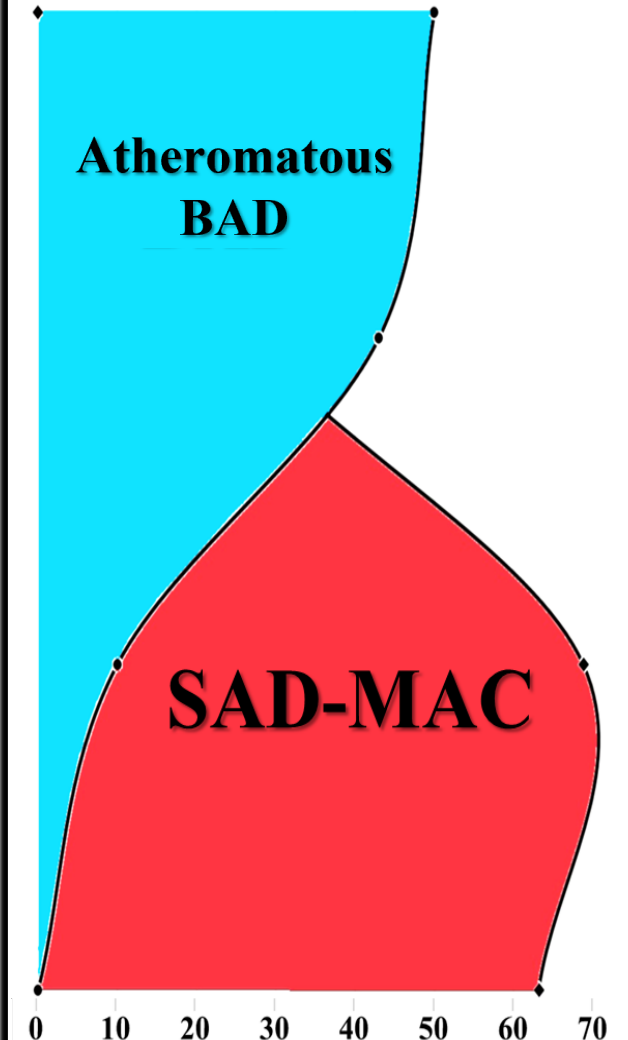
Site



Power



Type

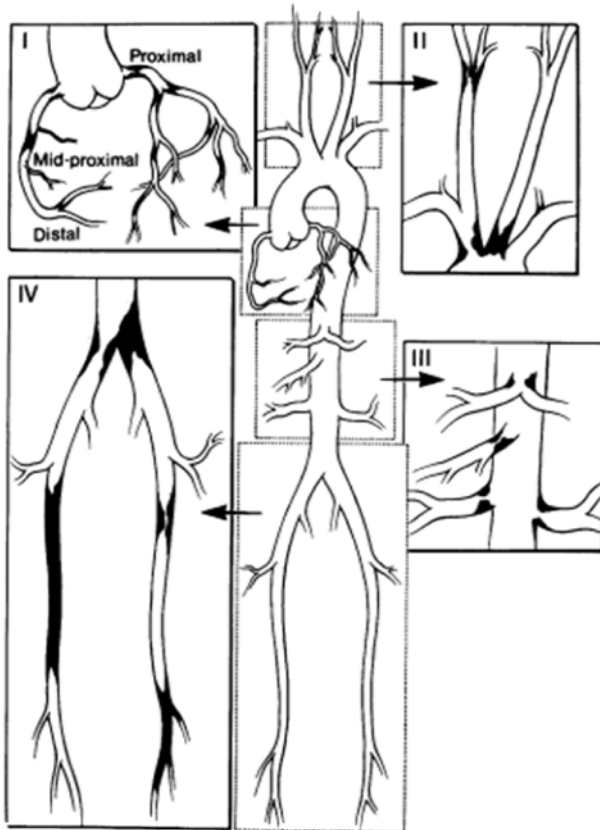


Industry missed the new PAD



Patterns of Atherosclerosis and their Surgical Significance

MICHAEL E. DEBAKEY, M.D.,* GERALD M. LAWRIE, M.D.,† DONALD H. GLAESER, D.Sc.‡



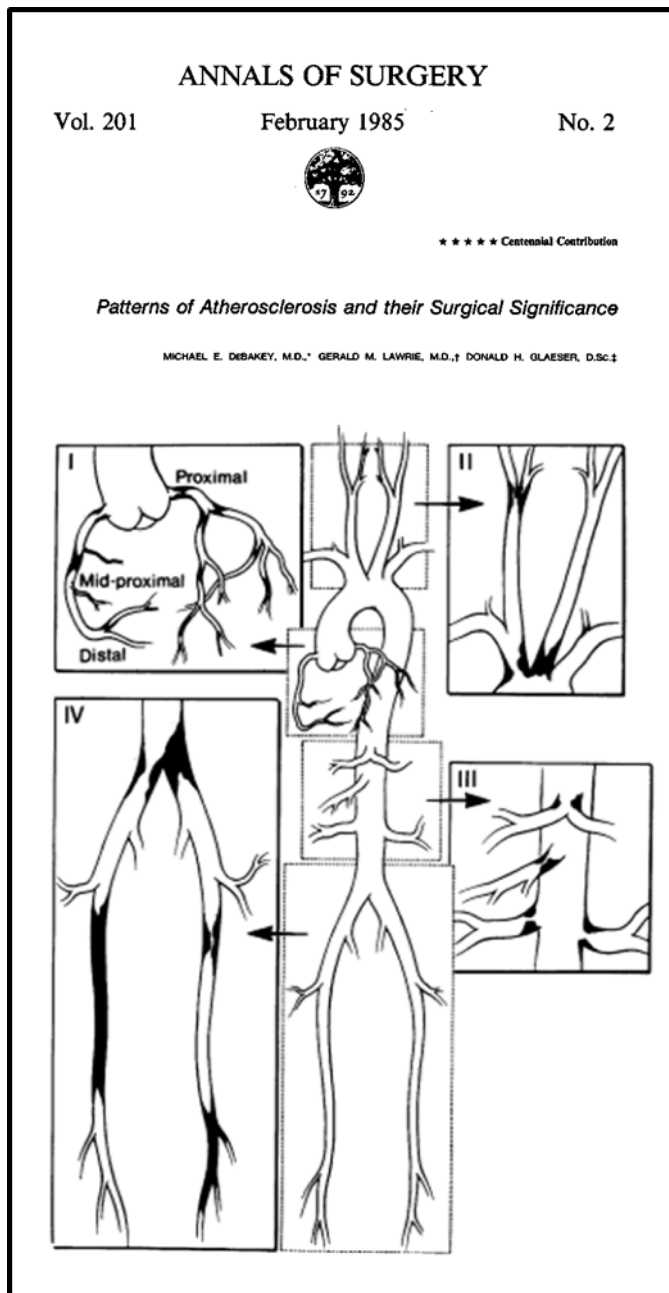
Happy days

Mean age 59 yrs

Only 5.7% of all pts had a diagnosis of atherosclerosis in more than one site during initial admission

The word “diabetes” compares only one time, and the word “dialysis” is absent

The word “calcium” or “calcification” is absent

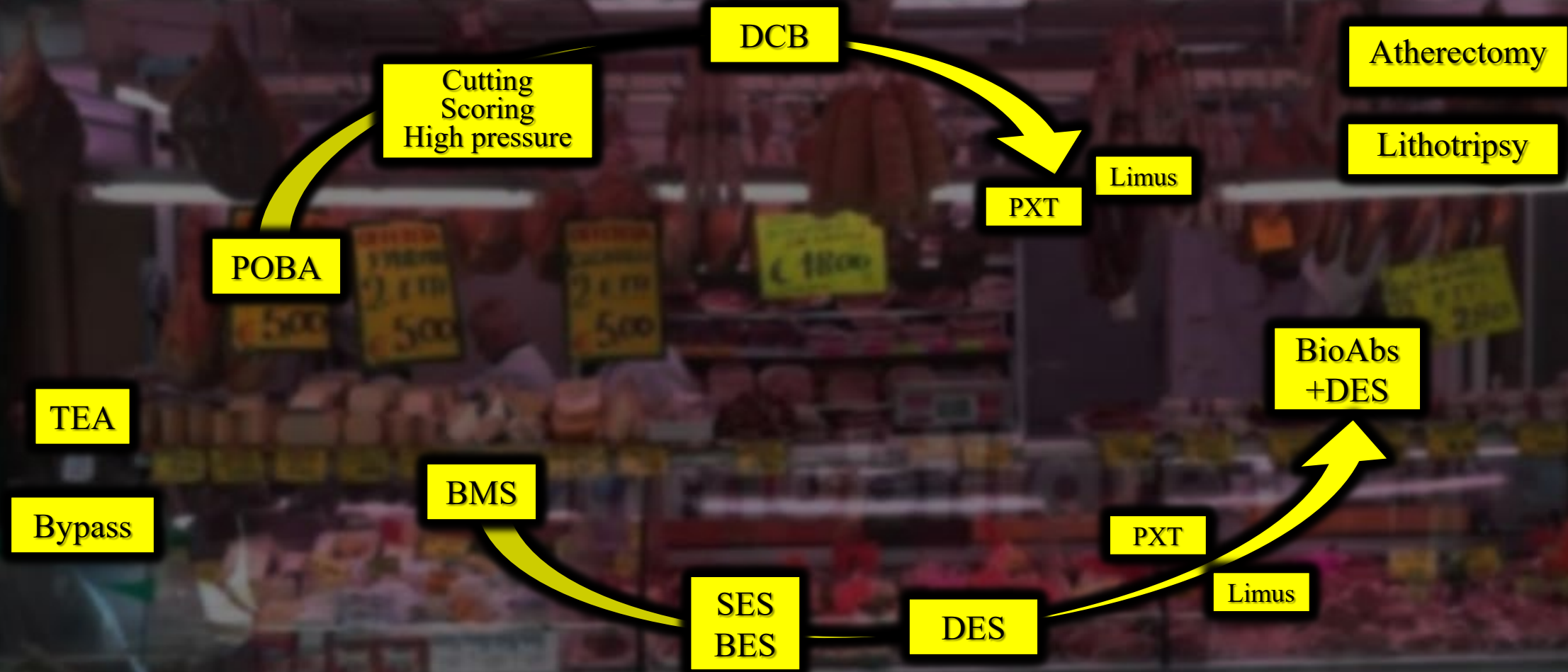


Happy days	Today: my CLTI pts
Mean age 59 yrs	Mean age 76 yrs
Only 5.7% of all pts had a diagnosis of atherosclerosis in more than one site during initial admission	- >70% heart disease - >40% brain disease
The word “diabetes” compares only one time, and the word “dialysis” is absent	- 86% DM - >20% ESRD-HD
The word “calcium” or “calcification” is absent	>80% calcified lesion

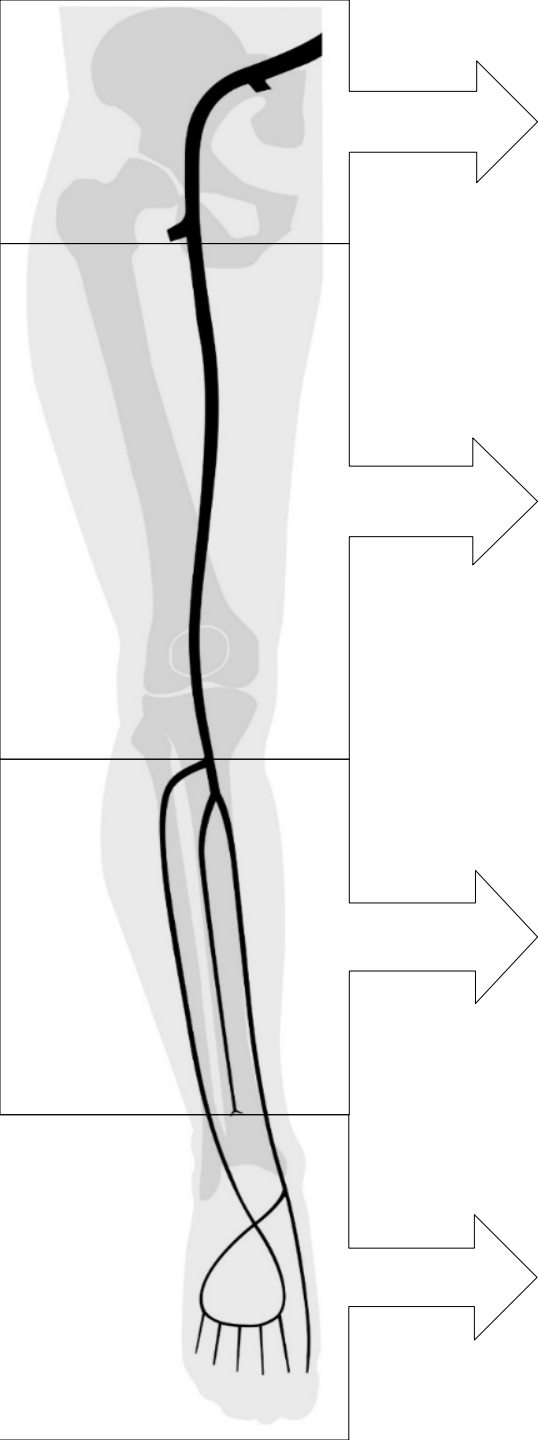
Butcher and delicatessen shop



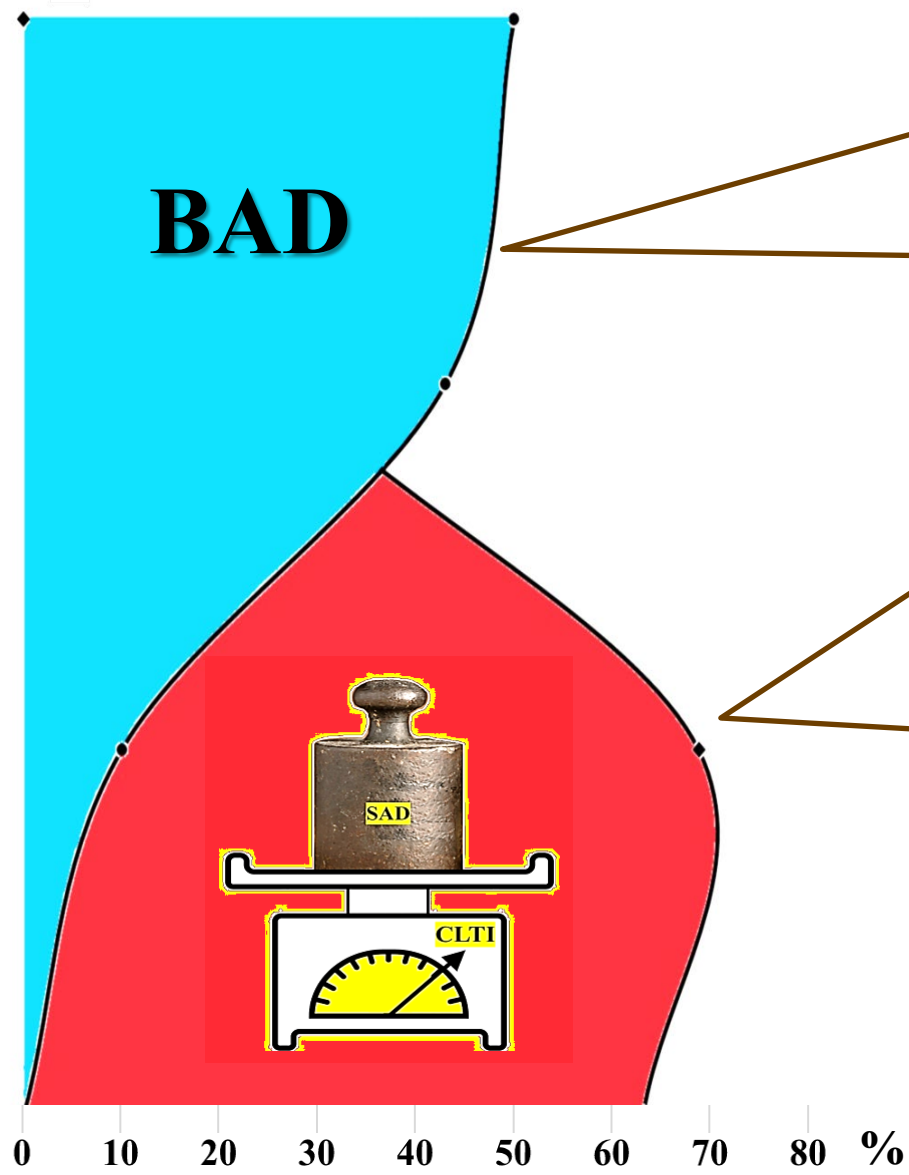
Revascularization shop



What's your budget?

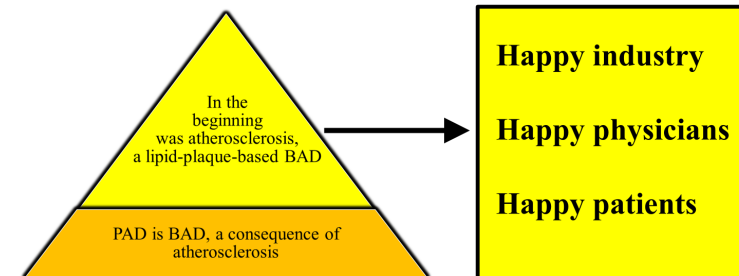


Prevalence of obstructive (>50%) lesions (%)

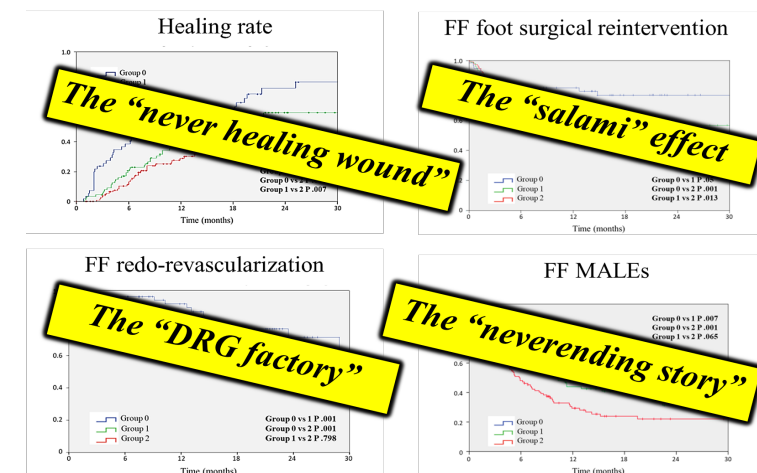


Happy days

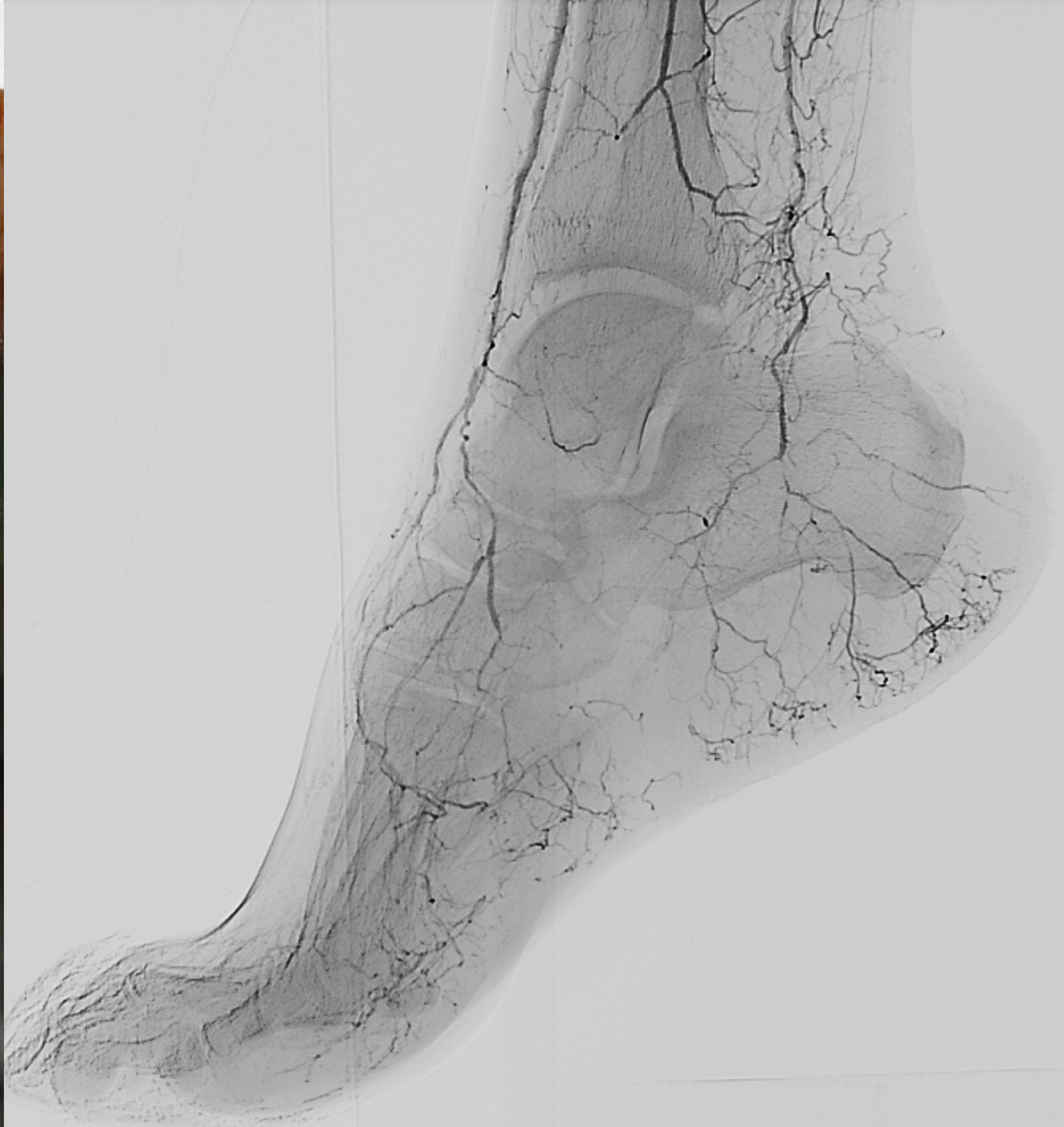
The PAD dogma

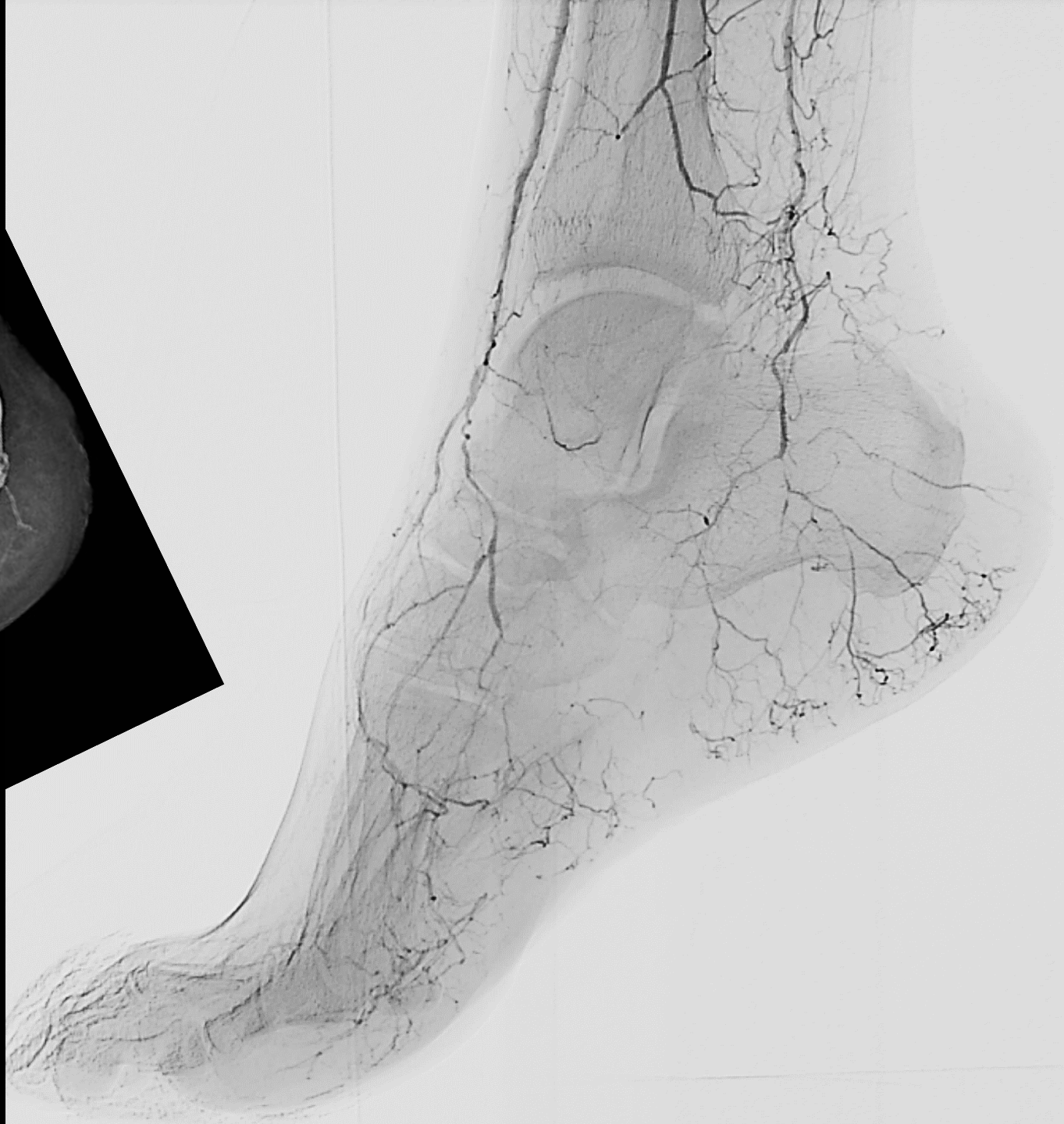


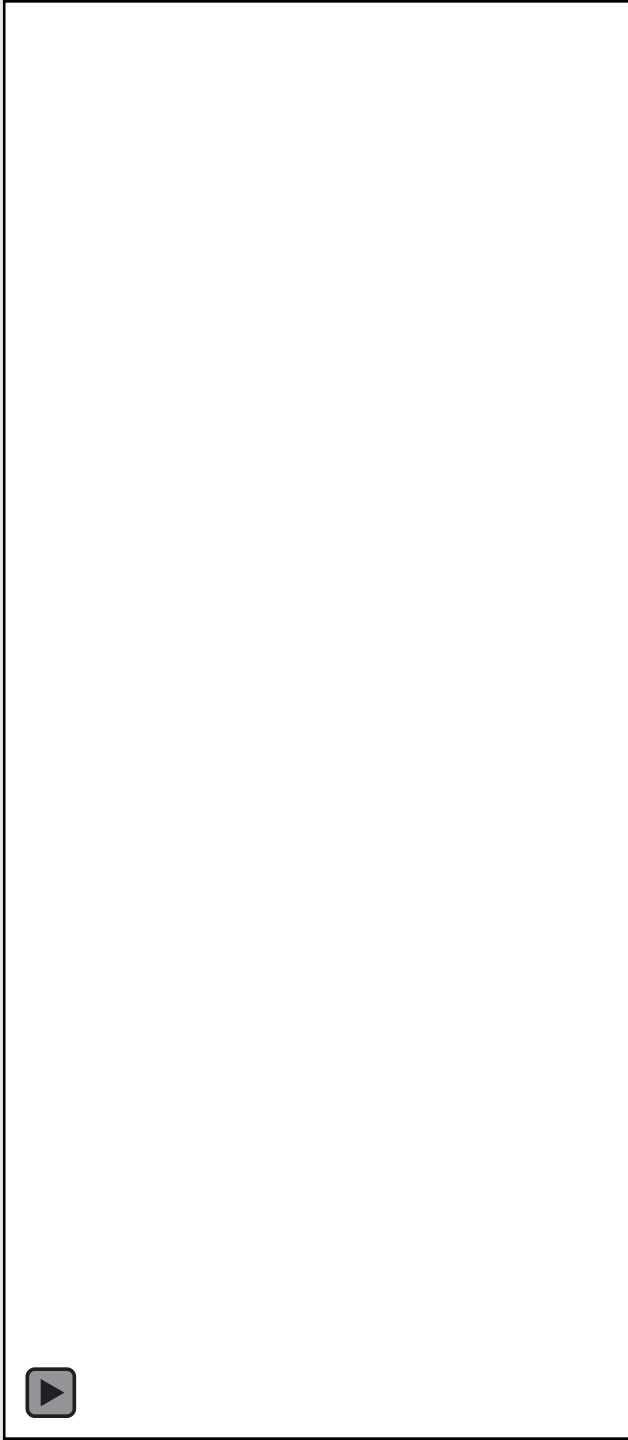
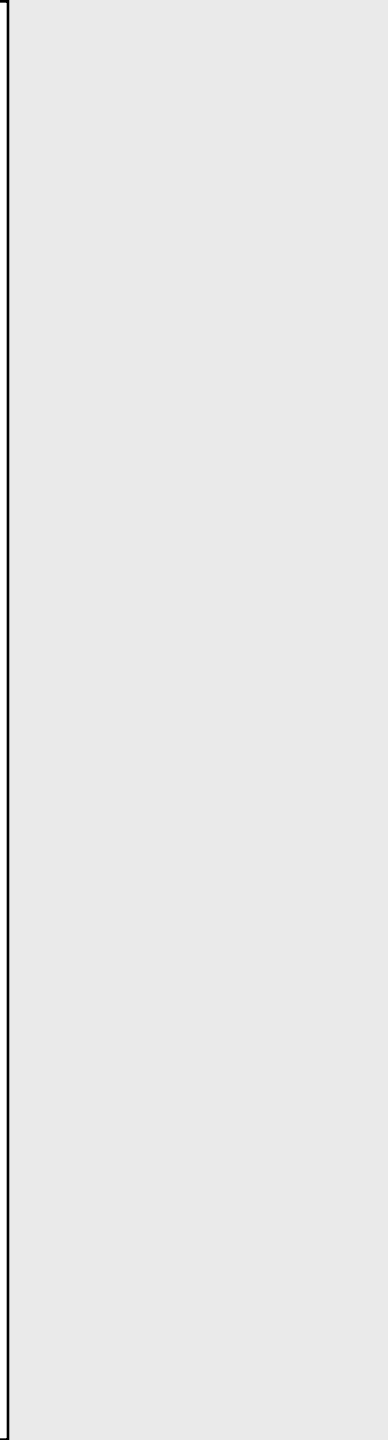
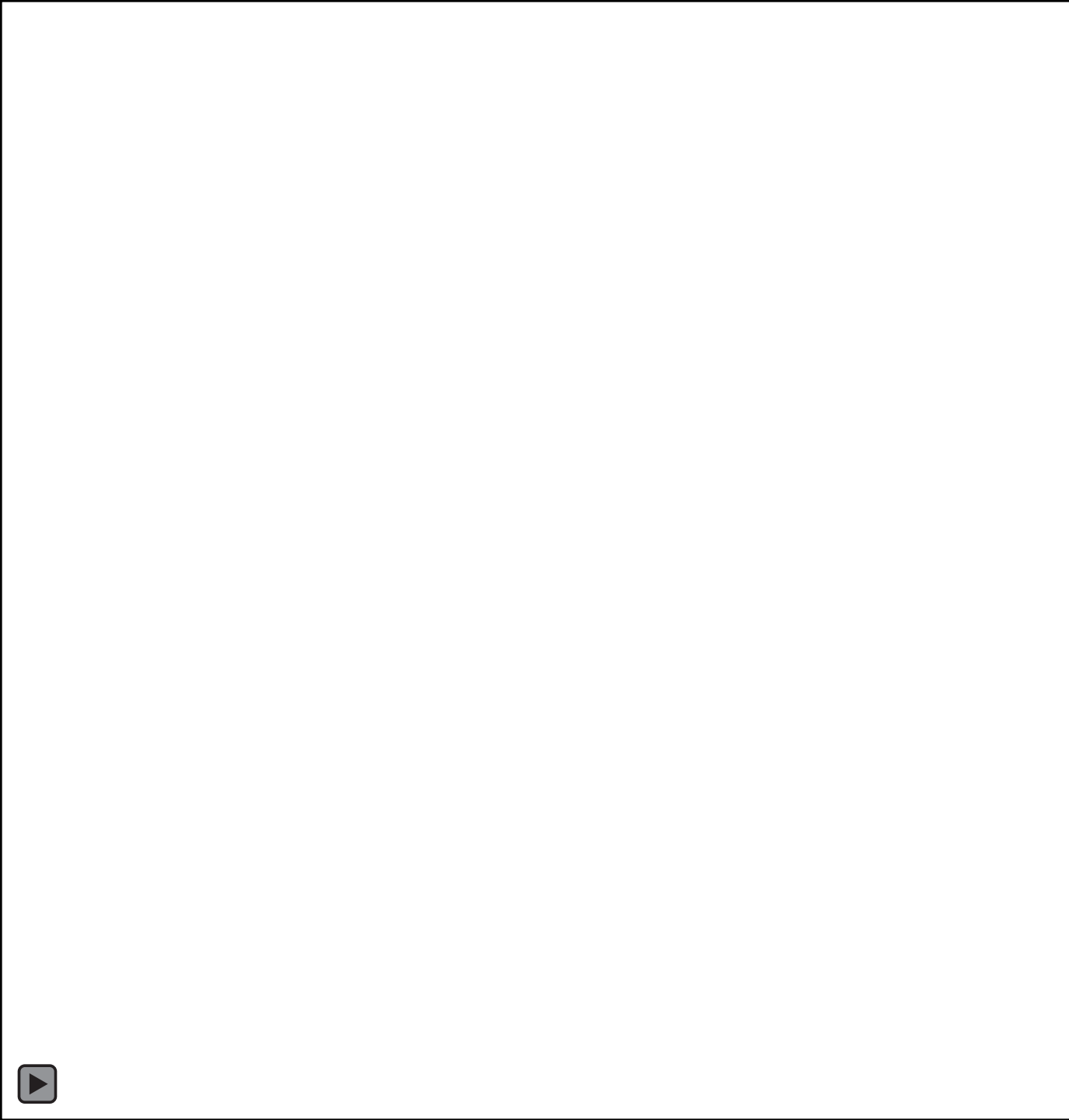
Today

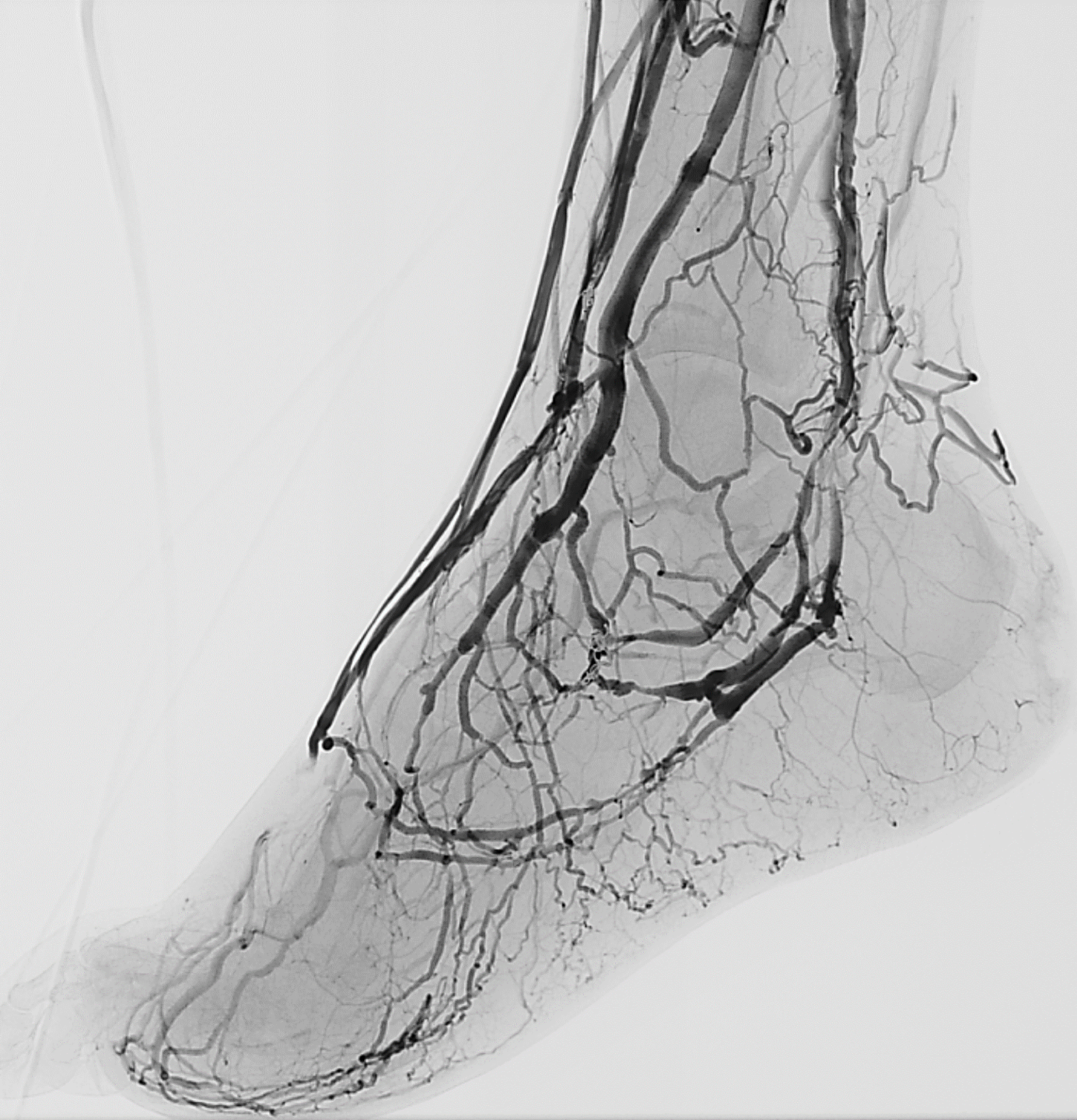


The only new element for the
SAD-MAC pts is the FVA













The pedal MAC score provides a simple, objective tool to stratify patient's and limb risk and tailor revascularization strategies, guiding treatment decisions in CLTI pts.