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Clinical Research

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Anschutz Medical Campus

Peripheral Artery Disease Basics/Risk Factors

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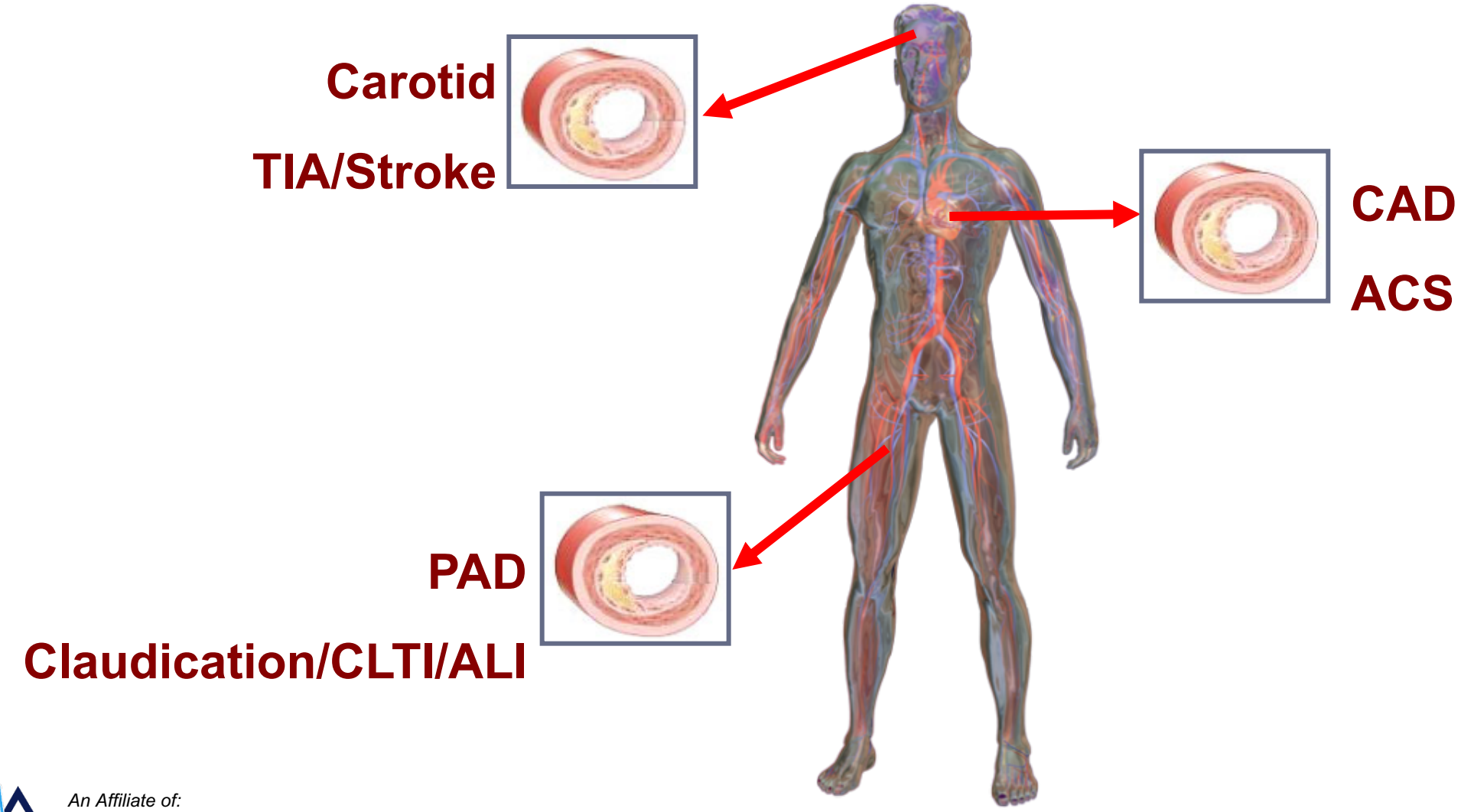
Peripheral Artery Disease

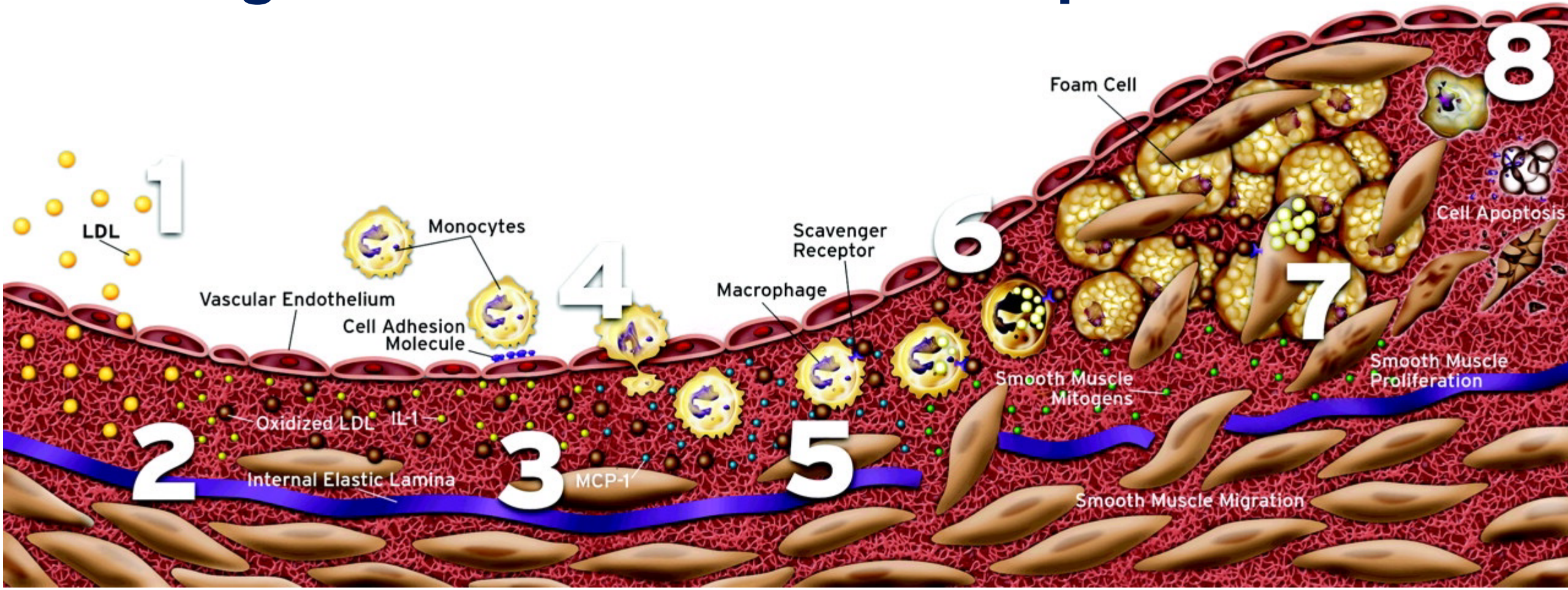
- **Underlying cause is atherosclerosis**
  - **Diffuse and progressive process**
  - **Variable distribution**
  - **Variable clinical presentation**
- **All dependent on the regional circulation involved**
  - **Size of affected artery**
  - **Structure of affected artery**
  - **Local and regional flow**
  - **Changes in microcirculatory alterations**
  - **End organ damage**

Faxon DP et al. Circulation 2004;109:2617-25

Atherosclerosis is a Systemic Disease



Stages of atherosclerotic Plaque Formation



1) LDL moves into subendothelium 2) LDL oxidized by macrophages/smooth muscle cells 3) Release of growth factors/cytokines 4) attracts additional monocytes 5) Monocytes transform to macrophages 6) Macrophages ingest LDL to make foam cells 7) Foam cell accumulation and 8) Smooth muscle cell proliferation result in plaque growth

Faxon DP et al. Circulation 2004;109:2617-25

Peripheral Artery Disease

- **Atherosclerosis locates in Predictable regions in the arterial tree with flow instabilities**
  - **Large to medium sized arteries**
  - **Branch points**
  - **Bifurcations**
  - **Vessel curvature**
- **Carotid arteries – (Considered part of PAD in Canada)**
- **Aorta and its branches – (PAD in US)**
  - **Iliac arteries**
  - **Lower extremity arteries**

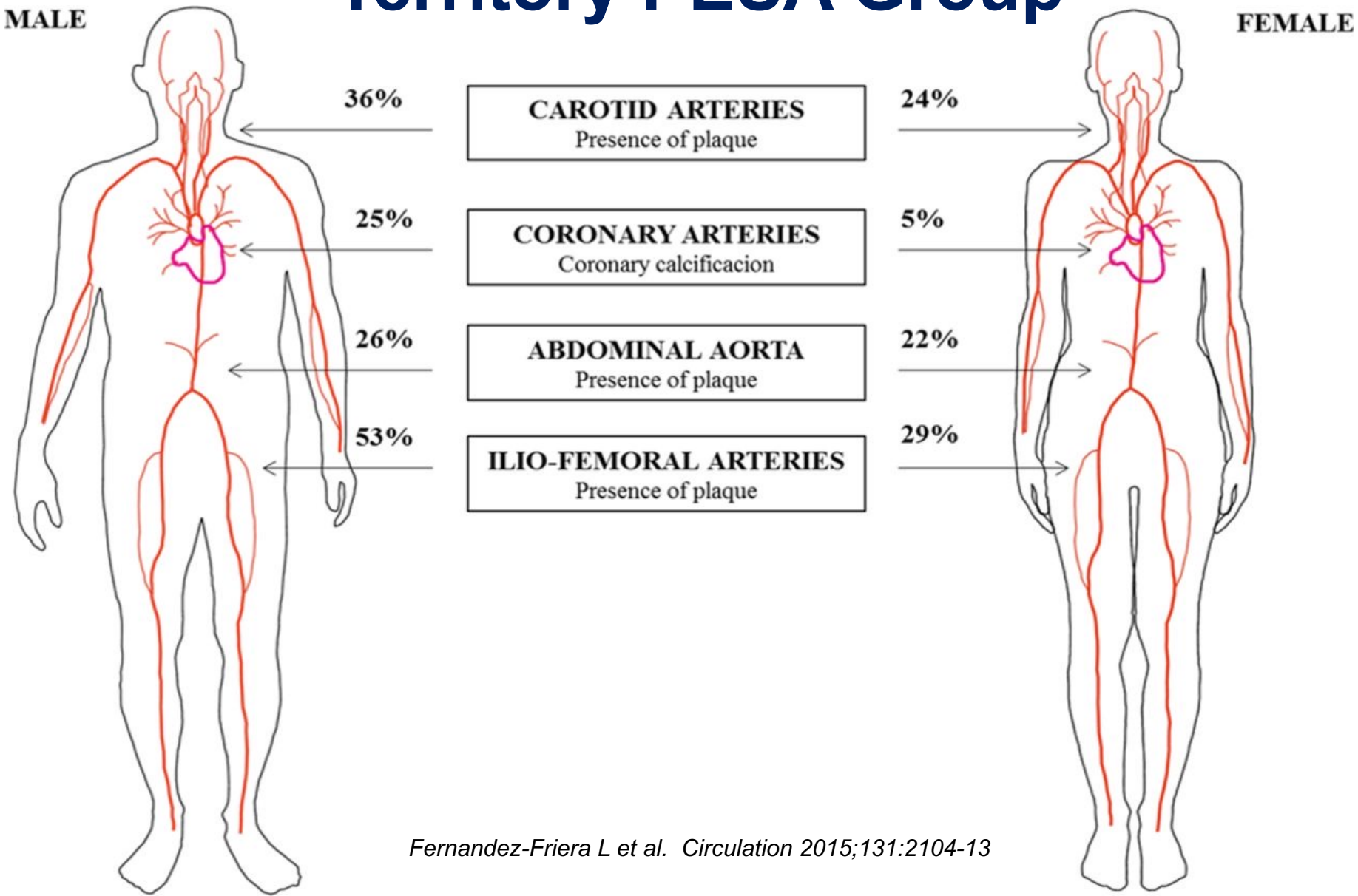
Davies PF et al. Biorheology 2002:39:299-306

Peripheral Artery Disease

- Atherosclerosis in the various beds begins early in life
- Progression of early subclinical atherosclerosis (PESA)
- Screened patients age 40-54 years age with no cardiovascular history
  - Duplex ultrasound to examine carotid and aorta/iliofemoral arteries for plaque
  - CT to examine the coronary arteries for calcification
- They screened a total of 4066 patients over 4.5 years
  - 2573 men
  - 1493 women
- Males were more likely to have plaque formation in all beds

Fernandez-Friera L et al. Circulation 2015;131:2104-13

Prevalence of Subclinical Atherosclerosis by Vascular Territory PESA Group



Fernandez-Friera L et al. Circulation 2015;131:2104-13

Peripheral Artery Disease (PAD)

- The presence of a stenosis or occlusion in the aorta or arteries of the limbs
- Usually caused by atherosclerosis
- Associated with an increased risk of death, myocardial infarction, and stroke
- May impair walking or cause critical limb ischemia

Peripheral Artery Disease

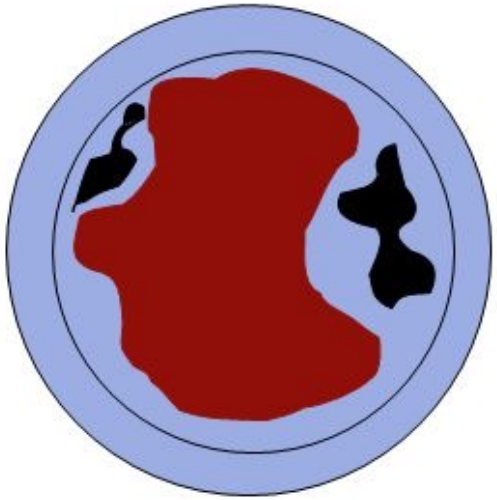
- Claudication – calf/buttock pain when ambulating
  - Often described by blocks walked prior to pain onset
  - Pain stops quickly with rest
  - Is reproducible at same distance
- Chronic Limb Threatening Ischemia (CLTI)
  - Pain in foot at rest
  - Non healing pedal ulcers
  - Pedal gangrene
- Acute Limb Ischemia
  - Acute arterial obstruction and limb threat

Heterogeneity in Biology

Hyperlipidemia, Smoking, Hypertension, Inflammation, Stress, Diabetes

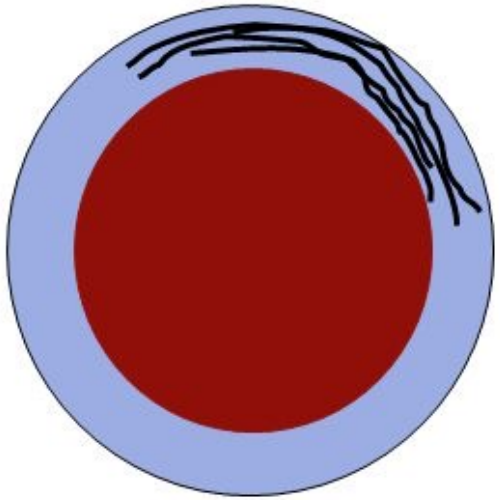
Renal Dysfunction, Diabetes
(Calcium & Phosphate Regulation, Osteogenesis, Local Cellular Dysfunction)

Intimal/subintimal Disease



Low ABI
≤ 0.9

Medial Calcification



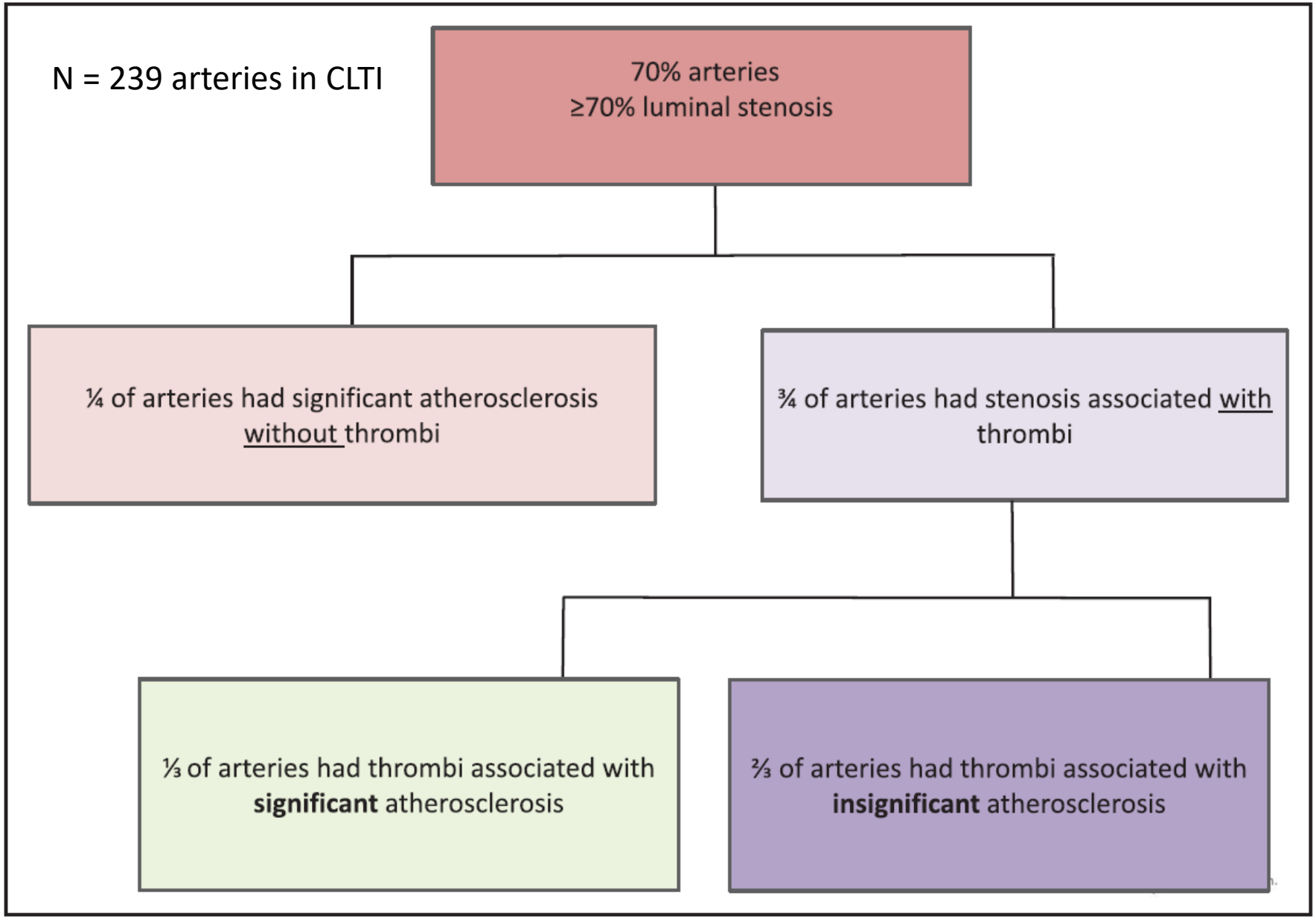
High ABI
≥ 1.3

Quehenberger O, Dennis EA. N Engl J Med 2011;365:1812-1823.

Pathology of PAD vs CAD Events

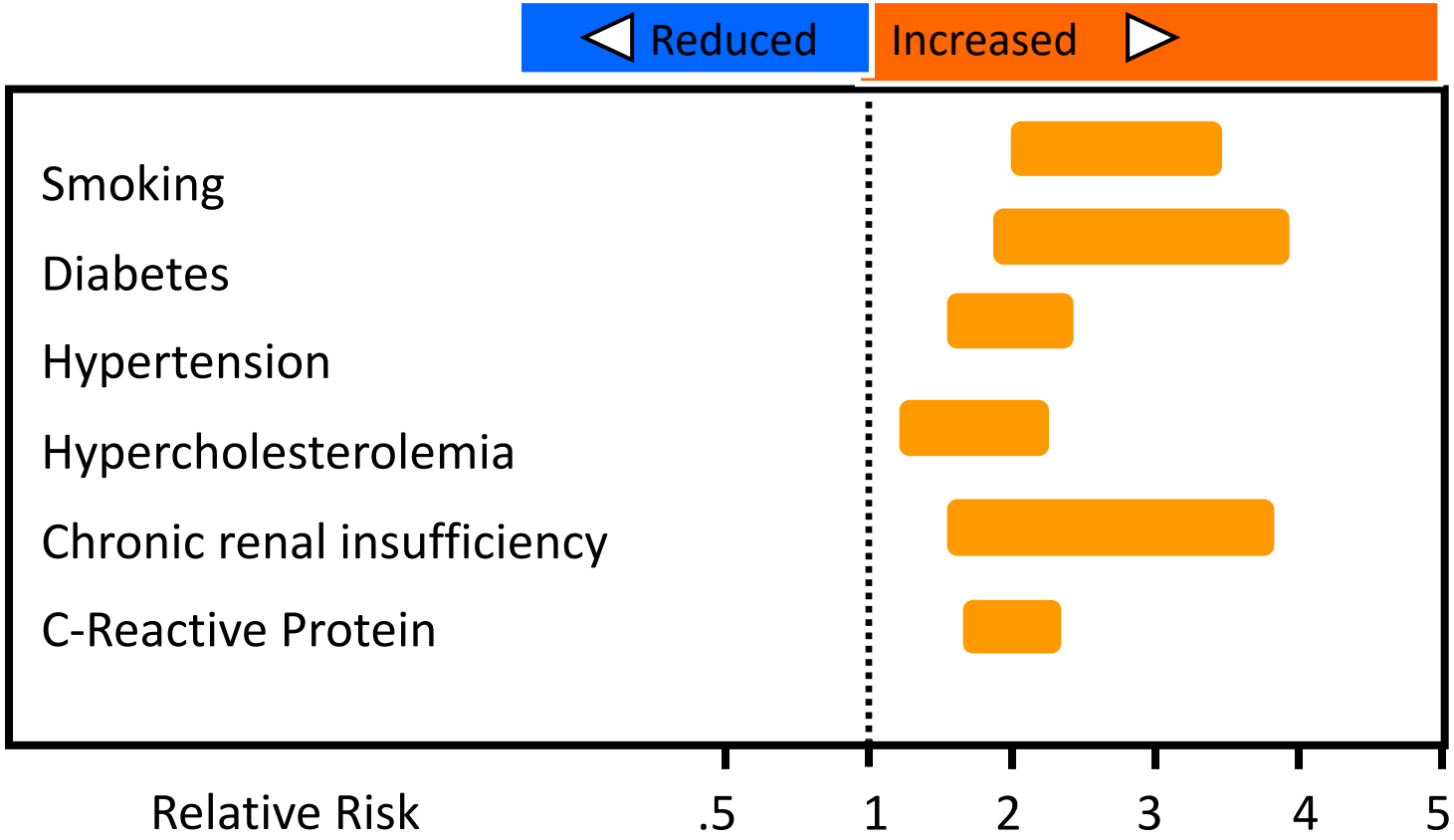
- Both CAD and PAD are luminal thrombosis as primary issue
- CAD - Acute Coronary Syndrome
  - Primarily due to luminal thrombosis associated with atherosclerosis
  - Plaque rupture of thin capped fibroatheroma (2/3)
  - Pathological intimal thickening with plaque erosion (1/3)
- PAD – Chronic Limb Threatening Ischemia
  - Primarily due to luminal thrombosis not associated with atherosclerosis
  - Study examining the limbs of amputees for CLTI
  - 70% of the arteries showed ≥70% stenosis

Narula N et al. Arterioscler Thromb Vasc Biol 2020;40:1982-89



Narula N et al. Arterioscler Thromb Vasc Biol 2020;40:1982-89

Risk Factors for PAD



Selvin E et al. Circulation 2004;110:738-43

Smoking and PAD

- **Stronger risk factor for PAD than CAD (Edinburgh Artery Study)**

- **Smoking, Type II Diabetes, hypertension, and hypercholesterolemia**
  - **Accounted for 75% of PAD risk**
  - **In males in Health Professional Follow-up Study**

Price JF et al. Eur Heart J 1999;20:344-53
Joosten MM et al. JAMA 2012;308:1660-67

Smoking and PAD continued

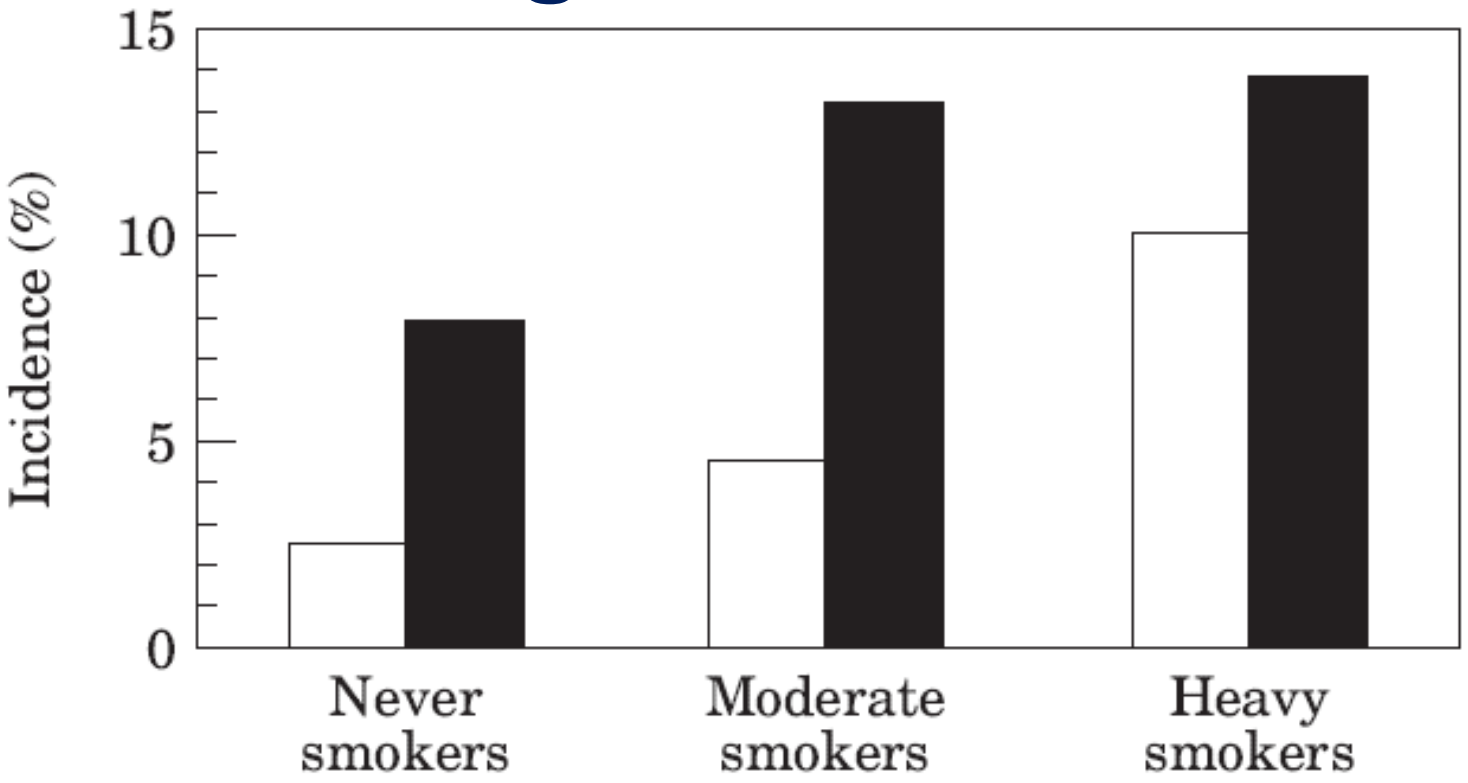


Figure 1 **Incidence (%) of peripheral arterial disease (□) and coronary artery disease (■) in never smokers (pack-years=0), moderate smokers (0 <packyears ≤25) and heavy smokers (packyears >25).**

Price JF et al. Eur Heart J 1999;20:344-53

Diabetes and PAD

- **Diabetes increases risk of PAD**
  - **Rates of claudication 3.5 times with than without diabetes**
  - **Adversely modifies the clinical course of PAD**

- **Diabetes most common cause of amputation in US**
  - **45-70% of all nontraumatic amputations**

Kannel WB et al. J Am Geriatr Soc 1985;53:13-18
CDC Morb Mortal Wkly Rep 1998;14:649-52

Population Characteristics of Ischemic Amputations

Table 1. Population Characteristics of Ischemic Amputations in Minnesota, 2005-2008[a]

Characteristic	All Amputations (n = 4,302)	Minor Amputations (n = 2,470)	Major Amputations (n = 1,831)
Age, median (IQR), y	67 (56-79)	65 (54-76)	70 (59-81)
Male sex, %	65.4	67.5	62.5
Urban county residence, %	65.1	66.0	63.9
Diabetes, %	72.3	79.4	62.8
Length of stay, median (IQR), d	7 (4-12)	6 (4-10)	9 (6-14)
Inpatient charges, median (IQR), $	32,129 (17,980-57,761)	27,377 (16,087-47,737)	39,512 (21,414-73,174)
Inpatient hospitalization costs, median (IQR), $	12,434 (7,402-21,714)	10,609 (6,525-18,127)	15,246 (8,992-26,912)

Abbreviation: IQR, interquartile range.

[a] A minor amputation is any amputation below the ankle, and a major amputation is any amputation at or above the ankle; 1 amputation was at an unspecified site.

Peacock JM et al. Prev Chronic Dis 2011;8:A141

Dyslipidemia and PAD

- **Abnormalities in lipid profile more common in PAD**
  - **Higher LDL**
  - **Lower HDL**

- **Relative risk for PAD increases for each 10 mg/dl increase in total cholesterol**

Newman AB et al. Circulation 1993;88:837-45

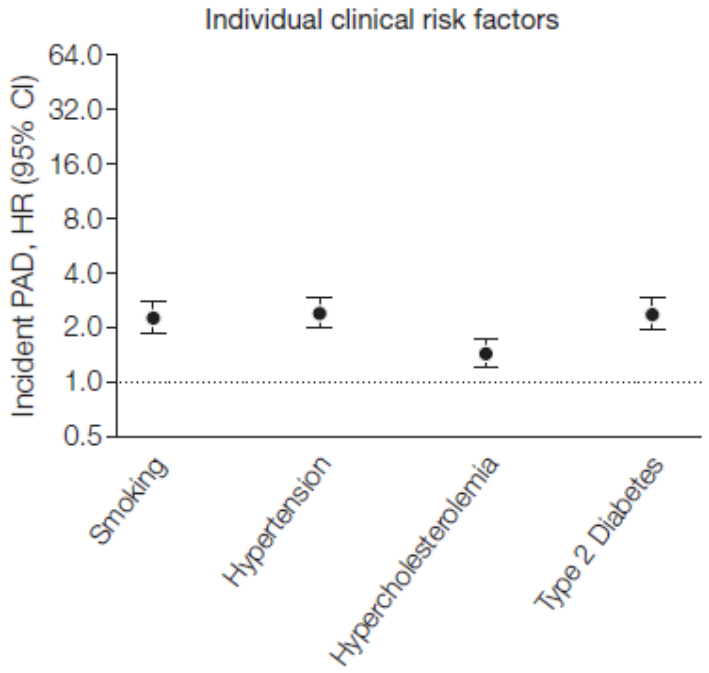
Dyslipidemia and PAD

- **Importantly these risk factors are additive**

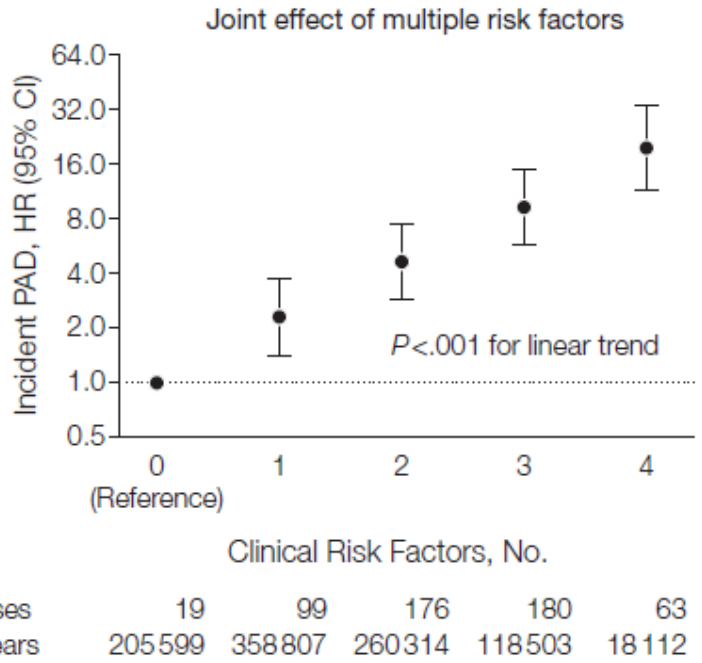
- **The figures in the next slide from Health Professionals Followup Study show the individual and then then additive risk of PAD with smoking, diabetes, hypertension, and dyslipidemia**

Joosten MM et al. JAMA 2012;308:1660-67

PAD According to Individual & Joint Clinical Risk Factors



Risk factor group				
No. of cases	412	377	325	129
Person-years	496 549	349 279	397 481	64 080
PAR (95% CI), %	44 (33-53)	41 (31-50)	17 (7-26)	14 (10-19)
Reference group				
No. of cases	125	160	212	408
Person-years	464 785	612 504	563 853	897 253



No. of cases	19	99	176	180	63
Person-years	205 599	358 807	260 314	118 503	18 112

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Joosten MM et al. JAMA 2012;308:1660-67

Risk Factors and PAD

- There are several modifiable risk factors in PAD

- Smoking cessation
- Diabetes management
- LDL cholesterol reduction
- Hypertension control

- Improvements in these can reduce events and prolong life in patients with PAD