

Guide to Lower Extremity Peripheral Arterial Disease (PAD)

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Disclosure

Consultant: AbbVie; Corcept; Novo Nordisk

Research Grant: Cleerly; Janssen; Massachusetts
General Hospital/PCORI; Novartis; Novo Nordisk



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Peripheral Vascular Disease

Group of diseases affecting blood vessels that includes atherosclerotic conditions, vasculitides, vasospasm, venous thrombosis, venous insufficiency, and lymphatic disorders



Braunwald's Heart Disease (15th ed). 2016

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Peripheral Arterial Disease

Disorder of blood flow to either the upper or lower extremities:

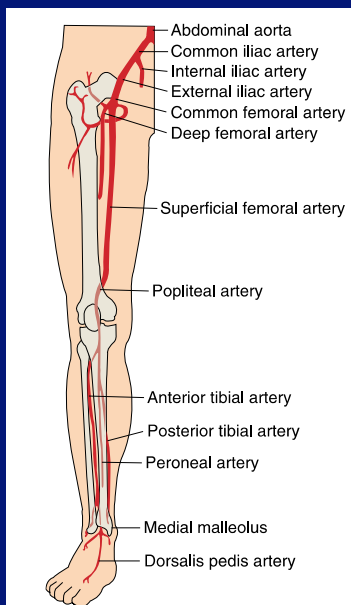
- Atherosclerosis
- Thrombosis/embolism
- Vasculitis
- Fibromuscular dysplasia
- Entrapment



Braunwald's Heart Disease (15th ed). 2016

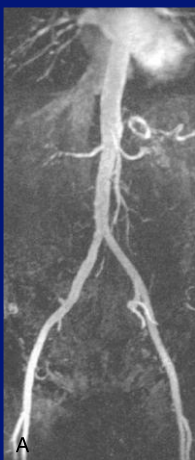
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Vascular Anatomy of the Lower Extremity



Lower Extremity Vascular Anatomy

Aorto-Iliac



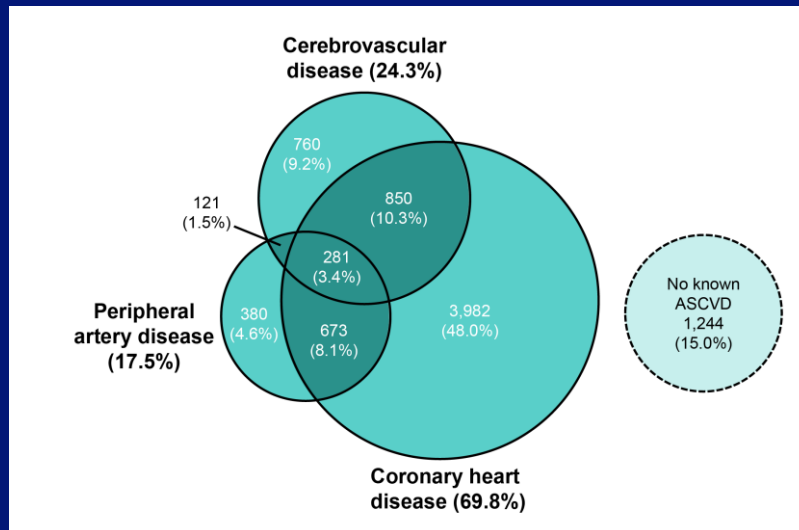
Femoropopliteal



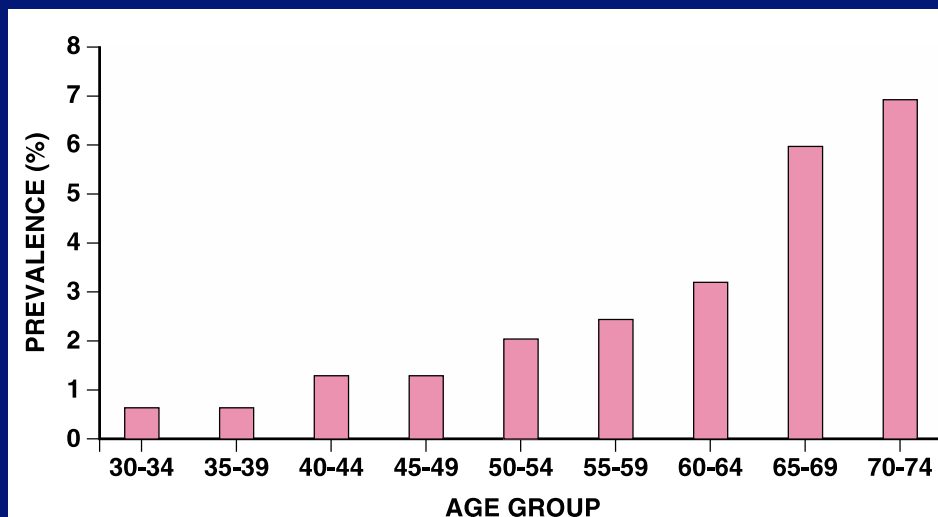
Infrapopliteal



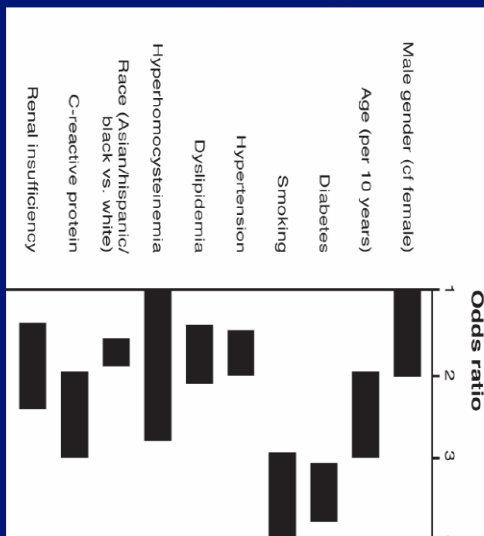
Epidemiology of Peripheral Arterial Disease n=8,291 Patients in the SOUL Trial



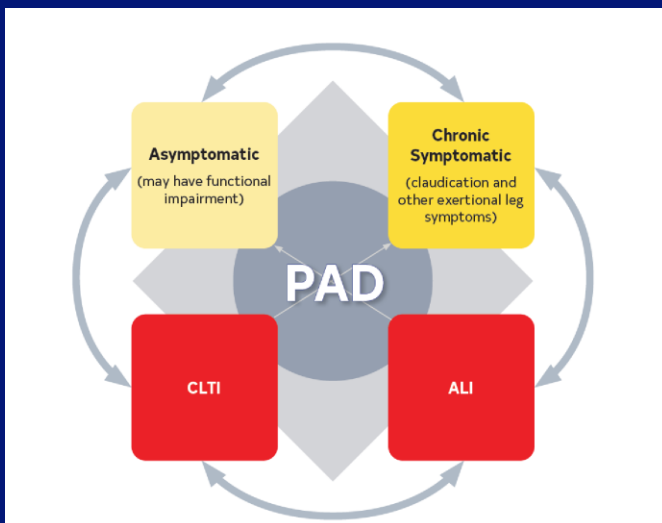
Epidemiology of Peripheral Arterial Disease



Risk Factors for Development of Peripheral Arterial Disease



Clinical Subsets of Patients with PAD



Multiple Comorbidities in Patients with PAD

Table 1. Characteristics Associated With Intermittent Claudication vs Other Leg Symptom Categories Among Men and Women Aged 55 Years or Older With Peripheral Arterial Disease (N = 460)*

	Intermittent Claudication (n = 150)†	Atypical Exertional Leg Pain		No Exertional Leg Pain		Leg Pain on Exertion and Rest (n = 88)
		Carry On (n = 41)	Stop (n = 90)	Active (n = 63)‡	Inactive (n = 28)§	
Age, mean (SD), y	70.7 (8.4)	72.0 (7.6)	71.3 (8.6)	74.7 (7.8)	75.5 (8.7)	71.1 (8.6)
Men	64.0	73.2	56.7	71.4	53.6	40.9
Black	13.3	7.3	12.4	12.7	35.7	27.3
Ankle-brachial index, mean (SD)	0.61 (0.14)	0.70 (0.12)	0.64 (0.14)	0.70 (0.12)	0.65 (0.15)	0.66 (0.16)
Neuropathy, mean (SD)	3.5 (3.7)	4.3 (4.3)	3.1 (3.6)	4.2 (4.3)	5.7 (5.3)	5.6 (5.8)
Obesity¶	44.7	39.0	40.0	34.9	46.4	53.4
Current and past smoking	86.7	80.5	85.6	79.4	82.1	83.0
Diabetes	26.7	24.4	26.7	30.2	39.3	48.9
Disk disease	29.3	29.3	31.1	19.0	28.6	40.9
Spinal stenosis	7.2	9.7	13.6	1.8	8.9	20.8
Hip or knee arthritis	16.0	4.9	11.1	4.8	17.9	14.8
Lower-extremity revascularization	45.3	22.0	40.0	42.9	28.6	40.9
Depression#	25.9	5.1	18.8	19.3	4.2	32.9
≥3 Comorbidities	43.3	29.3	38.9	36.5	60.7	68.2
Report leg pain during the 6-min walk	88.6	72.5	83.1	33.3	53.6	76.1

High Risk Populations for PAD

- Age ≥65 y
- Age 50–64 y, with risk factors for atherosclerosis (eg, diabetes mellitus, history of smoking, hyperlipidemia, hypertension), chronic kidney disease, or family history of PAD
- Age <50 y, with diabetes mellitus and 1 additional risk factor for atherosclerosis
- Individuals with known atherosclerotic disease in another vascular bed (eg, coronary, carotid, subclavian, renal, mesenteric artery stenosis, or AAA)

Guideline Recommendations for PAD

In patients at increased risk of PAD

- Take a comprehensive history regarding exertional leg symptoms (claudication, ischemic rest pain, non-healing wounds)
- Perform a vascular examination (assess pulses, listen for bruits, inspect feet)
- Perform non-invasive BP in both arms at least once

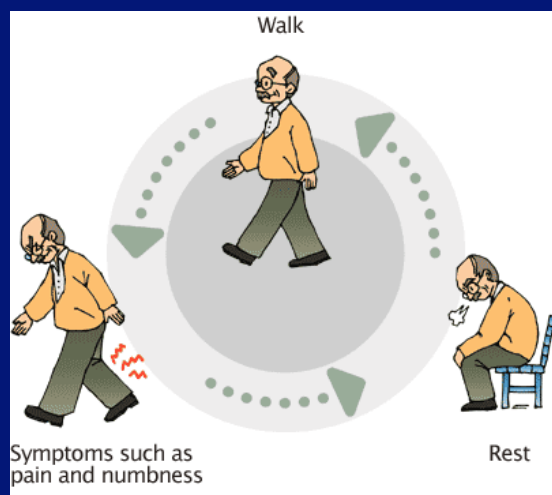


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Presentation of Peripheral Arterial Disease

Claudication

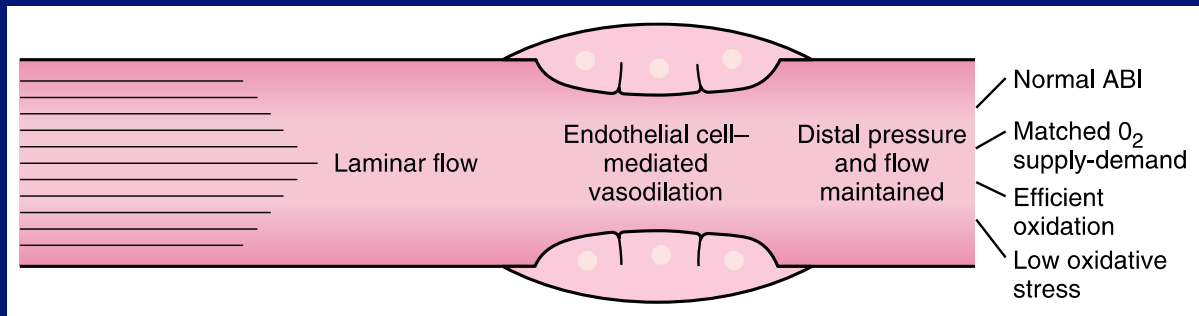
Fatigue, discomfort, cramping, or pain of vascular origin in the muscles of the lower extremities that is consistently induced by exercise and consistently relieved by rest (within 10 min)



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Pathophysiology of Peripheral Arterial Disease

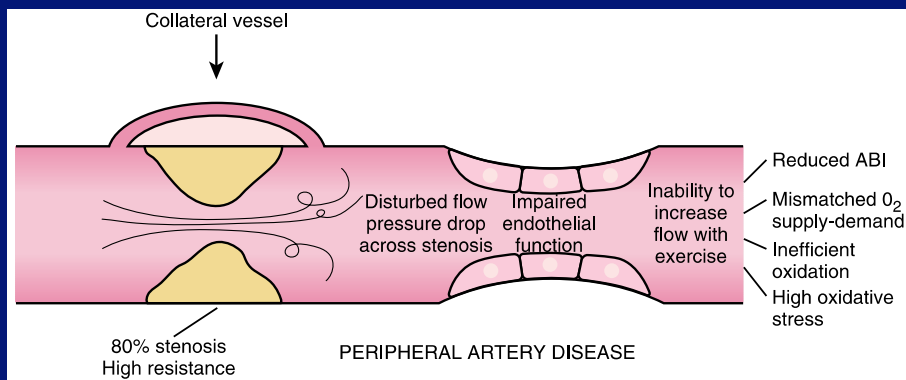
Normal Peripheral Blood Flow



Pathophysiology of Peripheral Arterial Disease

Claudication

Fatigue, discomfort, cramping, or pain of vascular origin in the muscles of the lower extremities that is consistently induced by exercise and consistently relieved by rest (within 10 min)



Findings Suggestive of Peripheral Arterial Disease

History

- Claudication
- Other non–joint-related exertional lower extremity symptoms (not typical of claudication)
- Impaired walking function
- Ischemic rest pain

Physical Examination

- Abnormal lower extremity pulses
- Vascular bruit
- Nonhealing lower extremity wound or gangrene
- Other suggestive lower extremity physical findings (eg, elevation pallor/dependent rubor)



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Pathophysiology of Peripheral Arterial Disease

Claudication

Fatigue, discomfort, cramping, or pain of vascular origin in the muscles of the lower extremities that is consistently induced by exercise and consistently relieved by rest (within 10 min)

<i>Discomfort</i>	<i>Arterial Stenosis</i>
Shoulder, Biceps, Forearm	Subclavian, Axillary
Buttock/Hip, Thigh	Aorta, Iliac, Common Femoral
Calf, Ankle	Superficial Femoral, Popliteal
Ankle, Foot	Tibial, Peroneal



Braunwald's Heart Disease. 15th ed. 2016

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Differential Diagnosis of Exertional Extremity Pain

Vascular	Non-Vascular
Atherosclerosis	Radiculopathy (Spinal Stenosis, Herniated Disks)
Thrombosis/Embolism	Arthritis
Vasculitis (Thromboangiitis obliterans, Takayasu arteritis, Giant Cell)	Venous Insufficiency
Aortic Coarctation	Myositis
Fibromuscular Dysplasia	Glycogen Storage Disease (Type V) McArdle's Syndrome
Radiation	
Extravascular Entrapment (Endofibrosis of external iliac artery, Popliteal Entrapment, Thoracic Outlet)	



Braunwald's Heart Disease. 15th ed. 2016

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Alternative Diagnoses of PAD (Normal ABI)

Condition	Location	Characteristic	Exercise	Rest	Position
Arthritis	Joints	Aching discomfort	Variable	Not relieved (quickly)	Better when not weight bearing
Nerve root compression	Radiates down leg	Sharp, burning	Variable (may worsen with walking)	Induced by certain positions	Improved by changing
Spinal stenosis	Buttocks, hips	Pain, weakness, bilateral	Worse with standing and extending spine	Relieved but can take a long time to improve	Better with flexion of spine
Baker's Cyst	Behind calf	Swelling, tenderness (constant)	Worse	Present	None
Venous claudication	Entire leg, worse in the calf	Tight, bursting pain	Worsened	Subsides slowly	Relieved with leg raise
Compartment syndrome	Calf	Tight, bursting pain after running	Induces	Subsides slowly	Muscular patients



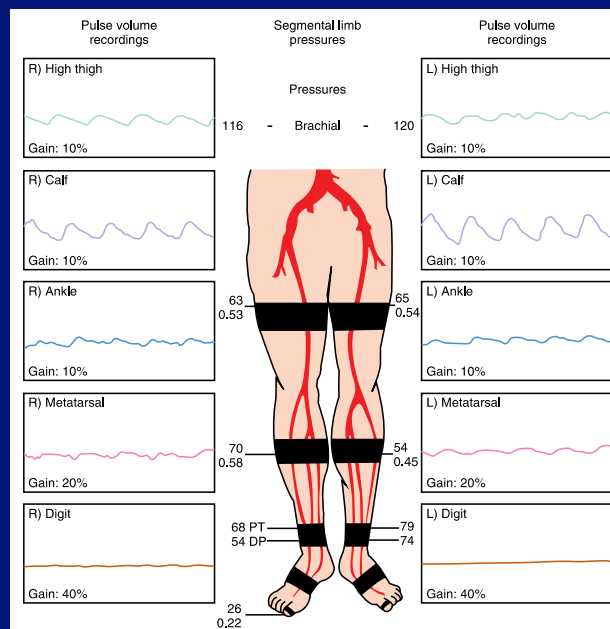
J Am Coll Cardiol. 2024; 83 (24): 2497

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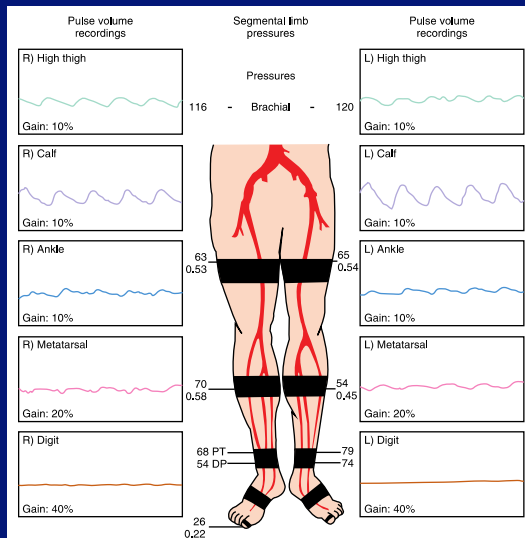
Guideline Recommendations for PAD

COR	LOE	Recommendations
I	B-NR	In patients with history or physical examination findings suggestive of PAD, the resting ABI is recommended to establish the diagnosis.
I	C-LD	Resting ABI results should be reported as abnormal (ABI ≤ 0.90), borderline (ABI 0.91–0.99), normal (1.00–1.40), or noncompressible (ABI >1.40).
I	B-NR	Patients with suspected PAD and normal/borderline ABI, should undergo exercise treadmill ABI to evaluate for PAD
3: NB	B-NR	In patients not at increased risk of PAD and without history or physical examination findings suggestive of PAD, screening for PAD with the ABI is not recommended.

Diagnostic Criteria for Peripheral Arterial Disease



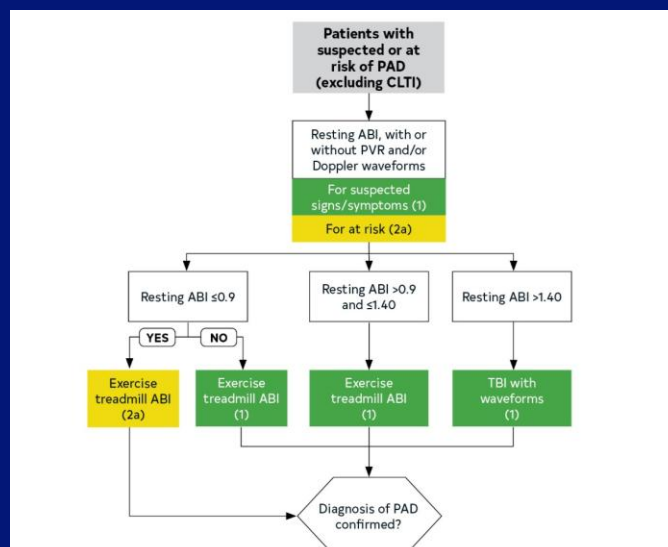
Diagnostic Criteria for Peripheral Arterial Disease



>1.40 – Noncompressible
 0.9-1.40 – Normal
 0.5- <0.9 – PAD
 <0.5 - Critical Limb Ischemia

Decrease in the ABI >25%
 with Exercise is consistent
 with PAD

Diagnostic Criteria for Peripheral Arterial Disease

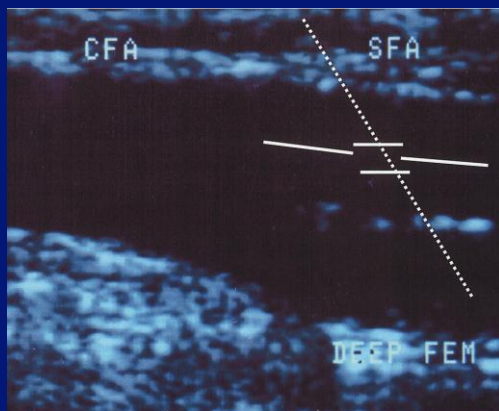


Guideline Recommendations for PAD

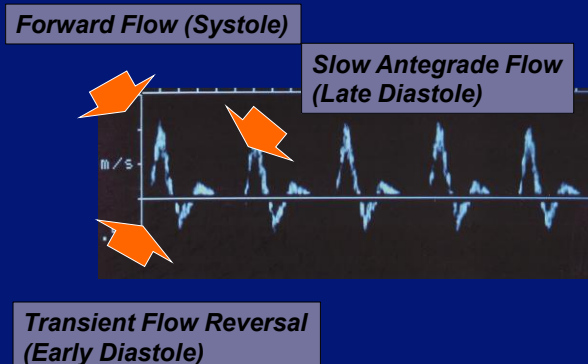
COR	LOE	Recommendations
1	B-NR	In patients with functionally limiting claudication with inadequate response to GDMT (including structured exercise) for whom revascularization is being considered , duplex ultrasound, computed tomography angiography (CTA), magnetic resonance angiography (MRA), or catheter angiography of the lower extremities is useful for assessment of anatomy and severity of disease and to determine potential revascularization strategy.

Arterial Duplex

Grey Scale Doppler

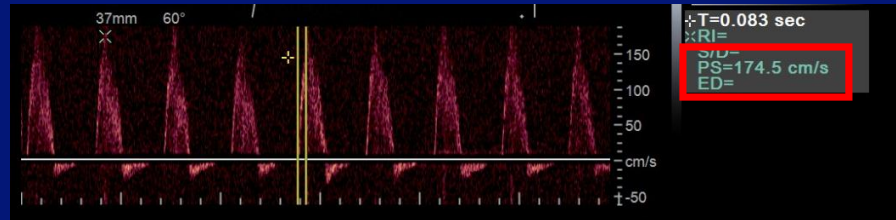


Pulse Doppler

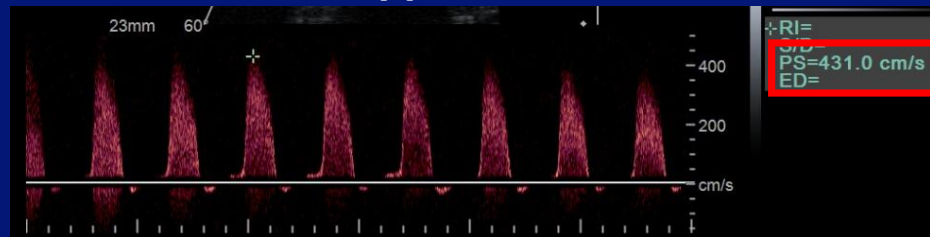


Arterial Duplex

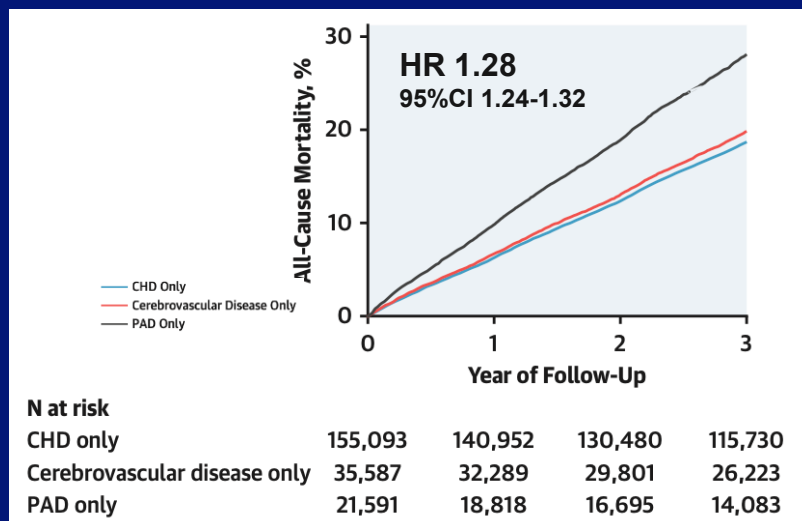
Normal Pulse Doppler – L CFA



Abnormal Pulse Doppler – R CFA



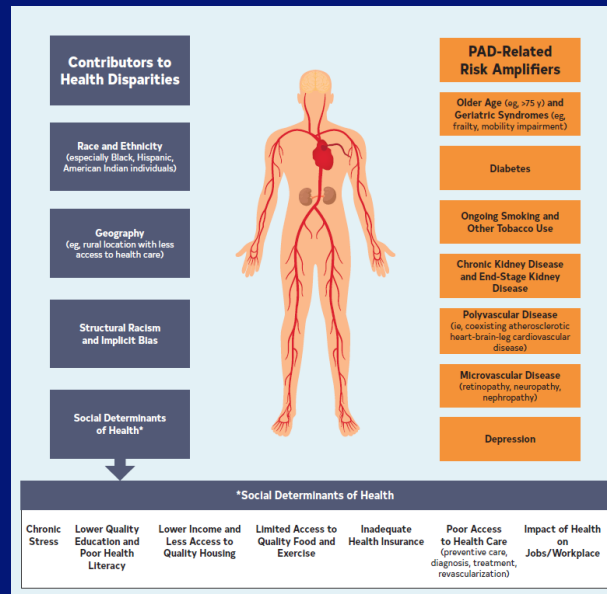
Risk of Death Associated with Peripheral Arterial Disease



Peripheral Arterial Disease

*Cerebrovascular
Coronary*

Potential Contributors to Poor Outcomes in PAD



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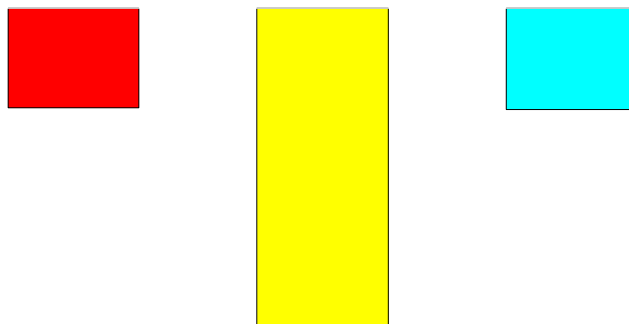
Guideline Recommendations for PAD

COR	LOE	Recommendation
Ila	B-NR	A screening duplex ultrasound for AAA is reasonable in patients with symptomatic PAD.

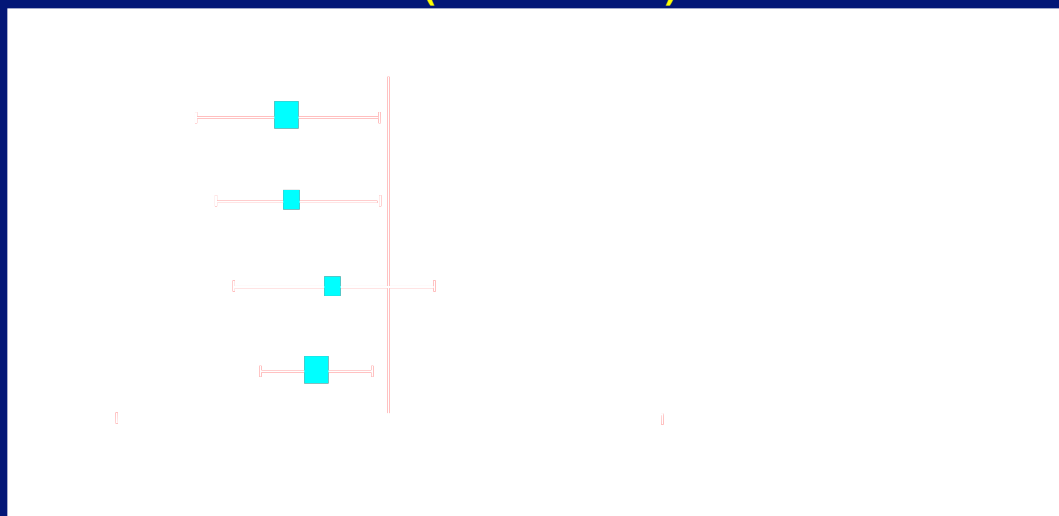
COR	LOE	Recommendations
I	A	Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit.

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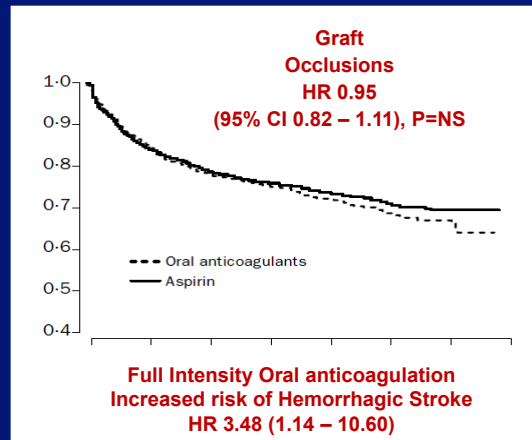
CAPRIE trial: Risk reduction in specific subgroups



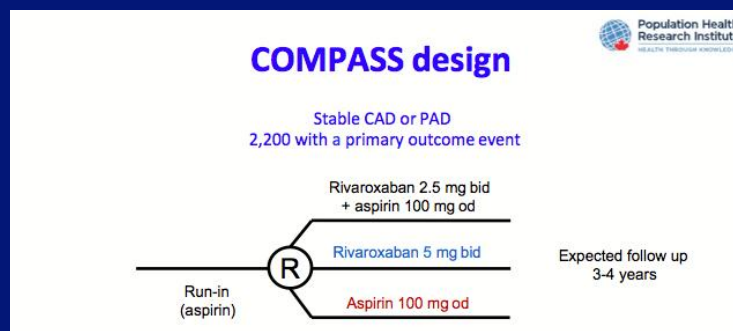
Aspirin + Clopidogrel for Peripheral Arterial Disease (CHARISMA)



Outcomes with DAPT and Anti-Coagulation Following Peripheral Revascularization



Risk of CV Death, MI, Stroke in Patients with PAD *n=7,470 Patients with PAD*



Risk of CV Death, MI, Stroke in Patients with PAD

n=7,470 Patients with PAD



PAD Patients in COMPASS

PAD Groups	Number of patients
All Patients	7,470
Symptomatic PAD Limbs	4,129
Carotid Disease	1,919
CAD + Low ABI (<0.90) only	1,422

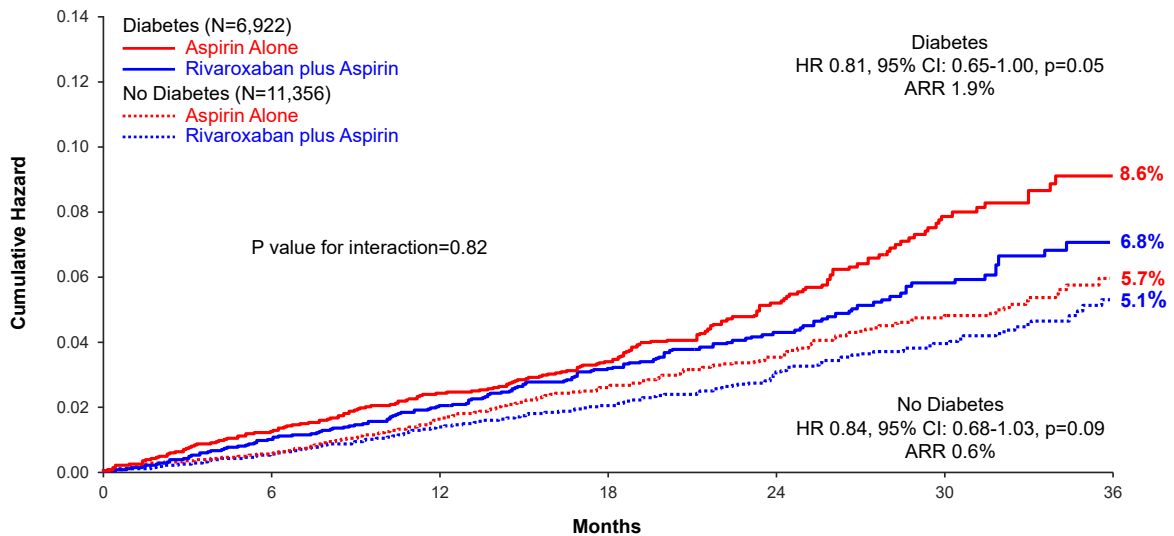
Mean Follow-up: 21 months

Risk of CV Death, MI, Stroke in Patients with PAD

n=7,470 Patients with PAD

Outcome	R + A N=2,492	R N=2,474	A N=2,504	Riva + aspirin vs. aspirin		Riva vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
MACE	126 (5.1)	149 (6.0)	174 (6.9)	0.72 (0.57-0.90)	0.005	0.86 (0.69-1.08)	0.19
MI	51 (2.0)	56 (2.3)	67 (2.7)	0.76 (0.53-1.09)	-	0.84 (0.59-1.20)	-
Stroke	25 (1.0)	43 (1.7)	47 (1.9)	0.54 (0.33-0.87)	-	0.93 (0.61-1.40)	-
CV Death	64 (2.6)	66 (2.7)	78 (3.1)	0.82 (0.59-1.14)	-	0.86 (0.62-1.19)	-

All-Cause Death



Bhatt DL, Eikelboom JW, Connolly SJ, et al, Yusuf S. *Circulation*. 2020.

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Trial Design

NCT02504216

6,564 Patients with Symptomatic Lower Extremity PAD* Undergoing Peripheral Revascularization

*Ankle Brachial Index < 0.90 and Imaging Evidence of Occlusive Disease

ASA 100 daily for all Patients
Clopidogrel at Investigator's Discretion

Randomized 1:1 Double Blind

Rivaroxaban 2.5 mg twice daily

Stratified by
Revascularization Approach
(Surgical or Endovascular)
and Use of Clopidogrel

Placebo

Follow up Q6 Months, Event Driven, Median f/u 28 Months

Primary Efficacy Endpoint: Acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke or cardiovascular death

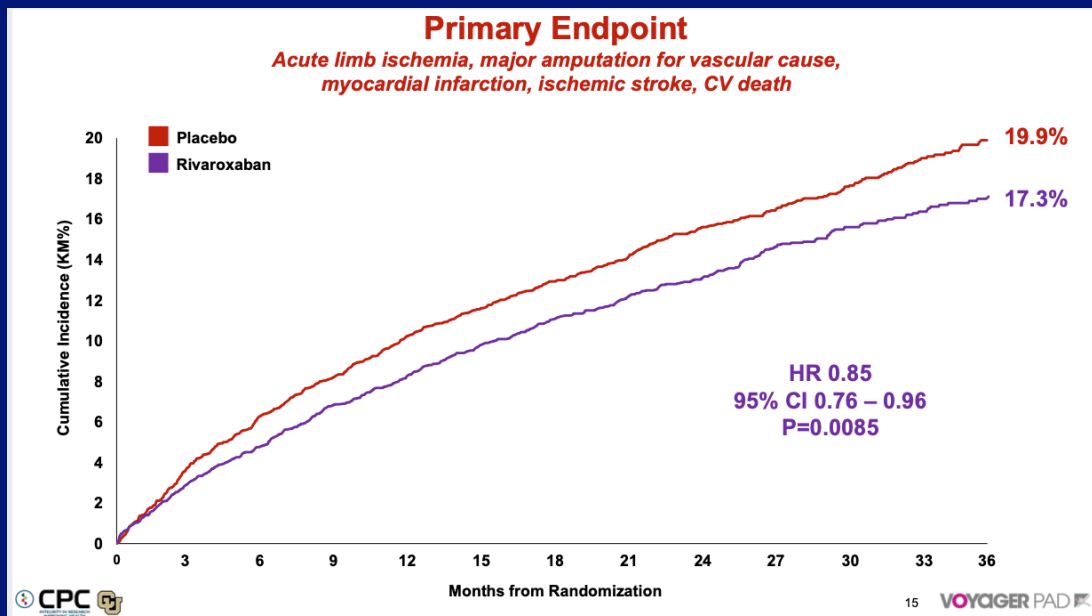
Principal Safety Outcome: TIMI Major Bleeding



Capell WH, Bonaca MP, Nehler MR...Hiatt WR. *AHJ* 2018

6 VOYAGER PAD

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Guideline Recommendations for Symptomatic PAD

COR	LOE	Recommendations
1	A	In patients with symptomatic PAD, single antiplatelet therapy is recommended to reduce the risk of MACE.
1	B-R	In patients with symptomatic PAD, single antiplatelet therapy with clopidogrel alone (75 mg daily) is recommended to reduce the risk of MACE.
1	A	In patients with symptomatic PAD, low dose rivaroxaban (2.5mg twice daily combined with low-dose aspirin) is recommended to reduce the risk of MACE and MALE.
1	C-LD	In patients with symptomatic PAD, single antiplatelet therapy with aspirin alone (range, 75–325 mg daily) is recommended to reduce the risk of MACE.

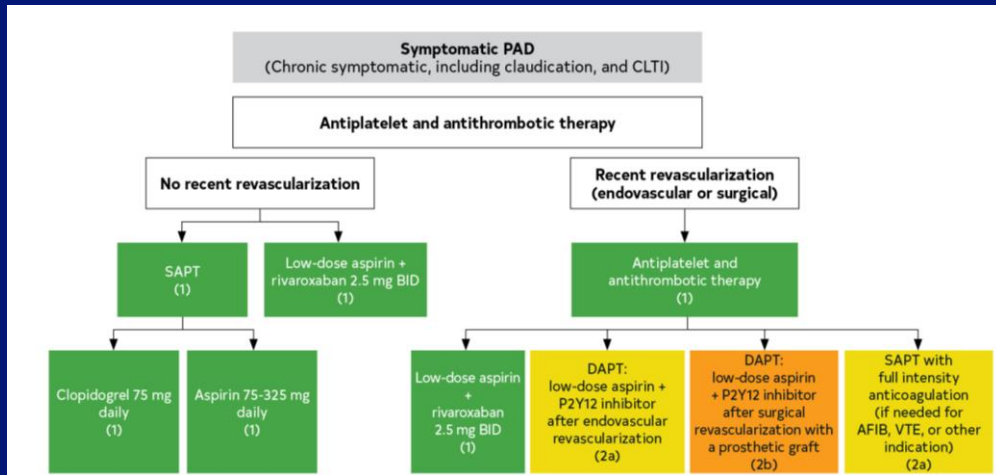
Guideline Recommendations for Symptomatic PAD

1	B-R	After endovascular or surgical revascularization for PAD, antiplatelet therapy is recommended.
1	A	After endovascular or surgical revascularization for PAD, low-dose rivaroxaban (2.5 mg twice daily) combined with low-dose aspirin is recommended to reduce the risk of MACE and MALE.
2a	C-LD	After endovascular revascularization for PAD, dual antiplatelet therapy with a P2Y12 antagonist and low-dose aspirin is reasonable for at least 1 to 6 months.

Guideline Recommendations for PAD

COR	LOE	Recommendations
III: Harm	A	In patients with PAD without another indication (eg, atrial fibrillation), full-intensity oral anticoagulation should not be used to reduce the risk of MACE and MALE.

Summary – Antiplatelet Therapy for PAD



Guideline Recommendations for PAD

COR	LOE	Recommendations
1	A	In patients with PAD, treatment with high-intensity statin therapy is indicated, with an aim of achieving a $\geq 50\%$ reduction in LDL-C level.
2a	B-R	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.
2a	B-R	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.

Guideline Recommendations for PAD

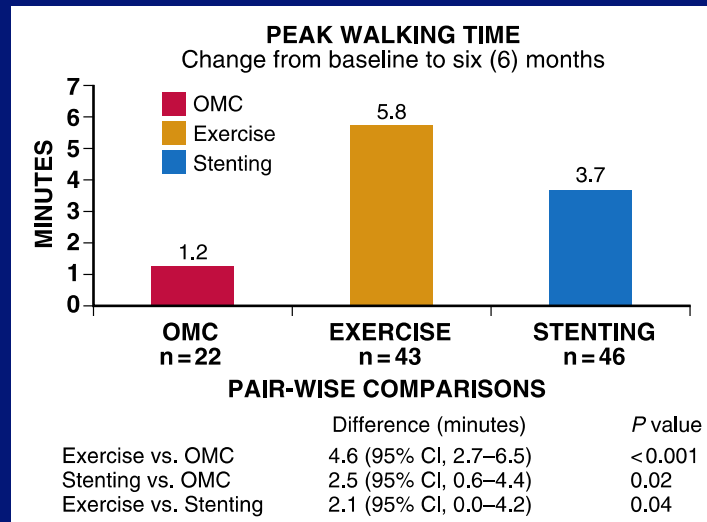
	High Intensity	Moderate Intensity	Low Intensity
LDL lowering†	≥50%	30%–49%	<30%
Statins	Atorvastatin 40 mg–80 mg Rosuvastatin 20 mg–40 mg	Atorvastatin 10 mg–20 mg Rosuvastatin 5 mg–10 mg Simvastatin 20mg–40 mg‡	Simvastatin 10 mg
		Pravastatin 40 mg–80 mg Lovastatin 40 mg–80 mg Fluvastatin XL 80 mg Fluvastatin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

Guideline Recommendations for PAD

COR	LOE	Recommendations
1	A	In patients with PAD and hypertension, antihypertensive therapy should be administered to reduce the risk of MACE.
1	B-R	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.
1	B-R	In patients with PAD and hypertension, the selective use of ACE/ARB is recommended to reduce the risk of MACE.

Exercise Therapy Increases Walking Time

n=111 Patients in the CLEVER Trial



Murphy TP et al. *Circulation*; 2012. 125: 130

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Guideline Recommendations for PAD

COR	LOE	Recommendations
I	A	In patients with claudication, cilostazol is recommended to improve symptoms and increase walking distance.
I	A	In patients with chronic symptomatic PAD, supervised exercise therapy is recommended to improve walking performance, functional status, and QOL.
I	B-R	In patients with functionally limiting claudication, SET or a structured community-based exercise program should be offered as an initial treatment option.



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Guideline Recommendations for PAD

COR	LOE	Recommendations
2a	B-NR	In patients with functionally limiting claudication and an inadequate response to GDMT (including structured exercise), revascularization is a reasonable treatment option to improve walking function and QOL.
3: Harm	B-NR	In patients with claudication who have had an adequate clinical response to GDMT (including structured exercise), revascularization is not recommended.



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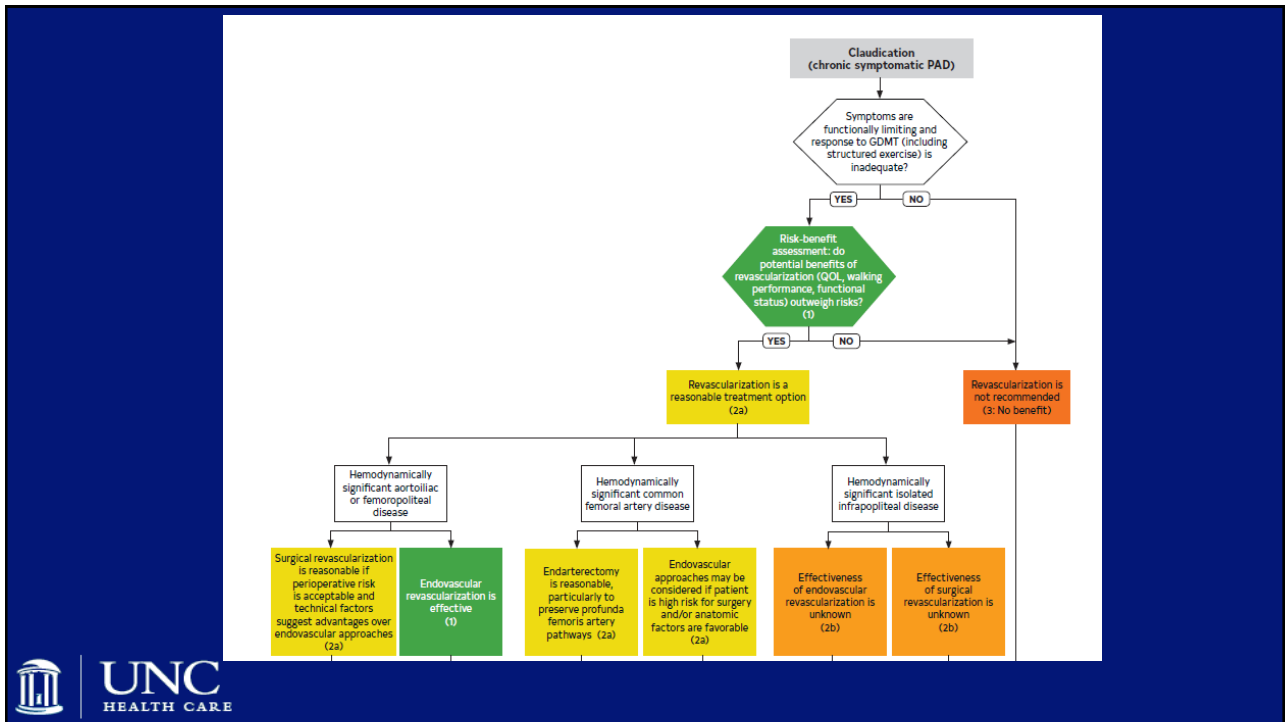
Guideline Recommendations for PAD - Revascularization

COR	LOE	Recommendations
I	A	In patients with functionally limiting claudication and hemodynamically significant aortoiliac or femoropopliteal disease with inadequate response to GDMT (including structured exercise), endovascular revascularization is effective to improve walking performance and QOL.
IIa	B-R	In patients with functionally limiting claudication and hemodynamically significant common femoral artery disease with inadequate response to GDMT (including structured exercise), surgical endarterectomy is reasonable, especially if endovascular approaches adversely affect profunda femoris artery pathways.
IIb	C-LD	In patients with functionally limiting claudication and isolated hemodynamically significant infrapopliteal disease with inadequate response to GDMT (including structured exercise), the effectiveness of endovascular revascularization is unknown.



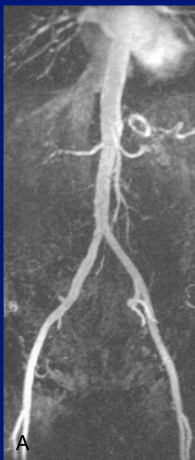
J Am Coll Cardiol. 2024; 83 (24): 2497

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Guidelines for Endovascular Revascularization in Patients Who Fail Medical Tx

*Aorto-Iliac**Femoropopliteal**Infrapopliteal*

I

I

IIb

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Endovascular Revascularization in Patients Who Fail Medical Tx



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Presentation of Peripheral Arterial Disease

Acute Limb Ischemia

Acute (<2 wk), severe hypoperfusion of the limb characterized by the 6 P's:

- Pain
- Pallor
- Pulselessness
- Poikilothermia (cold)
- Paresthesias
- Paralysis



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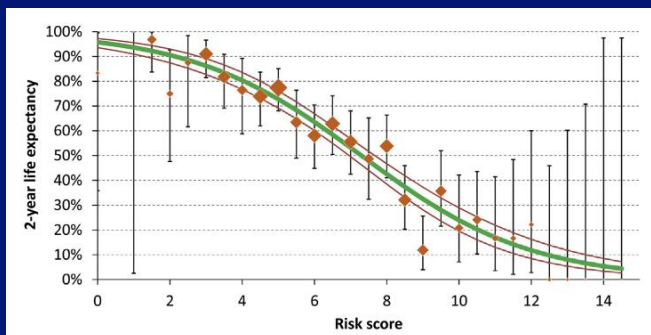
Presentation of Peripheral Arterial Disease

Critical Limb Ischemia

Chronic (≥ 2 wk) ischemic rest pain, nonhealing wound/ulcers, or gangrene in 1 or both legs attributable to objectively proven arterial occlusive disease.



Risk Associated with Critical Limb Ischemia



Cause of Death

Cardiac - 29%
Vascular - 10%
SCD - 8%
Non-CV 46%
Unknown 7%

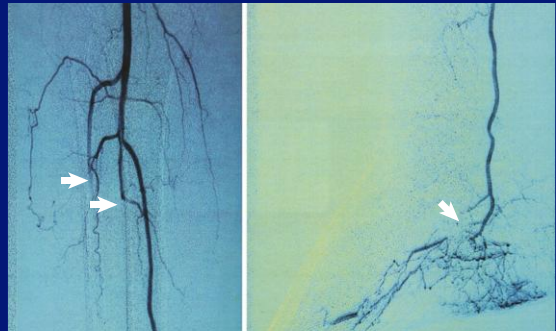
Variables	Score*
Nonambulatory status	2.0
Rutherford class	
5	1.5
6	3.0
Cerebrovascular disease	1.0
Hemodialysis	2.0
BMI, kg/m ²	
18.0-19.9	1.0
<18.0	2.0
Age, yrs	
65-79	1.5
≥ 80	3.0
Ejection fraction, %	
40-49	1.5
<40	2.0

J Am Coll Cardiol Interv 2014; 7: 1444

Thromboangiitis Obliterans (Buerger's Disease)

Segmental vasculitis involving the distal arteries, veins, and nerves of young (~40) people who smoke

Treatment – tobacco cessation. Amputations occur in ~40% of pts who continue to smoke



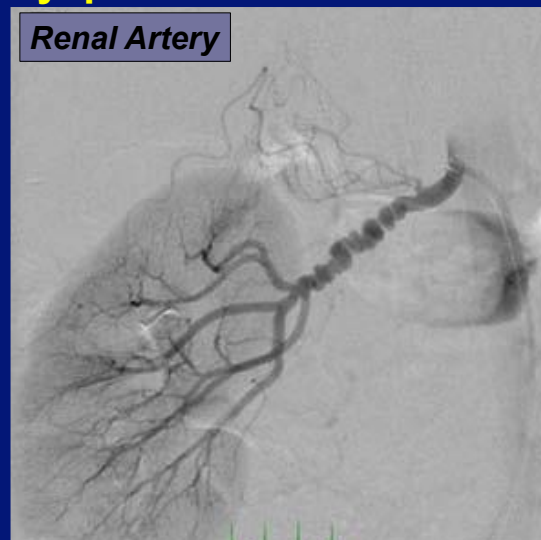
Fibromuscular Dysplasia

Effects medium-large artery (typically renal, carotid) in young, white women

Can present with poorly controlled HTN or tinnitus

Angiography shows a beaded appearance

Treatment is balloon angioplasty



Fibromuscular Dysplasia

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Circulation. 2014; 129: 1048

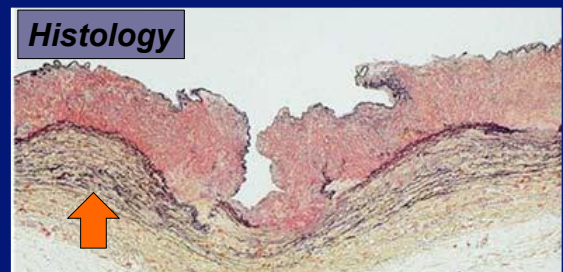
Fibromuscular Dysplasia

Effects medium-large artery (typically renal, carotid) in young, white women

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Angiography shows a beaded appearance

Treatment is balloon angioplasty



Circulation. 2014; 129: 1048

Top Ten Guidelines Based Recommendations for Patients with PAD

1. Evaluate pts at increased risk for PAD
2. Perform ABIs in those in whom PAD is suspected
3. Imaging (CTA, MRA) only needed for those in whom revascularization is being considered
4. Screen pts with PAD for AAA
5. Smoking cessation should be advised for all pts with PAD
6. Many options for anti-thrombotic pharmacotherapy including aspirin, clopidogrel, or ASA/low dose riva
7. All pts with PAD need aggressive statin therapy
8. Anti-HTN therapy (preferably ACEi/ARB) is indicated in pts with PAD
9. Pts w/ claudication benefit from supervised exercise program (Cardiac rehab now reimbursable from CMS)
10. Revascularization is indicated in pts with persistent claudication despite medical therapy and exercise, acute limb ischemia or critical limb ischemia.

