

L'arteriopatia obliterante nel paziente in dialisi: diagnosi ed interventistica endovascolare



Roberto Ferraresi

Peripheral Interventional Unit
Diabetic Foot Center



CLINICA SAN CARLO
PADERNO DUGNANO (MI)

Vincenzo Foppa, 1462

"The miracle of the salvaged foot"

Cappella Portinari, S. Eustorgio Church
Milan, Italy

Disclosure

Roberto Ferraresi, MD

No conflict of interest with this presentation

BAD & SAD, who is the enemy in CLTI?

SAD-MAC: brothers in arm

Obstruction patterns in CLTI

Weapons and soldiers: the CLTI-PAD war

Jungle patrols: extreme below-the-ankle guerilla

Mercy for patients

ANNALS OF SURGERY

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No. 2



1985

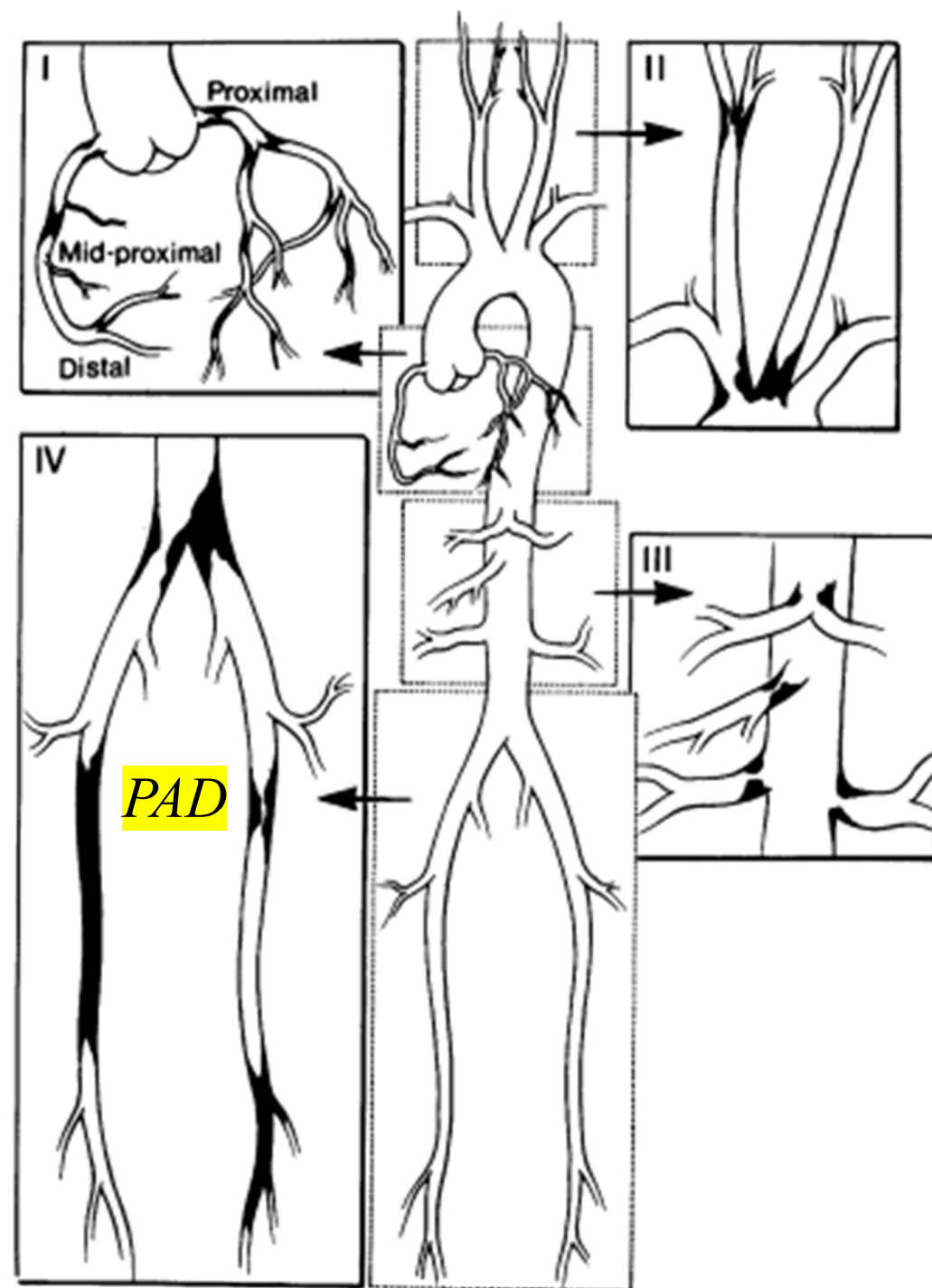
***** Centennial Contribution

Patterns of Atherosclerosis and their Surgical Significance

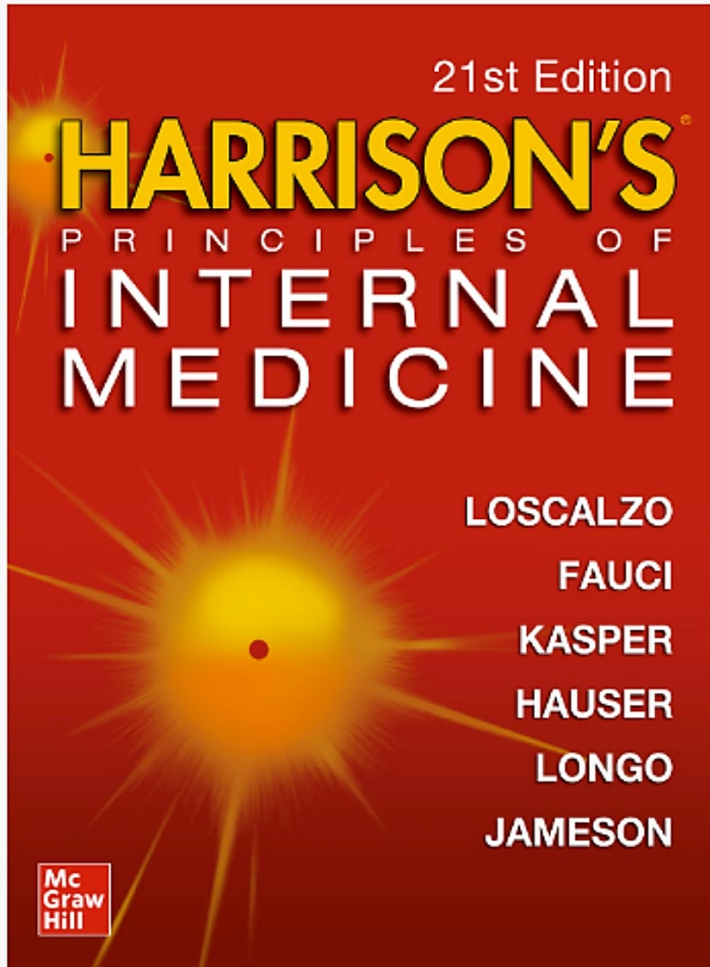
MICHAEL E. DeBAKEY, M.D.* GERALD M. LAWRIE, M.D.,† DONALD H. GLAESER, D.Sc.‡

- 13.827 from 1948 to 1983
- mean age 59 yrs, No DM, No ESRD-HD, No calcium/calcification

“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”



1985 → 2022



Chapter 281: Arterial Diseases of the Extremities - Peripheral Artery Disease

Mark A. Creager; Joseph Loscalzo

Atherosclerosis is the leading cause of PAD.

Segmental lesions that cause stenosis or occlusion are usually localized to **large and medium-size vessels**.

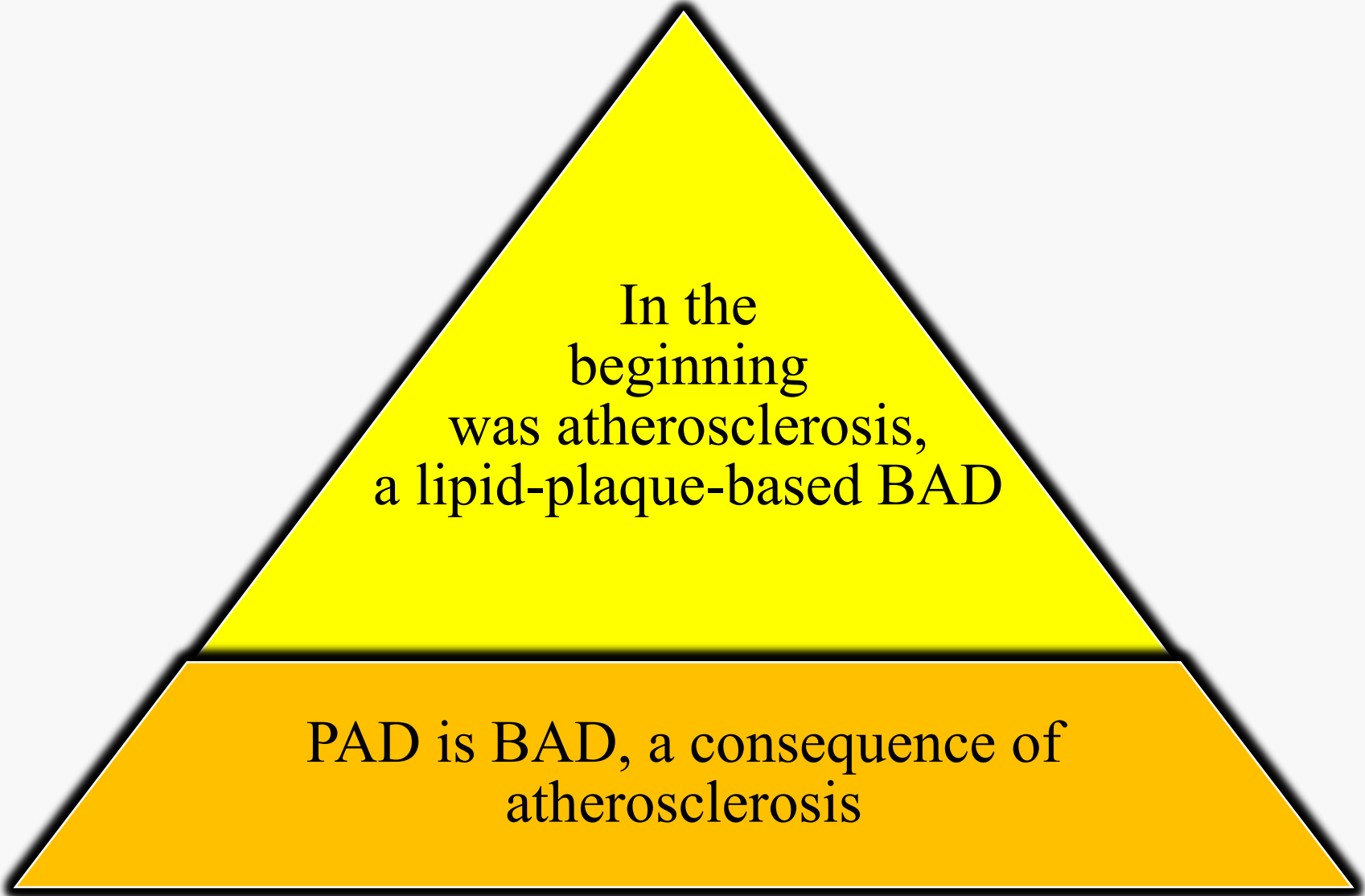
The primary sites of involvement are:

- abdominal aorta and iliac arteries (30% of pts)
- femoral and popliteal arteries (80–90% of pts)
- and the more distal vessels, including the tibial and peroneal arteries (40–50% of pts).

Foot arteries are not mentioned

1985 → 2022

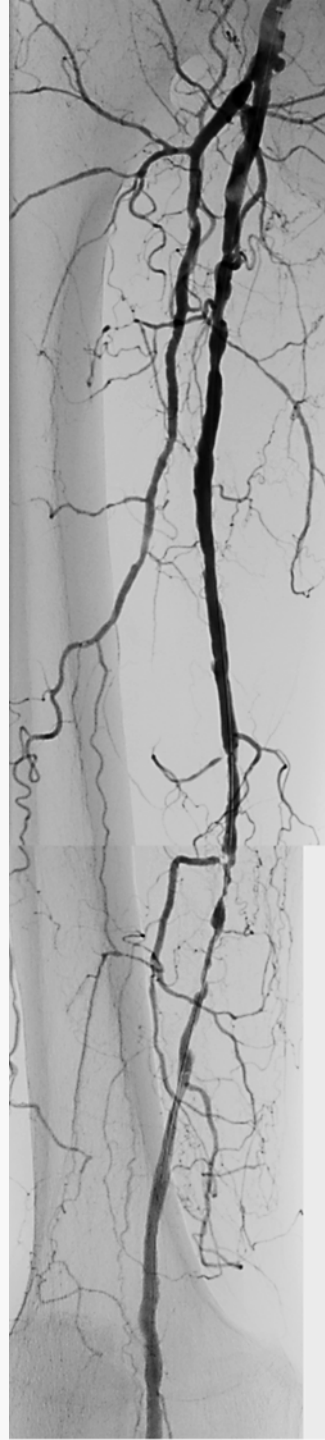
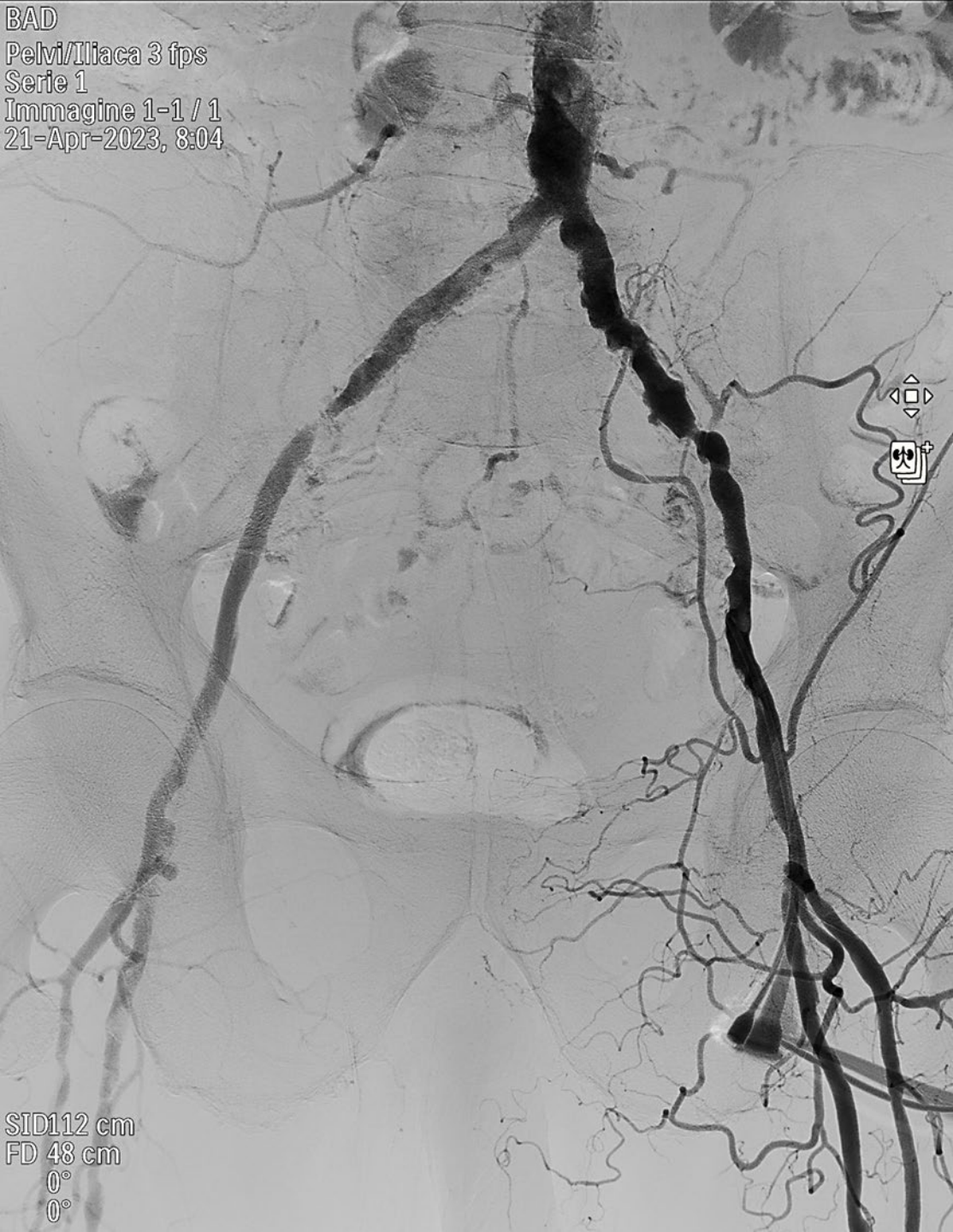
The PAD dogma



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

PAD is BAD, a consequence of
atherosclerosis

Patient A:
A pure BAD pt





TREATMENT





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



SID112 cm
FD 48 cm
LA05°
CRAN

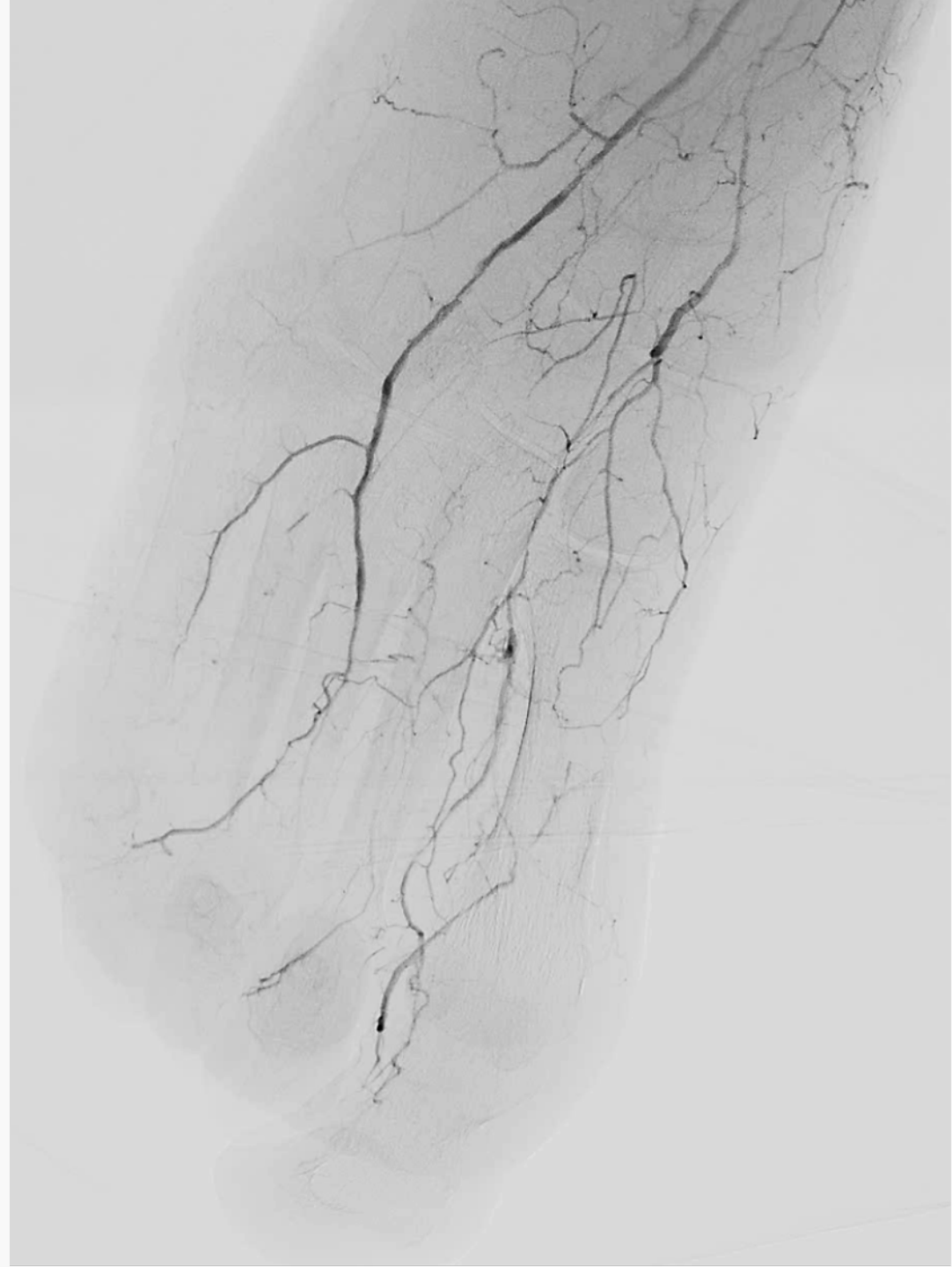


Patient B:
a BAD & SAD pt

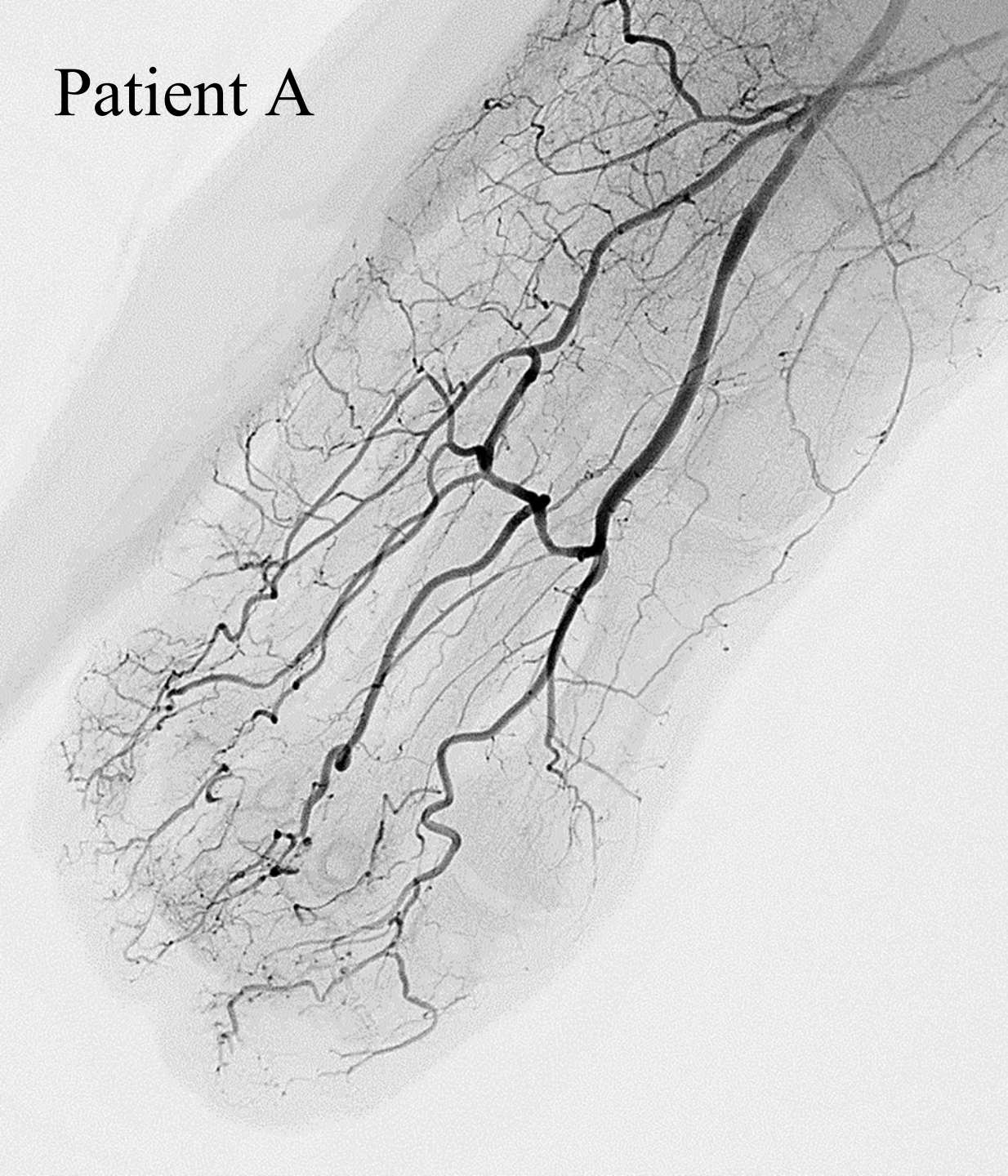




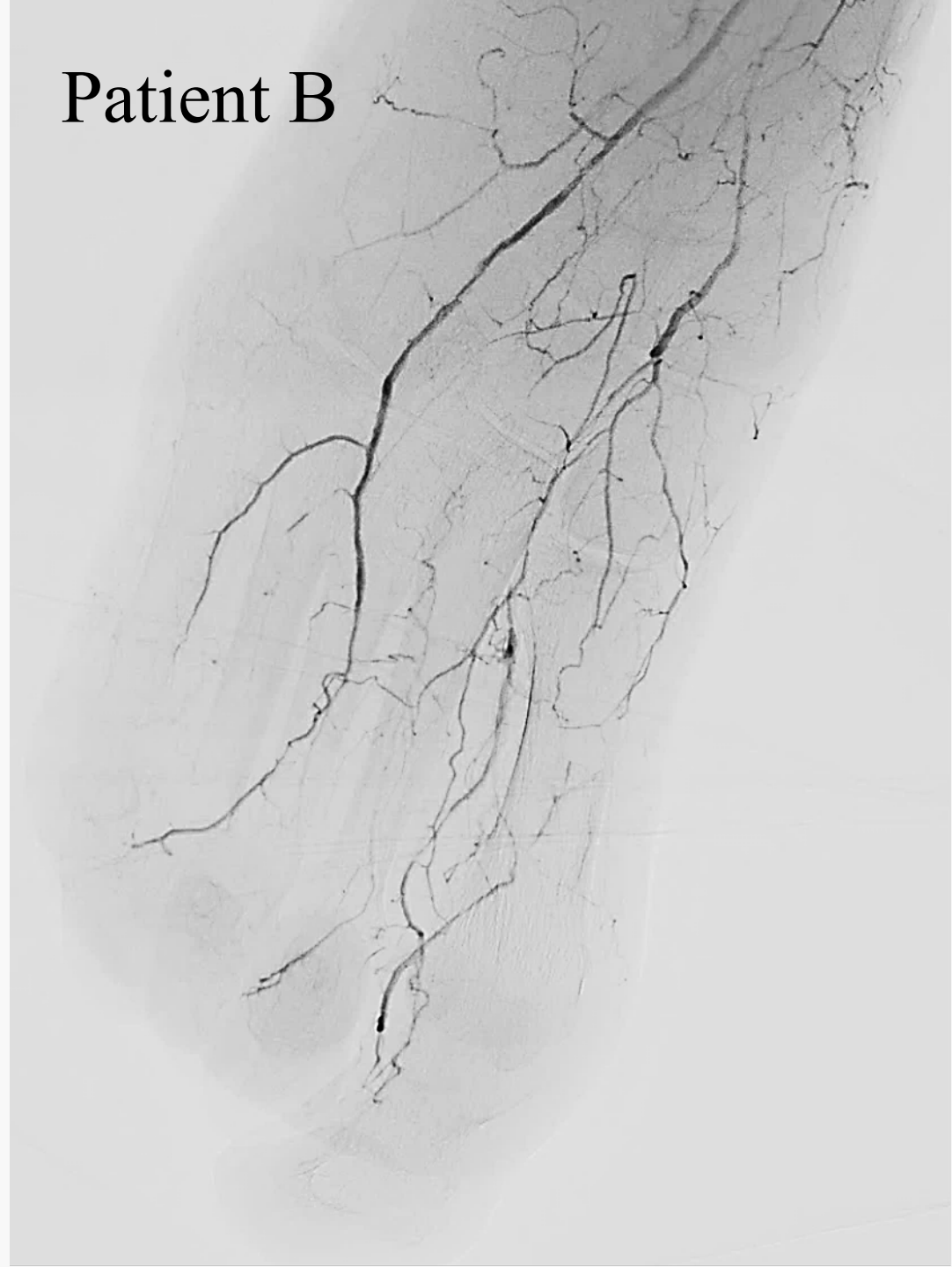




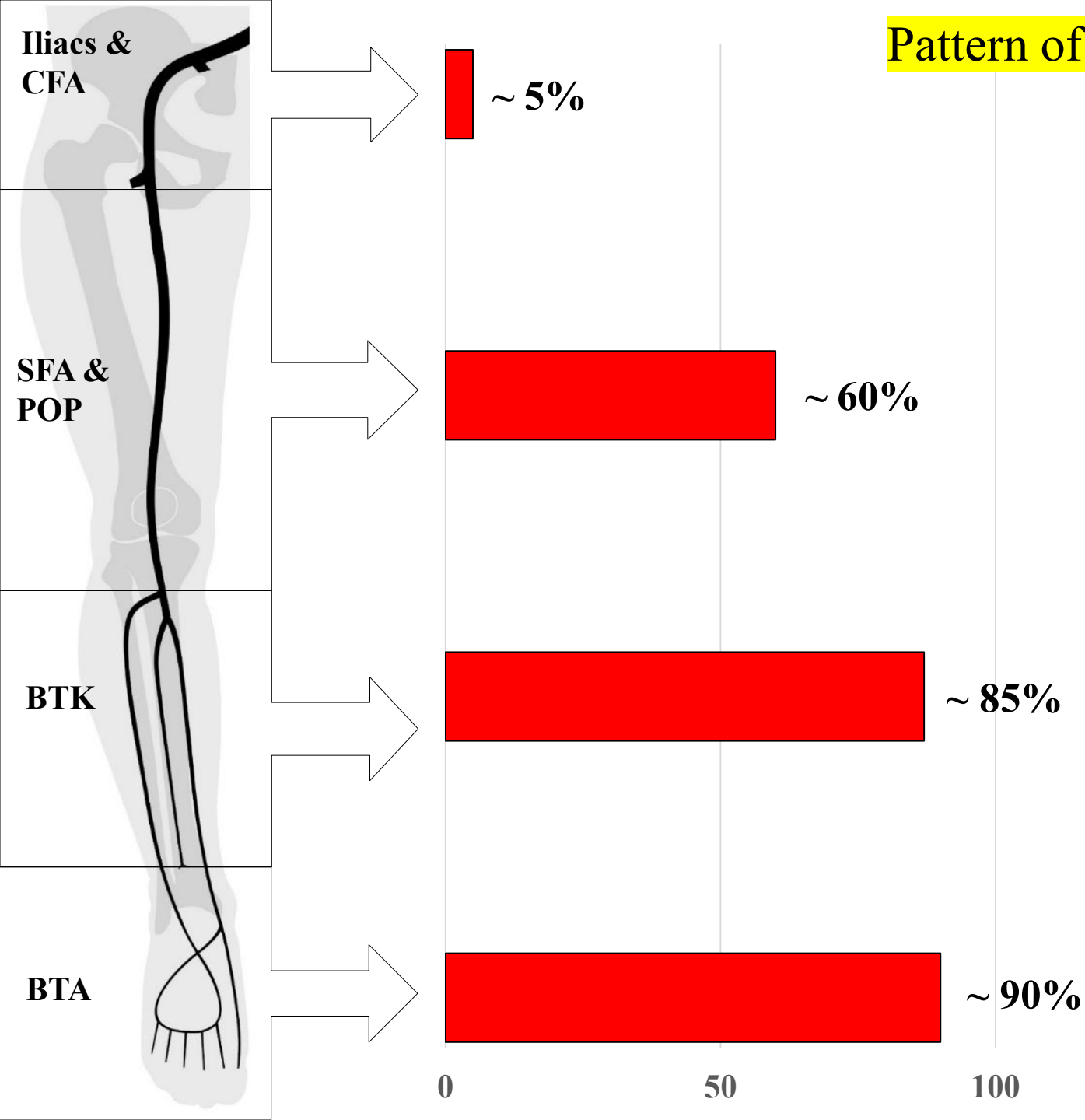
Patient A



Patient B



Pattern of PAD in CLTI pts



© 2018 EDIZIONI MINERVA MEDICA
 The Journal of Cardiovascular Surgery 2018 October;59(5):655-64
 Online version at <http://www.minervamedica.it>
 DOI: 10.23750/S0021-9509.18.10572-6

ORIGINAL ARTICLE
 RECENT DEVELOPMENTS IN THE MANAGEMENT OF THE DIABETIC FOOT

**BAD transmission and SAD distribution:
 a new scenario for critical limb ischemia**

Roberto FERRARESI ¹*, Giovanni MAURI ², Fabrizio LOSURDO ³, Nicola TROISI ⁴,
 Diego BRANCACCIO ⁵, Carlo CARAVAGGI ⁶, Luca NERI ⁷

Piaggese A, Apelqvist J (eds): The Diabetic Foot Syndrome.
 Front Diabetes. Basel, Karger, 2018, vol 26, pp 60–69

**Indications to ischemic foot
 revascularization**

R. Ferraresi, F. Losurdo, R. Lorenzoni, M. Ferraris, M. Caminiti

**Interventional Treatment of the
 Below the Ankle Peripheral
 Artery Disease** **119**

Roberto Ferraresi, Luis Mariano Palena, Giovanni Mauri, and
 Marco Manzi

3 **Small artery disease in
 critical limb ischemia:
 innocent bystander or
 leading actor?**

Roberto Ferraresi, Roberto Nerla, Fabrizio Losurdo, Doriana Ferrara,
 Antonietta Cucci, Andrea Casini, Maurizio Caminiti, Giacomo Clerici

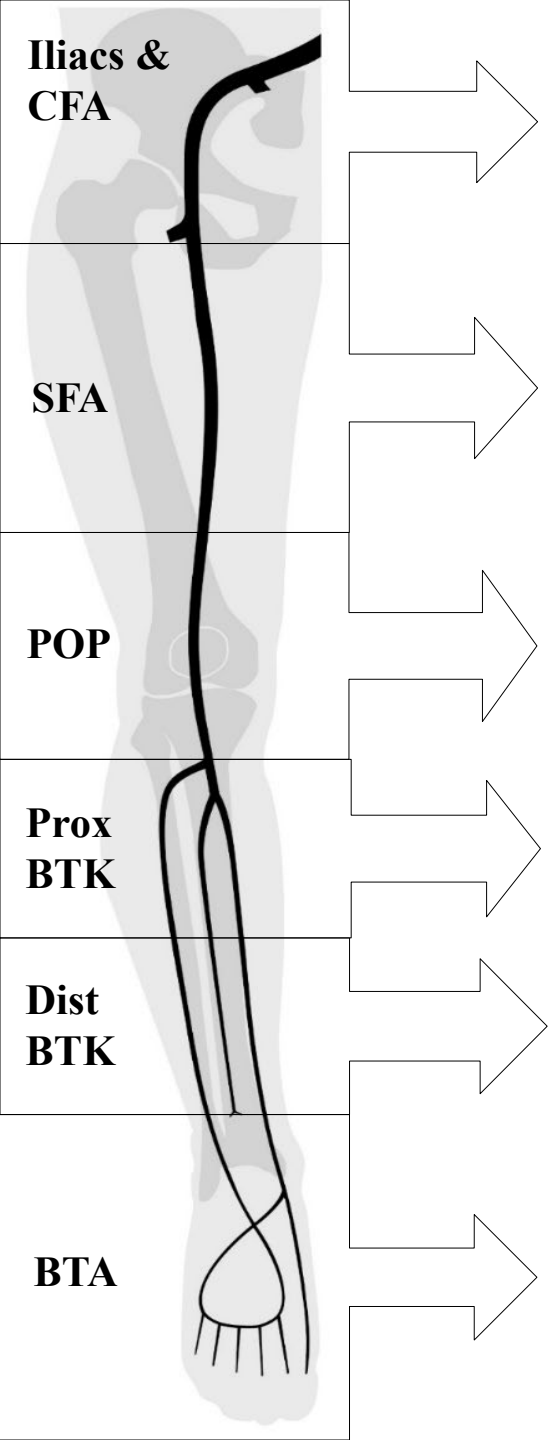
Clinical Investigation

**ENDOVASCULAR
 THERAPY**

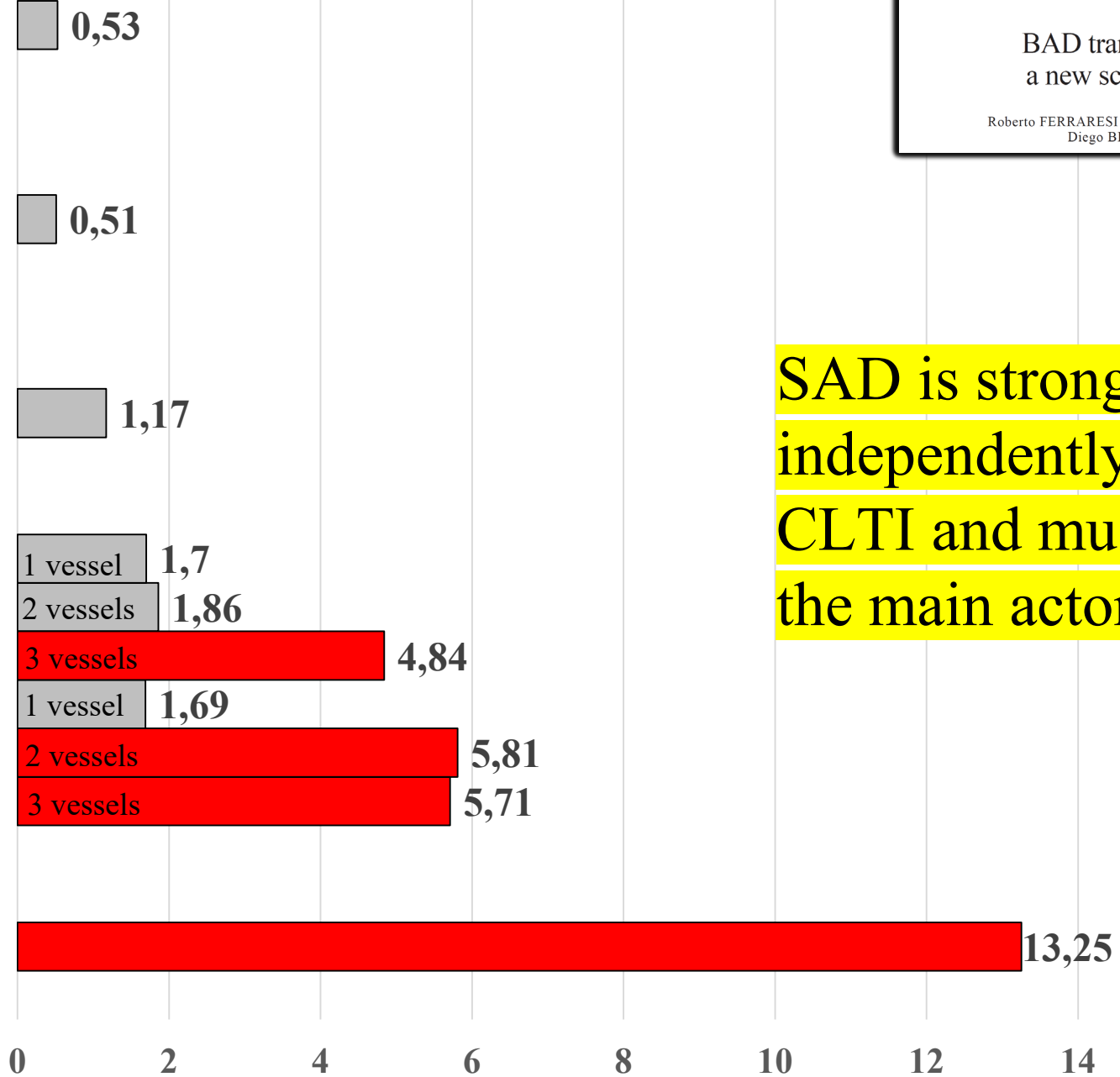
Journal of Endovascular Therapy
 1-14
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 DOI: 10.1177/152662202096309

**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**

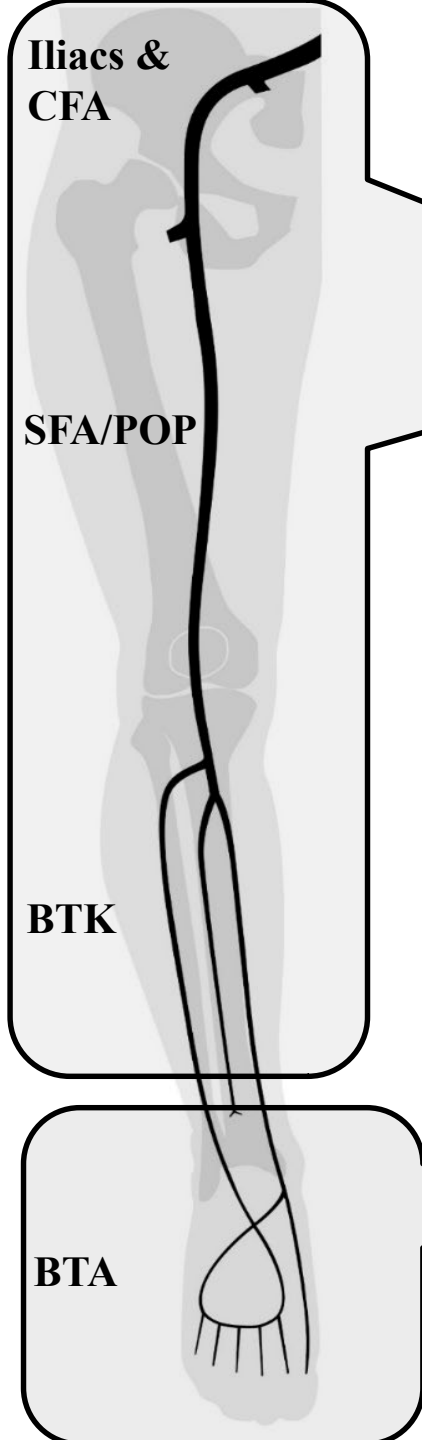
Roberto Ferraresi, MD¹, Alessandro Ucci, MD², Alessandra Pizzuto, MD³,
 Fabrizio Losurdo, MD⁴, Maurizio Caminiti, MD⁴, Daniela Minnella, MD⁴,
 Andrea Casini, MD⁵, Giacomo Clerici, MD⁴, Miguel Montero-Baker, MD⁴,
 and Joseph Mills, MD⁴



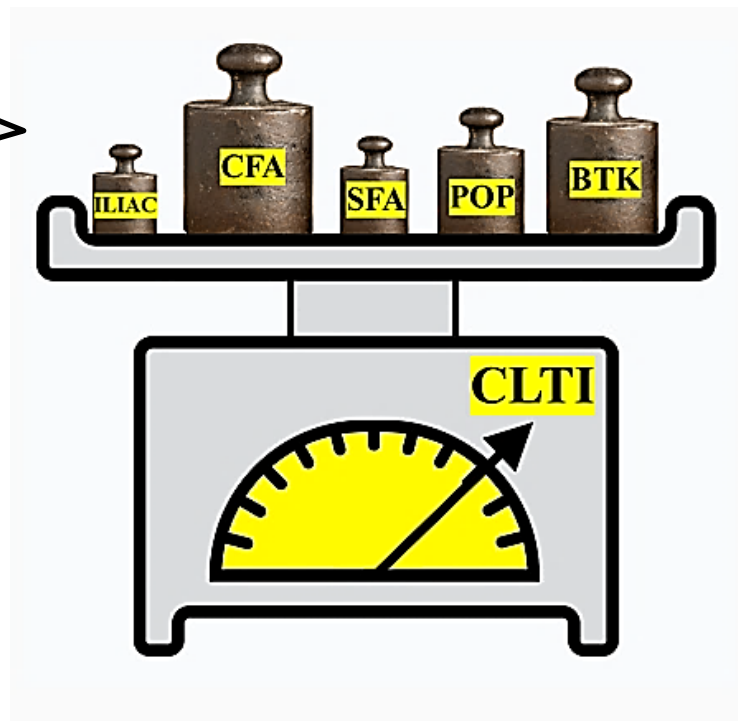
**Risk factors for CLTI
 Odds Ratio (95% CI)**



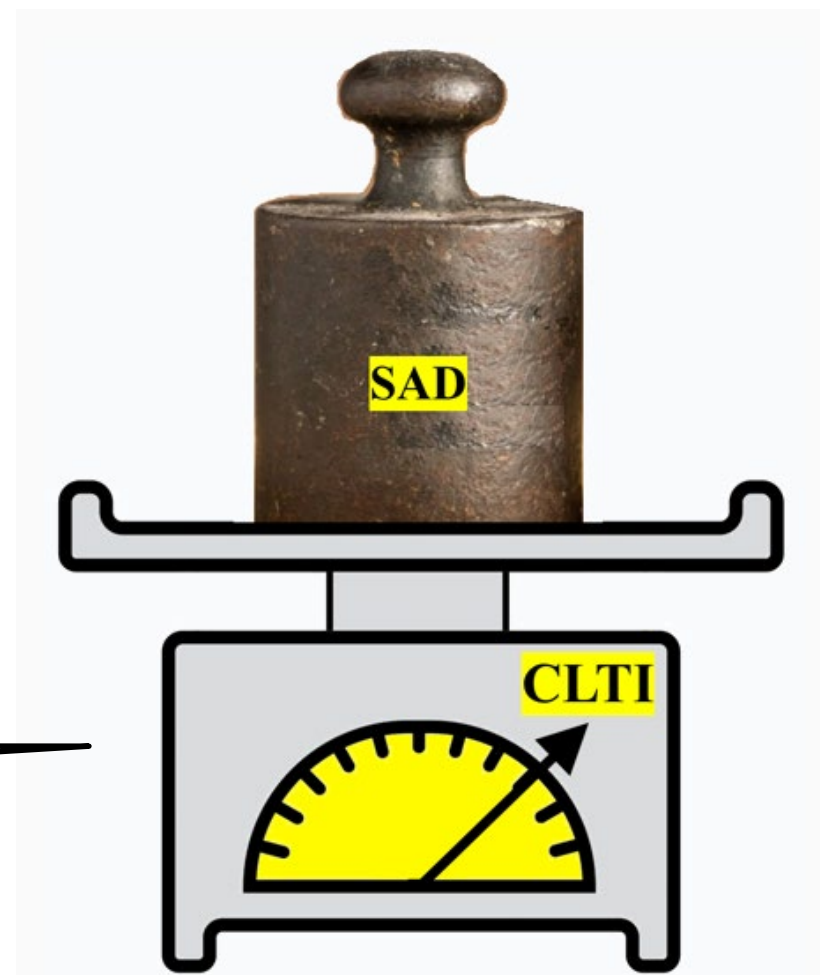
SAD is strongly and independently associated with CLTI and must be considered the main actor in CLTI



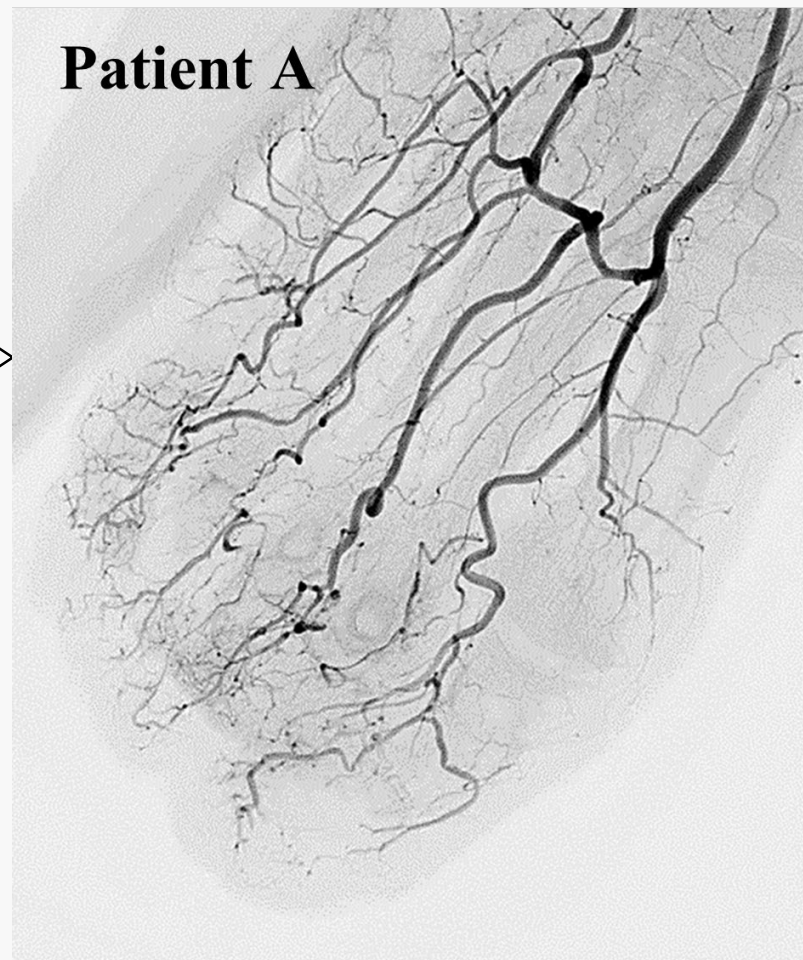
BAD → transmission failure



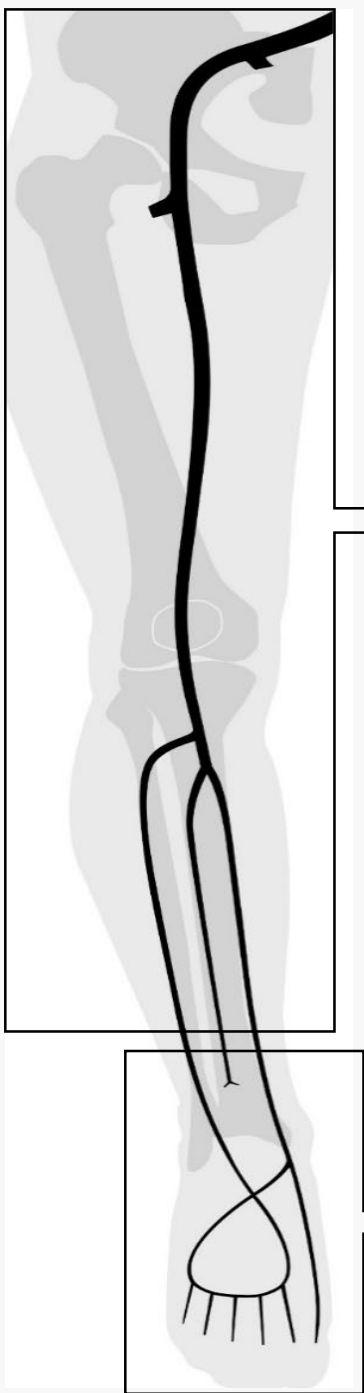
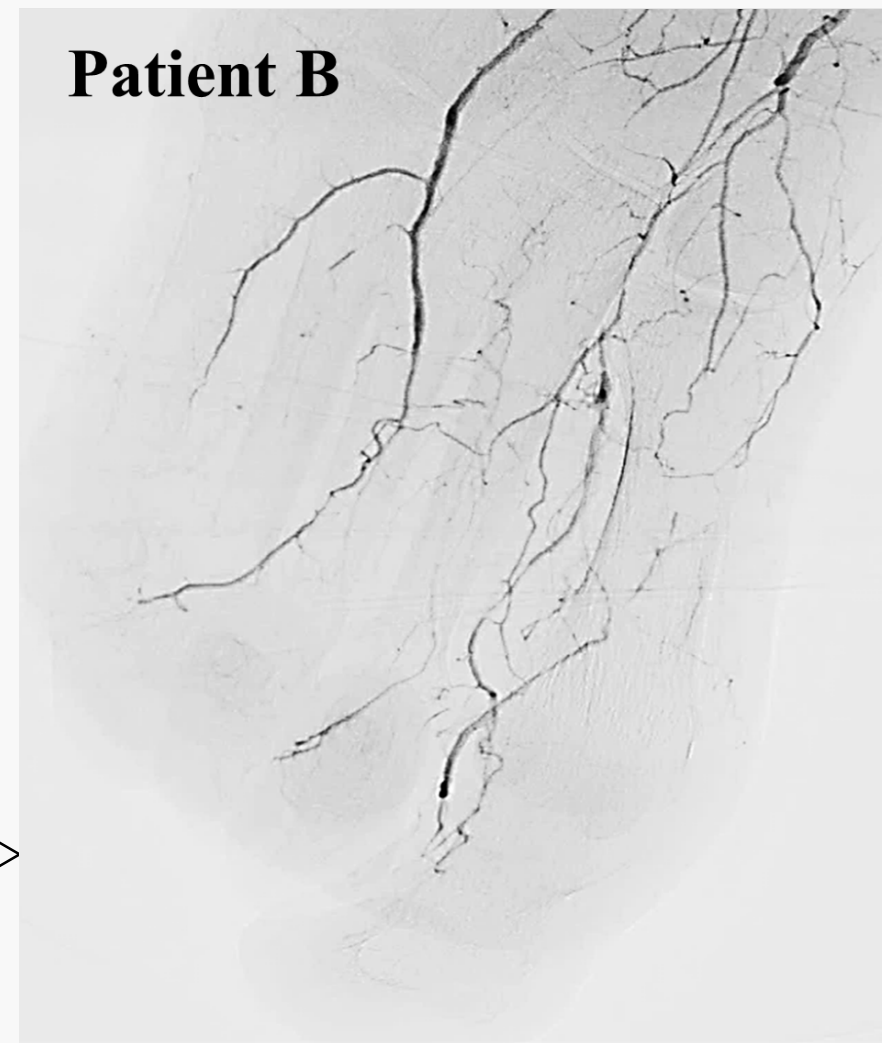
SAD → distribution failure



BAD → transmission failure



SAD → distribution failure



BAD & SAD, who is the enemy in CLTI?

SAD-MAC: brothers in arm

Obstruction patterns in CLTI

Weapons and soldiers: the CLTI-PAD war

Jungle patrols: extreme below-the-ankle guerilla

Mercy for patients

What is MAC?

VÄI.

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

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

Von

Dr. J. G. Monckeberg.

Medial Arterial Calcification

JACC State-of-the-Art Review

Peter Lanzer, MD,^a Fadil M. Hannan, DPM,^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

MAC was firstly described
in 1903 by Monckeberg

MAC = accumulation of calcium
phosphate (CaP) in the form of
hydroxyapatite crystals within the medial
layer of the arterial wall resulting in its
progressive petrification

Most common in patients with old age,
diabetes and/or renal failure

Medial Arterial Calcification

JACC State-of-the-Art Review

Peter Lanzer, MD,^a Fasil 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

In the past, MAC was considered an innocent bystander. However, studies now demonstrate that MAC can be considered **the silent killer of the cardiovascular system** because MAC is a strong marker of future cardiovascular events and death.

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}

MAC & PAD are strongly associated

MAC and elevated ABI are associated with foot ulcer, occlusive PAD and amputation

Prevalence of Nonatheromatous Lesions in Peripheral Arterial Disease

W. Charles O'Neill, Kum Hyun Han, Thomas M. Schneider, Randolph A. Hennigar

Arterioscler Thromb Vasc Biol. 2015;35:439-447

- 176 upper and lower leg arteries from amputations of 60 pts with PAD
- The most common findings were **calcification of the media (72% of arteries)**..., with the presence of atheromas in only 23% of arteries.

The bulk of vascular calcification in the lower extremities is medial rather than intimal

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 A



Patient B

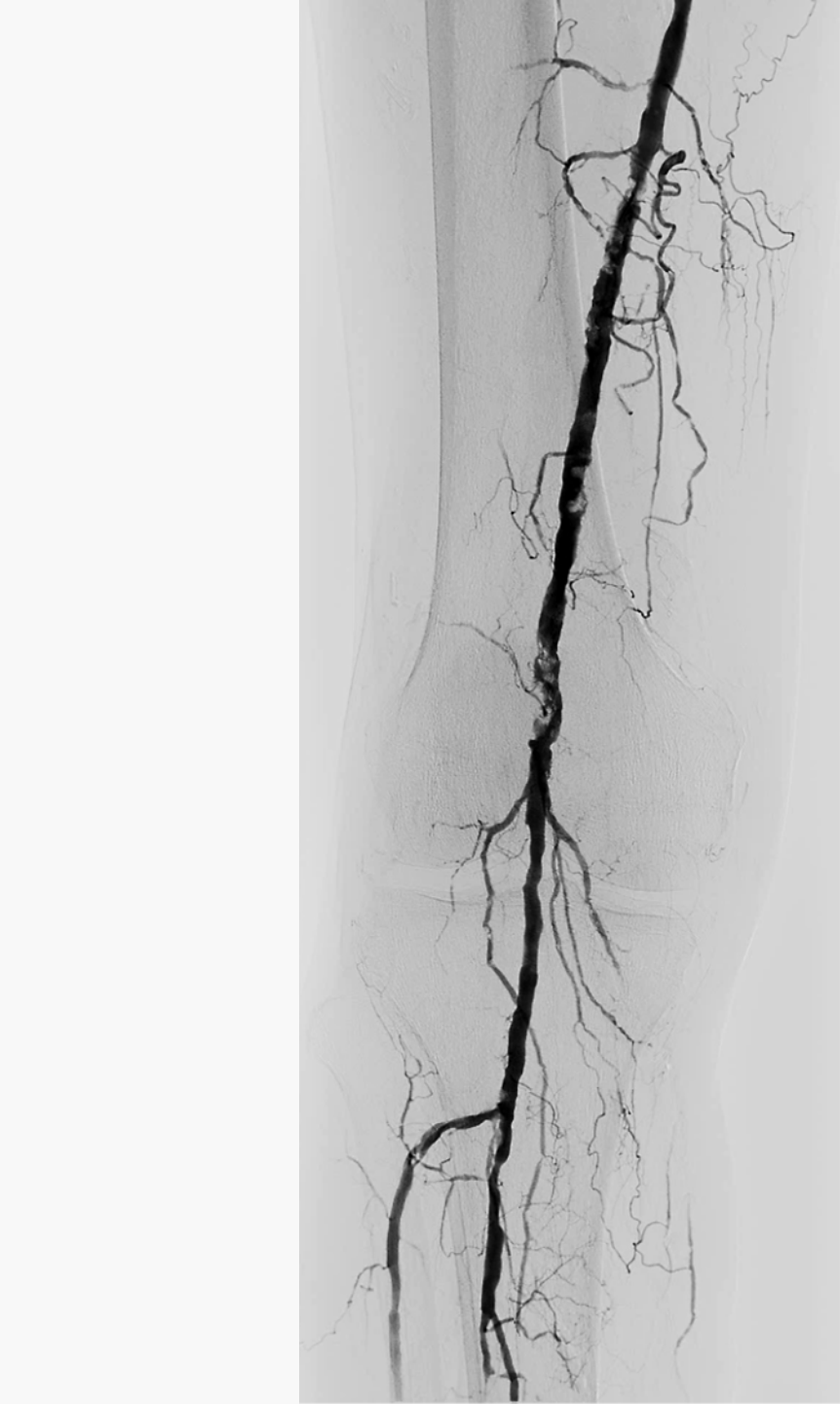


Patient B



Just a foot
problem?

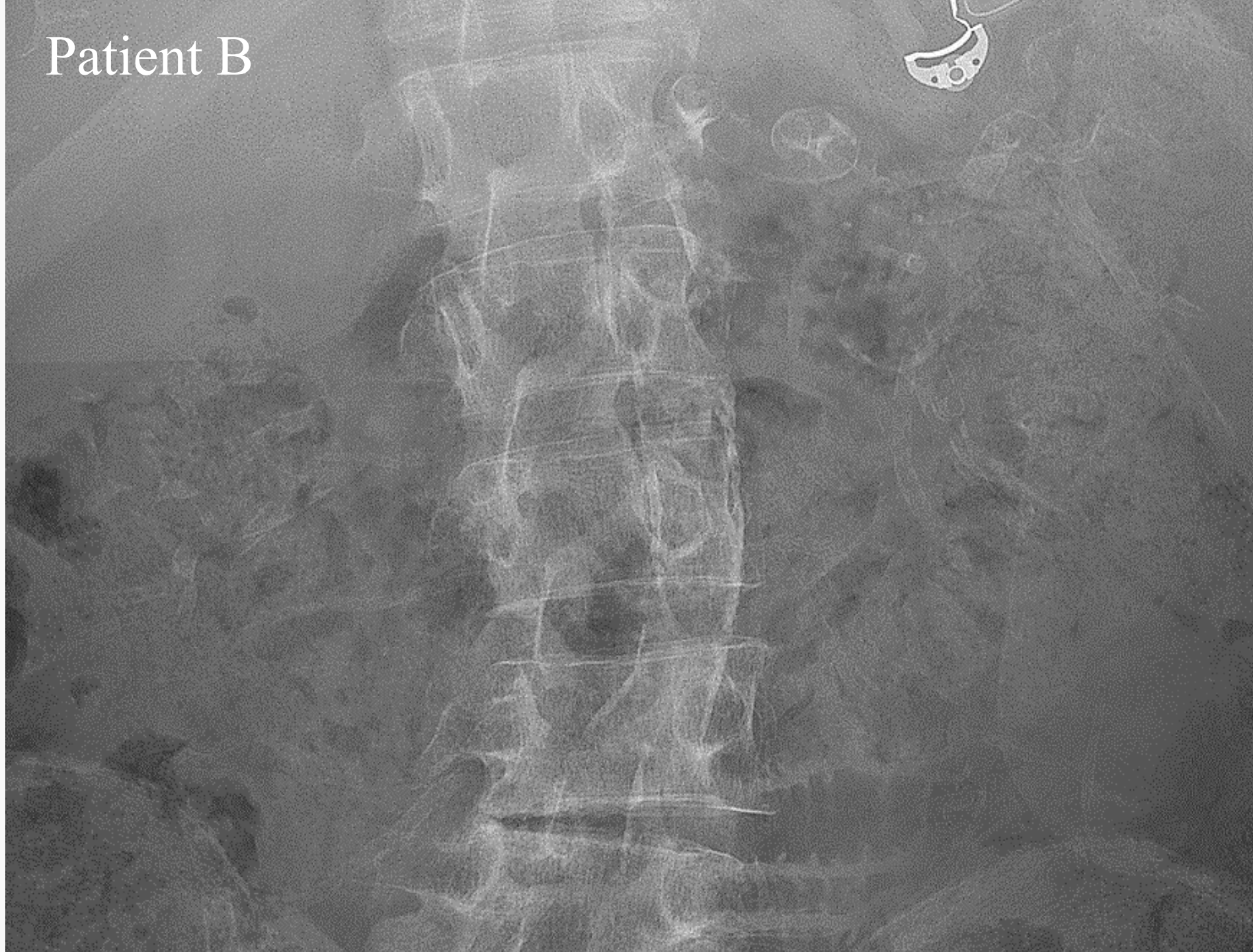
Patient B



Patient B



Patient B



Patient B



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 %

5-steps MAC-score

1		yes = 1 or no = 0
2	≥ 2 cm?	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

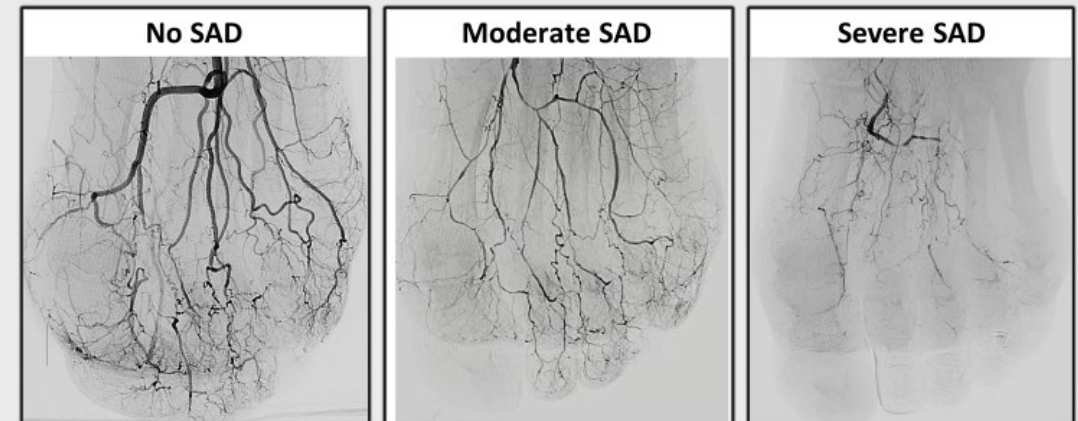
Sum all points up →

- 0-1 = no MAC
- 2-3 = moderate MAC
- 4-5 = severe MAC

SAD-score is difficult!

- Contrast dye/multiple injections
- Movement artifacts
- Spasm/slow flow
- Evaluation is subjective

We can get a true SAD-score only in a minority of pts, we need something easier and feasible in every pt!



Clinical Investigation

JOURNAL OF
ENDOVASCULAR
THERAPY

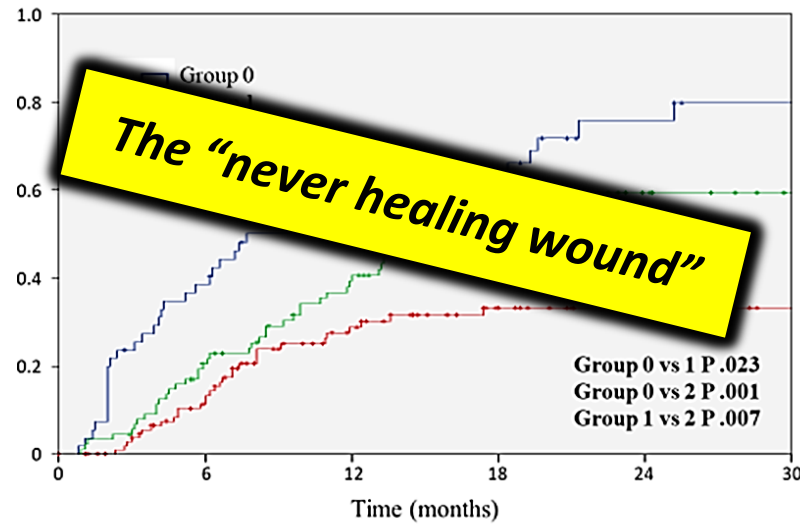
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DOI: 10.1177/1526402820966309
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SAGE

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

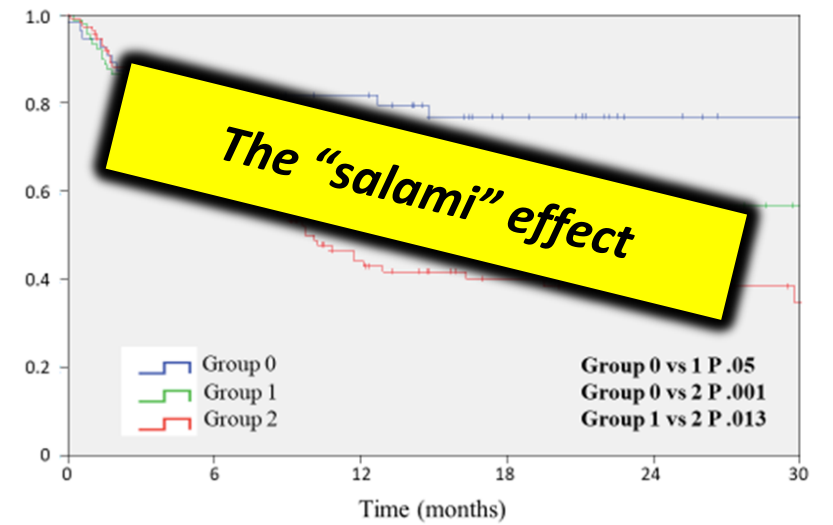
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Patient's
outcomes by
MAC-score
groups

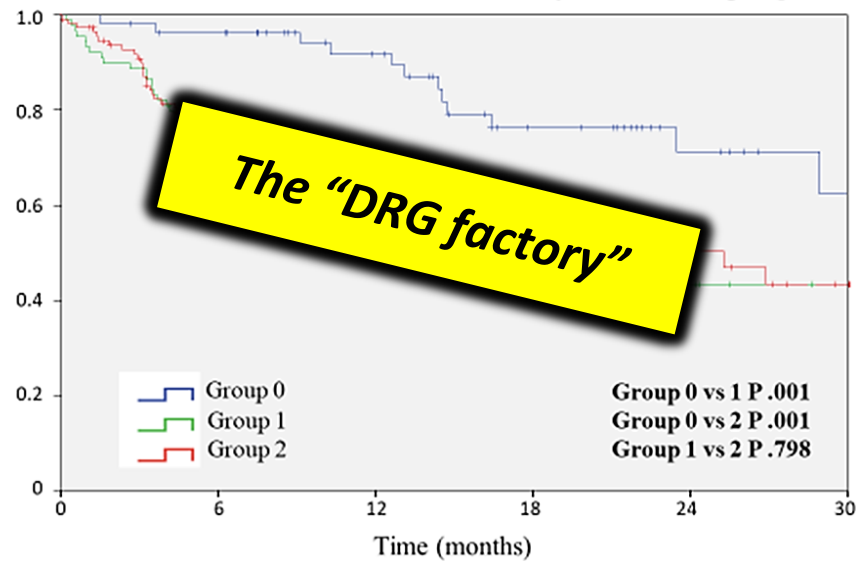
Healing rate



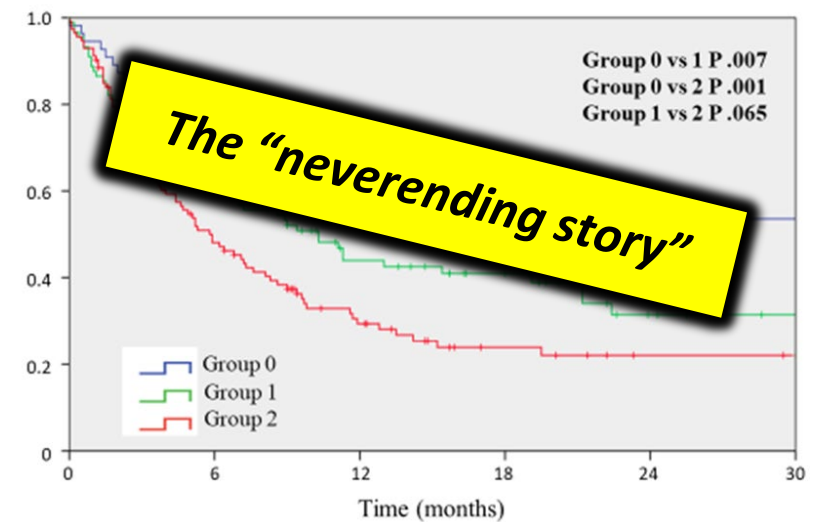
FF foot surgical reintervention



FF redo-revascularization



FF MALEs



The MAC score is a simple, practical tool and a strong independent predictor of:

- Inframalleolar arterial disease
- Major amputation
- Failure to improve WIfI ischemia grade after infrainguinal percutaneous revascularization
- Technical failure of inframalleolar angioplasty

- Liu IH et al. Pedal arterial calcification score is associated with risk of major amputation in chronic limb-threatening ischemia. *J Vasc Surg*. Published online September 2, 2021:S0741-5214(21)01978-9
- DiBartolomeo AD et al. Medial Arterial Calcification Score is Associated with Increased Risk of Major Limb Amputation. *J Vasc Surg*. Published online July 30, 2023:S0741-5214(23)01726-3
- Liu IH et al. Pedal arterial calcification score is associated with hemodynamic change and major amputation after infrainguinal revascularization for chronic limb-threatening ischemia. *J Vasc Surg*. Published online July 15, 2022:S0741-5214(22)01883-3
- So JM et al. Medial Arterial Calcification and the Risk of Amputation of Diabetic Foot Ulcer in Patients With Diabetic Kidney Disease. *J Korean Med Sci*. 2023 May 29;38(21):e160.
- Sato Y et al. Prediction of technical failure of inframalleolar angioplasty in patients with chronic limb-threatening ischemia. *EJVS* 2022
- Davies M, Hart J. Pedal Medial Arterial Calcification Influences Outcomes of Isolated Inframalleolar Interventions. *JVS Abstracts*. Peripheral endovascular procedures. Volume 78, issue 4, e115, october 2023- DOI:<https://doi.org/10.1016/j.jvs.2023.08.05>

SAD-MAC is a single non-atherosclerotic disease and must be considered the main actor in CLTI

CLTI-pts with high SAD-MAC score present at 2yy:

- only 30% healing rate
- higher risk of major amputation, rev. failure & foot and vascular reinterventions

These no-option CLTI pts should be considered for alternative therapies such as:

- primary major amputation
- palliative care
- foot vein arterialization

BAD & SAD, who is the enemy in CLTI?

SAD-MAC: brothers in arm

Obstruction patterns in CLTI

Weapons and soldiers: the CLTI-PAD war

Jungle patrols: extreme below-the-ankle guerilla

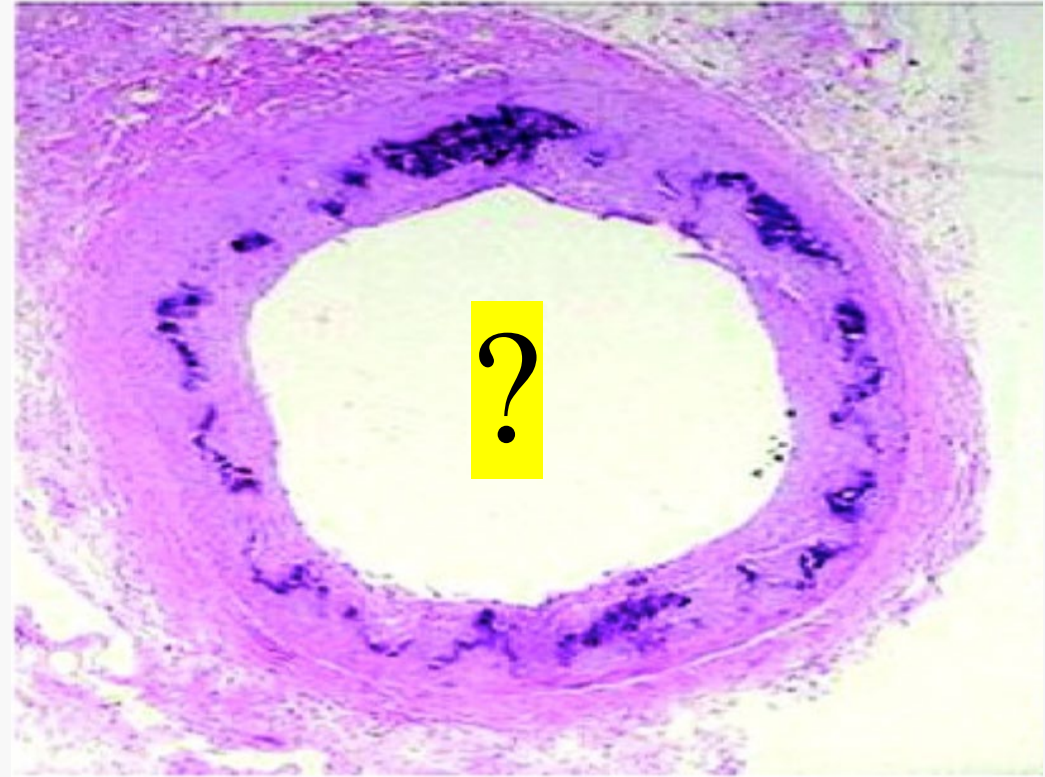
Mercy for patients

Open question

MAC is outside the lumen, in the vessel wall and, in itself, is not obstructing the lumen.

How can be MAC responsible of SAD? What is the material obstructing the lumen?

Intimal Thickening (IT) could be the answer



Amann K. Media calcification and intima calcification are distinct entities in chronic kidney disease. Clin J Am Soc Nephrol. 2008;3:1599-605.

VÄI.

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

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

Von

Dr. J. G. Monckeberg.

In the highest degrees of MAC, the artery is transformed into a rigid tube..., on such vessels there is usually a diffuse intimal overgrowth

Monckeberg, 1903

**Prevalence of Nonatheromatous Lesions
in Peripheral Arterial Disease**

W. Charles O'Neill, Kum Hyun Han, Thomas M. Schneider, Randolph A. Hennigar

Arterioscler Thromb Vasc Biol. 2015;35:439-447

- The most common findings were calcification of the media (72% of arteries) and intimal thickening without lipid (68% of arteries), with the presence of atheromas in only 23% of arteries.
- Nonatheromatous intimal thickening was frequently severe, resulting in complete occlusion in some vessels.

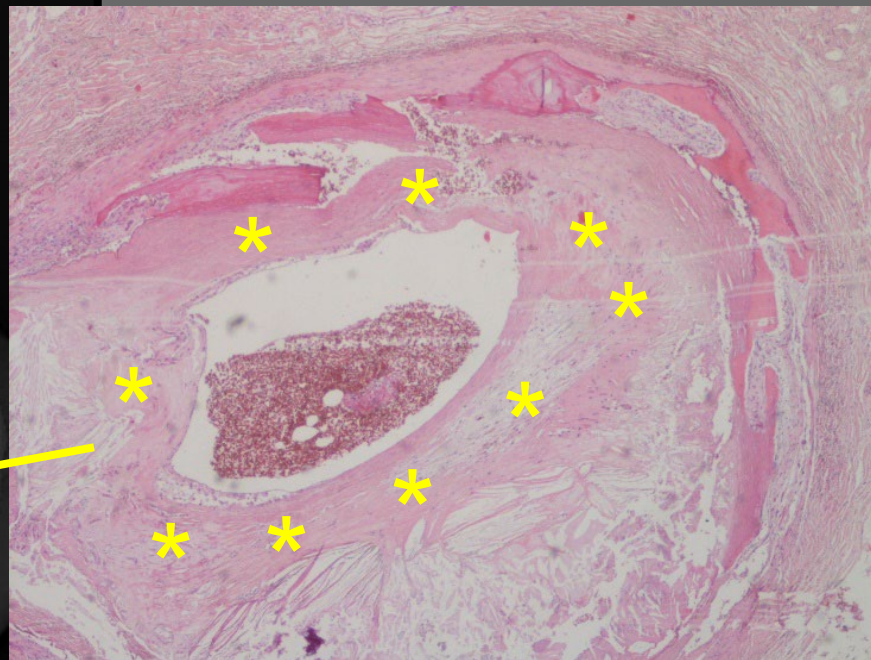
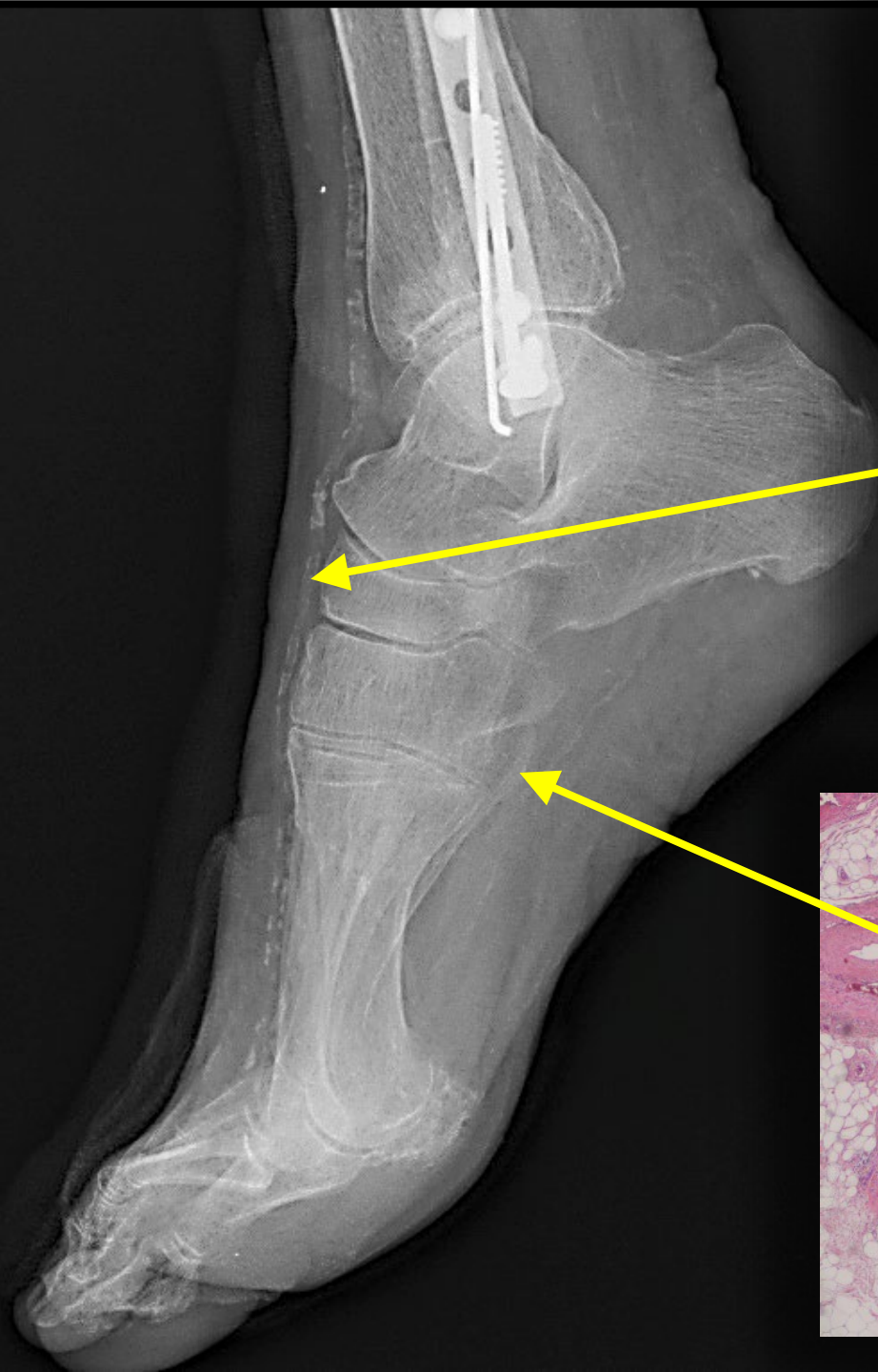


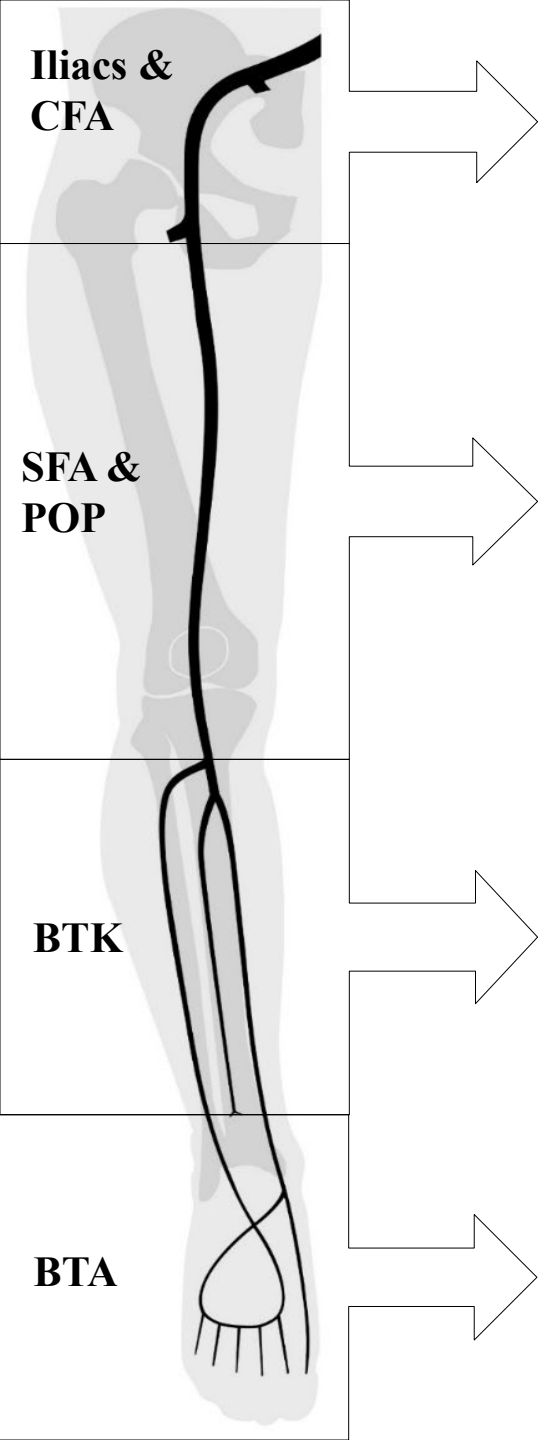
Anatomo-pathological study on amputated limbs (26) due to CLTI

Preliminary results

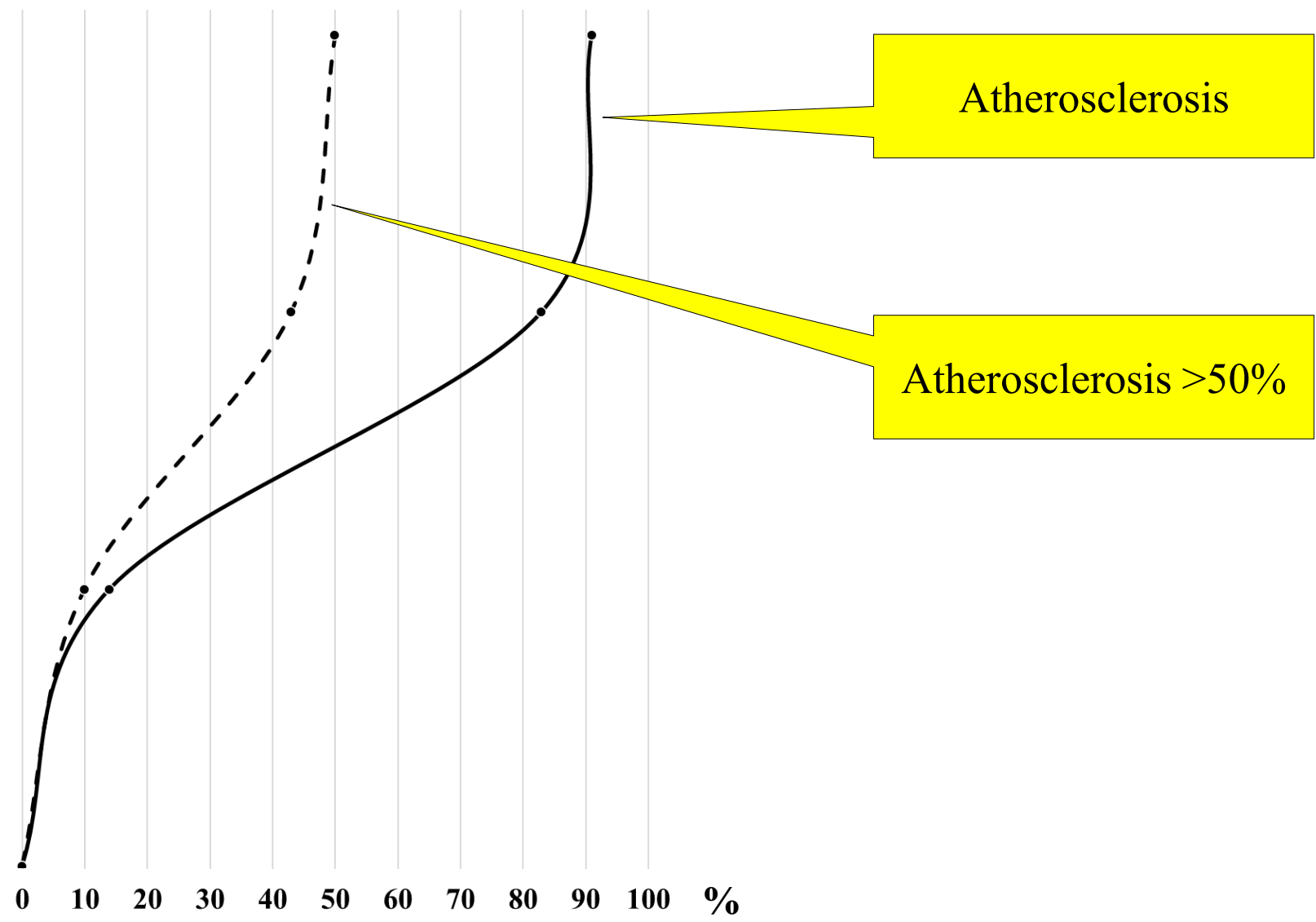
Parma's study

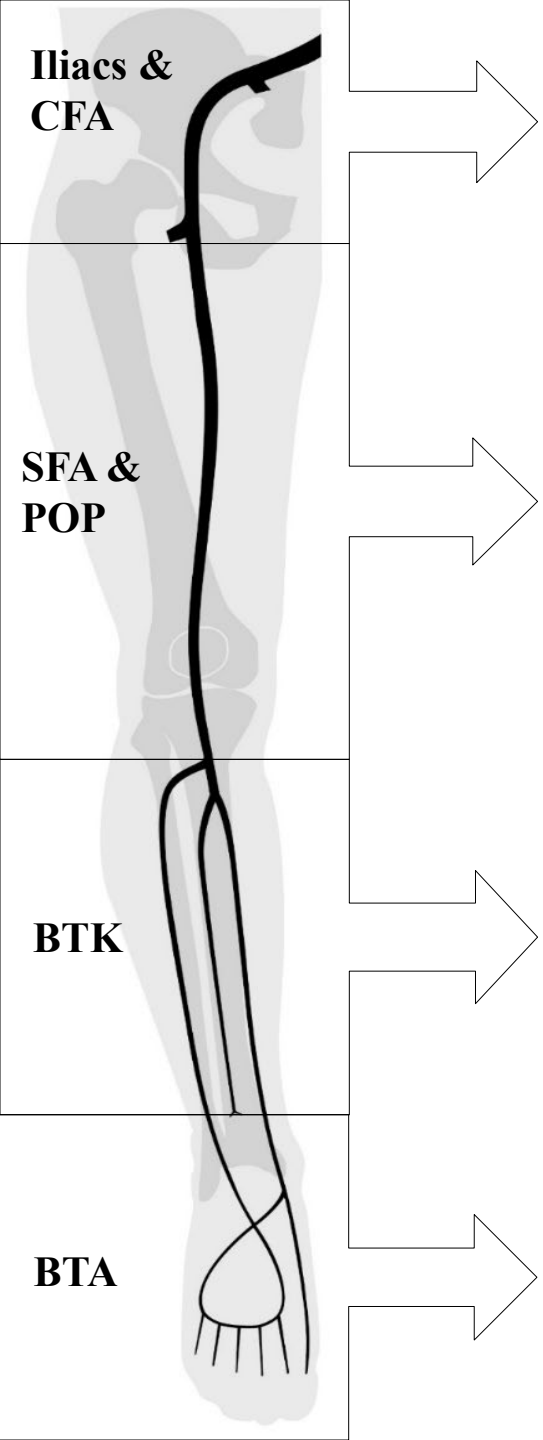




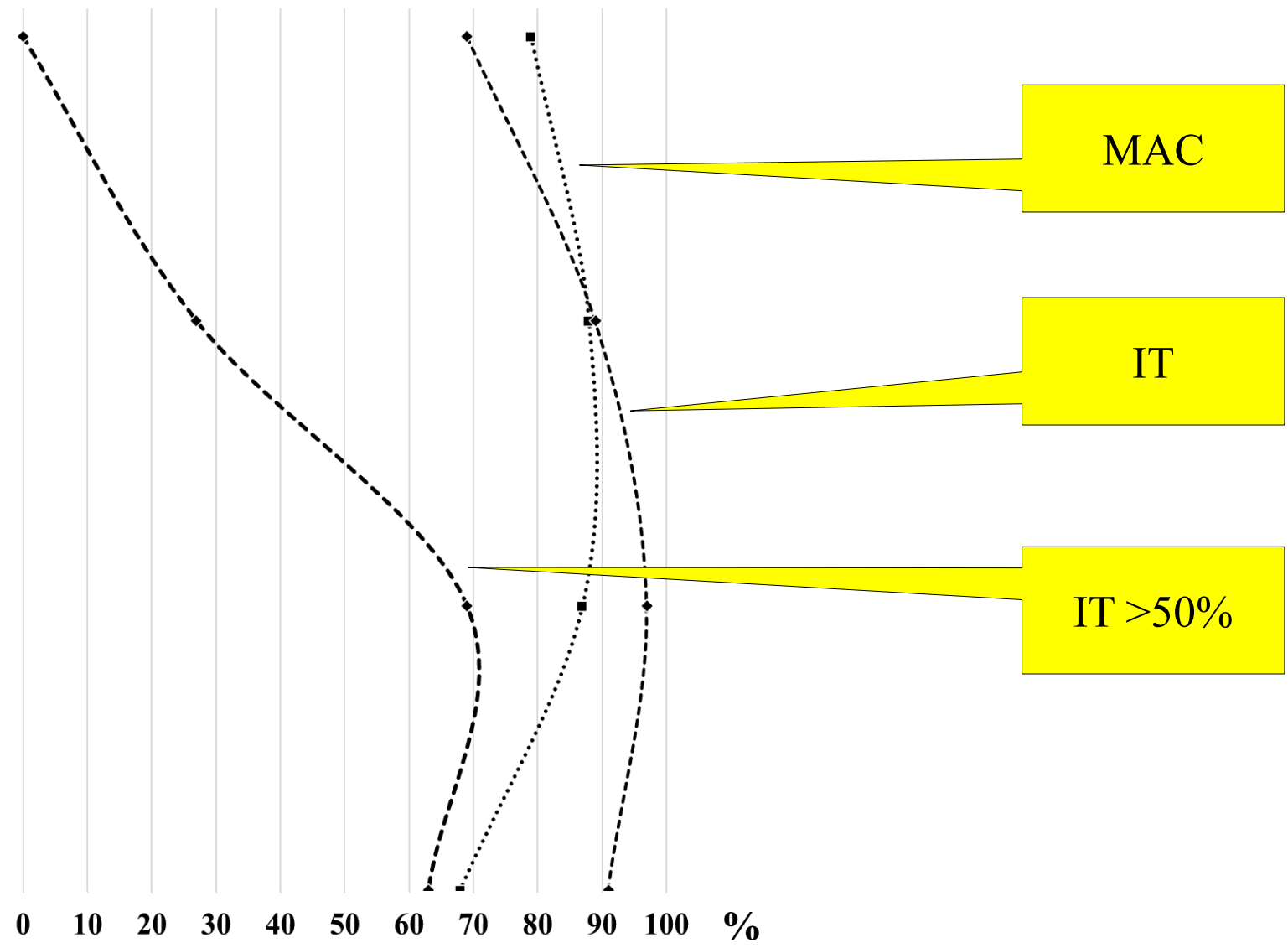


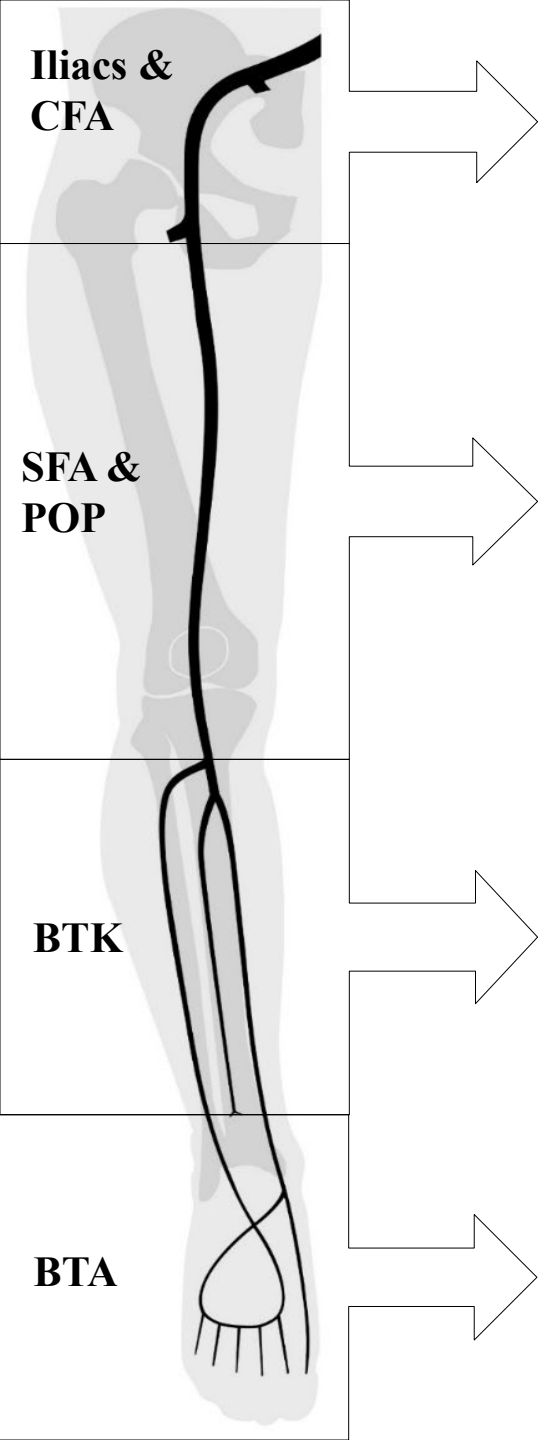
Prevalence of atheromatous lesions (%)



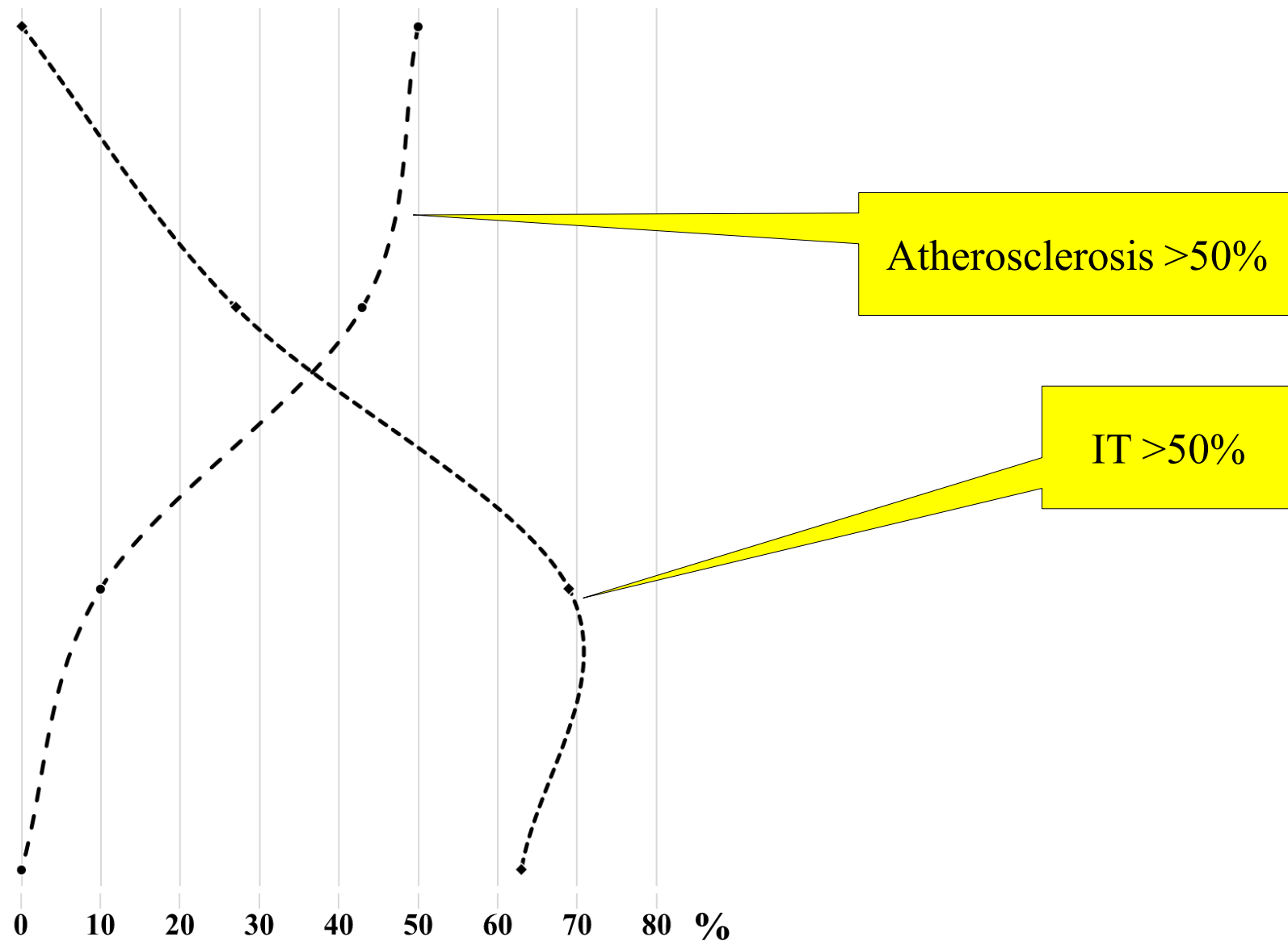


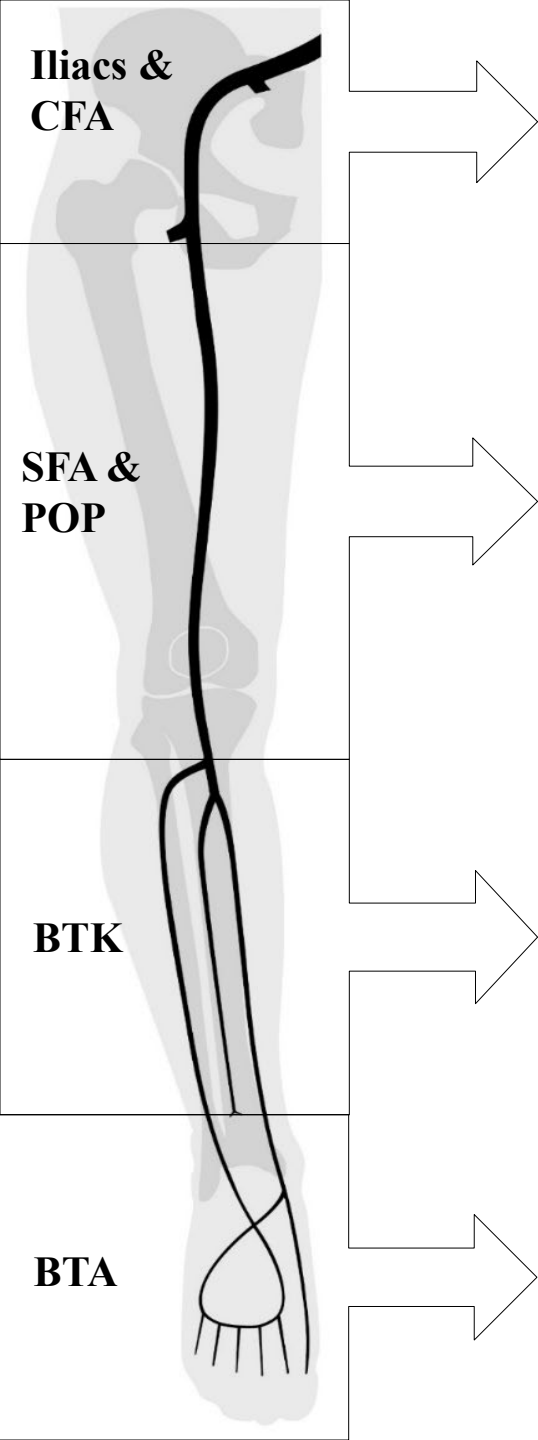
Prevalence of MAC and IT (%)



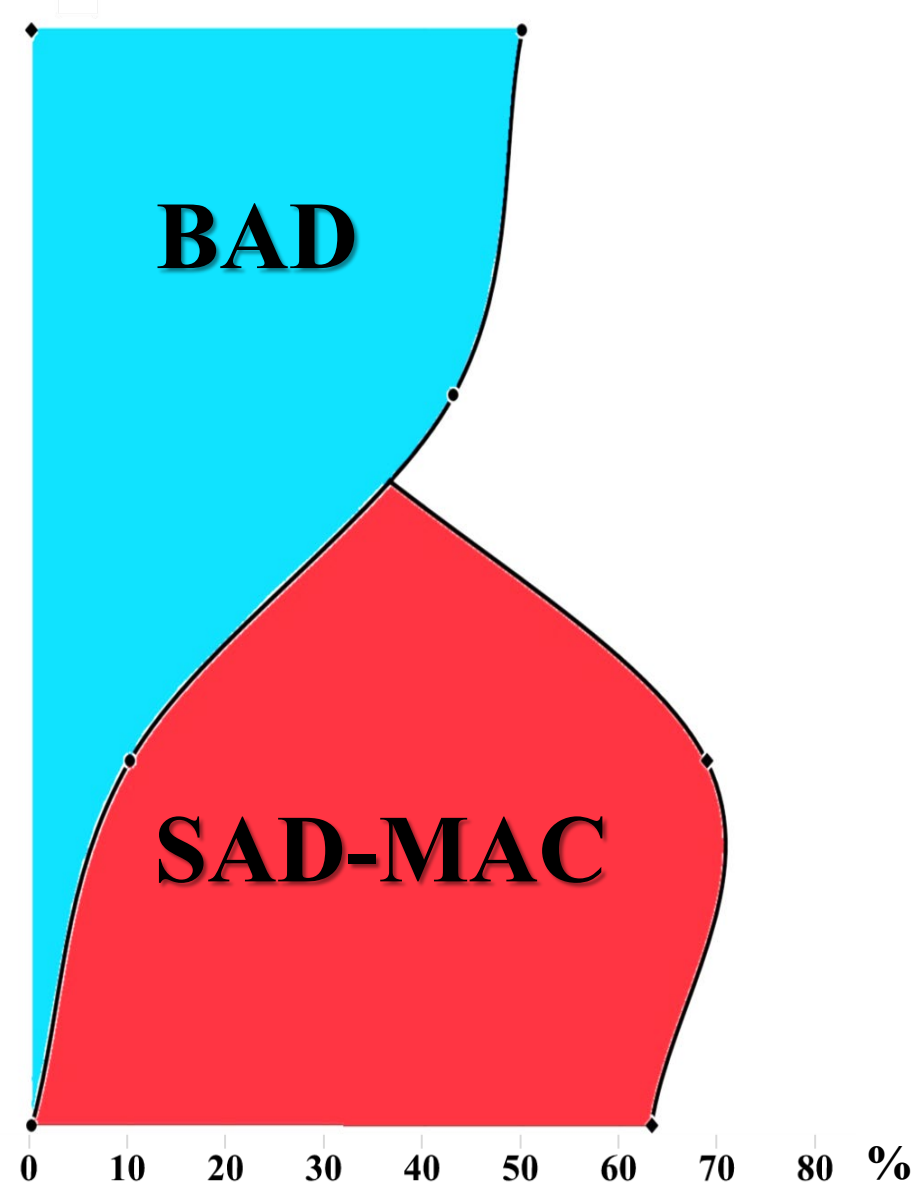


Prevalence of obstructive (>50%) lesions (%)





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



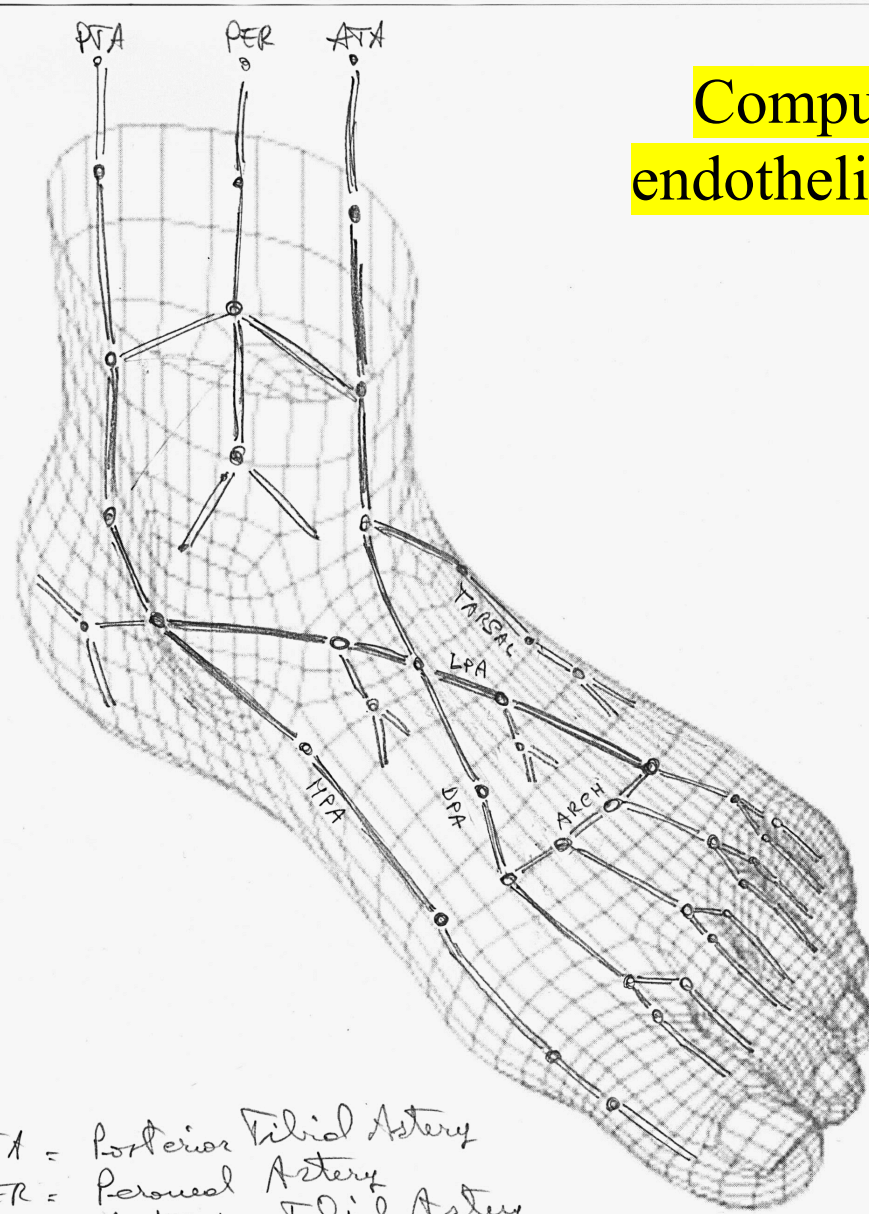
MAC



Arterial wall stiffness

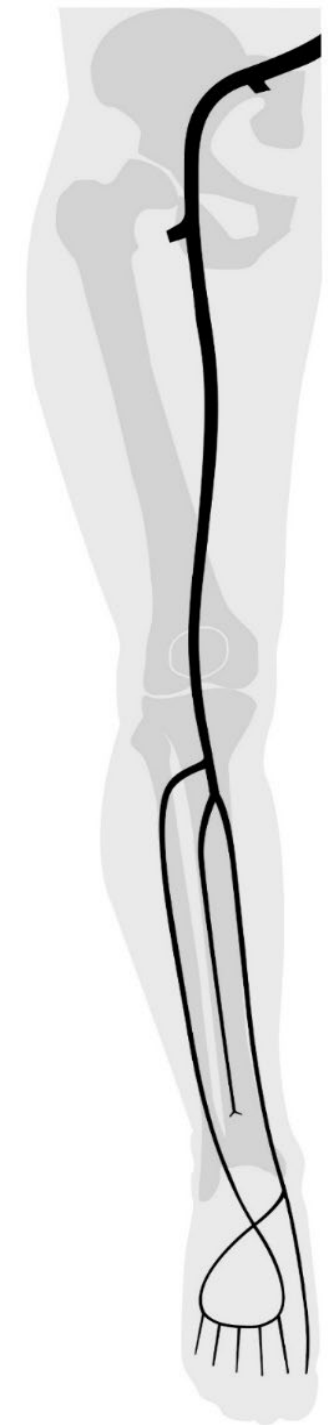
Why does MAC lead to IT & SAD?

Computational model-based analysis of endothelial SS of the lower limb arterial tree

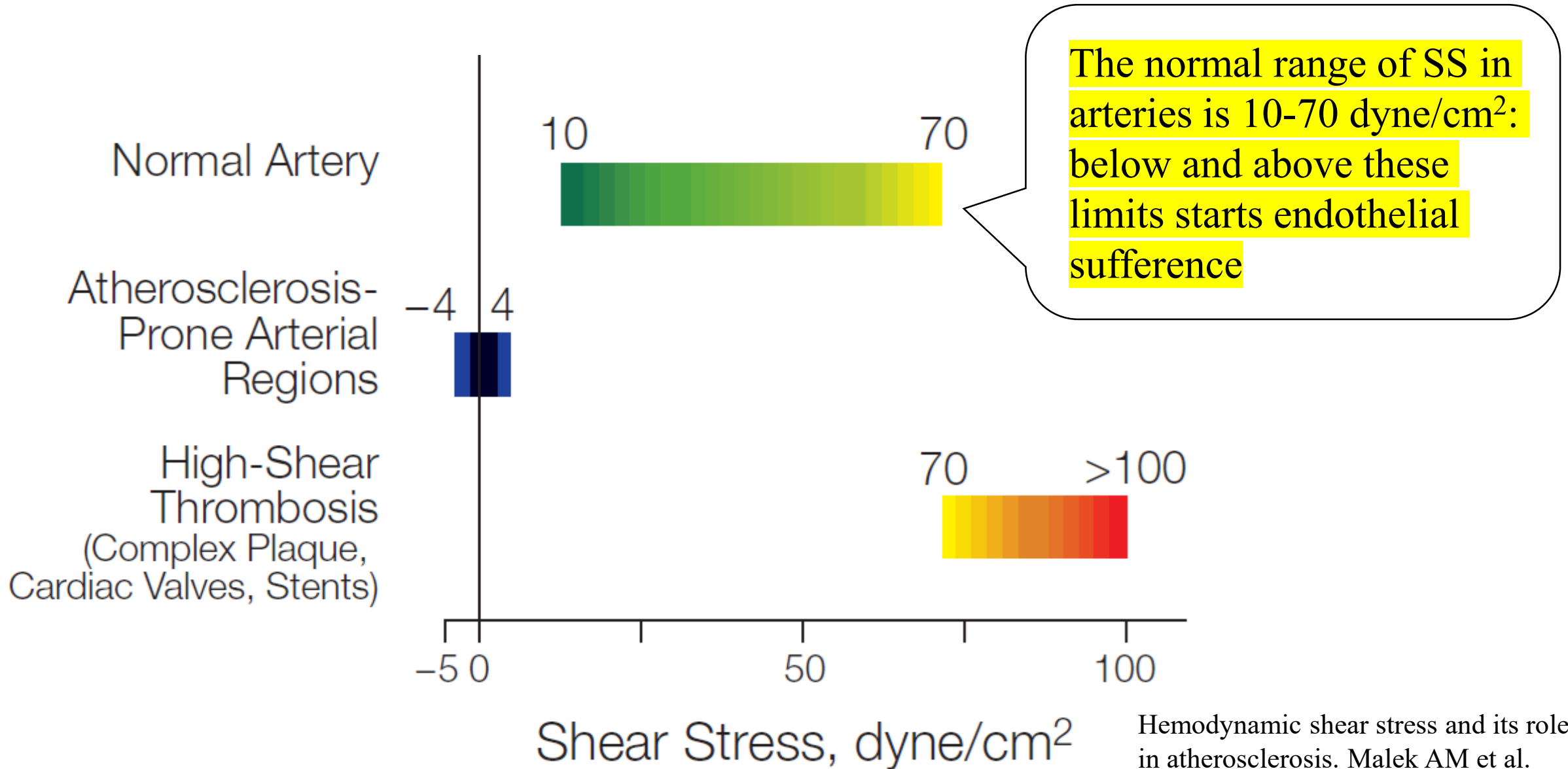


- PTA = Posterior Tibial Artery
- PER = Peroneal Artery
- ATA = Anterior Tibial Artery
- LPA = Lateral Plantar Artery
- MPA = Medial Plantar Artery
- DPA = Dorsalis Pedis Artery

Preliminary results



Range of wall shear stress magnitude

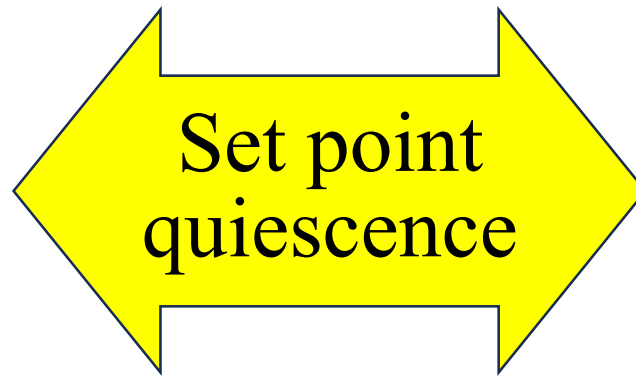


Hemodynamic shear stress and its role in atherosclerosis. Malek AM et al. JAMA 1999;282(21):2035-42

Range of wall shear stress magnitude



Inward remodeling



Outward remodeling

SS modification \rightarrow tau (dyne/cm²)

0 20 40 60 80 100 120

SFA-POP



□ x 1.0 Baseline

□ x 1.5

□ x 2.0

□ x 2.5

■ x 3.0

■ x 3.5

■ x 4.0

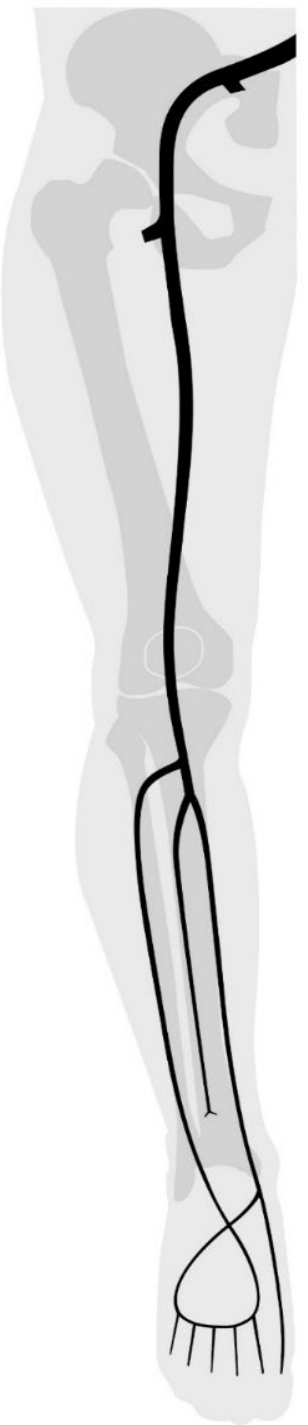


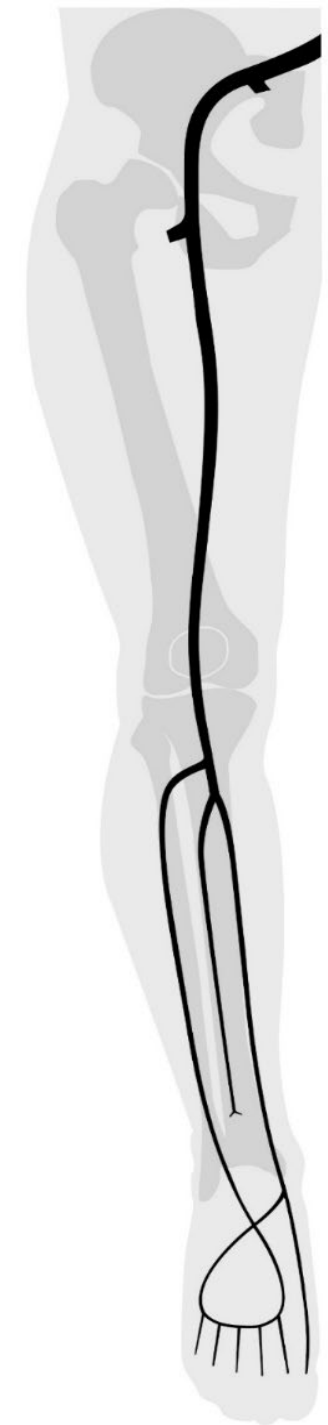
Increasing
stiffness

BTK

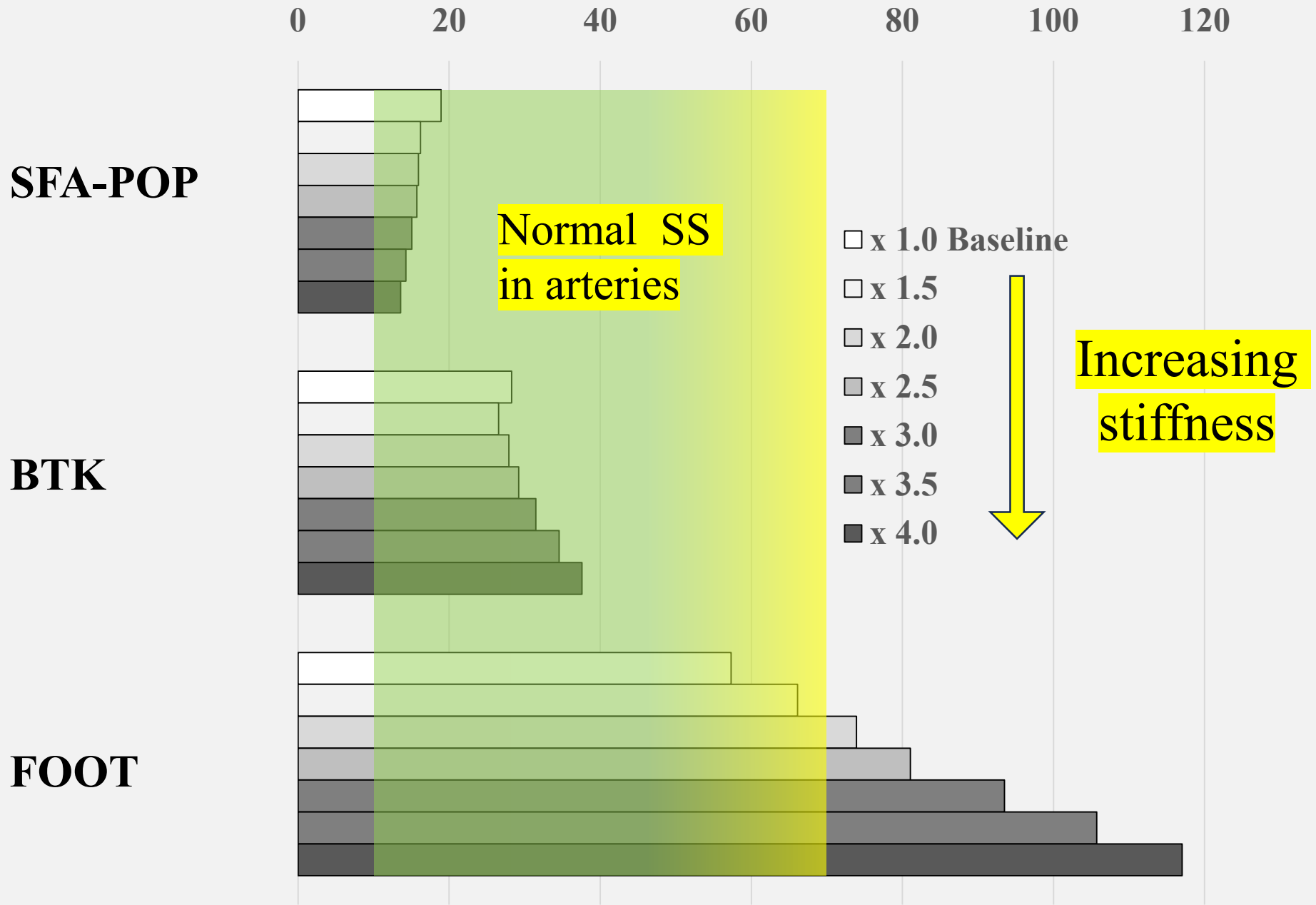


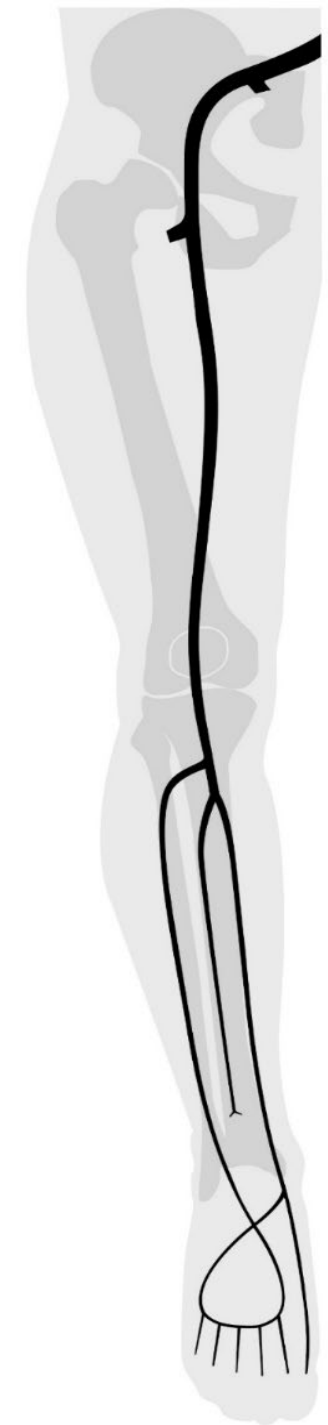
FOOT





SS modification \rightarrow tau (dyne/cm²)





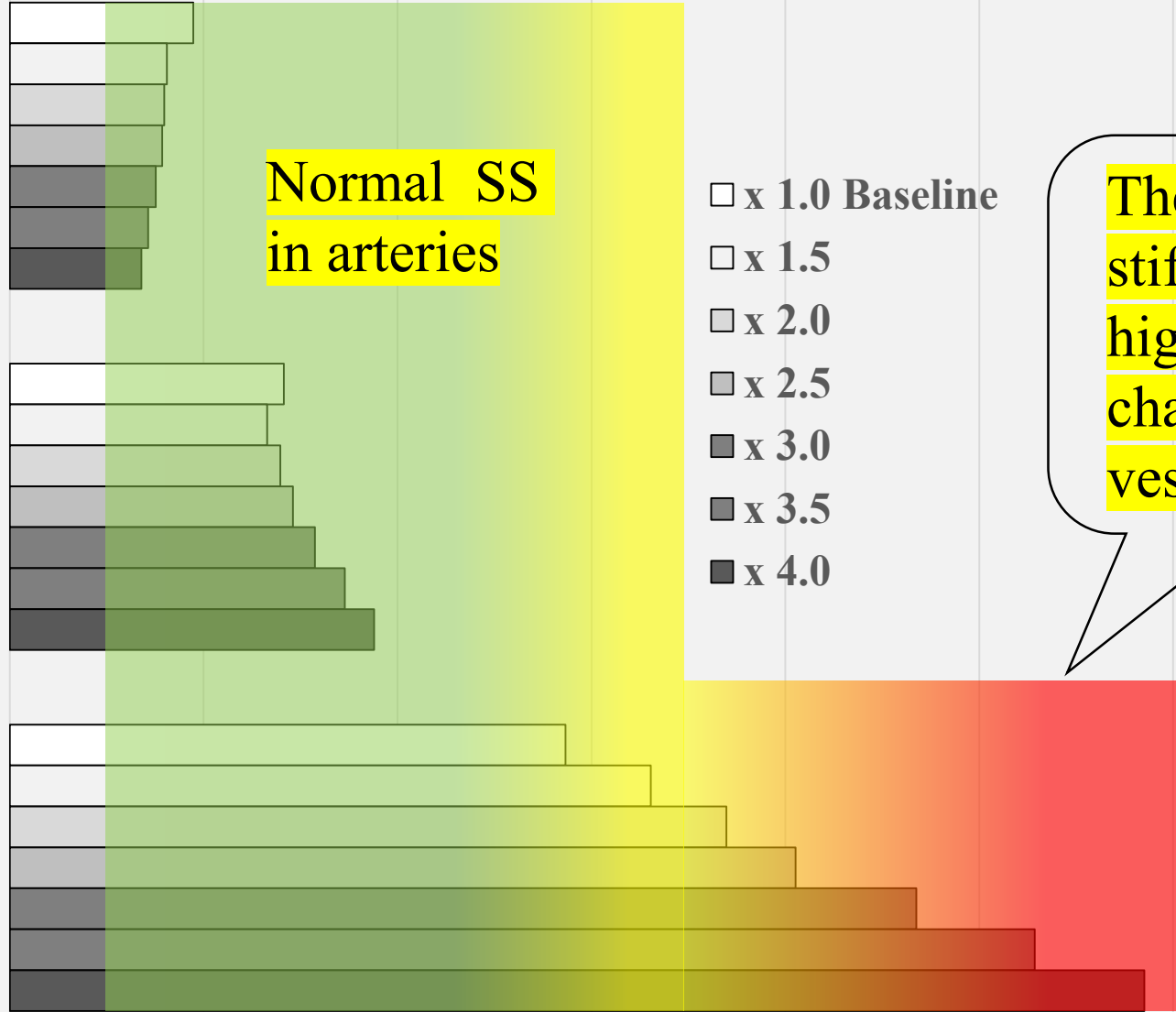
SS modification \rightarrow tau (dyne/cm²)

SFA-POP

BTK

FOOT

0 20 40 60 80 100 120



The higher the stiffness, the higher the SS change in small vessels

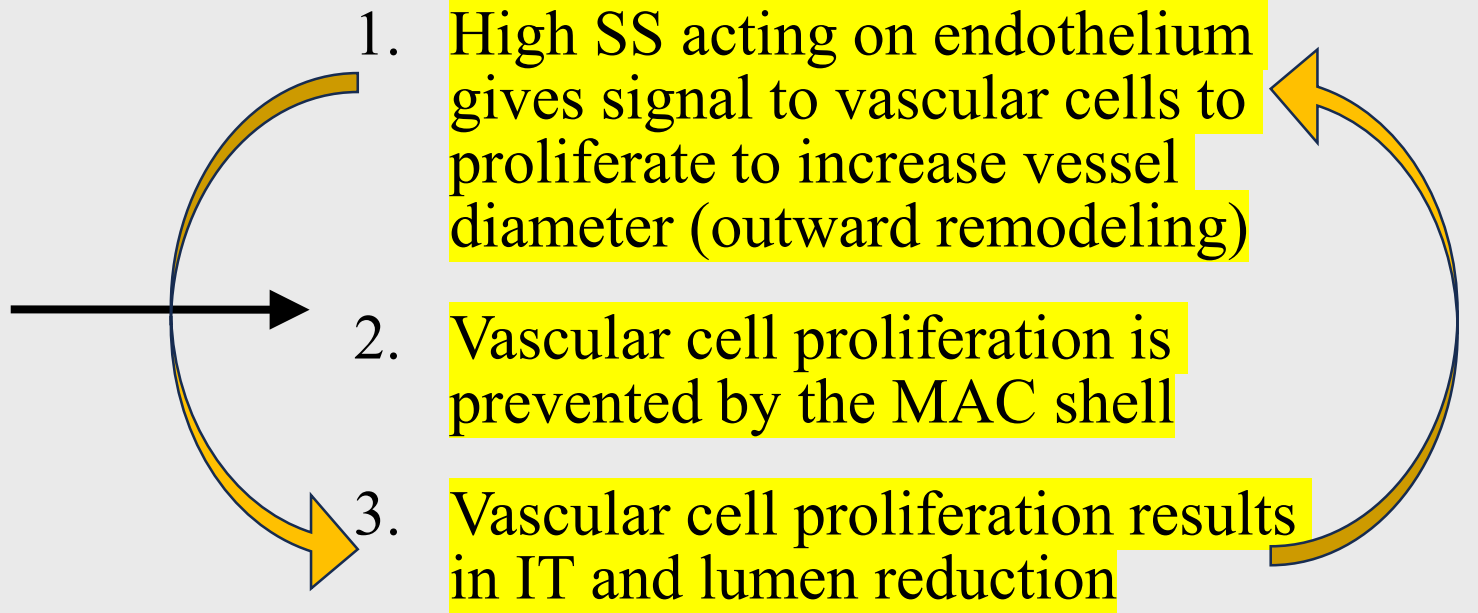
MAC



Arterial wall stiffness



Flexibility failure



FRACTURE OF ARTERIES.*

OSKAR KLOTZ.

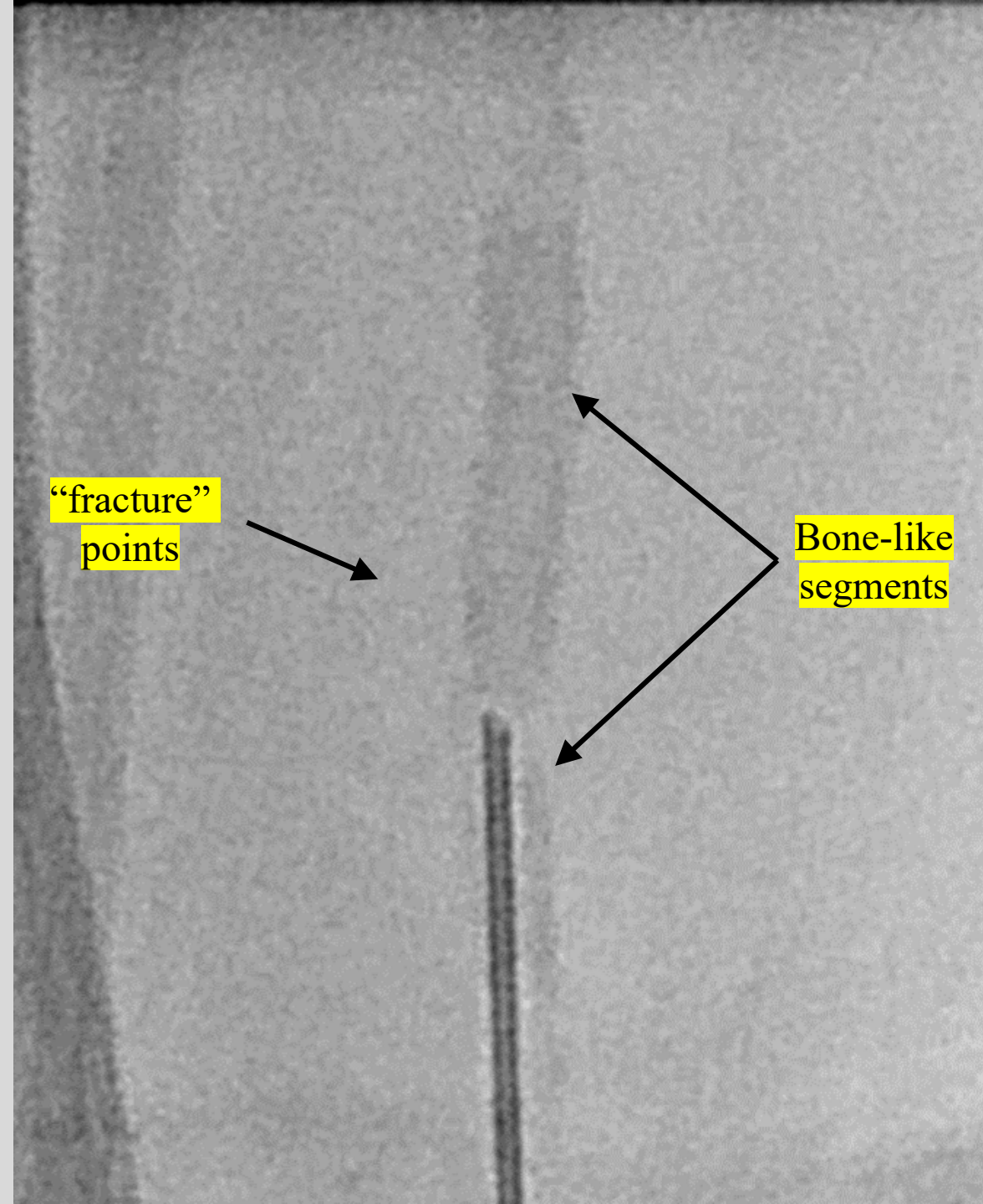
(From the Pathological Laboratories, University of Pittsburgh, Pittsburgh, Pa.)

* Received for publication May 26, 1916.

When an artery suffers advanced calcification acute flexion may fracture some of the calcareous rings, particularly when the tortuous course of the vessel does not permit it to move readily nor to adapt a more easy curve in the surrounding tissues



FRACTURE OF CALCAREOUS RING OF MEDIA WITH CALLUS FORMATION.





MAC



Arterial wall stiffness



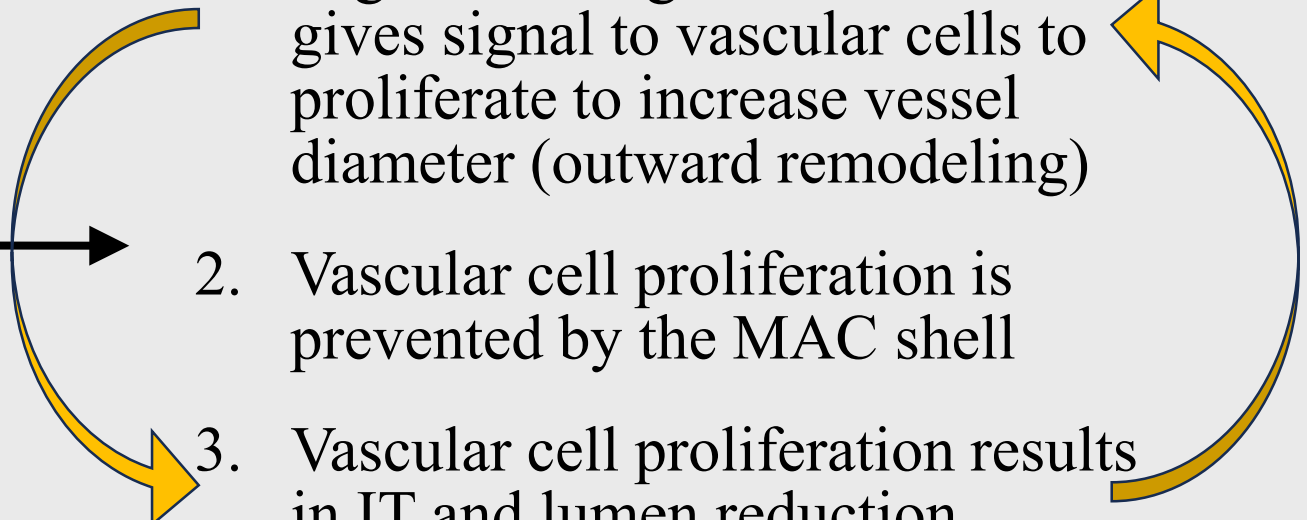
Flexibility failure



1. High SS acting on endothelium gives signal to vascular cells to proliferate to increase vessel diameter (outward remodeling)

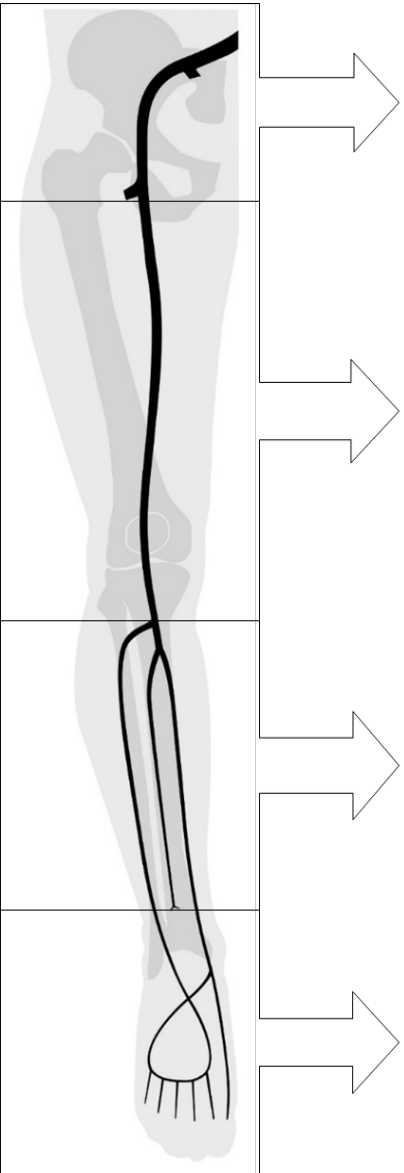
2. Vascular cell proliferation is prevented by the MAC shell

3. Vascular cell proliferation results in IT and lumen reduction

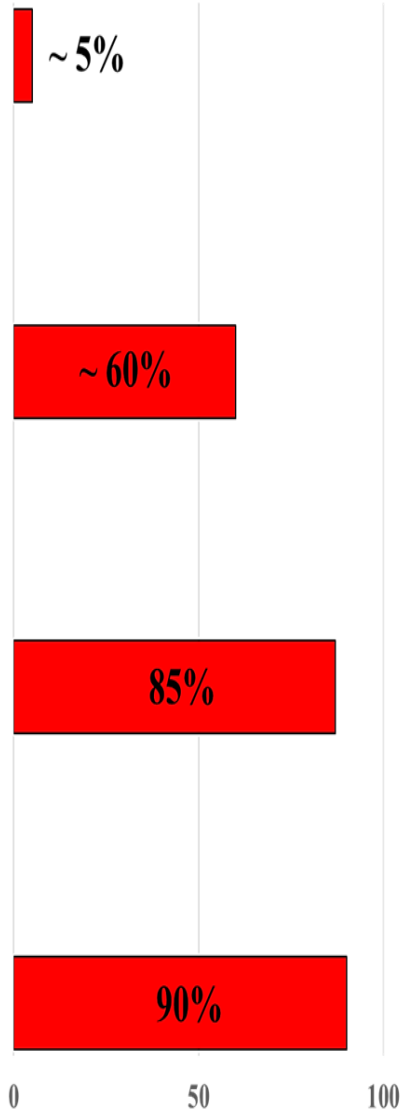


Arterial stiffness could be associated with arterial fractures leading to IT, stenosis, turbulence & thrombosis

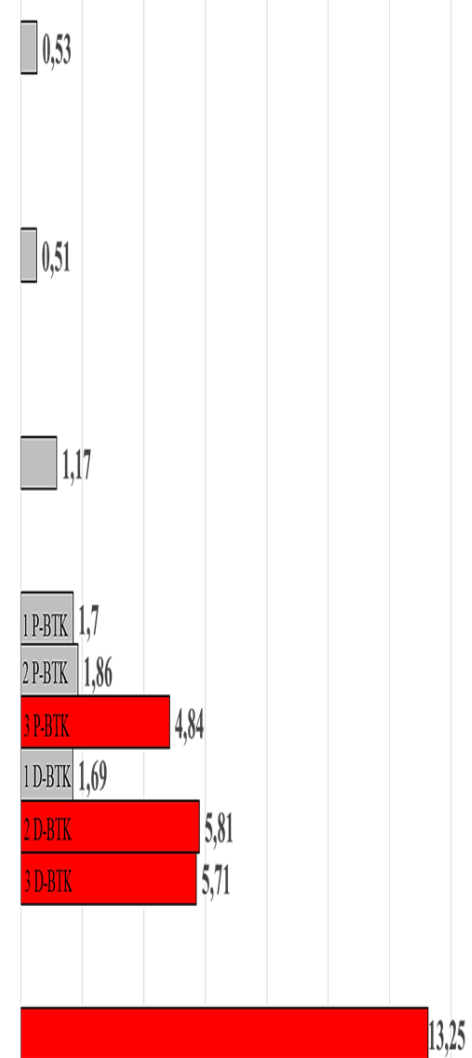
CLTI



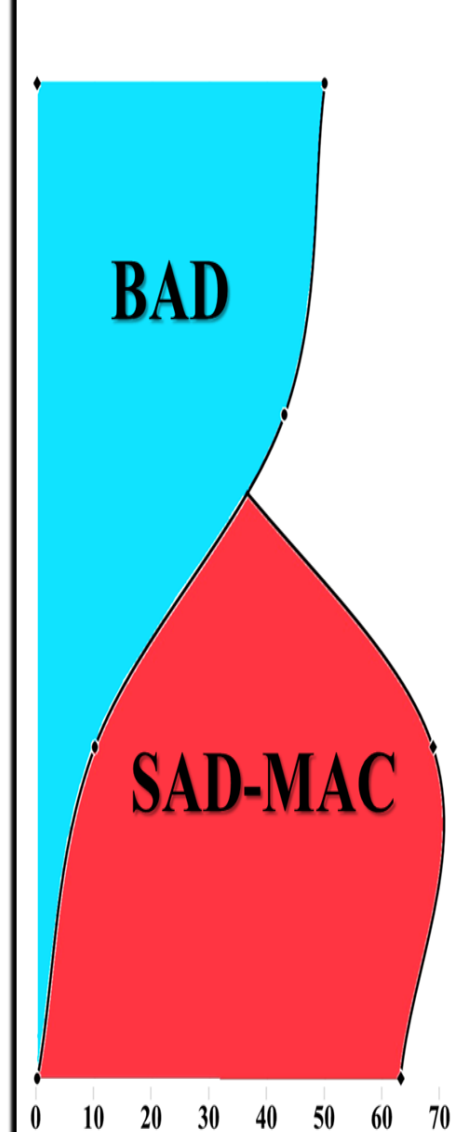
Site



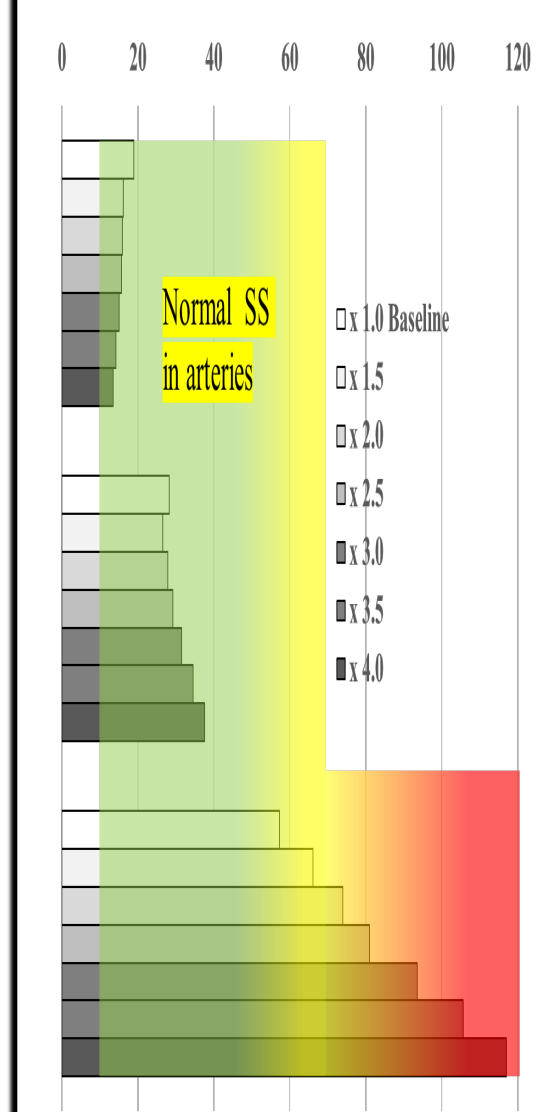
Power



Type



Stiffness = FSS



BAD & SAD, who is the enemy in CLTI?

SAD-MAC: brothers in arm

Obstruction patterns in CLTI

Weapons and soldiers: the CLTI-PAD war

Jungle patrols: extreme below-the-ankle guerilla

Mercy for patients

The fake PAD dogma

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

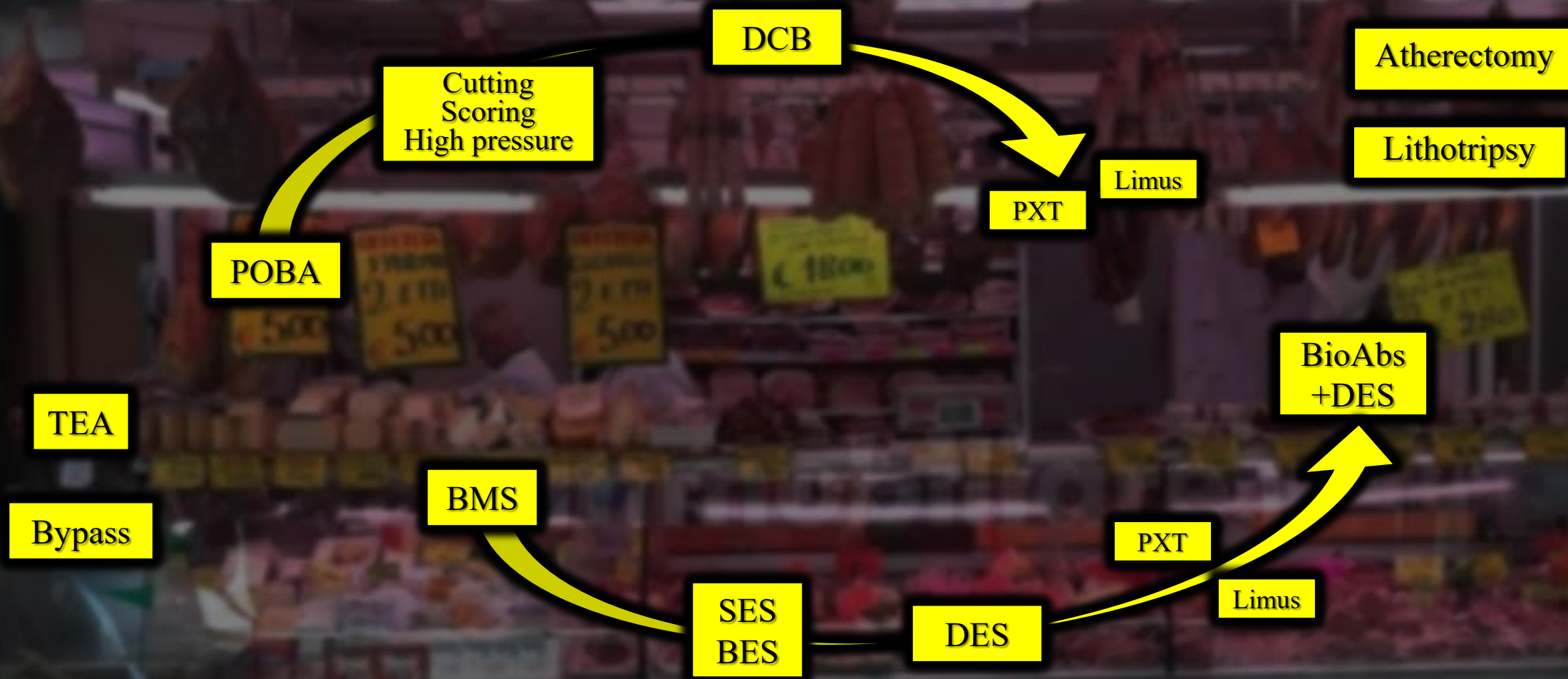
PAD is BAD, a consequence of atherosclerosis

We are fighters of BAD, and we have developed great weapons: TEA, bypass, POBA, stents, drug elution, statins, anti-PLTs, NOA etc.

Butcher and delicatessen shop

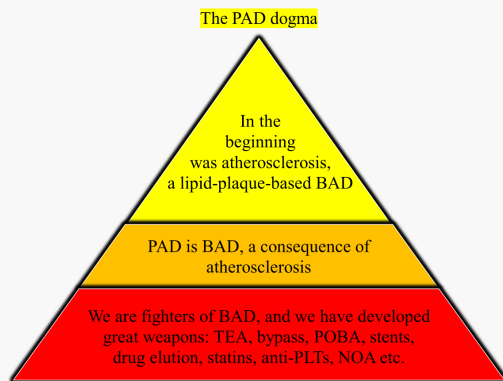


Revascularization shop



What's your budget?

The uncriticizable PAD dogma



Great weapons market → happy industry



Happy SUPERHEROES

ICEP 2016

International Course
Endovascular Procedures

Rome
November 2016
3th - 4th - 5th
13th Edition

Crediti ECM

Università di Roma
Società Italiana di Radiologia Medica
POLICLINICO CASILINO

Sede del Convegno: Aula Nuovo Policlinico Casilino

BAD & SAD, who is the enemy in CLTI?

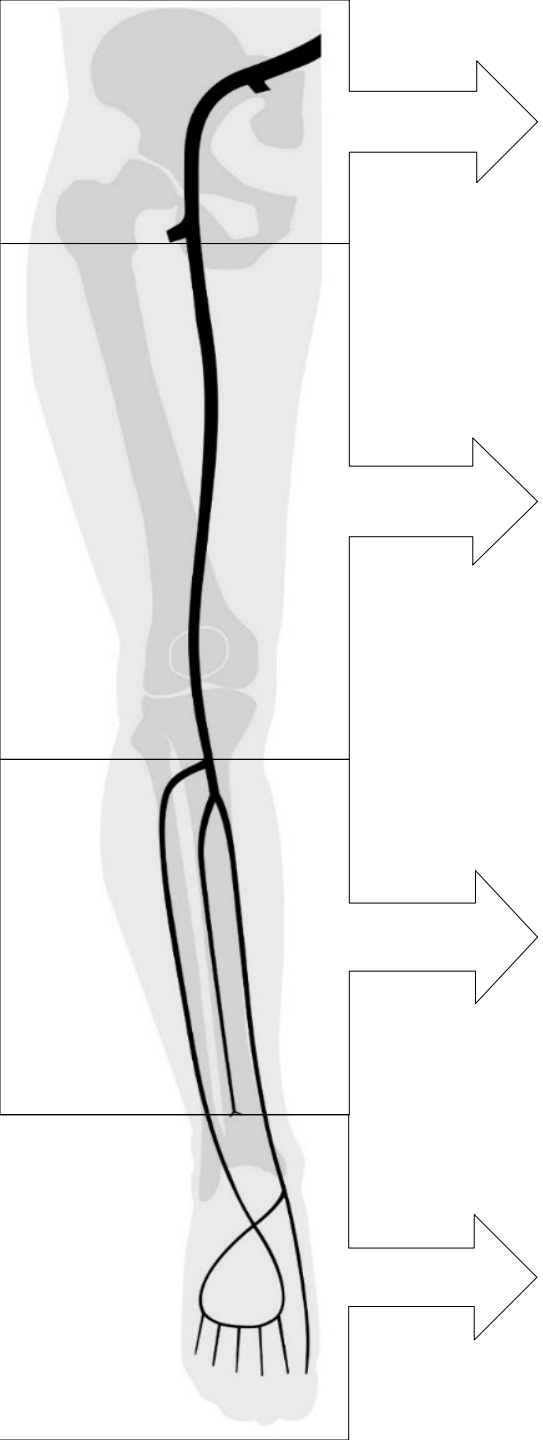
SAD-MAC: brothers in arm

Obstruction patterns in CLTI

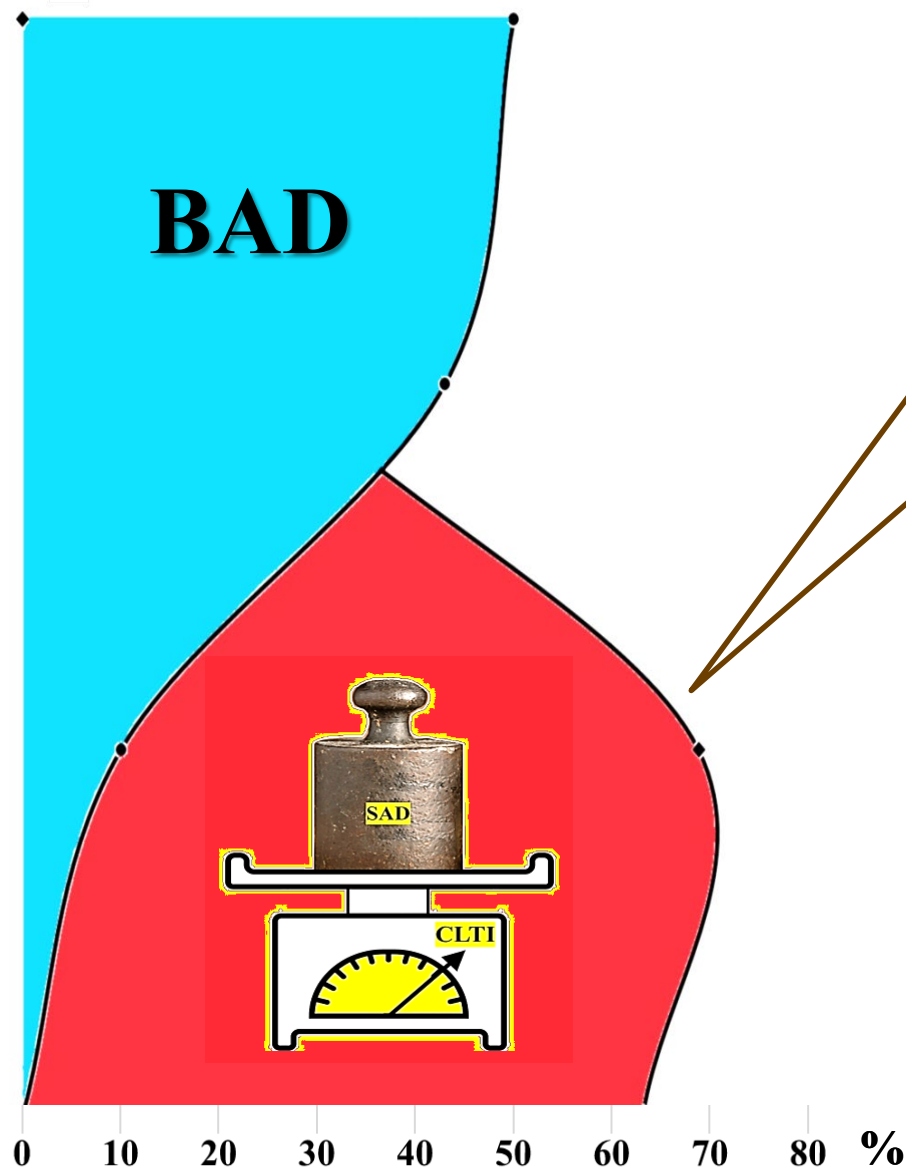
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Jungle patrols: extreme below-the-ankle guerilla

Mercy for patients



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



PAD dogma

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

PAD is BAD, a consequence of atherosclerosis

We are fighters of BAD, and we have developed great weapons: TIA, bypass, POBA, stents, drug eluting, stents, and DES, NSA, etc.

Happy industry

Happy superheroes

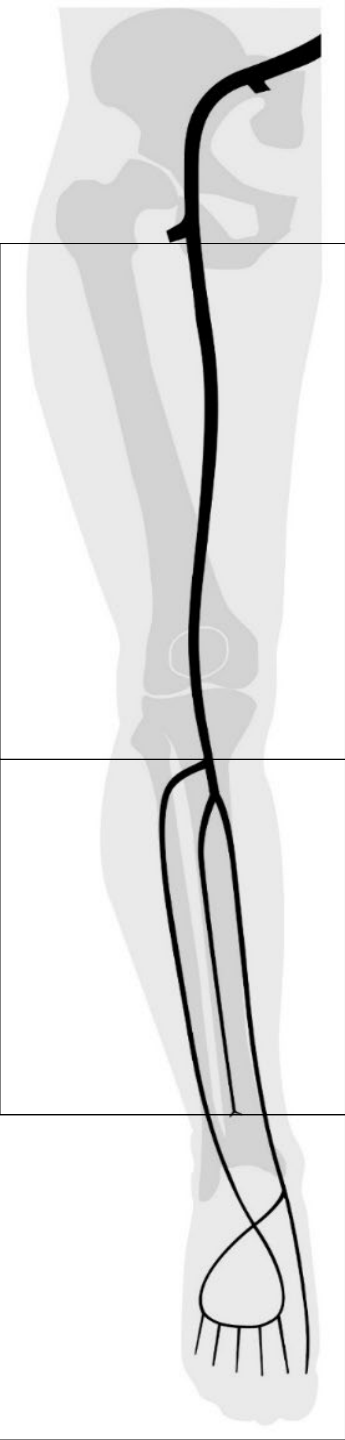
Revascularization shop

What's your budget?

Angiosome concept

Direct rev. results in improved wound healing and limb salvage rates compared with indirect rev.

GVGs: successful rev. in CLTI, particularly in patients with tissue loss, nearly always requires restoration of in-line (pulsatile) flow to the foot

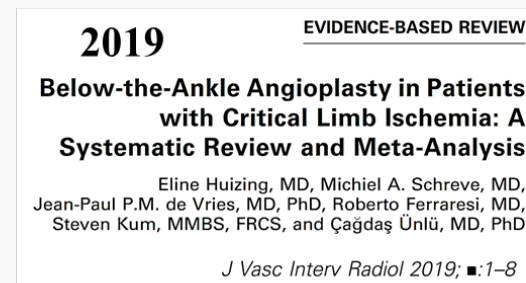


SFA-POP artery PTA
>20.000 pts in published
studies with many RCT

BTK artery PTA >10.000
pts in published studies
with many RCT

BTA artery PTA < 1000 pts

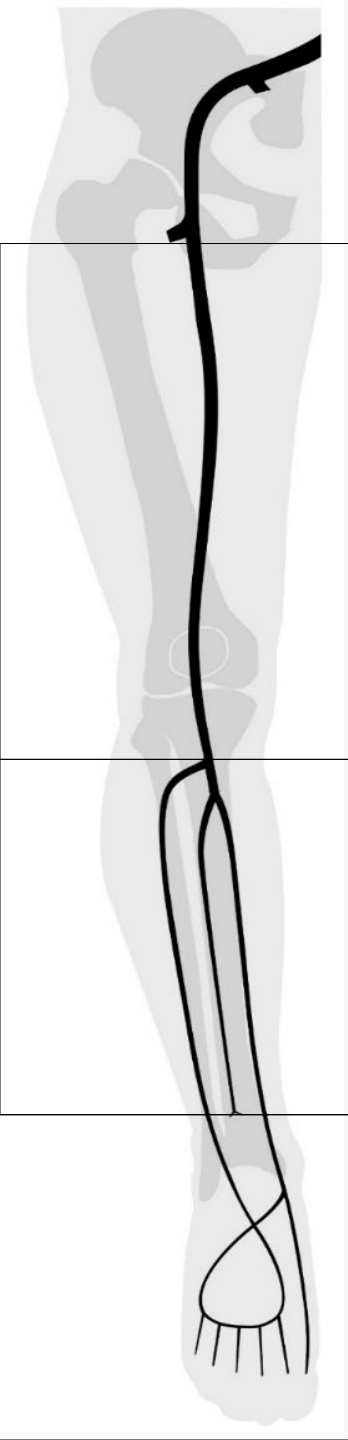
- Heterogeneous articles: prospective, retrospective, non-randomized, not controlled cohort studies; small sample size
- Different endovascular approaches: POBA, DCB, DES, BMS, ped-plant-loop, SUBI-ENDO, orbital atherectomy, retrograde approach, angiosome-guided, blush-guided.....
- Lack of studies assessing limb salvage, wound healing, symptoms, restenosis, reintervention and complications



10 studies on 524 legs



10 studies on 643 pts



SFA-POP artery PTA

>20.000 pts in published studies with many RCT

BTK artery PTA >10.000

pts in published studies with many RCT

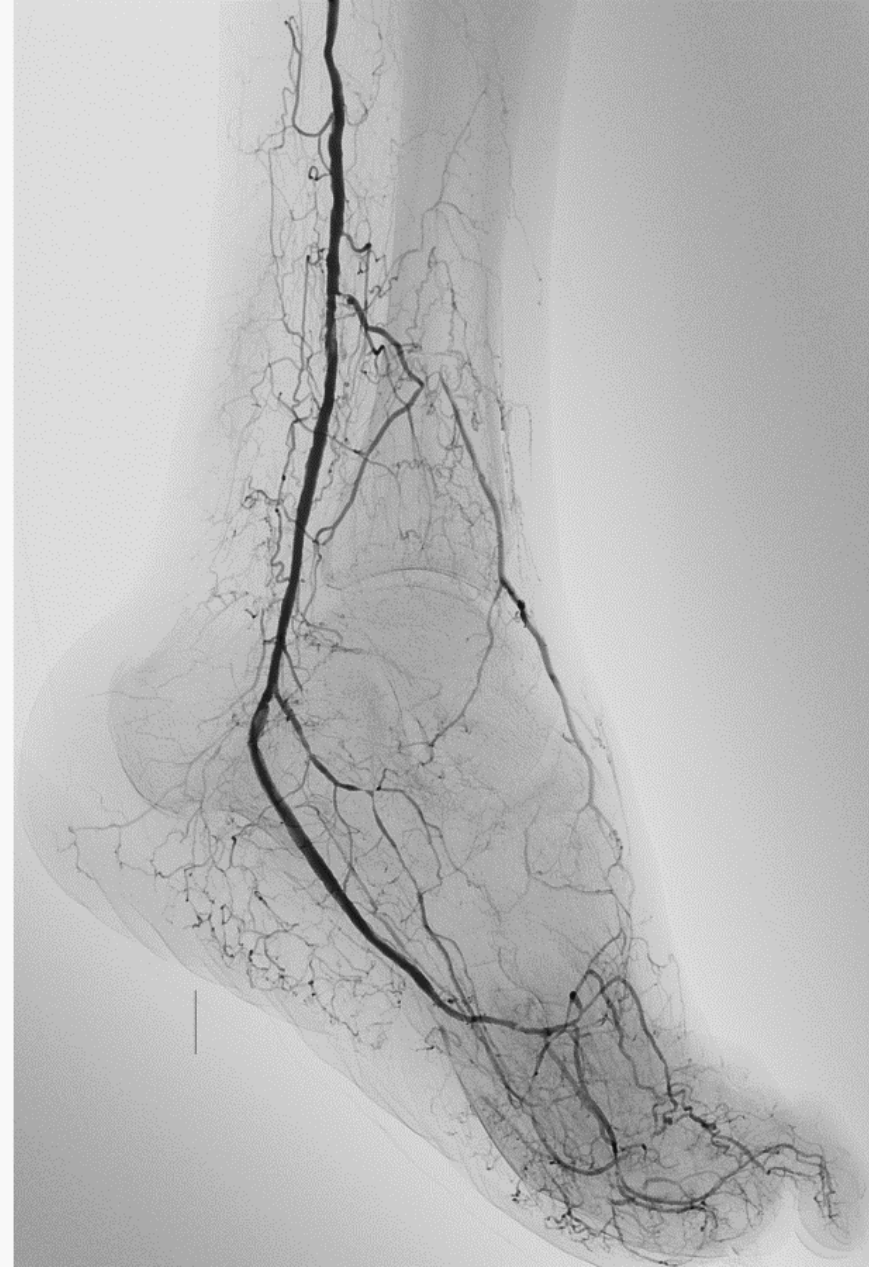
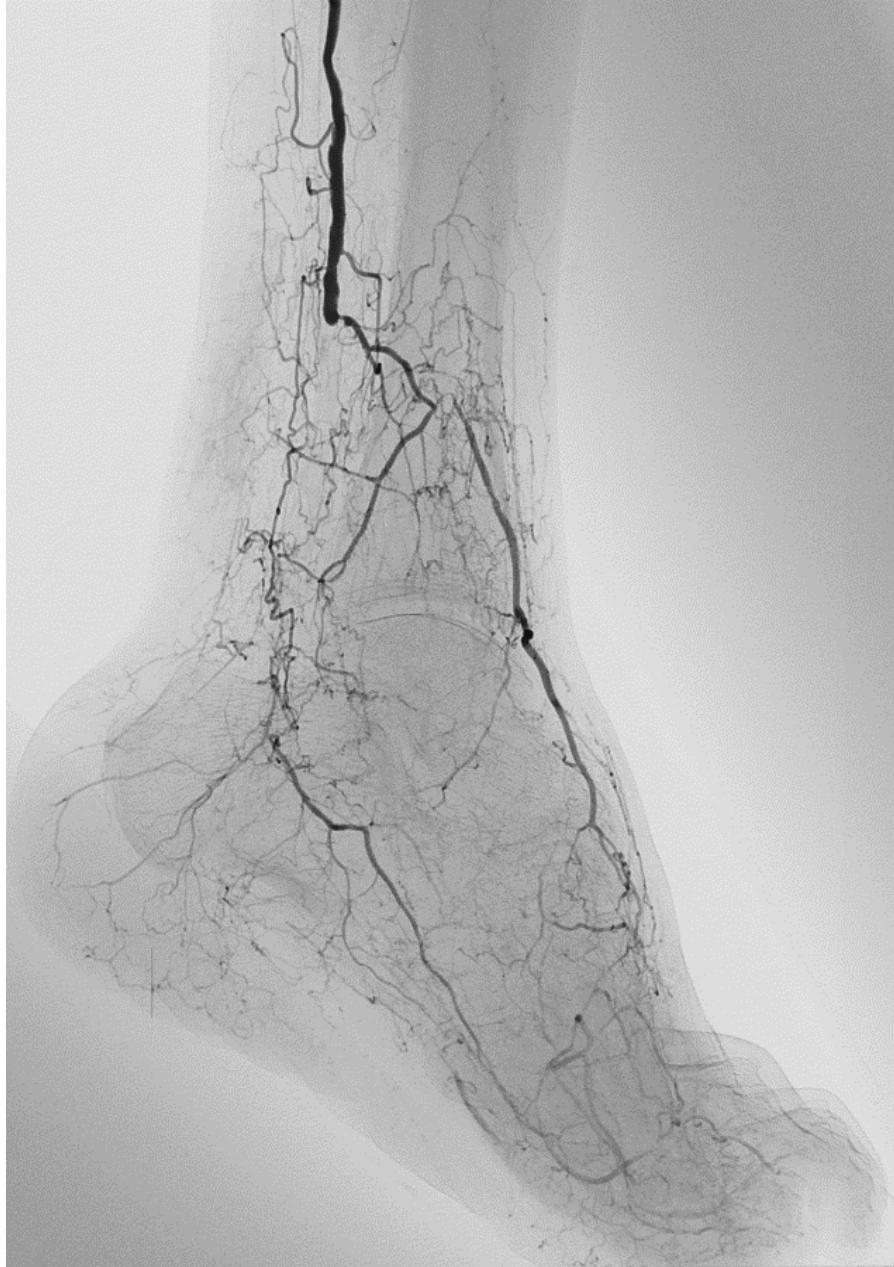
BTA artery PTA < 1000 pts

BTA angioplasty is safe & feasible with high technical success rate

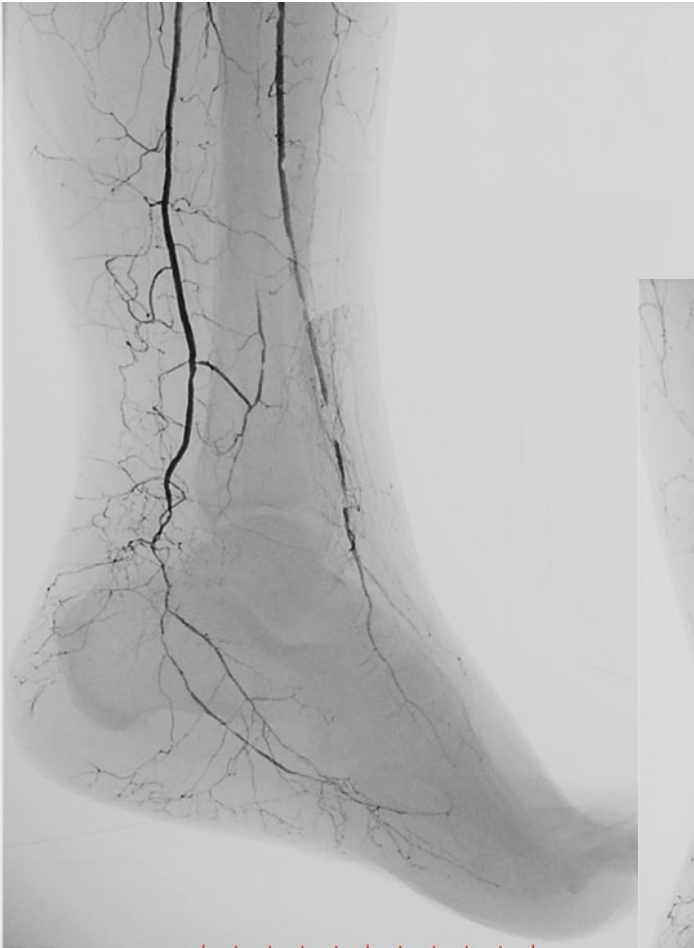
It is difficult to understand the criteria used to apply or not BTA PTA:

- Two different techniques: Yes-BTA-PTA vs No-BTA-PTA?
- Two different physicians: aggressive vs non-aggressive?
- Two different diseases: treatable vs non-treatable?

Most, predominantly BAD, pts can be successfully treated



Few SAD-MAC pts can be successfully treated



Most predominantly SAD-MAC pts have no option





BAD & SAD, who is the enemy in CLTI?

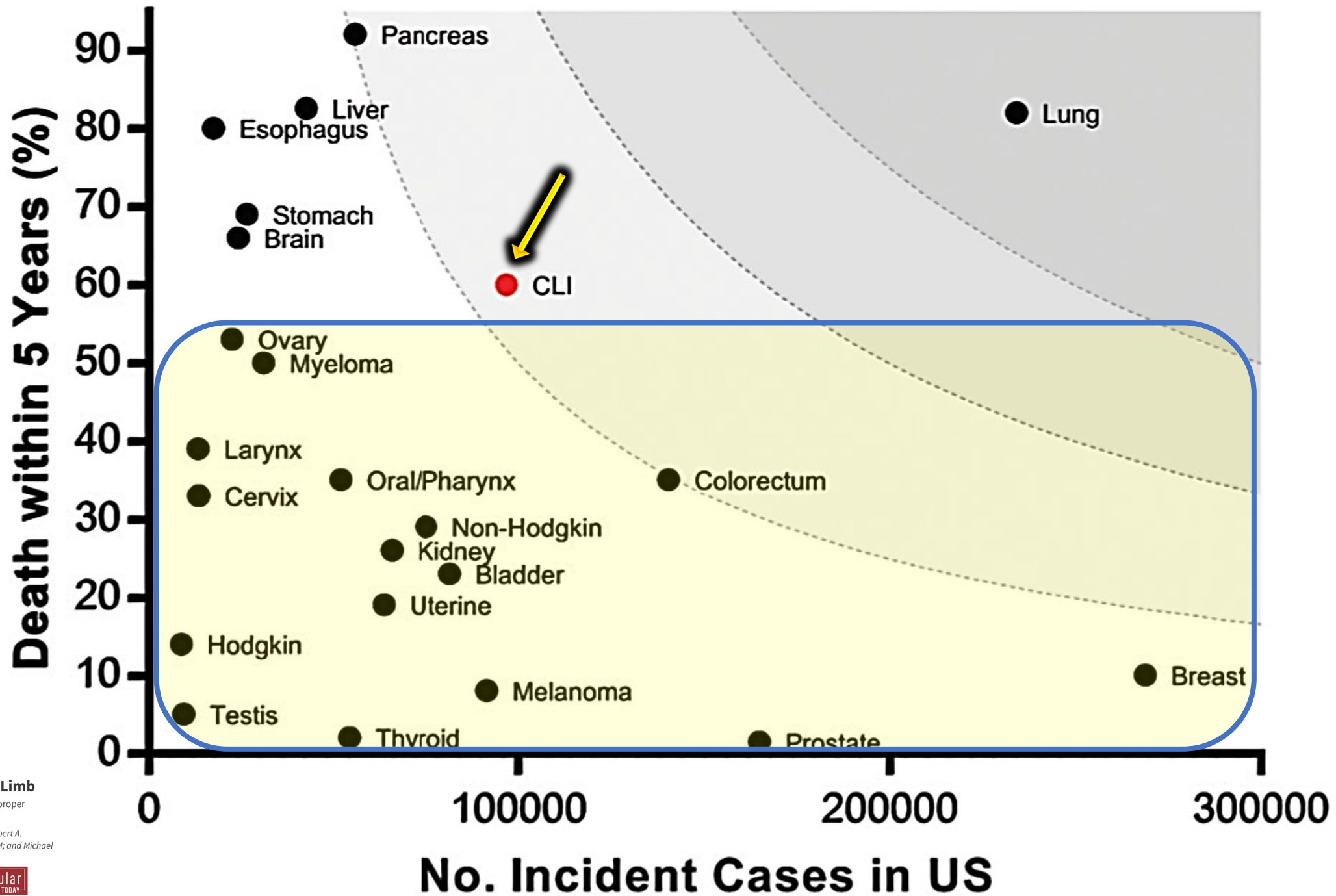
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Mercy for patients



May 2019

Critical Limb Ischemia: A Threat to Life and Limb

CLI is an underdiagnosed and undertreated deadly disease that requires proper diagnostic imaging and increased awareness.

By Jihad A. Mustapha, MD; Barry T. Katzen, MD; Richard F. Neville, MD, FACS; Robert A. Lookstein, MD; Thomas Zeller, MD, PhD; Larry E. Miller, PhD; Vickie R. Driver, DPM; and Michael R. Jaff, DO

GVGs - Raccomandation 6

Offer primary amputation or *palliation* to patients with limited life expectancy, poor functional status (eg, nonambulatory), or an unsalvageable limb after *shared decision-making*

Palliative care consultants, where available, may be a valuable resource to optimize symptom management in pts with limited goals of care

“When is it TOO Much? Best Practice Critical Limb Ischemia in 2024”

TOO much is when:

1. You treat patients without considering the true cause of CLTI and the complexity of vascular involvement
2. You act like a superhero, thinking that you have no limits and forgetting that Medicine is service, not circus acrobatics!
3. You are a slave of industrial medicine and waste public and private money for nothing
4. You sell patients impossible dreams without any realistic vision