Peripheral Artery Disease

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Disclosures

- None

Goals and Objectives

- Describe the epidemiology and risk factors.
- Identify the important history and physical exam findings.
- Describe the initial workup and management.
- Recognize some of the indications for invasive management.

What is PAD?

- Chronic atherosclerosis leading to plaque buildup in arteries of the lower extremities resulting in arterial insufficiency.

- Generally defined as an ankle-brachial index of < 0.9 in the presence of atherosclerotic vascular disease.

Epidemiology

- It is a major global health problem affecting more than 200 Million people.
- Data from the US suggests that 8.5 million Americans are living with PAD with a strong age-dependent increase.
- The prevalence is increasing significantly largely due to an aging population.

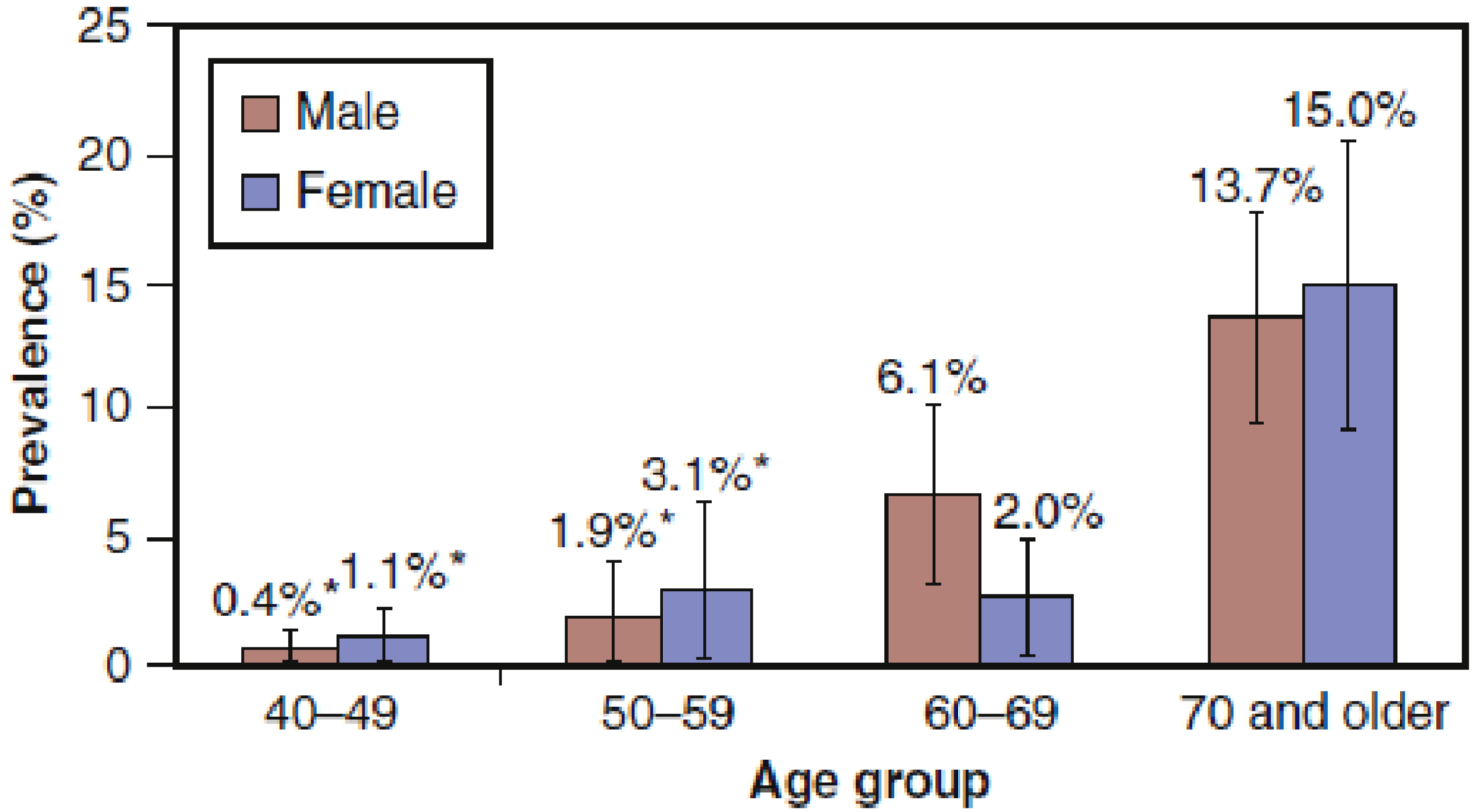


Figure 107.2 Estimated age-specific prevalence of PAD in the United States from the National Health and Nutrition Examination Survey 1999–2000. *Relative standard error >30%. (From Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. *Circulation*. 2004;110(6):738–743.)

Risk Factors

- Age
- Smoking
- Diabetes
- HTN
- Hyperlipidemia
- Chronic kidney disease
- Low socioeconomic status

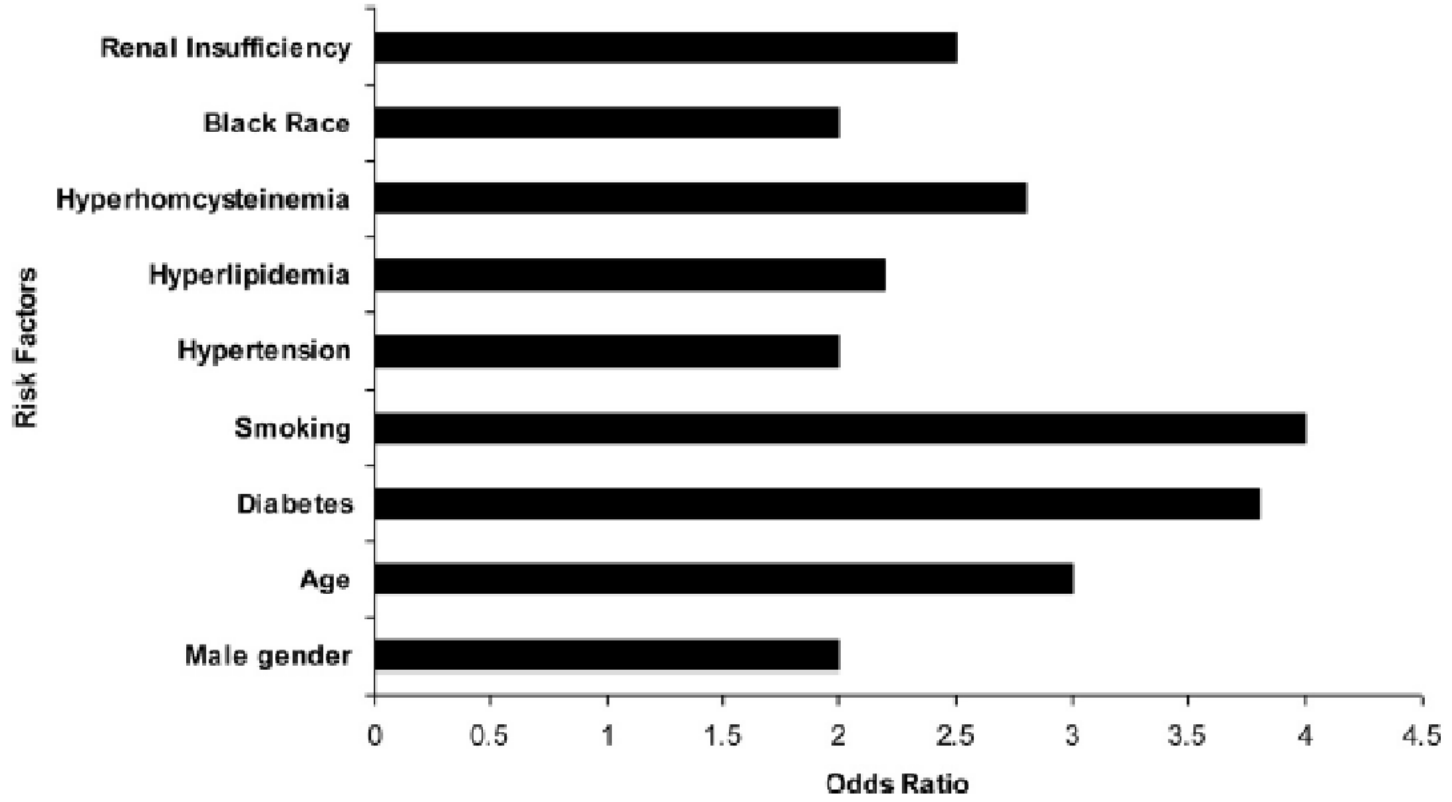
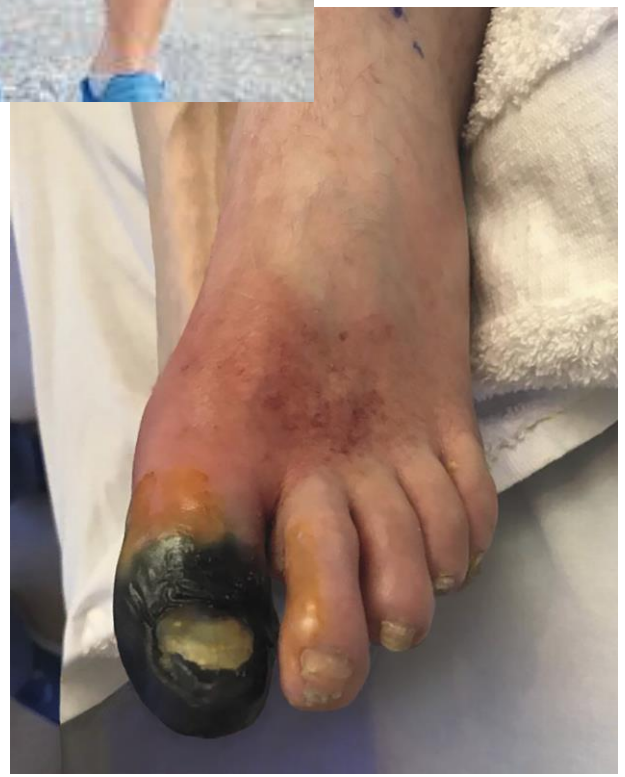


Fig 1. The approximate odds ratios (ORs) for risk factors associated with the development of peripheral arterial disease (PAD). Adapted from Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II).[9]

Clinical Presentation

- Asymptomatic
- Claudication (to limp)
  - Pain with ambulation
- CLI/CLTI
  - Ischemic rest pain
  - Tissue loss



Diagnosis of PAD

- History
  - Critically important
- Physical exam

- Diagnostic imaging
  - Non-invasive testing
  - Cross sectional imaging

Differential diagnosis

- Arthritis
- Spine disease, radiculopathy, neurogenic claudication
- Neuropathy
- Venous disease
- Fibromyalgia

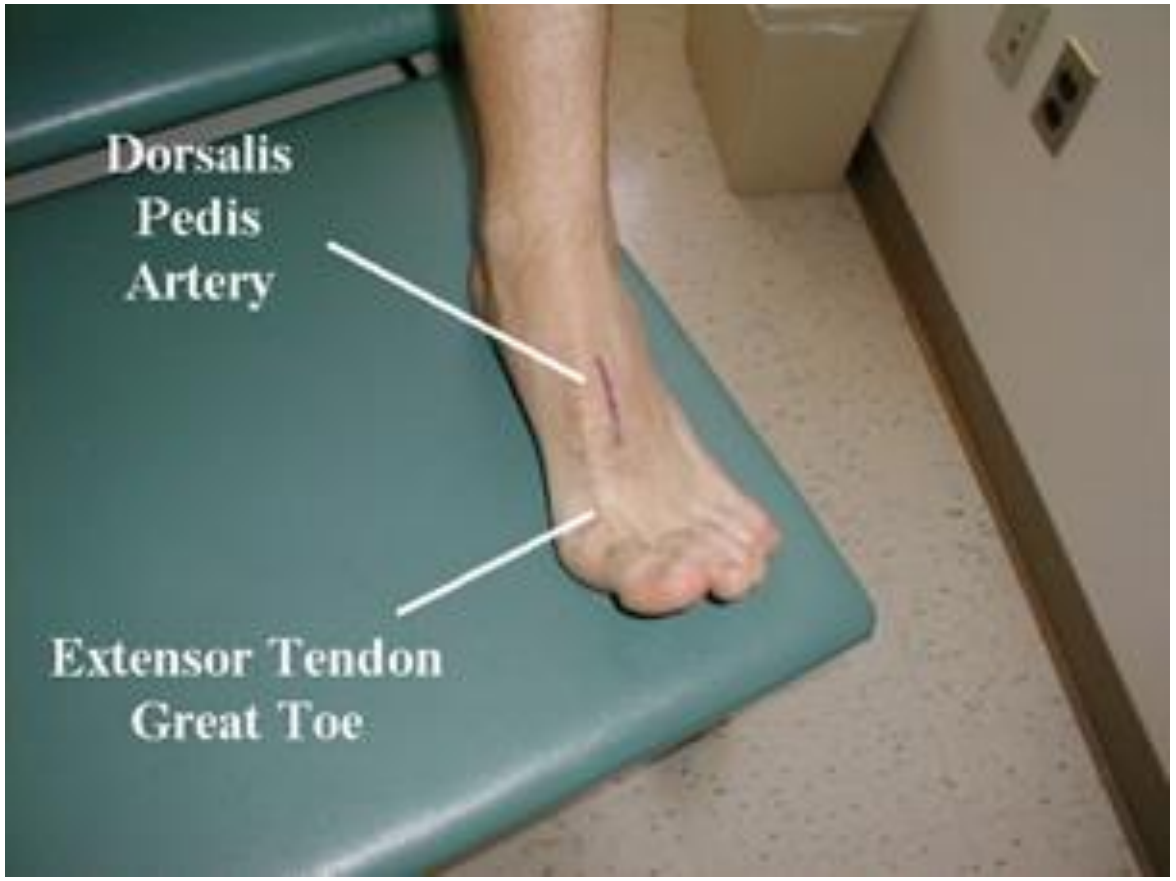
Key history in PAD

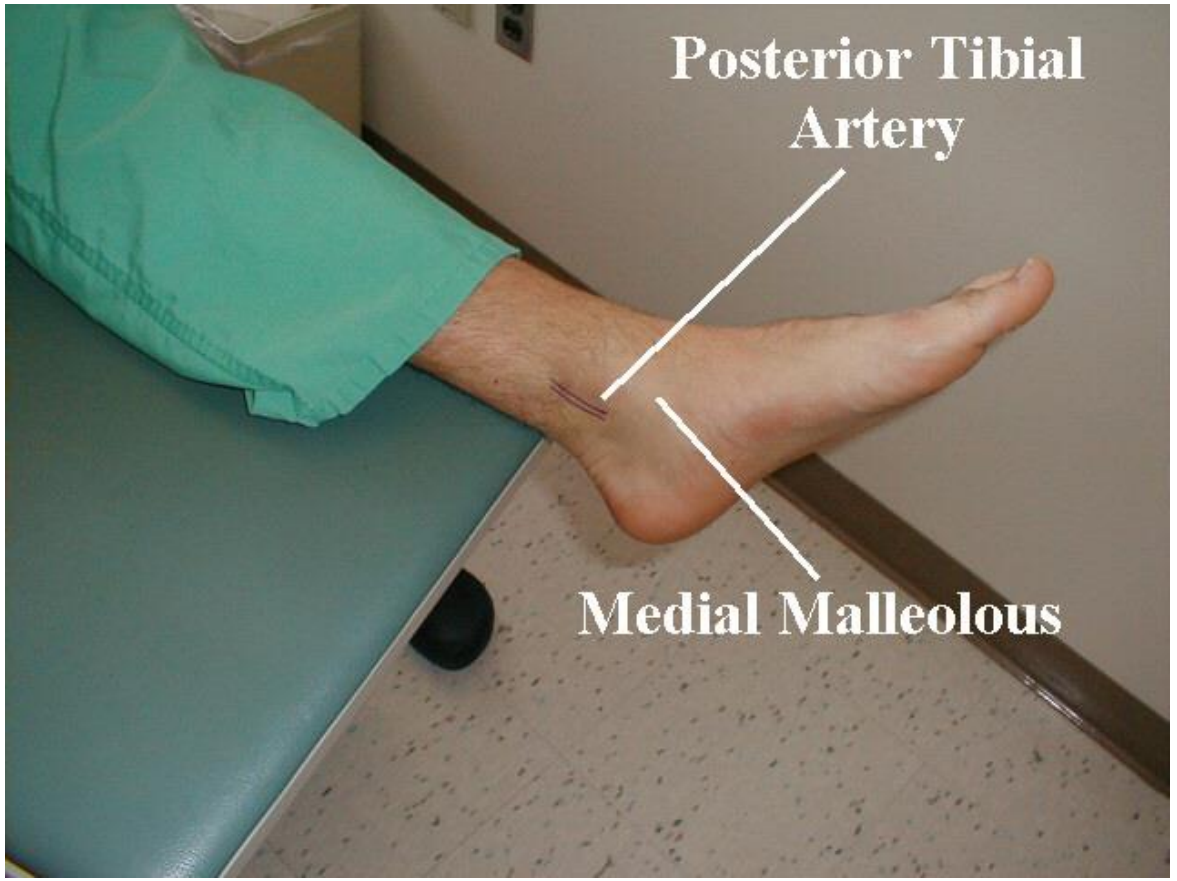
- Peripheral artery disease
  - Claudication
    - Predominantly affects the calf muscles
    - Less commonly affects more proximal muscle groups
    - Almost exclusively occurs with walking
    - Reproducible and very predictable i.e. at exactly ¼ mile I get cramping
    - Relieved with rest
  - Ischemic rest pain
    - Predominantly affects the feet and toes
    - Rarely affects more proximal legs
    - Is generally constant but can be worse at night and with elevation of the legs
    - Can be associated with decreased sensation or “pins and needles”

Key physical exam findings in PAD

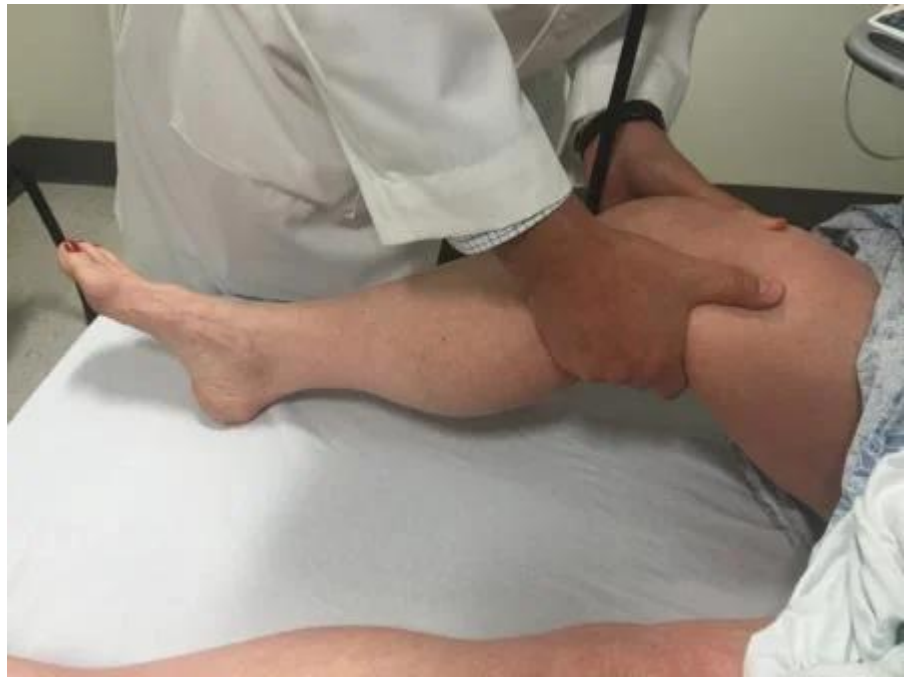
- Skin color and temperature
  - Cool
  - Rubor with pallor on elevation is highly suggestive
  - Cyanosis is a very late stage finding
- Lack of hair
- Thickened nails
- Wounds
  - Tend to be distal on the toes and on the dorsum of the foot
  - Painful
- Pulse exam
  - Femoral
  - Popliteal
  - AT/PT/DP
  - Doppler exam

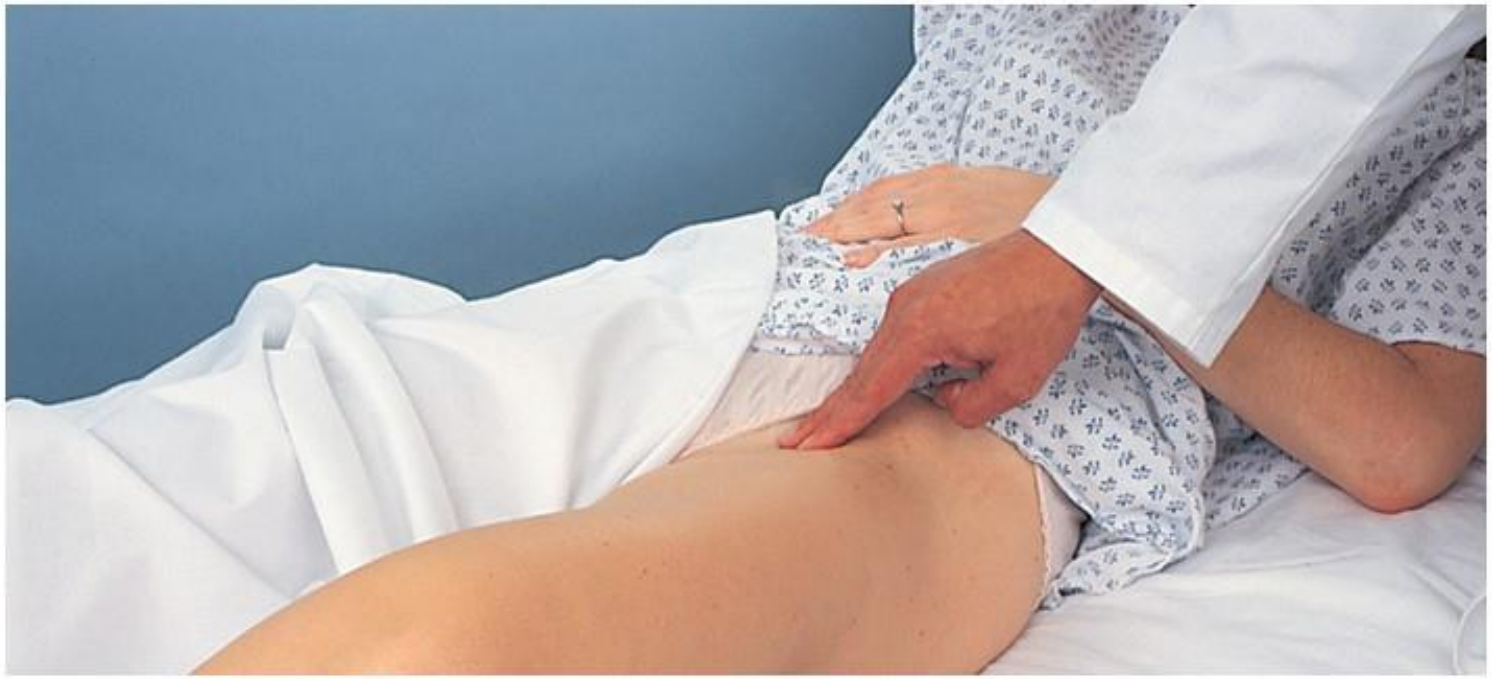
Pulse Examination





Pulse Examination





Differential diagnosis

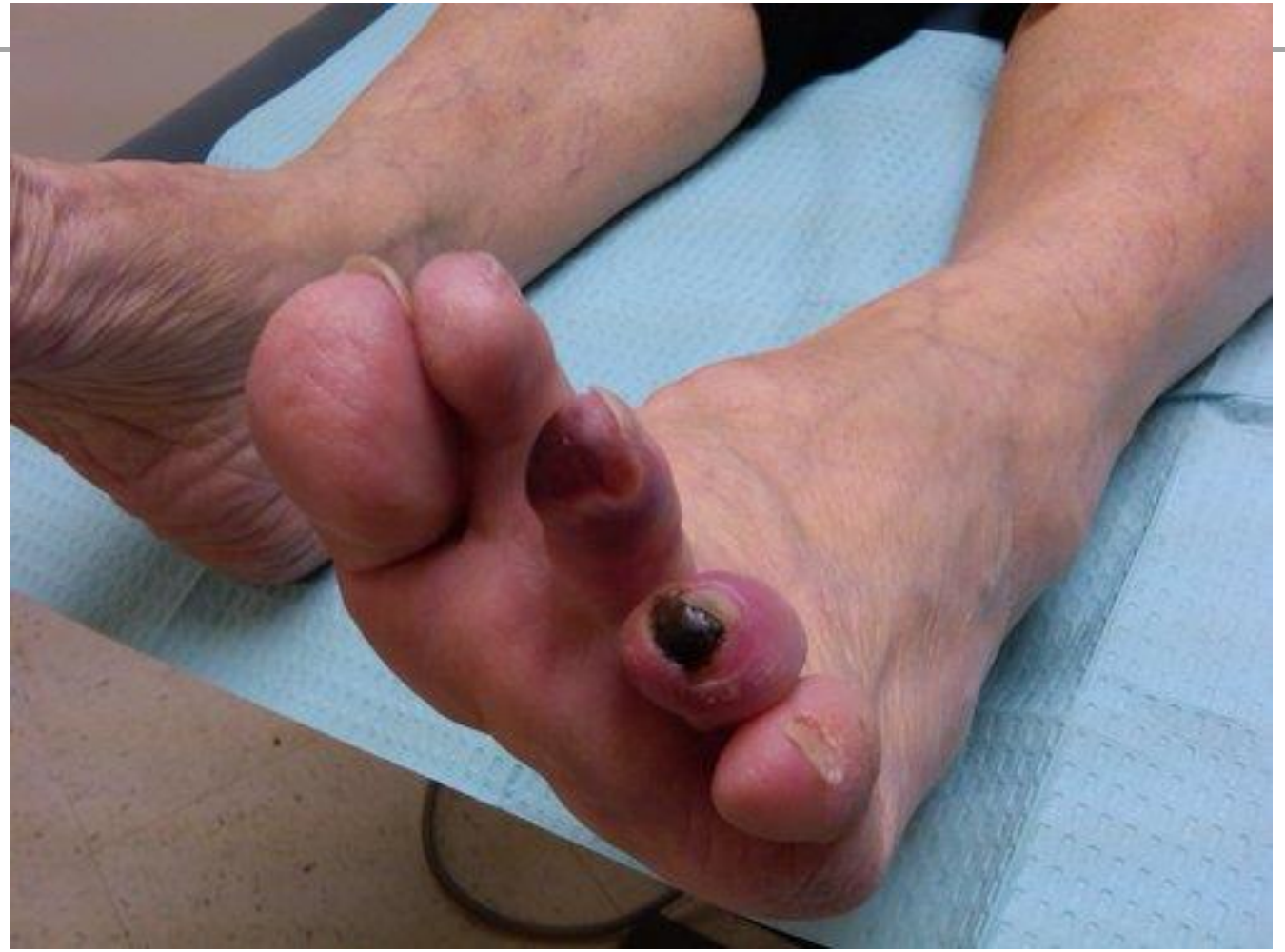
- Arthritis
  - Predominantly affects joints
  - Pain is not rapidly relieved with rest
- Spine disease, radiculopathy, neurogenic claudication
  - Electric shocks, radiating and shooting pains, burning, sensory changes, positional
- Neuropathy
  - Numbness, burning, “pins and needles”, “walking on eggshells”
- Venous disease
  - Dull ache, worse at the end of the day and with prolonged standing, swelling, ulceration on the legs or ankles
- Fibromyalgia
  - Diffuse
- Diabetic foot ulcer
  - Pressure areas of the foot
  - Painless
- Raynaud's
  - Color change
  - Cold exposure

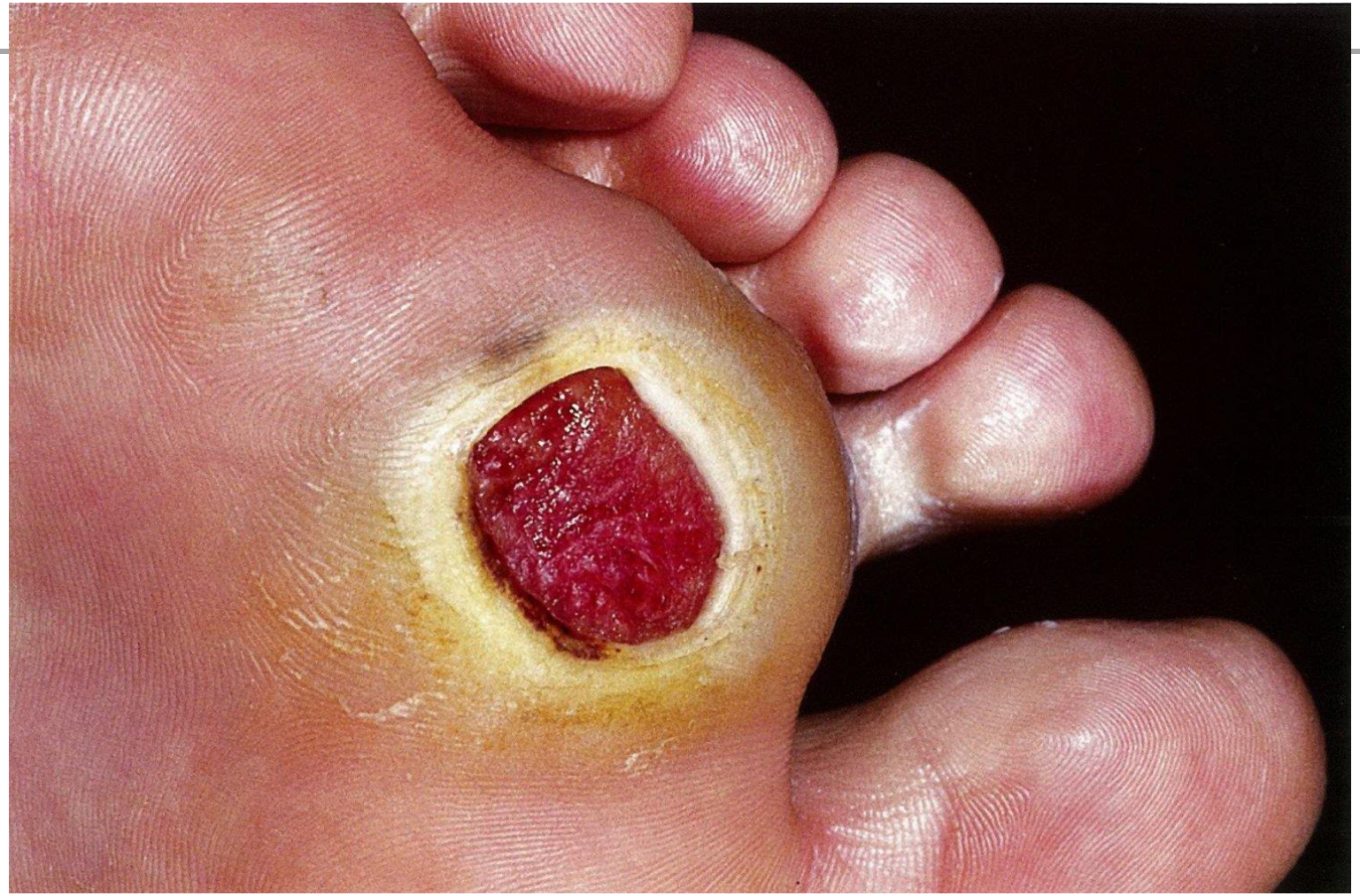
TABLE 19.4 Differential Diagnosis of Common Leg Ulcers

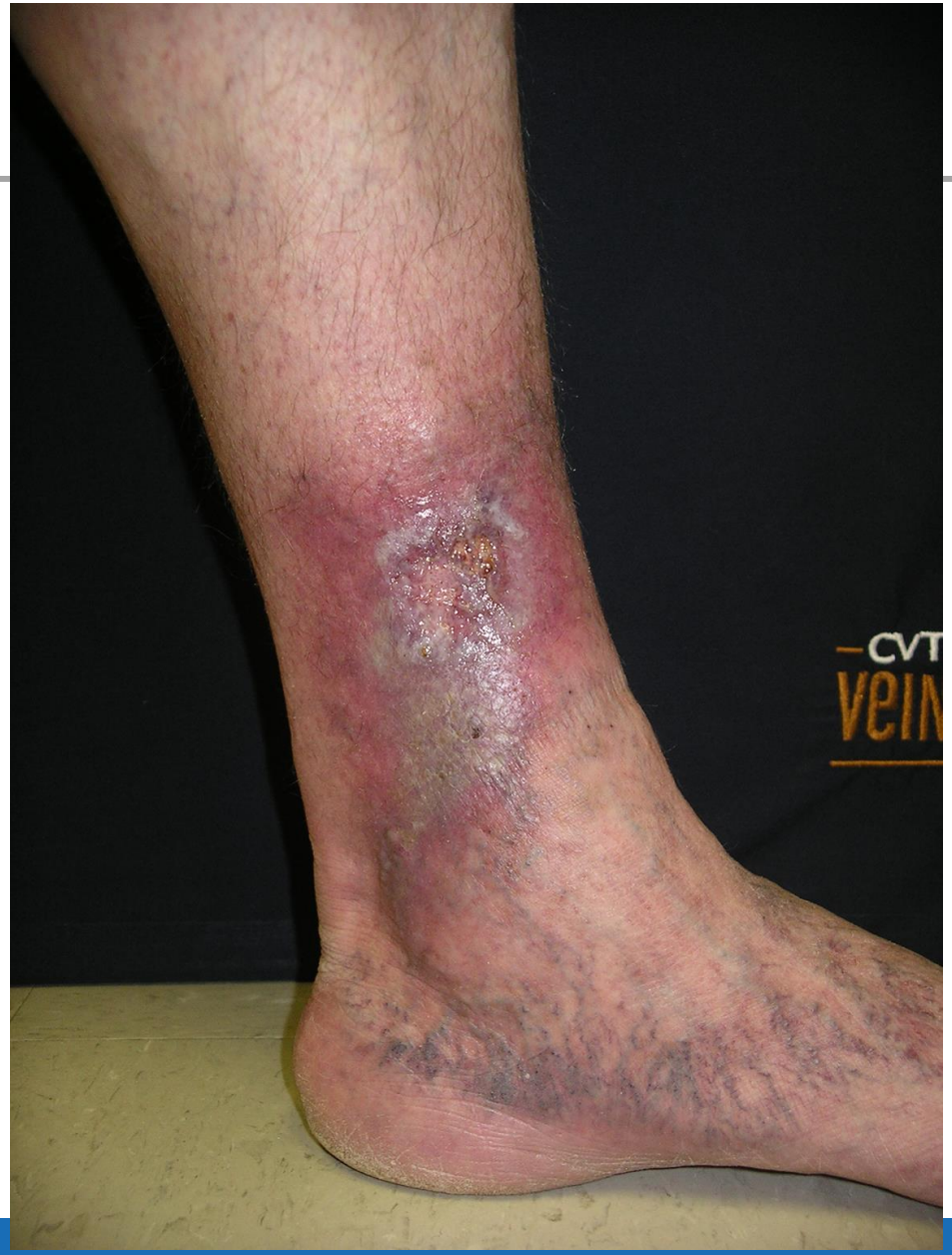
	CHARACTERISTIC					
Type	Usual Location	Pain	Bleeding With Manipulation	Lesion Characteristics	Surrounding Inflammation	Associated Findings
Ischemic ulcer	Distal, on the dorsum of the foot or toes	Severe, particularly at night; relieved by dependency	Little or none	Irregular edge; poor granulation tissue	Absent	Trophic changes of chronic ischemia; absence of pulses
Neurotrophic ulcer	Under calluses or pressure points (e.g., plantar aspect of the first or fifth metatarsophalangeal joint)	None	May be brisk	Punched out, with a deep sinus	Present	Demonstrable neuropathy
Venous stasis ulcer	Lower third of the leg (gaiter area)	Mild; relieved by elevation	Venous ooze	Shallow, irregular shape; granulating base; rounded edges	Present	Lipodermatofibrosis, pigmentation

TABLE 19.5 Characterization of Areas of Ulceration and Tissue Loss

Ulcer Location	Ulcer Etiology	Clinical Appearance	Treatment
Toes, distal forefoot	Arterial insufficiency	Dry/wet gangrene	Revascularization
Weight-bearing surface	Diabetic neuropathy	Callus, "heaped up"	Offloading
Medial malleolus	Venous insufficiency	Beefy red, brown staining of skin	Compression, venous intervention





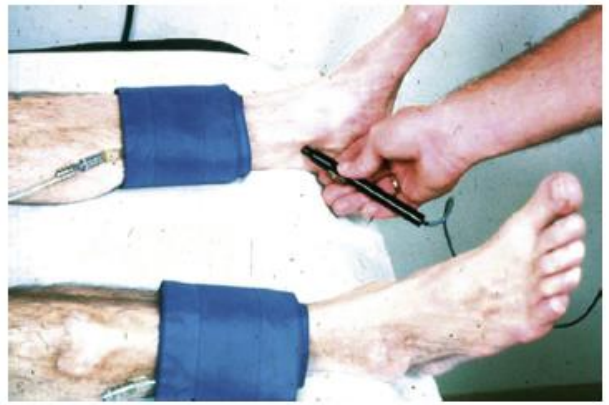


Imaging studies in the diagnosis of PAD

- Physiologic studies vs. anatomic studies
- Non-invasive vascular testing, aka vascular lab testing
  - Ankle brachial index/Pulse volume recording
  - Arterial duplex
- Cross-sectional imaging
  - CTA
  - MRA

ABI/PVR

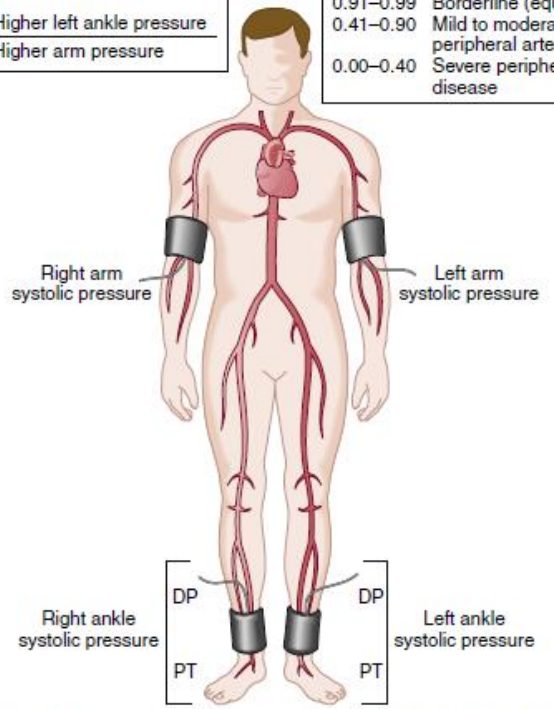
- The best first test for PAD
- Physiologic study
- Provides minimal anatomic information



A

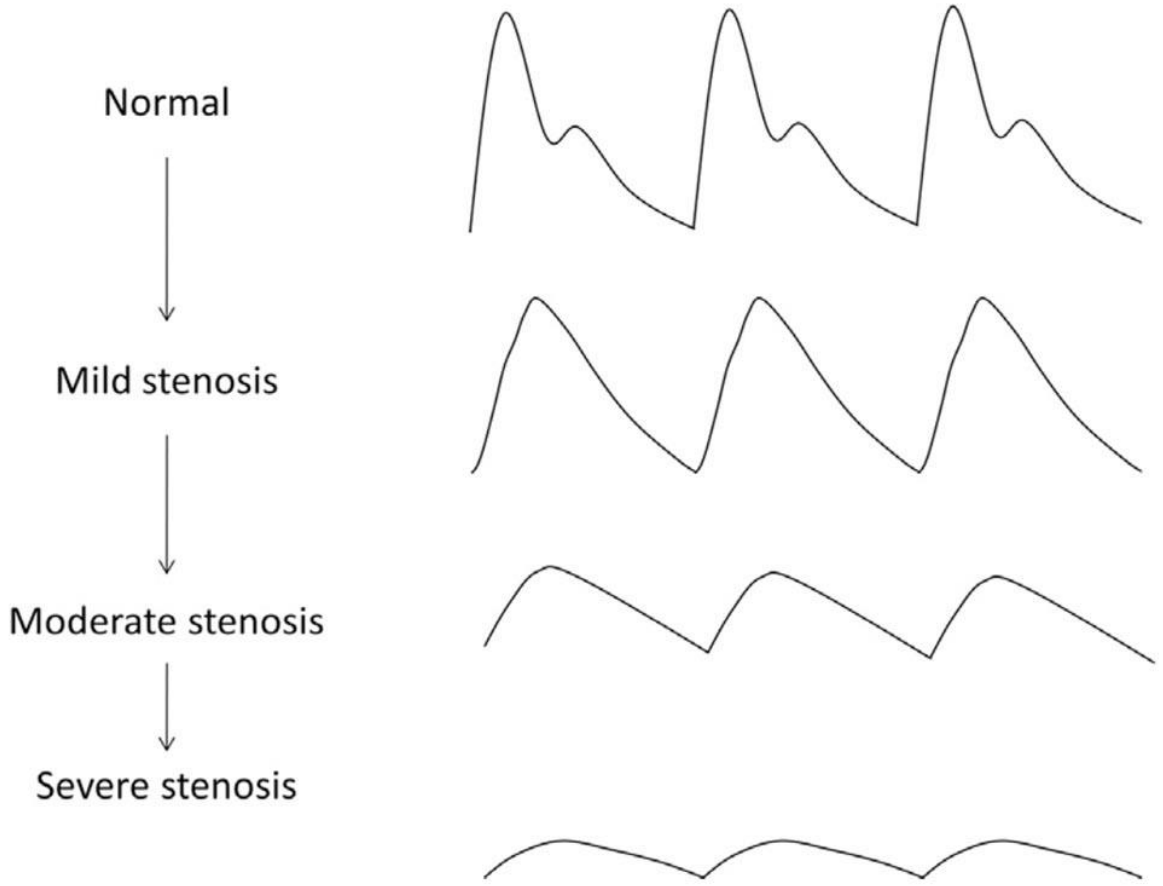
Right ABI	Higher right ankle pressure / Higher arm pressure
Left ABI	Higher left ankle pressure / Higher arm pressure

Interpretation of ABI	
>1.30	Noncompressible
1.00–1.29	Normal
0.91–0.99	Borderline (equivocal)
0.41–0.90	Mild to moderate peripheral arterial disease
0.00–0.40	Severe peripheral arterial disease



B

Figure 21.4 (**A**) Method for measurement of ankle pressure. The cuff is placed just above the ankle, and pressure is measured over the dorsalis pedis and posterior tibial arteries. The higher of the two is used to estimate perfusion pressure at the ankle. (**B**) Method for measurement of the ankle–brachial index (ABI). The higher of the two brachial pressures and the higher of the two ankle pressures are used for calculation of the index. The patient should be supine and resting for at least 5 minutes before the measurements are made. *DP*, dorsalis pedis; *PT*, posterior tibial. (From Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med.* 2001;344:1608–1621.)


Normal
Mild stenosis
Moderate stenosis
Severe stenosis

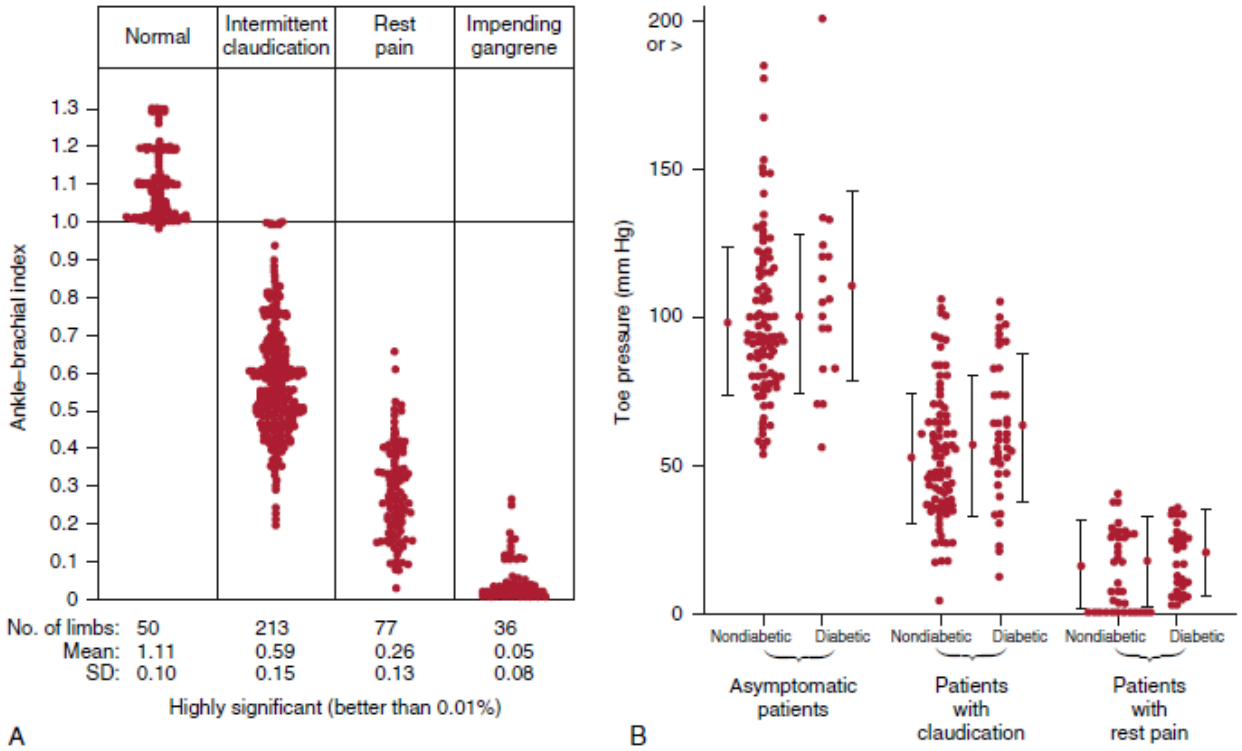


Figure 21.6 (**A**) Relationship of the ankle–brachial index to functional impairment produced by the occlusive process. *SD*, standard deviation. (**B**) Toe blood pressure grouped according to symptoms and the presence of diabetes in patients with arterial disease. Mean and SDs for the nondiabetic and diabetic subgroups and for the two groups combined are indicated by *vertical bars*. ([A] Modified from Yao JST. Hemodynamic studies in peripheral arterial disease. *Br J Surg.* 1970;57:761; [B] Modified from Ramsey DE, Manke DA, Sumner DS. Toe blood pressure: a valuable adjunct to ankle pressure measurement for assessing peripheral arterial disease. *J Cardiovasc Surg.* 1983;24:43–48.)

Recommendations: Diagnosis of peripheral arterial disease (*PAD*)

		Grade	*Level of evidence*
2.1.	We recommend using the ABI as the first-line noninvasive test to establish a diagnosis of PAD in individuals with symptoms or signs suggestive of disease. When the ABI is borderline or normal (>0.9) and symptoms of claudication are suggestive, we recommend an exercise ABI.	1	A
2.2.	We suggest against routine screening for lower extremity PAD in the absence of risk factors, history, signs, or symptoms of PAD.	2	C
2.3.	For asymptomatic individuals who are at elevated risk, such as those aged >70, smokers, diabetic patients, those with an abnormal pulse examination, or other established cardiovascular disease, screening for lower extremity PAD is reasonable if used to improve risk stratification, preventive care, and medical management.	2	C
2.4.	In symptomatic patients who are being considered for revascularization, we suggest using physiologic noninvasive studies, such as segmental pressures and pulse volume recordings, to aid in the quantification of arterial insufficiency and help localize the level of obstruction.	2	C
2.5.	In symptomatic patients in whom revascularization treatment is being considered, we recommend anatomic imaging studies, such as arterial duplex ultrasound, CTA, MRA, and contrast arteriography.	1	B

ABI, Ankle-brachial index; *CTA*, computed tomography angiography; *MRA*, magnetic resonance angiography.

Recommendations for Resting ABI and Additional Physiological Testing
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

Resting ABI

COR	LOE	Recommendations
1	B-NR	1. In patients with history or physical examination findings suggestive of PAD (Table 6), the resting ABI, with or without ankle pulse volume recordings (PVR) and/or Doppler waveforms, is recommended to establish the diagnosis.[1,2]
1	B-NR	2. The resting ABI should be reported as abnormal (ABI ≤0.90), borderline (ABI 0.91-0.99), normal (ABI 1.00-1.40), or noncompressible (ABI >1.40).[3]

Recommendations for Resting ABI and Additional Physiological Testing (Continued)		
COR	**LOE**	**Recommendations**
2a	B-NR	3. In patients at increased risk of PAD (Table 5), screening for PAD with the resting ABI, with or without ankle PVR and/or Doppler waveforms, is reasonable.[4–9]
3: No Benefit	B-NR	4. In patients not at increased risk of PAD (Table 5) and without history or physical examination findings suggestive of PAD (Table 6), screening for PAD with the ABI is not recommended.[10,11]
Exercise ABI and Additional Physiological Testing		
1	B-NR	5. In patients with suspected PAD, toe pressure/toe-brachial index (TBI) with waveforms should be performed when the resting ABI is >1.40 (noncompressible).[12–17]
1	B-NR	6. Patients with suspected chronic symptomatic PAD (ie, exertional nonjoint-related leg symptoms) and normal or borderline resting ABI (>0.90 and ≤1.40, respectively) should undergo exercise treadmill ABI testing to evaluate for PAD.[18,19]
2a	B-NR	7. In patients with PAD and an abnormal resting ABI (≤0.90), the exercise treadmill ABI test can be useful to objectively assess the functional status and walking performance.[20–25]
2a	C-LD	8. In patients with chronic symptomatic PAD, it is reasonable to perform segmental leg pressures with PVR and/or Doppler waveforms in addition to the resting ABI to help delineate the anatomic level of PAD.[26,27]
2a	B-NR	9. In patients with suspected CLTI, it is reasonable to use toe pressure/TBI with waveforms, transcutaneous oxygen pressure ($TcPO_2$), and/or skin perfusion pressure (SPP) in addition to ABI for assessment of arterial perfusion and to establish the diagnosis of CLTI.[13,28–37]

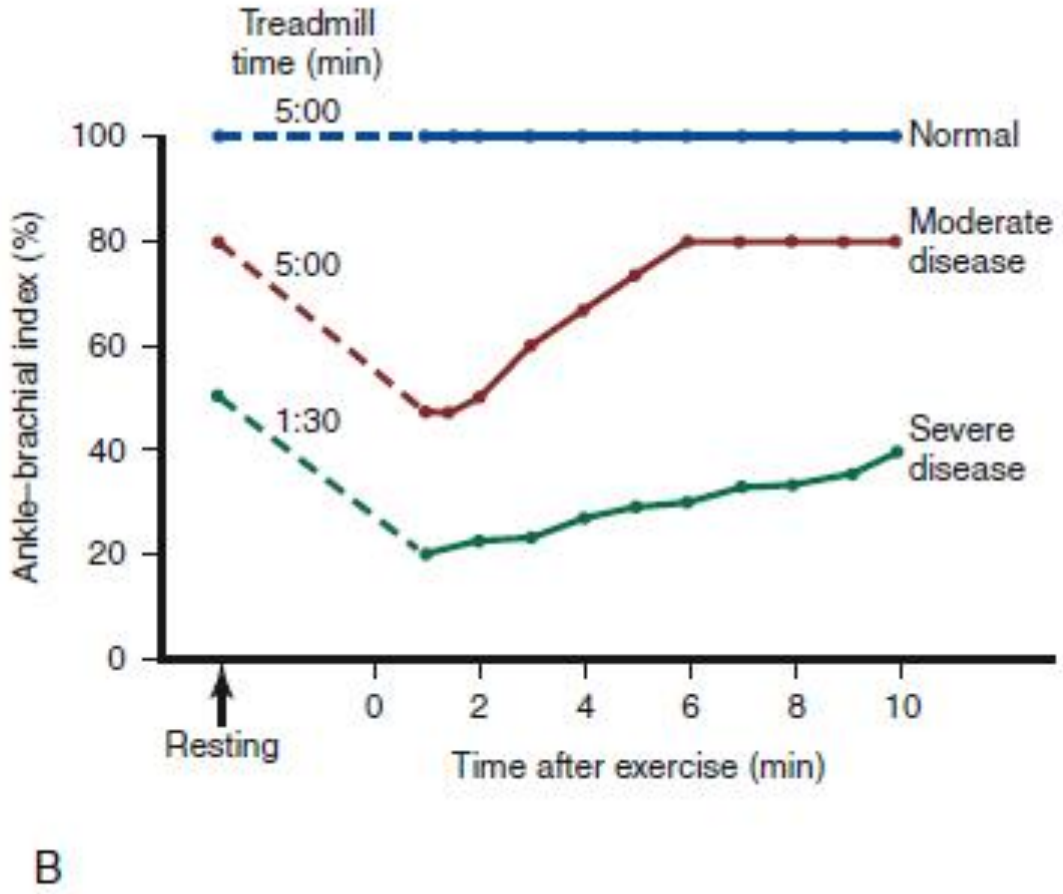


Figure 21.10 (**A**) Patient undergoing a standard treadmill test. Pressure cuffs are left in position at the arms and ankles to allow immediate measurement on stopping. (**B**) Examples of exercise test results in patients with various degrees of peripheral arterial occlusive disease. The resting ankle–brachial indices are noted, followed by similar measurements immediately after exercise and for several minutes thereafter.

Arterial duplex

- Non-invasive anatomic study

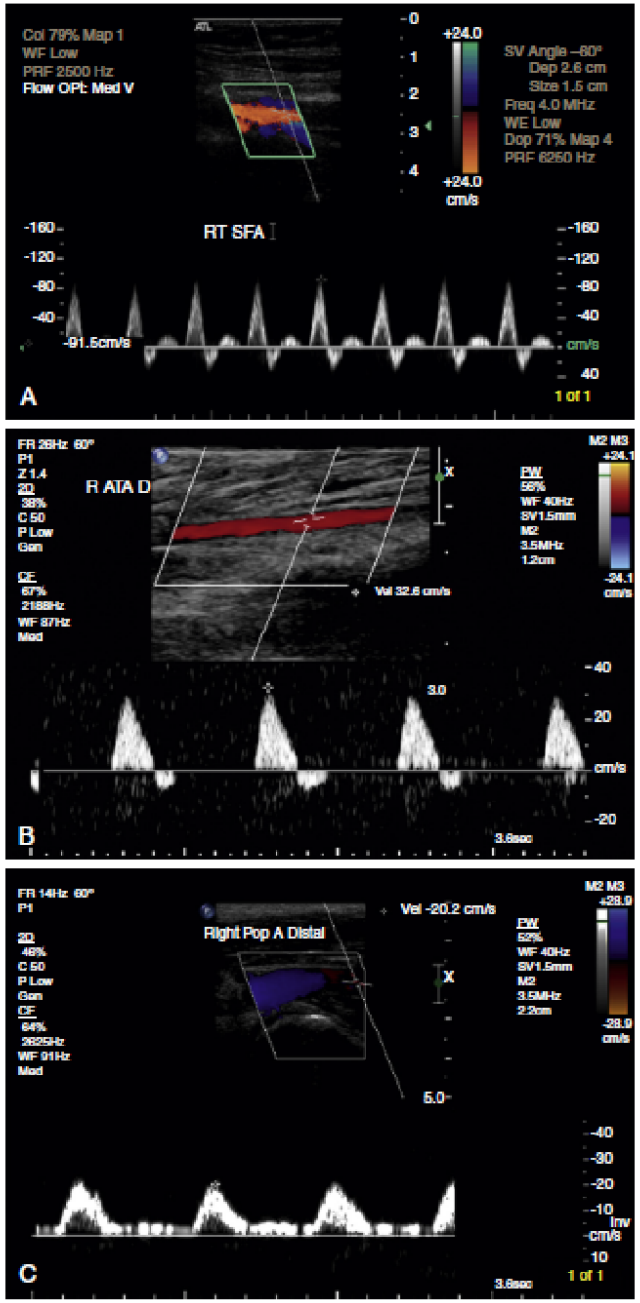


Figure 21.2 Normal and Dampened Velocity Waveforms Obtained with a Duplex Scanner. (**A**) Normal triphasic velocity waveform. (**B**) Biphasic velocity waveform. (**C**) Monophasic velocity waveform.

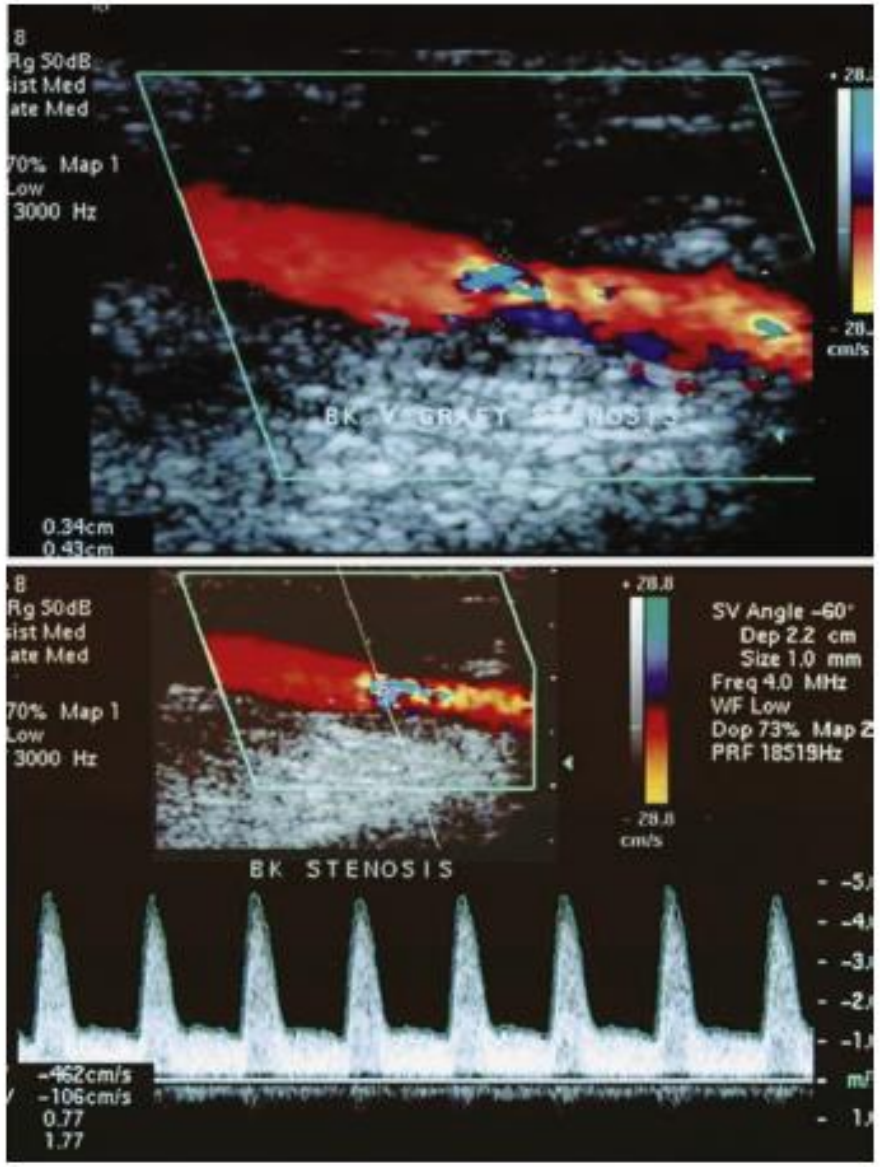


Figure 22.2 Color duplex image and velocity spectra of an arterial vein bypass graft stenosis. *Top image,* Color aliasing occurs at the stenosis when mean velocity is greater than 28 cm/s and extends for several vessel diameters downstream. *Bottom image,* Velocity spectra recording at the stenosis "flow jet" indicates a peak velocity of 426 cm/s and spectral broadening of highly disturbed, turbulent flow.

Cross sectional imaging

- CTA
  - Provides excellent anatomic detail
  - Limited evaluation of distal vessels and those which are heavily calcified

- MRA
  - Limited evaluation of plaque characteristics
  - “Flow study”

Natural History of PAD

- Progression
- Amputation
- Mortality

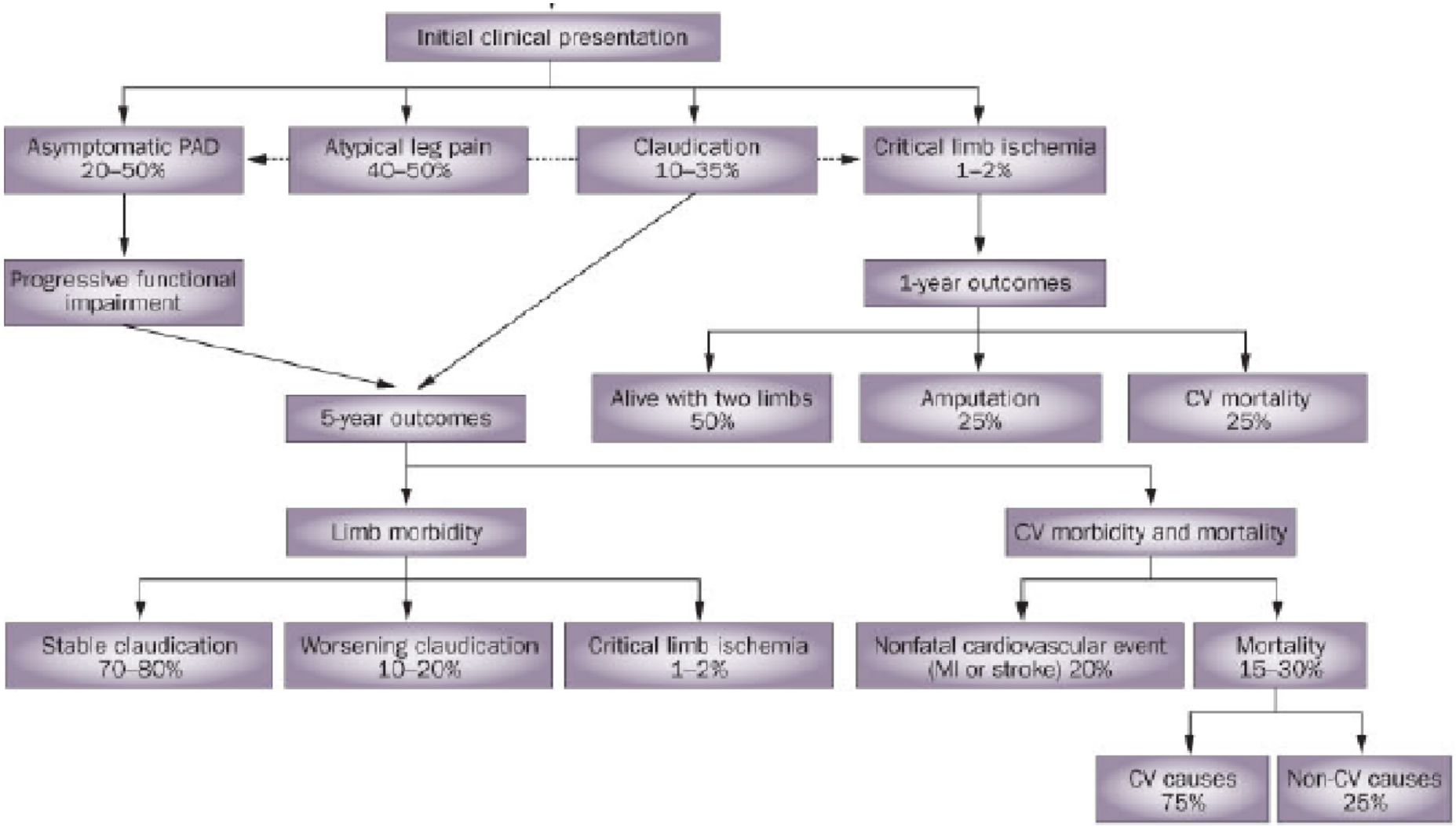
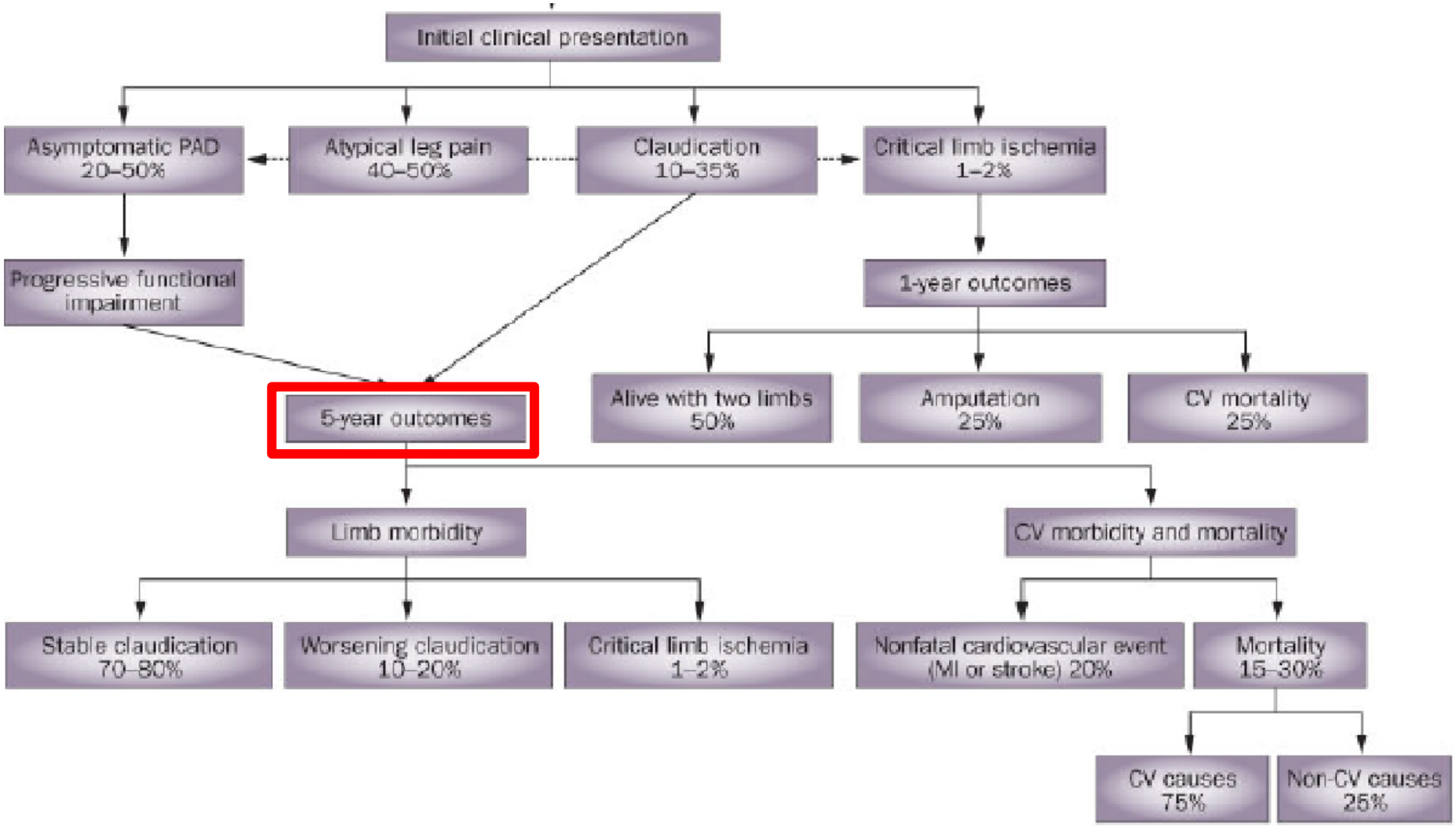


Figure 1 | Clinical presentation, natural history, and outcomes in patients with atherosclerotic PAD. Abbreviations: CV, cardiovascular; MI, myocardial infarction; PAD, peripheral artery disease. Permission obtained from Wolters Kluwer Health © Weitz, J. I. *et al.* Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation* **94** (11), 3026–3049 (1996).



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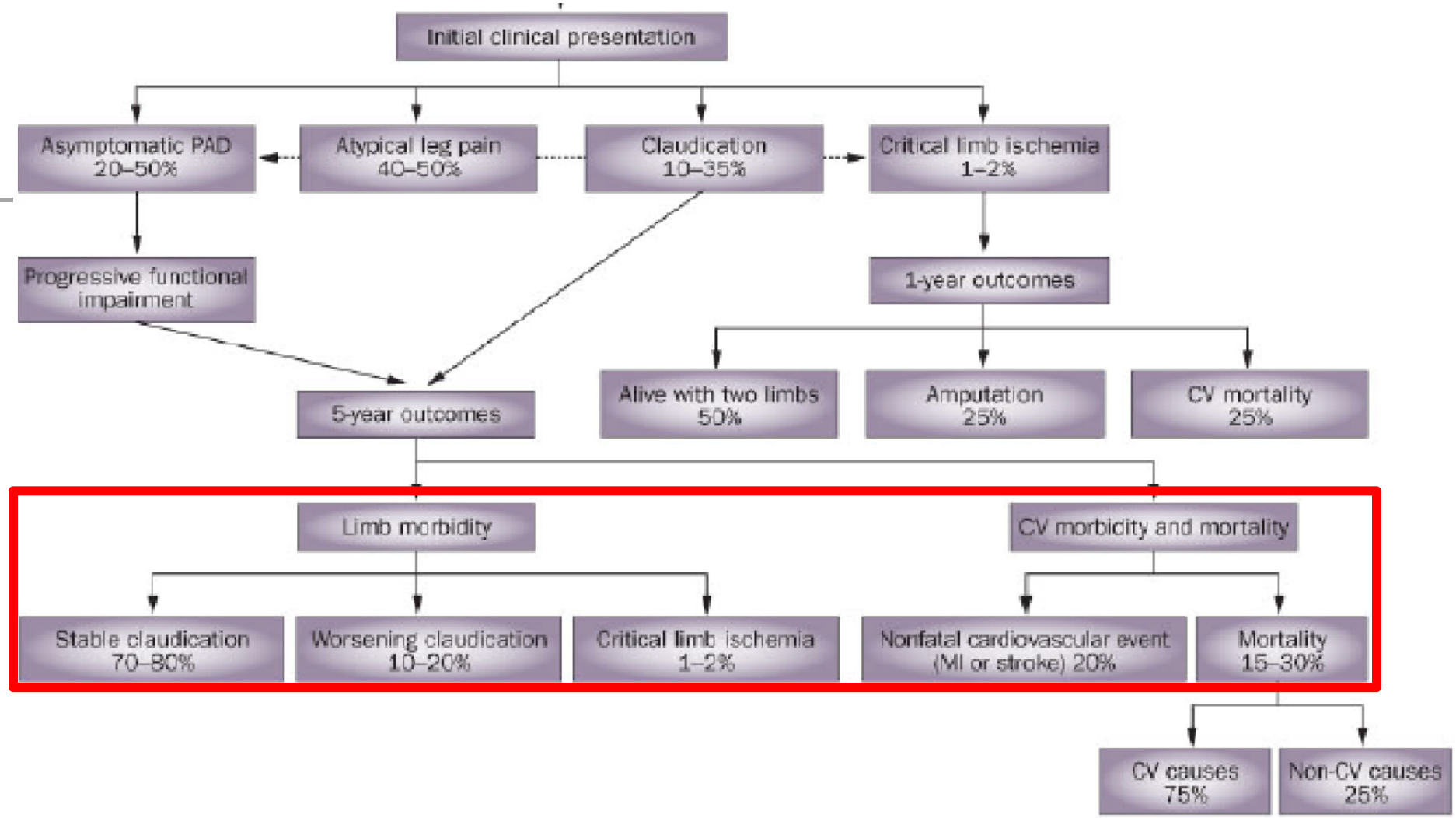

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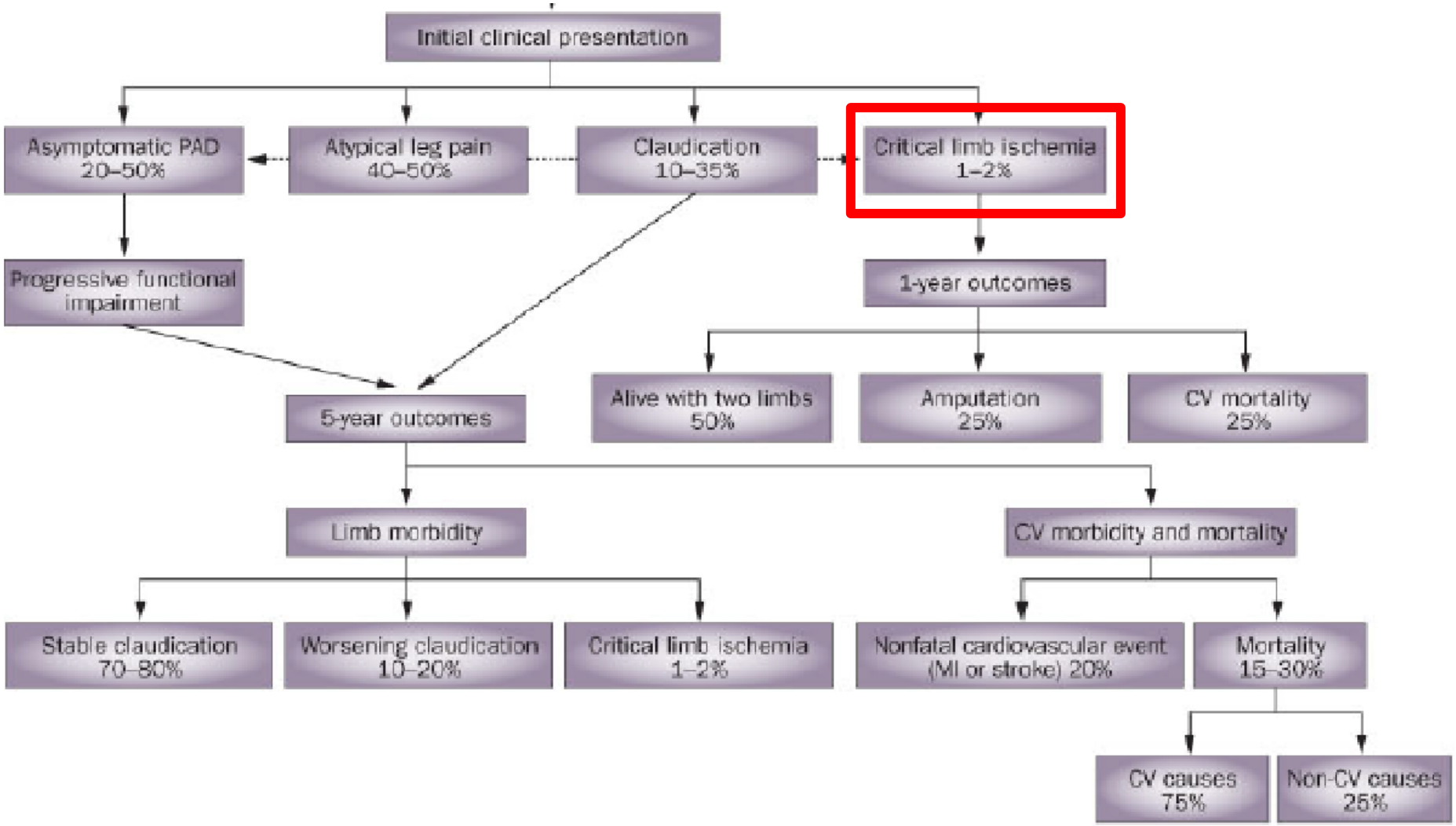

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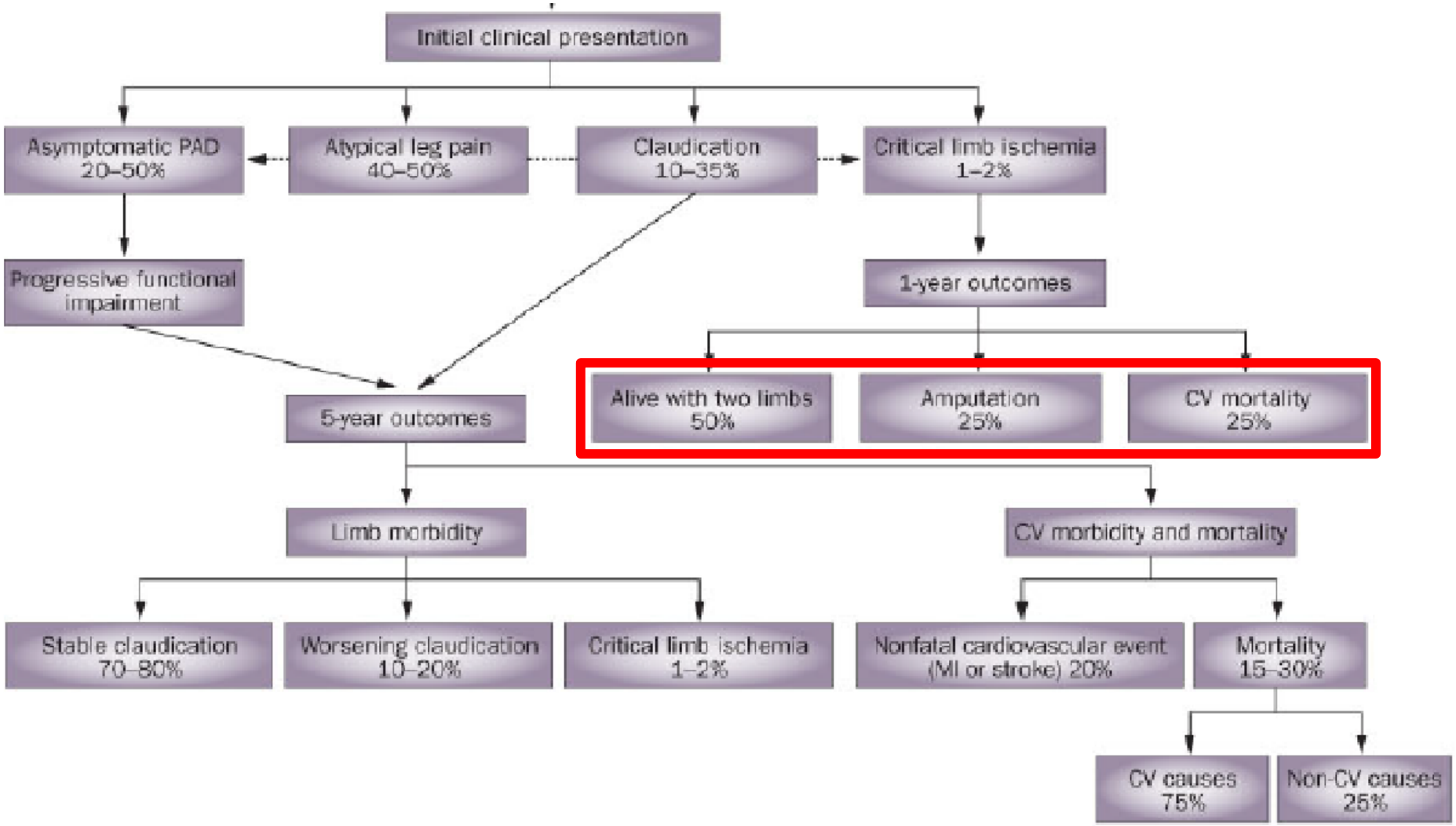

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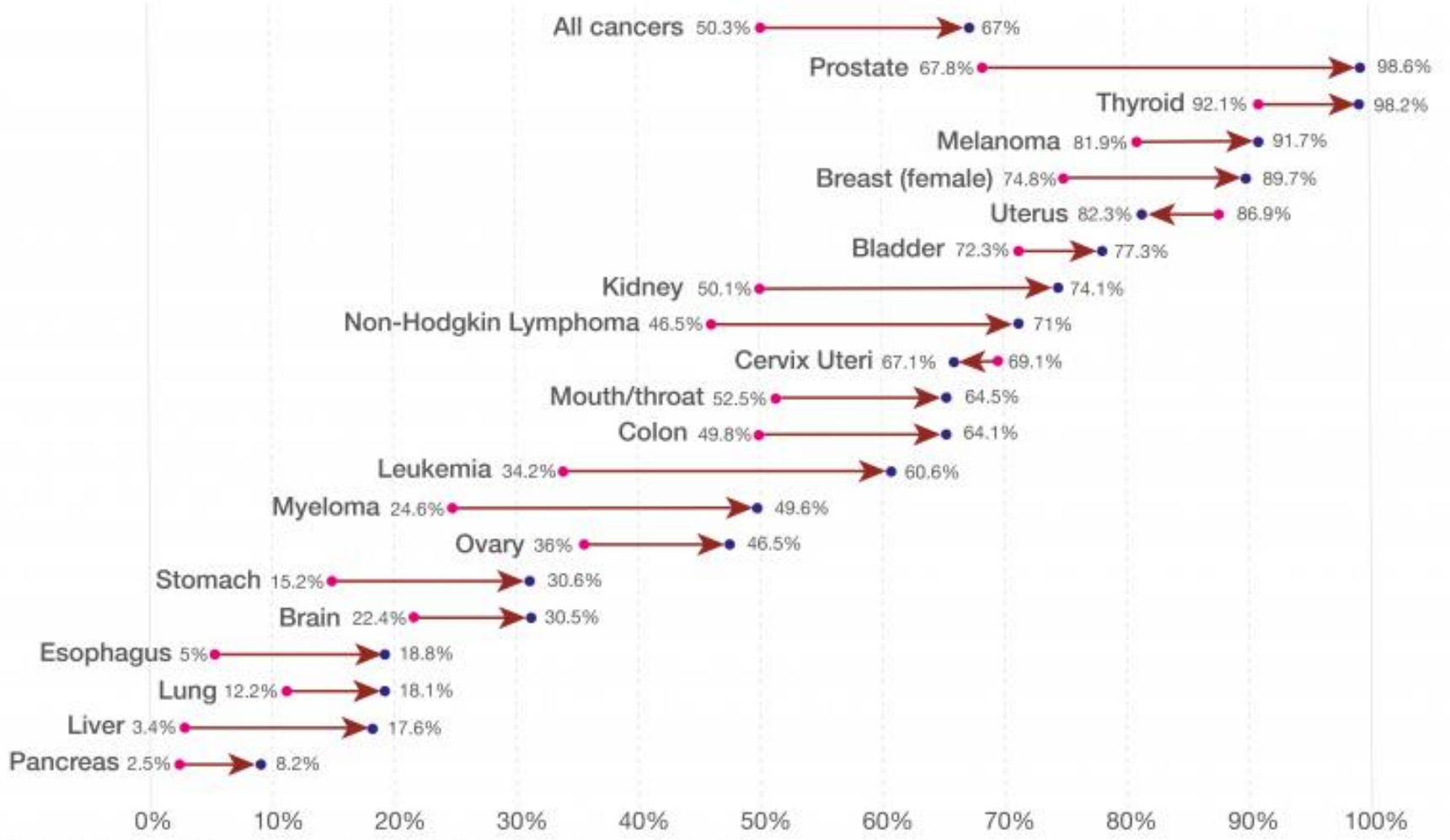
Five-year cancer survival rates in the USA

Average five-year survival rates from common cancer types in the United States, shown as the rate over the period 1970-77 [●] and over the period 2007-2013 [●]: 1970-77 → 2007-2013

This five-year interval indicates the percentage of people who live longer than five years following diagnosis.

Our World in Data



Based on data by Journal of the National Cancer Institute; Surveillance, Epidemiology and End Results Program.
The data visualization is available at OurWorldinData.org. There you find research and more visualizations on this topic.

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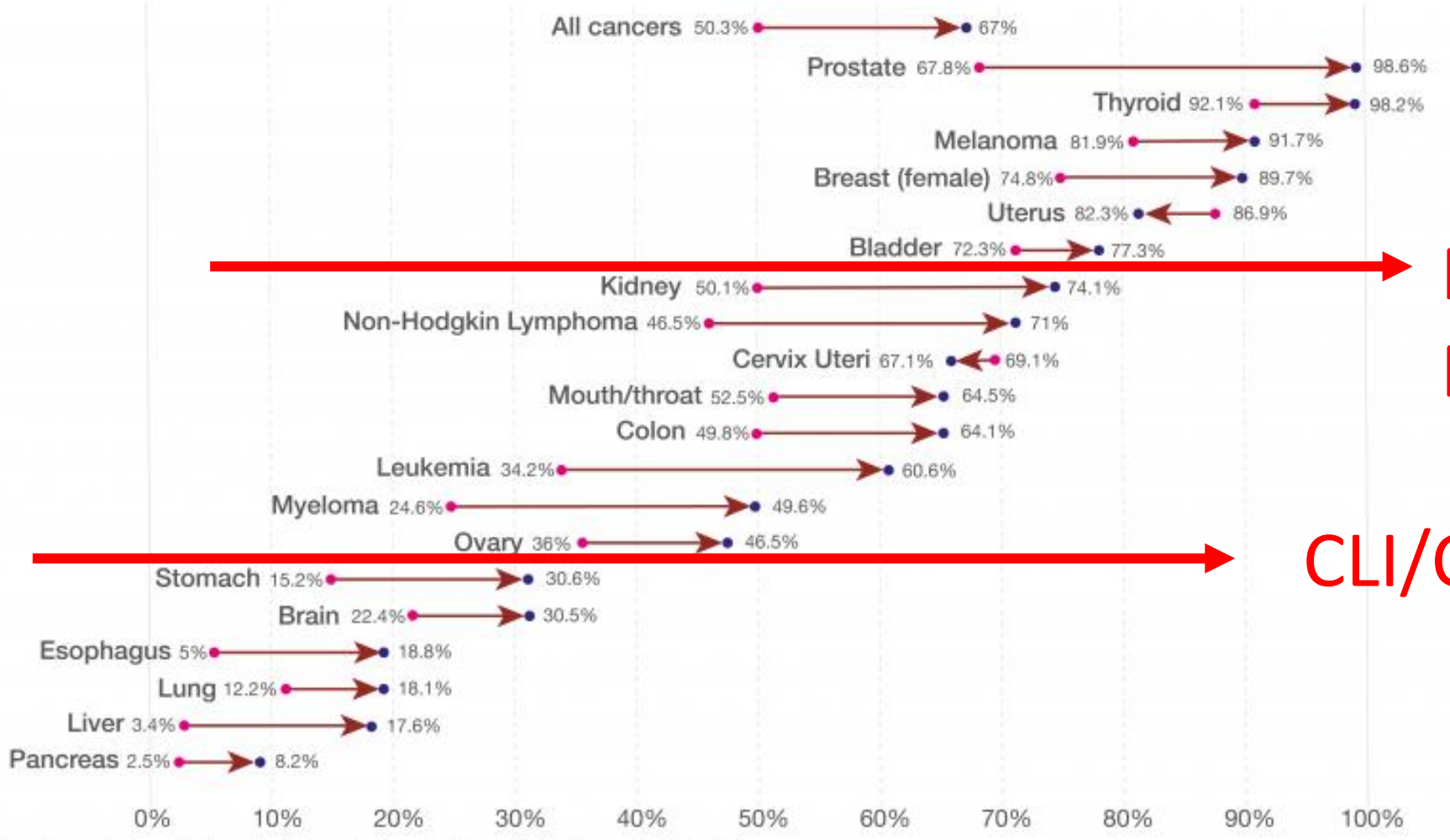

Mild PAD

CLI/CLTI

Based on data by Journal of the National Cancer Institute; Surveillance, Epidemiology and End Results Program.
The data visualization is available at OurWorldinData.org. There you find research and more visualizations on this topic.

Guidelines

- Society for Vascular Surgery
- ACC/AHA
- ESVS

Diagnosis of PAD

Recommendations: Diagnosis of peripheral arterial disease (*PAD*)

		Grade	*Level of evidence*
2.1.	We recommend using the ABI as the first-line noninvasive test to establish a diagnosis of PAD in individuals with symptoms or signs suggestive of disease. When the ABI is borderline or normal (>0.9) and symptoms of claudication are suggestive, we recommend an exercise ABI.	1	A
2.2.	We suggest against routine screening for lower extremity PAD in the absence of risk factors, history, signs, or symptoms of PAD.	2	C
2.3.	For asymptomatic individuals who are at elevated risk, such as those aged >70, smokers, diabetic patients, those with an abnormal pulse examination, or other established cardiovascular disease, screening for lower extremity PAD is reasonable if used to improve risk stratification, preventive care, and medical management.	2	C
2.4.	In symptomatic patients who are being considered for revascularization, we suggest using physiologic noninvasive studies, such as segmental pressures and pulse volume recordings, to aid in the quantification of arterial insufficiency and help localize the level of obstruction.	2	C
2.5.	In symptomatic patients in whom revascularization treatment is being considered, we recommend anatomic imaging studies, such as arterial duplex ultrasound, CTA, MRA, and contrast arteriography.	1	B

ABI, Ankle-brachial index; *CTA*, computed tomography angiography; *MRA*, magnetic resonance angiography.

Recommendations for Resting ABI and Additional Physiological Testing
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

Resting ABI

COR	LOE	Recommendations
1	B-NR	1. In patients with history or physical examination findings suggestive of PAD (Table 6), the resting ABI, with or without ankle pulse volume recordings (PVR) and/or Doppler waveforms, is recommended to establish the diagnosis.[1,2]
1	B-NR	2. The resting ABI should be reported as abnormal (ABI ≤0.90), borderline (ABI 0.91-0.99), normal (ABI 1.00-1.40), or noncompressible (ABI >1.40).[3]

Initial therapy for PAD

- The most important element of treatment for patients with PAD is reducing their risk of death due to cardiovascular causes.

Initial therapy for PAD

- Risk factor reduction
  - Smoking cessation
  - Control of hyperlipidemia
  - Control of HTN
  - Control of Diabetes
- Medical therapy
  - Aspirin
  - Statins
  - Cilostazol
- Structured exercise

5.4. Smoking Cessation for PAD

Recommendations for Smoking Cessation for PAD Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	**LOE**	**Recommendations**
1	A	1. Patients with PAD who smoke cigarettes or use any other forms of tobacco should be advised at every visit to quit or encouraged to maintain cessation.[1–3]
1	A	2. Patients with PAD who smoke cigarettes or use any other forms of tobacco should be assisted in developing a plan for quitting that includes pharmacotherapy (ie, varenicline, bupropion, and/or nicotine replacement therapies) combined with counseling, and/or referral to a smoking cessation program.[4–9]
1	B-NR	3. Patients with PAD should be advised to avoid exposure to secondhand tobacco smoke in all indoor or enclosed spaces, including work, home, transportation vehicles, and public places.[10–14]

5.2. Lipid-Lowering Therapy for PAD

Recommendations for Lipid-Lowering Therapy for PAD
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	A	1. In patients with PAD, treatment with high-intensity statin therapy is indicated, with an aim of achieving a ≥50% reduction in low-density lipoprotein cholesterol (LDL-C) level.[1–3]
2a	B-R	2. In patients with PAD who are on maximally tolerated statin therapy and have an LDL-C level of ≥70 mg/dL, it is reasonable to add PCSK9 inhibitor therapy.[1,4–6]
2a	B-R	3. In patients with PAD who are on maximally tolerated statin therapy and have an LDL-C level of ≥70 mg/dL, it is reasonable to add ezetimibe therapy.[1,7]

Table 11. High-, Moderate-, and Low-Intensity Statin Therapy*

	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering†	≥50%	30%-49%	<30%
Statins	Atorvastatin 40–80 mg Rosuvastatin 20–40 mg	Atorvastatin 10–20 mg Rosuvastatin 5–10 mg Simvastatin 20–40 mg‡ Pravastatin 40–80 mg Lovastatin 40–80 mg Fluvastatin XL 80 mg Fluvastatin 40 mg twice daily Pitavastatin 1–4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg

Percent LDL-C reductions with the statin medications used in clinical practice (atorvastatin, rosuvastatin, simvastatin) were estimated using the median reduction in LDL-C from the VOYAGER database.[16] Reductions in LDL-C for other statin medications (fluvastatin, lovastatin, pitavastatin, pravastatin) were identified according to FDA-approved product labeling in adults with dyslipidemia, primary hypercholesterolemia, and mixed dyslipidemia.[17]

FDA indicates US Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; and VOYAGER PAD, Vascular Outcomes Study of ASA [acetylsalicylic acid] Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease. Modified with permission from Grundy et al.[1] Copyright 2018 American Heart Association, Inc., and American College of Cardiology Foundation.

*Percent reductions are estimates from data across large populations. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice.[16]

†LDL-C lowering that should occur with the dosage listed below each intensity.

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.

Effect of alirocumab on cardiovascular outcomes after acute coronary syndromes according to age: an ODYSSEY OUTCOMES trial analysis

Peter R. Sinnaeve [1]*, Gregory G. Schwartz [2], Daniel M. Wojdyla [3], Marco Alings [4], Deepak L. Bhatt [5], Vera A. Bittner [6], Chern-En Chiang [7], Roger M. Correa Flores [8], Rafael Diaz [9], Maria Dorobantu [10], Shaun G. Goodman [11,12], J. Wouter Jukema [13], Yong-Un Kim [14], Robert Pordy [15], Matthew T. Roe [3], Rody G. Sy [16], Michael Szarek [17], Harvey D. White [18], Andreas M. Zeiher [19], and Ph. Gabriel Steg [20,21]; for the ODYSSEY OUTCOMES Investigators†

The NEW ENGLAND JOURNAL of MEDICINE

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Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

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5.3. Antihypertensive Therapy for PAD

Recommendations for Antihypertensive Therapy for PAD
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	A	1. In patients with PAD and hypertension, antihypertensive therapy should be administered to reduce the risk of MACE.[1–5]
1	B-R	2. In patients with PAD and hypertension, a systolic blood pressure (SBP) goal of <130 mm Hg and a diastolic blood pressure target of <80 mm Hg is recommended.[5–9]
1	B-R	3. In patients with PAD and hypertension, the selective use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers is recommended to reduce the risk of MACE.[10–12]

5.5. Diabetes Management for PAD

Recommendations for Diabetes Management for PAD
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	A	1. In patients with PAD and type 2 diabetes, use of glucagon-like peptide–1 agonists (liraglutide and semaglutide) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, and empagliflozin) are effective to reduce the risk of MACE.[1–12]
1	C-EO	2. In patients with PAD, management of diabetes should be coordinated among members of the health care team.
2b	B-NR	3. In patients with PAD and diabetes, glycemic control may be beneficial to improve limb outcomes.[13–16]

Recommendations: Medical treatment for intermittent claudication (*IC*)

		Grade	*Level of evidence*
4.1.	We recommend multidisciplinary comprehensive smoking cessation interventions for patients with IC (repeatedly until tobacco use has stopped).	1	A
4.2.	We recommend statin therapy in patients with symptomatic PAD.	1	A
4.3.	We recommend optimizing diabetes control (hemoglobin A_{1c} goal of <7.0%) in patients with IC if this goal can be achieved without hypoglycemia.	1	B
4.4.	We recommend the use of indicated β-blockers (eg, for hypertension, cardiac indications) in patients with IC. There is no evidence supporting concerns about worsening claudication symptoms.	1	B
4.5.	In patients with IC due to atherosclerosis, we recommend antiplatelet therapy with aspirin (75-325 mg daily).	1	A
4.6.	We recommend clopidogrel in doses of 75 mg daily as an effective alternative to aspirin for antiplatelet therapy in patients with IC.	1	B
4.7.	In patients with IC due to atherosclerosis, we suggest against using warfarin for the sole indication of reducing the risk of adverse cardiovascular events or vascular occlusions.	1	C
4.8.	We suggest against using folic acid and vitamin B_{12} supplements as a treatment of IC.	2	C
4.9.	In patients with IC who do not have congestive heart failure, we suggest a 3-month trial of cilostazol (100 mg twice daily) to improve pain-free walking.	2	A
4.10.	In patients with IC who cannot tolerate or have contraindications for cilostazol, we suggest a trial of pentoxifylline (400 mg thrice daily) to improve pain-free walking.	2	B

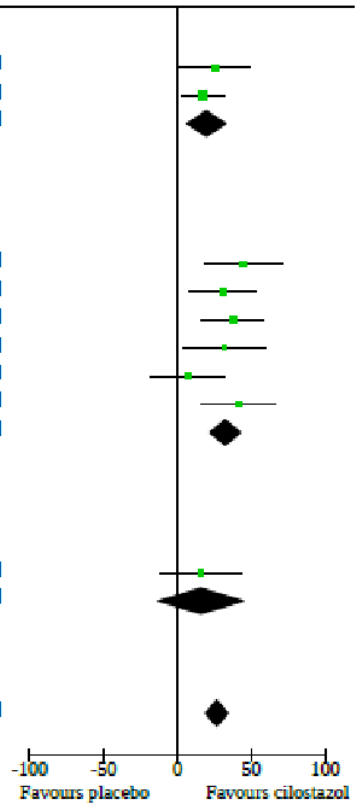
ACEI, Angiotensin-converting enzyme inhibitor; *PAD*, peripheral arterial disease.
A recommendation (4.11) for using ramipril in IC was originally made but subsequently deleted (see Supplementary Material on page 41S.e1, online only).

5.7. Medications for Leg Symptoms in Chronic Symptomatic PAD

Recommendations for Medications for Leg Symptoms in Chronic Symptomatic PAD Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	**LOE**	**Recommendations**
Cilostazol		
1	A	1. In patients with claudication, cilostazol is recommended to improve leg symptoms and increase walking distance.[1–4]
2b	B-R	2. In patients with PAD, cilostazol may be useful to reduce restenosis after endovascular therapy for femoropopliteal disease.[5–7]
3: Harm	C-LD	3. In patients with PAD and congestive heart failure of any severity, cilostazol should not be administered.[8–10]
Pentoxifylline		
3: No Benefit	B-R	4. In patients with chronic symptomatic PAD, pentoxifylline is not recommended for treatment of claudication.[11,12]
Chelation Therapy		
3: No Benefit	B-R	5. In patients with chronic symptomatic PAD, chelation therapy is not recommended for treatment of claudication.[13]

Analysis 1.1. Comparison 1: Cilostazol versus placebo, Outcome 1: Initial claudication distance (ICD)

Study or Subgroup	Cilostazol Mean	Cilostazol SD	Cilostazol Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Cilostazol 50 mg twice daily								
Beebe 1999	48.6	93.13	139	23.1	76.9	70	10.1%	25.50 [1.75 , 49.25]
Strandness 2002	34.3	60.6	128	17.2	43.6	63	25.3%	17.10 [2.06 , 32.14]
Subtotal (95% CI)			**267**			**133**	**35.4%**	**19.50 [6.80 , 32.21]**
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%								
Test for overall effect: Z = 3.01 (P = 0.003)								
1.1.2 Cilostazol 100 mg twice daily								
Beebe 1999	67.5	130.4	140	23.04	63.78	70	8.3%	44.46 [18.20 , 70.72]
Dawson 1998	38.9	68.34	52	8.3	33.5	25	11.0%	30.60 [7.85 , 53.35]
Dawson 2000	93.6	127.4	205	56.5	93.1	226	12.7%	37.10 [15.85 , 58.35]
Money 1998	85.9	108	119	54.2	114	120	7.2%	31.70 [3.55 , 59.85]
Otsuka Study 21-95-201	41.4	63.2	60	34.4	57.3	33	9.0%	7.00 [-18.26 , 32.26]
Strandness 2002	58.5	128.3	124	17.2	43.6	62	9.1%	41.30 [16.25 , 66.35]
Subtotal (95% CI)			**700**			**536**	**57.3%**	**32.19 [22.20 , 42.18]**
Heterogeneity: Chi² = 5.39, df = 5 (P = 0.37); I² = 7%								
Test for overall effect: Z = 6.32 (P < 0.00001)								
1.1.3 Cilostazol 150 mg twice daily								
Otsuka Study 21-95-201	50.1	70.3	53	34.4	60.1	33	7.3%	15.70 [-12.20 , 43.60]
Subtotal (95% CI)			**53**			**33**	**7.3%**	**15.70 [-12.20 , 43.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.10 (P = 0.27)								
Total (95% CI)			**1020**			**702**	**100.0%**	**26.49 [18.93 , 34.05]**
Heterogeneity: Chi² = 8.72, df = 8 (P = 0.37); I² = 8%								
Test for overall effect: Z = 6.87 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.99, df = 2 (P = 0.22), I² = 33.0%								



Recommendations for Exercise Therapy for PAD
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	A	1. In patients with chronic symptomatic PAD, SET is recommended to improve walking performance, functional status, and QOL.[7,16–28]
1	A	2. In patients with chronic symptomatic PAD, a structured community-based exercise program with behavioral change techniques is effective to improve walking performance, functional status, and QOL.[5–15]
1	A	3. In patients who have undergone revascularization for chronic symptomatic PAD, SET after revascularization is effective to improve walking performance, functional status, and QOL.[29–39]
1	B-R	4. In patients with functionally limiting claudication, SET or a structured community-based exercise program should be offered as an initial treatment option.[17,18,25,40]
2a	A	5. In patients with chronic symptomatic PAD, alternative programs of nonwalking structured exercise therapy (eg, arm ergometry, recumbent stepping) can be beneficial to improve walking performance, functional status, and QOL.[19,20,41–47]
2b	B-R	6. In patients with chronic symptomatic PAD, the usefulness of structured walking exercise therapy that avoids moderate to severe ischemic symptoms is uncertain.[5,45,48]
2b	B-R	7. In patients with chronic symptomatic PAD, the usefulness of unstructured exercise to improve walking performance, functional status, and QOL is uncertain.[10,12,28]

Recommendations: Exercise therapy

		Grade	*Level of evidence*
4.12.	We recommend as first-line therapy a supervised exercise program consisting of walking a minimum of three times per week (30-60 min/session) for at least 12 weeks to all suitable patients with IC.	1	A
4.13.	We recommend home-based exercise, with a goal of at least 30 minutes of walking three to five times per week when a supervised exercise program is unavailable or for long-term benefit after a supervised exercise program is completed.	1	B
4.14.	In patients who have undergone revascularization therapy for IC, we recommend exercise (either supervised or home based) for adjunctive functional benefits.	1	B
4.15.	We recommend that patients with IC be followed up annually to assess compliance with lifestyle measures (smoking cessation, exercise) and medical therapies as well as to determine if there is evidence of progression in symptoms or signs of PAD. Yearly ABI testing may be of value to provide objective evidence of disease progression.	1	C

ABI, Ankle-brachial index; *IC*, intermittent claudication; *PAD*, peripheral arterial disease.

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Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

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The NEW ENGLAND

Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial

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ORIGINAL ARTICLE

Rivaroxa peripher randomi

*Sonia S Anand, Jackie Katalin Keltai, Aldo P Dragos Vinereanu, Na Alvaro A Avezum, Ed Investigators**

Rivaroxaban in Peripheral Artery Disease after Revascularization

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Peripheral arterial disease				0.61
Yes	126/2492 (5.1)	174/2504 (6.9)	0.72 (0.57–0.90)	
No	253/6660 (3.8)	322/6622 (4.9)	0.77 (0.66–0.91)	

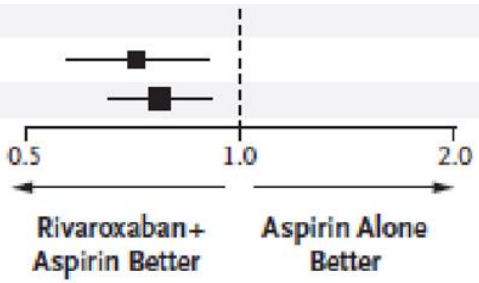

Figure 2. Subgroup Analyses for the Primary Outcome for the Comparison of Rivaroxaban plus Aspirin with Aspirin Alone.

The size of each box is proportional to the number of events. Arrows indicate that the limits of the confidence interval are not shown. The subgroup labeled "Western Europe" also includes participants in Israel, Australia, and South Africa. GFR denotes glomerular filtration rate.

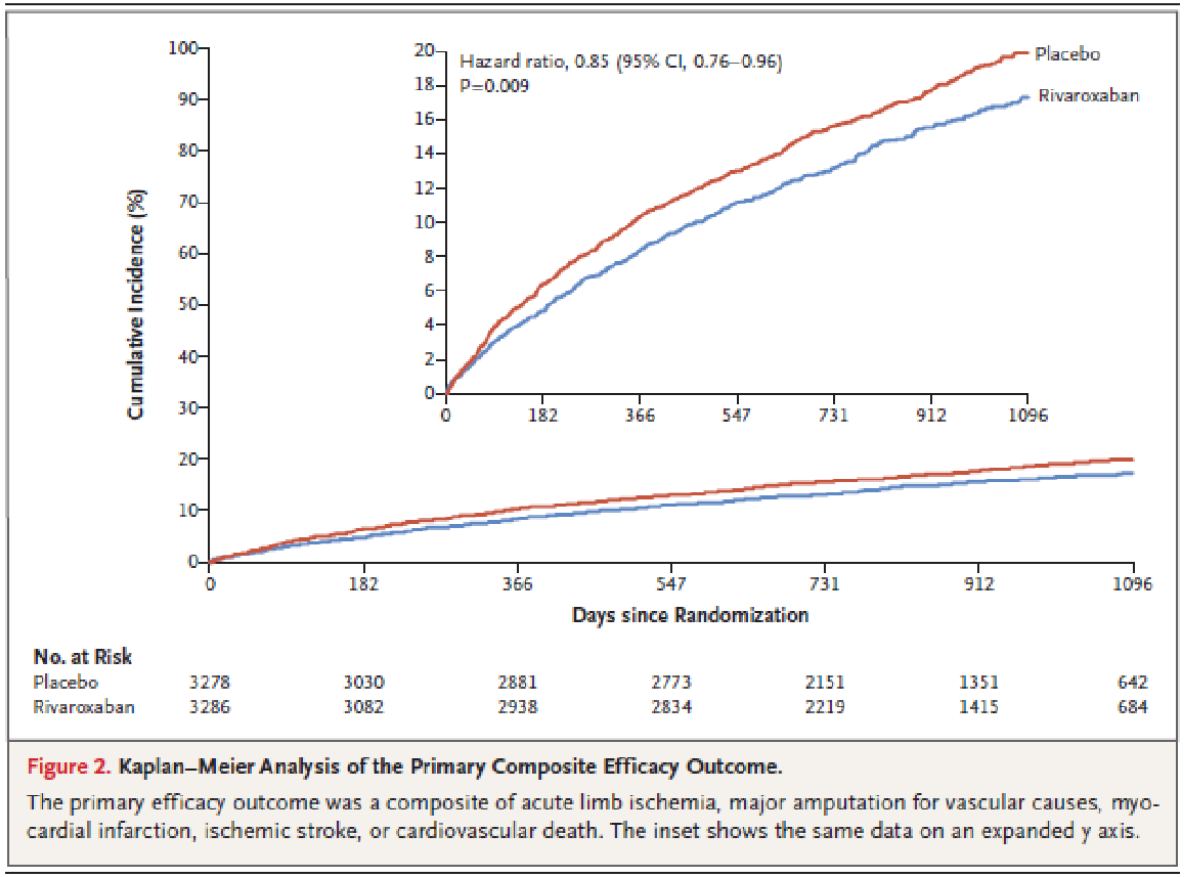

Figure 2. Kaplan–Meier Analysis of the Primary Composite Efficacy Outcome.

The primary efficacy outcome was a composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or cardiovascular death. The inset shows the same data on an expanded y axis.

Table 3. Safety Outcomes.*

Outcome	Rivaroxaban (N=3256)		Placebo (N=3248)		Hazard Ratio (95% CI)	P Value
	Patients with Event	K–M Estimate at 3 Yr	Patients with Event	K-M Estimate at 3 Yr		
	no. (%)	%	*no. (%)*	%		
Principal safety outcome: TIMI major bleeding	62 (1.90)	2.65	44 (1.35)	1.87	1.43 (0.97–2.10)	0.07
Intracranial hemorrhage	13 (0.40)	0.60	17 (0.52)	0.90	0.78 (0.38–1.61)	
Fatal bleeding	6 (0.18)	0.21	6 (0.18)	0.21	1.02 (0.33–3.15)	
Intracranial or fatal bleeding	17 (0.52)	0.74	19 (0.58)	0.97	0.91 (0.47–1.76)	
Secondary safety outcomes						
ISTH major bleeding	140 (4.30)	5.94	100 (3.08)	4.06	1.42 (1.10–1.84)	0.007
BARC major bleeding†	93 (2.86)	3.86	73 (2.25)	2.92	1.29 (0.95–1.76)	0.10

* Safety analyses included all patients who underwent randomization and had received at least one dose of trial medication. ISTH denotes International Society on Thrombosis and Haemostasis, and TIMI Thrombolysis in Myocardial Infarction.
† Bleeding Academic Research Consortium (BARC) major bleeding is defined as grade 3b or higher.

Table 2. Primary and Secondary Efficacy Outcomes.*

Outcome	Rivaroxaban (N=3286)		Placebo (N=3278)		Hazard Ratio (95% CI)	P Value
	Patients with Event	K–M Estimate at 3 Yr	Patients with Event	K–M Estimate at 3 Yr		
	no. (%)	%	*no. (%)*	%		
Primary efficacy outcome: acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes	508 (15.5)	17.3	584 (17.8)	19.9	0.85 (0.76–0.96)	0.009
Acute limb ischemia	155 (4.7)	5.2	227 (6.9)	7.8	0.67 (0.55–0.82)	
Major amputation for vascular causes	103 (3.1)	3.4	115 (3.5)	3.9	0.89 (0.68–1.16)	
Myocardial infarction	131 (4.0)	4.6	148 (4.5)	5.2	0.88 (0.70–1.12)	
Ischemic stroke	71 (2.2)	2.7	82 (2.5)	3.0	0.87 (0.63–1.19)	
Death from cardiovascular causes	199 (6.1)	7.1	174 (5.3)	6.4	1.14 (0.93–1.40)	
Secondary efficacy outcomes						
Acute limb ischemia, major amputation for a vascular cause, myocardial infarction, ischemic stroke, or death from coronary heart disease	433 (13.2)	14.7	528 (16.1)	18.2	0.80 (0.71–0.91)	<0.001
Unplanned index-limb revascularization for recurrent limb ischemia	584 (17.8)	20.0	655 (20.0)	22.5	0.88 (0.79–0.99)	0.03
Hospitalization for coronary or peripheral event of a thrombotic nature	262 (8.0)	8.7	356 (10.9)	12.1	0.72 (0.62–0.85)	<0.001
Acute limb ischemia, major amputation for a vascular cause, myocardial infarction, ischemic stroke, or death from any cause	614 (18.7)	20.6	679 (20.7)	23.2	0.89 (0.79–0.99)	0.03
Acute limb ischemia, major amputation for a vascular cause, myocardial infarction, stroke from any cause, or death from any cause	514 (15.6)	17.5	588 (17.9)	20.1	0.86 (0.76–0.96)	0.01
Death from any cause	321 (9.8)	11.1	297 (9.1)	10.9	1.08 (0.92–1.27)	0.34
Venous thromboembolism	25 (0.8)	0.8	41 (1.3)	1.7	0.61 (0.37–1.00)	

* All efficacy outcomes were analyzed on an intention-to-treat basis. K–M denotes Kaplan–Meier.

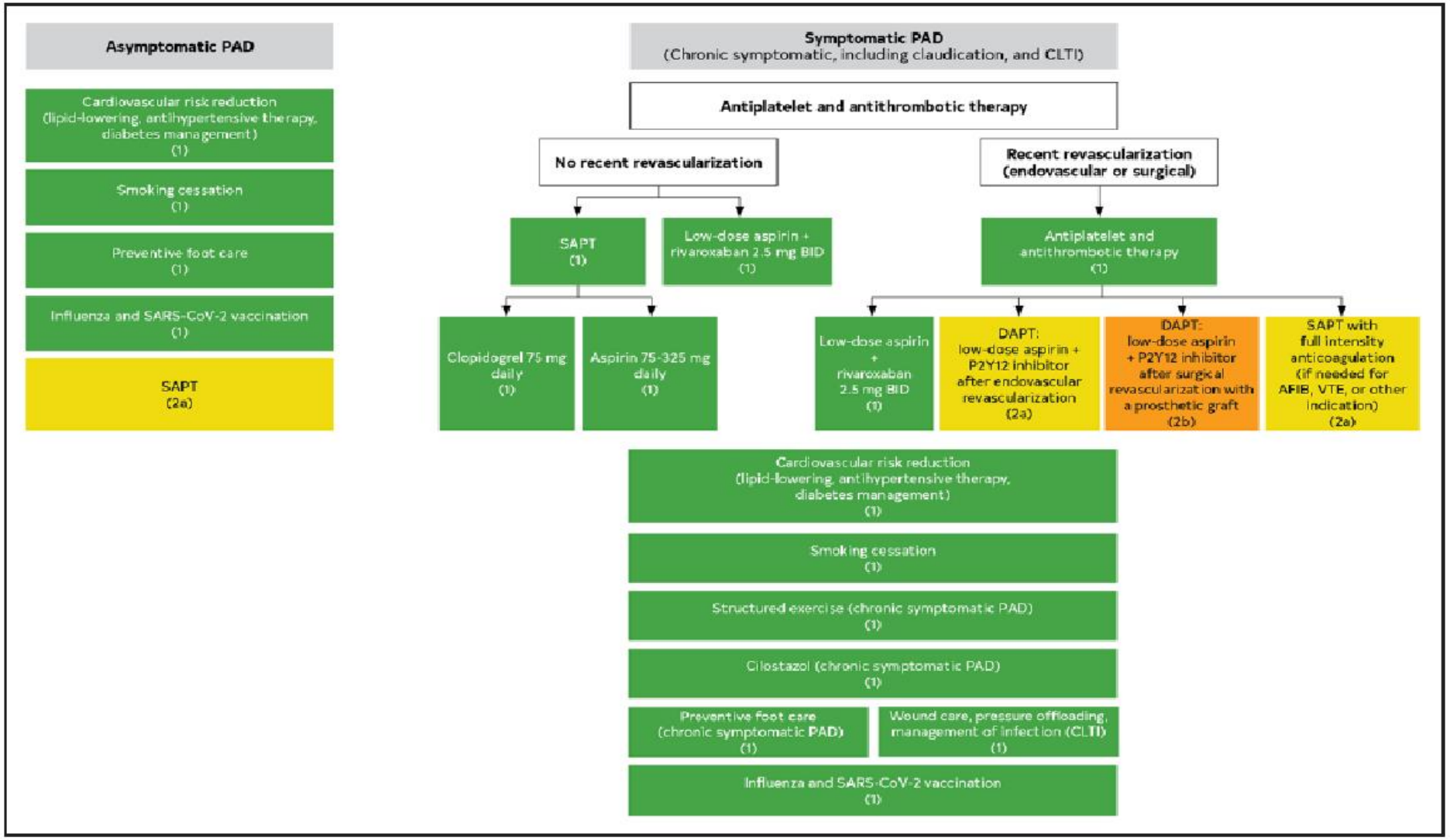

Figure 4. Medical Therapy and Foot Care for PAD.

Colors correspond to Table 3. Afib indicates atrial fibrillation; BID, 2 times daily; CLTI, chronic limb-threatening ischemia; DAPT, dual antiplatelet therapy; PAD, peripheral artery disease; SAPT, single antiplatelet therapy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; and VTE, venous thromboembolism.

When to intervene

- Claudication
- CLI/CLTI

Who to refer to

PROPUBLICA

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Health Care

Thousands of Patients May Be Undergoing Vascular Procedures Too Soon or Unnecessarily

by Annie Waldman, ProPublica, with data analysis by Alma Trotter and Fred Trotter, CareSet

Dec. 12, 2023, 5 a.m. EST

PROPUBLICA

Donate

Blocked Artery in Your Leg? Here's What You Should Know.

A ProPublica investigation found that some doctors overuse invasive treatments for peripheral artery disease. So we talked to experts to learn what vascular patients should know when seeking care.

Perspectives > Second Opinions

Who Is to Blame for the Rampant Overtreatment of Peripheral Artery Disease?

— The loudest critics are the biggest offenders

by Caitlin W. Hicks, MD, MS
August 13, 2023

Recommendations: General considerations on invasive treatment for intermittent claudication (*IC*)

		Grade	*Level of evidence*
5.1.	We recommend EVT or surgical treatment of IC for patients with significant functional or lifestyle-limiting disability when there is a reasonable likelihood of symptomatic improvement with treatment, when pharmacologic or exercise therapy, or both, have failed, and when the benefits of treatment outweigh the potential risks.	1	B
5.2.	We recommend an individualized approach to select an invasive treatment for IC. The modality offered should provide a reasonable likelihood of sustained benefit to the patient (>50% likelihood of clinical efficacy for at least 2 years). For revascularization, anatomic patency (freedom from hemodynamically significant restenosis) is considered a prerequisite for sustained efficacy.	1	C

EVT, Endovascular therapy.

Interventions

- Endovascular
  - Angioplasty
  - Stenting
  - Different therapies
- Surgical
  - Revascularization
  - Primary amputation

When to refer PAD patients

- Whenever the diagnosis is made

Who to refer PAD patients to

- Anyone who is qualified to care for these patients and who will provide comprehensive, quality, patient specific, and goal directed care.

Key points

- Importance of history and physical exam
- ABI is the best first test
- Risk factor reduction and medical therapy
- Indications for invasive intervention