School of Pharmacy
UNIVERSITY OF WISCONSIN–MADISON

Peripheral Artery Disease

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Objectives

- Define peripheral artery disease and describe the symptoms associated with it
- Identify the risk factors associated with peripheral artery disease
- Describe the treatment options for a patient with peripheral artery disease including risk factor modifications, medications, and revascularization techniques
- Identify other vascular diseases besides lower extremity peripheral artery disease
- Apply this information to a patient case

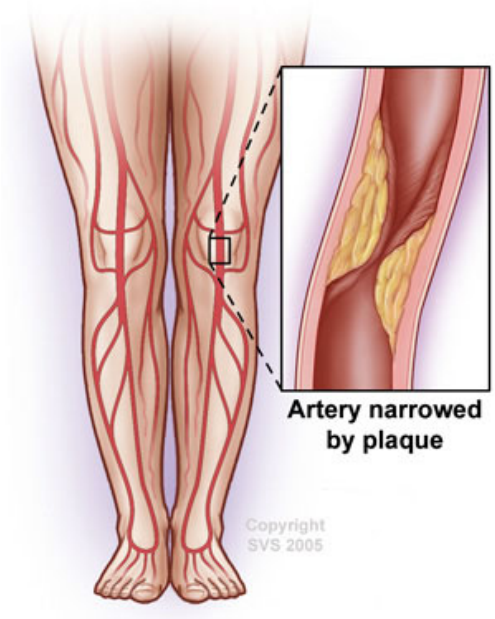
Patient Case

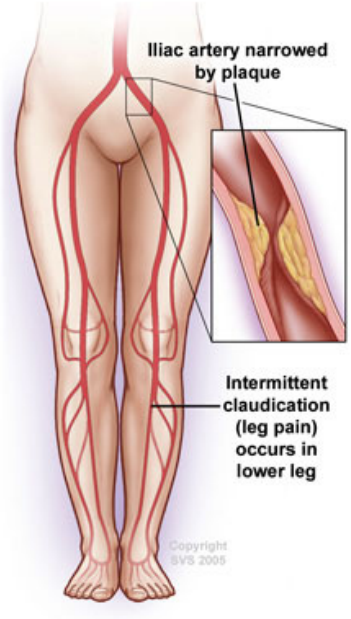
- JM is a 72 yo white female who presents to clinic for her yearly physical exam.
  - PMH: HTN, Type 2 DM x 10 years, dyslipidemia, smokes 1 ppd x 40 years
  - Meds:
    - Lisinopril 10mg po daily
    - Metoprolol 50mg po BID
    - Glipizide 5mg po BID
    - Atorvastatin 20mg po at bedtime
- JM mentions that she has been having leg pain with exercise over the past few months

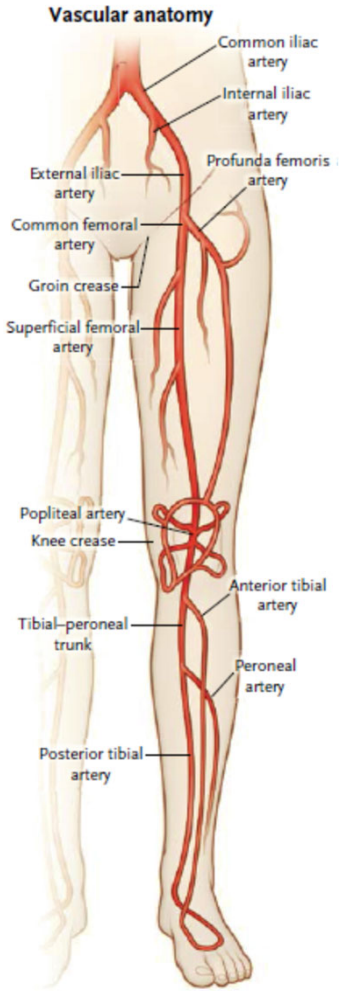
Peripheral Artery Disease (PAD)

- Disease of arteries excluding coronary and cerebral vessels
- Caused primarily by atherosclerosis and thromboembolic processes
  - Stenosis
  - Occlusive
  - Aneurysmal
- Alter the structure and function of arteries

PAD - Atherosclerosis







Available at http://www.vascularweb.org/vascularhealth/Pages/peripheral-artery-disease-%28-pad-%29-.aspx. Accessed on March 30, 2011.

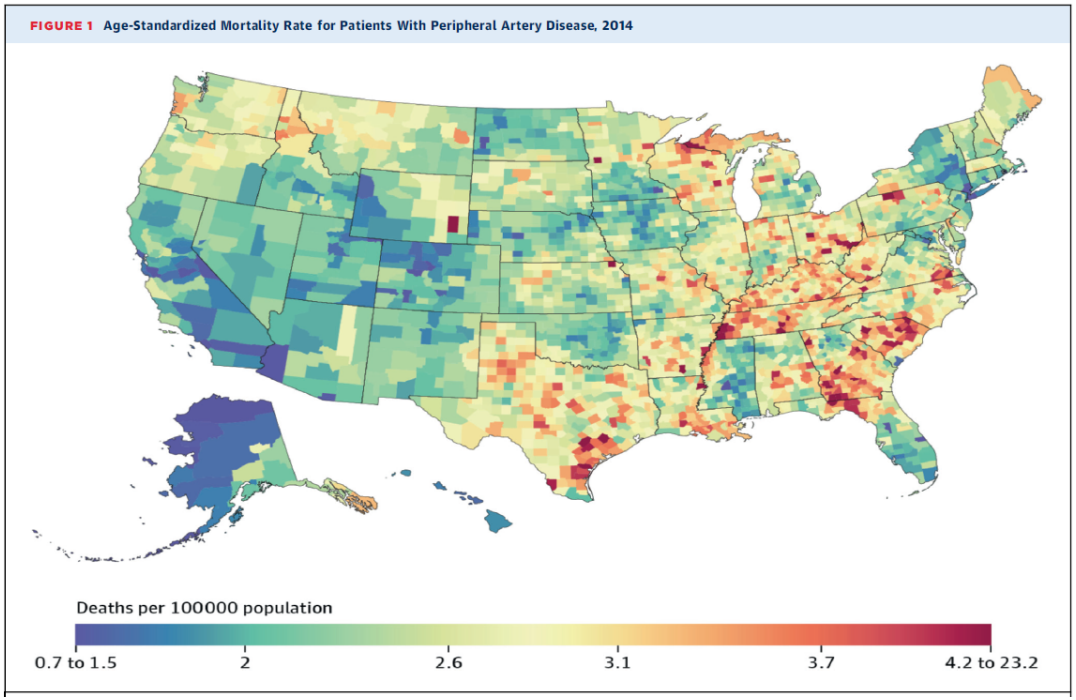
Epidemiology

- PAD affects ~8.5 million persons in US aged ≥ 40 years
- ~202 million people worldwide
- Underdiagnosed
  - Up to 2/3 of US adults with PAD (≥ 40 years) are asymptomatic
    - ¼ have severe PAD
  - In a telephone survey, 26% of adults expressed familiarity with PAD

AHA Heart Disease and Stroke Statistics – 2016 Update

Prognosis

- PAD is a marker for systemic atherosclerotic disease
- High mortality rate due to stroke and MI
- Low risk of losing a limb
  - 1.4% of patients with critical limb-threatening ischemia per year
  - Smokers and diabetics have a higher amputation risk
- Average life span decreased by 10 years
- Women with PAD have faster functional decline and greater mobility loss than men with PAD



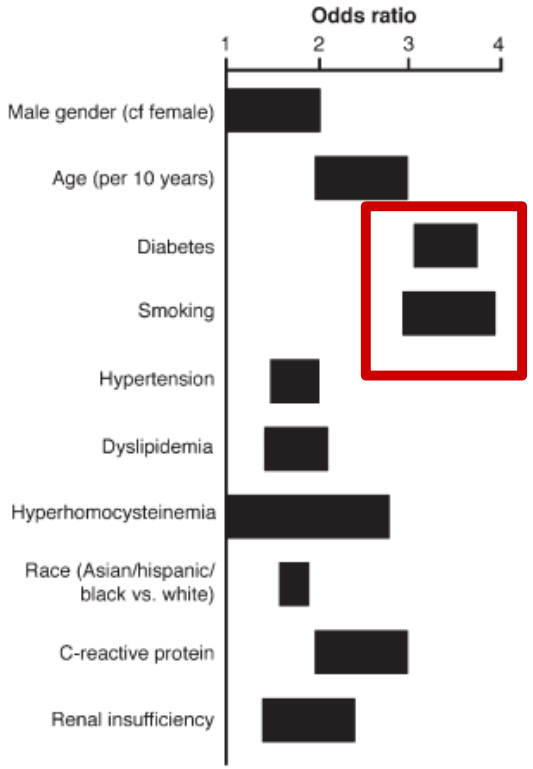
Jones et al. *JACC. 2018;* 71(3):352-362.

Risk Factors

- Race
- Gender
- Age
- Smoking
- Diabetes
- Hypertension
- Dyslipidemia
- Inflammatory Markers
- Hypercoagulable and hyperviscosity states
- Hyperhomocysteinemia
- Chronic Renal Insufficiency

Risk Factors

- Approximate range of odds ratios for risk factors for symptomatic PAD



Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg*. 2007;45(S Suppl):S5-S67.

Increased Risk of PAD

AHA/ACC Guidelines (2016)

- Age ≥ 65 years
- Age 50-64 years, with risk factors for atherosclerosis (e.g. DM, h/o smoking, hyperlipidemia, HTN) or family h/o PAD
- Age < 50 years with DM and 1 additional risk factor for atherosclerosis
- Individuals with known atherosclerotic disease is another vascular bed (e.g. coronary, carotid, subclavian, renal, mesenteric artery stenosis, or AAA)

AHA/ACC Guidelines 2016

Patient Case

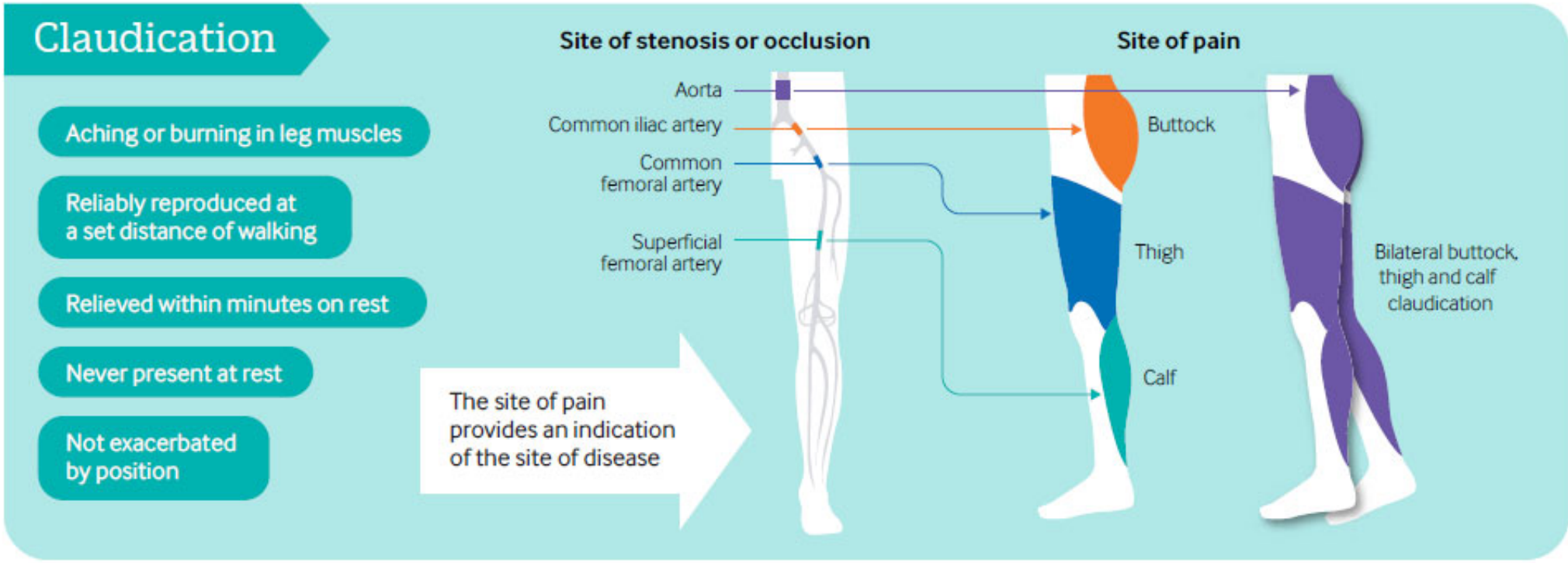
- JM is a 72 yo white female who presents to clinic for her yearly physical exam.
  - PMH: HTN, Type 2 DM x 10 years, dyslipidemia, smokes 1 ppd x 40 years
  - Meds:
    - Lisinopril 10mg po daily
    - Metoprolol 50mg po BID
    - Glipizide 5mg po BID
    - Atorvastatin 20mg po at bedtime

- What are JM's risk factors for PAD?

Symptoms

- Begin gradually
- Patients with PAD are often unaware of early symptoms
- 40% of patients experience no symptoms including leg pain
- ~10% present with intermittent claudication
- 50% have a variety of leg symptoms different from classic claudication
- Small minority present with ischemic pain at rest, ulceration, or gangrene

Intermittent Claudication



BMJ 2018;360:j5842

Non-PAD Causes of Leg Pain

Condition	Location	Characteristic	Effect of Exercise	Effect of Rest	Effect of Position	Other Characteristics
Symptomatic Baker's cyst	Behind knee, down calf	Swelling, tenderness	With exercise	Also present at rest	None	Not intermittent
Venous claudication	Entire leg, worse in calf	Tight, bursting pain	After walking	Subsides slowly	Relief speeded by elevation	History of iliofemoral deep vein thrombosis; edema; signs of venous stasis
Chronic compartment syndrome	Calf muscles	Tight, bursting pain	After much exercise (jogging)	Subsides very slowly	Relief with rest	Typically heavy muscled athletes
Spinal stenosis	Often bilateral buttocks, posterior leg	Pain and weakness	May mimic claudication	Variable relief but can take a long time to recover	Relief by lumbar spine flexion	Worse with standing and extending spine
Nerve root compression	Radiates down leg	Sharp lancinating pain	Induced by sitting, standing, or walking	Often present at rest	Improved by change in position	History of back problems; worse with sitting; relief when supine or sitting
Hip arthritis	Lateral hip, thigh	Aching discomfort	After variable degree of exercise	Not quickly relieved	Improved when not weight bearing	Symptoms variable; history of degenerative arthritis
Foot/ankle arthritis	Ankle, foot, arch	Aching pain	After variable degree of exercise	Not quickly relieved	May be relieved by not bearing weight	Symptoms variable; may be related to activity level or present at rest

Symptoms

- Pain at rest
  - Occurs when IC progresses to critical leg ischemia
  - Pain at night when patient is supine
  - Multilevel arterial involvement
- Ulcers
  - “Kissing ulcers”
  - Nonhealing ulcers
  - Dry gangrene
- Disuse atrophy
  - Loss of muscle mass in lower extremity

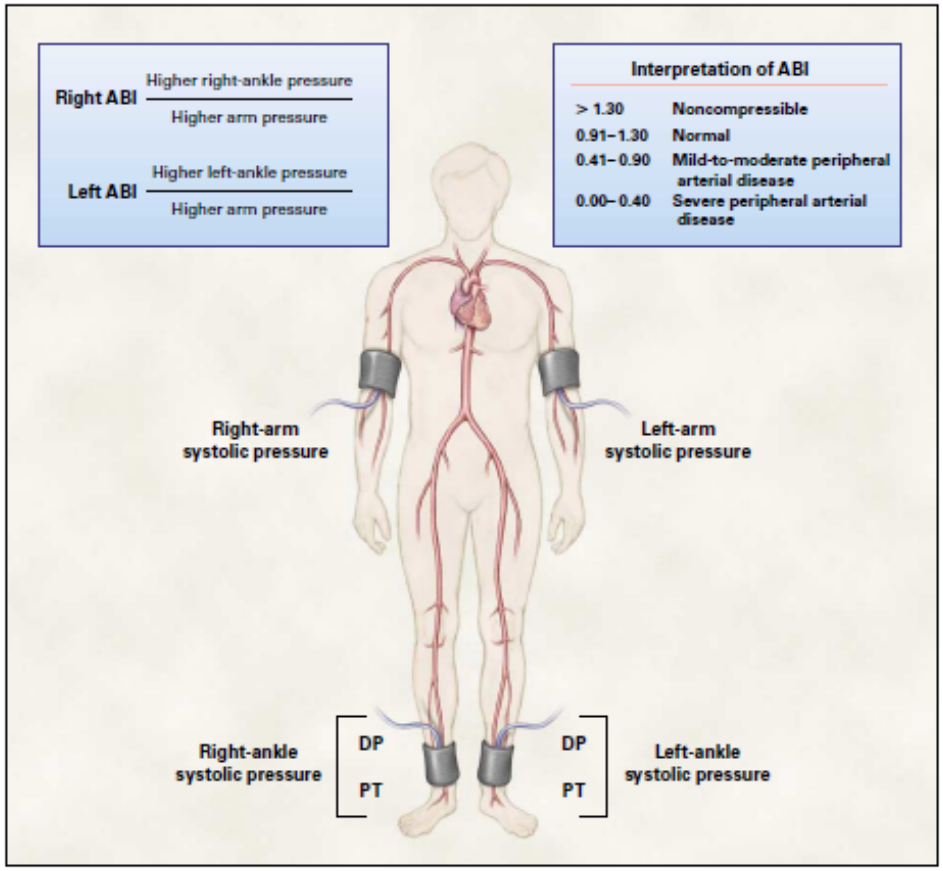
Video: http://www.nejm.org/doi/full/10.1056/NEJMvcm0807012

Diagnosis

For all patients at increased risk (previous slide):

- Clinical history
- Detailed physical exam
  - Quality of pulses
  - Signs of arterial insufficiency
- Systemic illnesses (hyperlipidemia, diabetes)
- Ankle-brachial systolic pressure index (ABI)
  - Higher systolic blood pressure in the pedal artery divided by the higher systolic pressure in the brachial arteries on the same side

Ankle-Brachial Index (ABI)

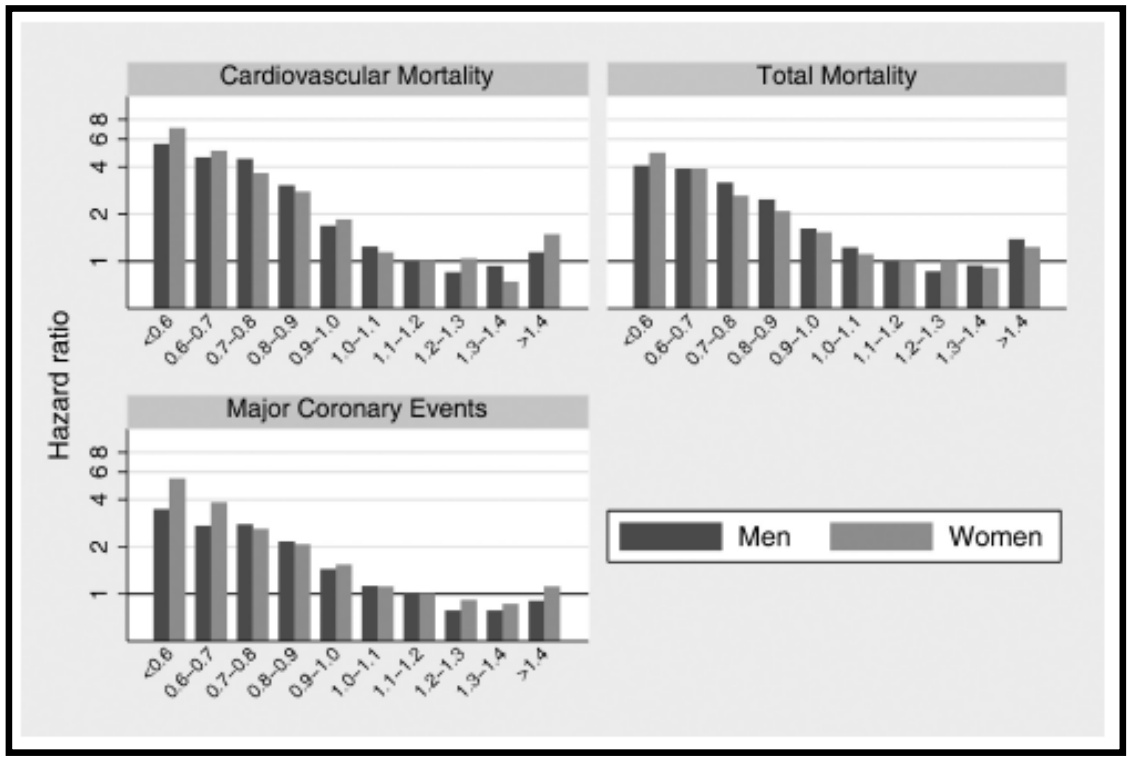


NEJM. 2007;356(12):1241-1250.

AHA/ACC Guidelines (2016)

- > 1.40: noncompressible
- 1.00-1.40: normal
- 0.91-0.99: borderline
- ≤ 0.90: abnormal
  - COR: I, LOR: C-LD

Ankle-Brachial Index (ABI)



Hazard ratios (unadjusted) by ankle-brachial index

Circulation. 2012;125:1449-1472.

Diagnosis

- Exercise treadmill ABI testing
- Toe-brachial index (TBI)
- Perfusion assessment measures
  - Examples: transcutaneous oxygen pressure, skin perfusion pressure
- Anatomic imaging assessment
  - Examples: duplex ultrasound scanning, magnetic resonance angiography (MRA), computed tomographic angiography (CTA), invasive angiography

Goals of Treatment

- Improve symptoms
- Prevent systemic complications of cardiovascular and cerebral atherosclerotic arterial disease

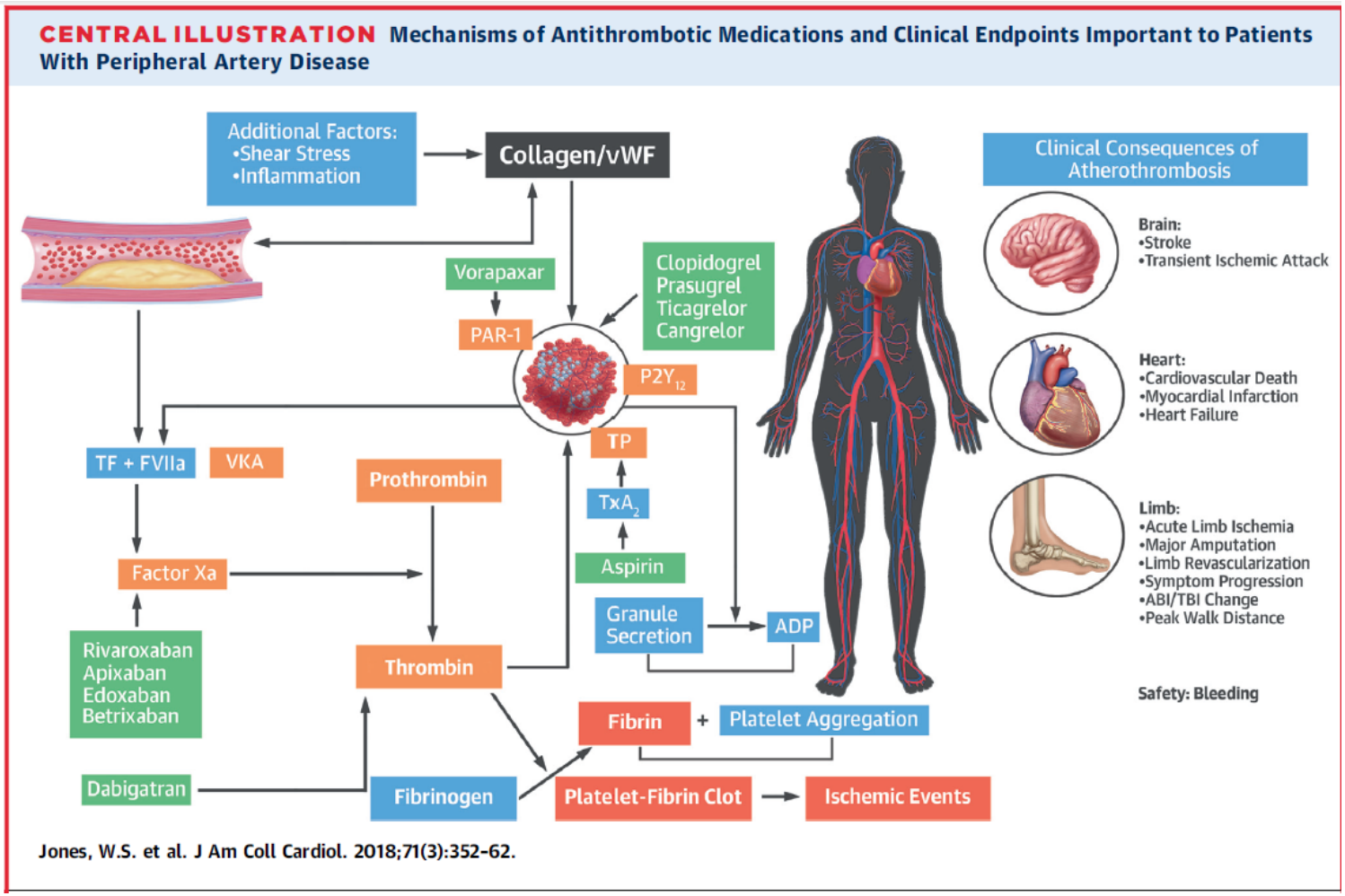
Treatment

- Improve symptoms → improve functional capacity
- Prevent systemic complications of cardiovascular and cerebral atherosclerotic arterial disease → treatment of risk factors

Treatment of Risk Factors

- Antithrombotic therapy
- Hyperlipidemia
- Hypertension
- Smoking cessation
- Diabetes

Antithrombotic Therapy



Antiplatelets

- AHA/ACC Guidelines (2016)
  - Antiplatelet therapy recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD
    - Aspirin alone (range: 75-325mg per day)
    - Clopidogrel alone (75mg per day)
      - COR: I, LOE: A
  - Asymptomatic patients with PAD (ABI ≤ 0.90), antiplatelet therapy is reasonable
      - COR: IIa, LOE: C-EO
  - Asymptomatic patients with borderline ABI (0.91-0.99), the usefulness of antiplatelet therapy is uncertain
      - COR: IIb, LOE: B-R

Antiplatelets

- AHA/ACC Guidelines (2016)
  - Effectiveness of dual antiplatelet therapy (aspirin + clopidogrel) in symptomatic patients is not well established
    - To reduce risk of CV ischemic events
      - COR: IIb, LOE: B-R
  - Dual antiplatelet therapy (aspirin + clopidogrel) may be reasonable in symptomatic patients after LE revascularization
    - To reduce the risk of limb-related events
      - COR: IIb, LOE: C-LD

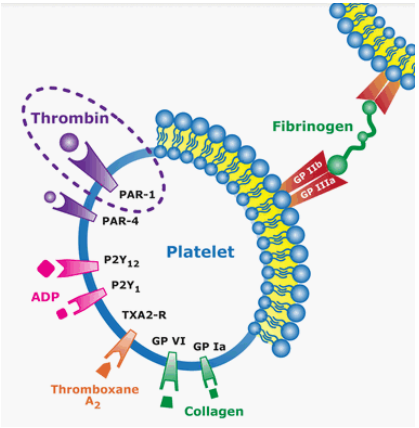
Antiplatelets

- Ticagrelor
  - Two recent studies
    - PEGASUS-TIMI 54: Ticagrelor + aspirin vs. aspirin
      - Patients with h/o MI (only 5% had PAD)
      - Greater absolute risk reduction with ticagrelor in post hoc analysis of PAD patients
    - EUCLID: ticagrelor vs. clopidogrel
      - Symptomatic PAD patients
      - No difference in CV death, MI, or stroke
      - Major bleeding similar
- No clinical trials have examined prasugrel in PAD patients
- ACC/AHA Guidelines (2016)
  - Overall clinical benefit of vorapaxar added to existing antiplatelet therapy in symptomatic patients is uncertain
    - COR: IIb, LOE: B-R

N Engl J Med 2017;376:32-40. J Am Coll Cardiol 2016;67:2719-2728.

Vorapaxar (Zontivity®)

- Reversible antagonist of protease-activated receptor-1 (PAR-1)
  - Inhibits thrombin-induced and thrombin receptor agonist peptide (TRAP)-induced platelet aggregation
- Metabolism: CYP3A4 and CYP2J2
- FDA Approved Indications: history of MI, established PAD
- Pharmacokinetics:
  - ≥80% inhibition of TRAP-induced platelet aggregation within 1 week
  - 50% inhibition of platelet aggregation at 4 weeks after d/c
- Dosing: 2.08mg daily in combo with ASA or clopidogrel
- Drug Interactions:
  - Avoid strong CYP3A4 inducers/Inhibitors, anticoagulants
- Boxed warning – Do not use in patients with h/o stroke, TIA, or ICH; or active pathological bleeding
- Caution in hepatic/renal impairment due to increased risk of bleeding
- Adverse Effects: Bleeding (any grade, 25%), Anemia (5%), Depression (2%), Rash (2%), Iron deficiency (<2%), Retinopathy (<2%)



Oral Anticoagulation

- AHA/ACC Guideline (2016)
  - Usefulness to improve patency after LE autogenous vein or prosthetic bypass is uncertain
    - COR: IIb, LOE: B-R
  - Anticoagulation should not be used to reduced the risk of CV ischemic events in PAD patients
    - COR: III (harm), LOE: A
- WAVE trial
  - Warfarin + aspirin: no benefit with full-dose anticoagulation
- COMPASS trial
  - Patients with stable atherosclerotic vascular disease (CAD, PAD, both)
  - Rivaroxaban (5mg BID) vs. rivaroxaban (2.5mg BID) + aspirin (100mg) vs. aspirin (100mg) alone
  - Stopped early due to benefit, aspirin + rivaroxaban arm better
    - Significantly lower rate of MI, stroke, CV death when compared to aspirin
    - Significantly higher rate of bleeding when compared to aspirin
- Rivaroxaban 2.5mg BID + low-dose aspirin approved late 2018

Hyperlipidemia

- Scandinavian Simvastatin Survival Study (4S)
  - Reduced incidence of IC from 3.6% (placebo) to 2.3% (simvastatin) over 5.4 years
- Simvastatin and atorvastatin improve pain-free walking time
- Non-cholesterol properties of statins may influence leg function in PAD patients
- AHA/ACC Guidelines (2016)
  - Treatment with a statin medication is indicated for all patients with PAD
    - COR: I, LOE: A

Pedersen TR, Kjekshus J, Pyorala K, *et al*. Effect of simvastatin on ischemic signs and symptoms in the Scandinanvian Simvastatin Survival Study (4S). *Am J Cardiol*. 1998;81:333-335.

Hyperlipidemia

- 2018 ACC/AHA guidelines on the management of blood cholesterol
  - PAD considered clinical ASCVD
    - Age ≤75 years
      - High-intensity statin
    - Age > 75 years OR if not candidate for high-intensity statin
      - Moderate-intensity statin

High-Intensity Statin	Moderate-Intensity Statin
Lowers LDL by approx. ≥ 50%	Lowers LDL by approx. 30 - <50%
Atorvastatin 40-80mg **Rosuvastatin 20** (40) **mg**	**Atorvastatin 10** (20) **mg** **Rosuvastatin** (5) **10mg** **Simvastatin 20-40mg** **Lovastatin 40mg** Fluvastatin XL 80mg **Fluvastatin 40mg BID** Pitavastatin 2-4mg

Hypertension

- Lowering blood pressure reduces CV and stroke risk
- BP Goals
  - Use other guidelines
- ACE-I may improve walking distances
- Beta-blockers do not worsen IC
  - Use with caution in patients with severe PAD

Hypertension

- AHA/ACC Guidelines (2016)
  - Antihypertensive therapy should be administered to all patients with HTN and PAD to reduce the risk of MI, stroke, HF, and CV death
    - COR: I, LOE: A
  - ACE-I or ARBs can be effective to reduce the risk of CV ischemic events
    - COR: IIa, LOE: A

Smoking Cessation

- AHA/ACC Guidelines (2016)
  - Patients who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit
    - COR: I, LOE: A
  - Patients who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (ie. varenicline, bupropion, and/or NRT) and/or referral to a smoking cessation program
    - COR: I, LOE: A
  - Patients with PAD should avoid exposure to environmental tobacco smoke at work, at home, and in public places
    - COR: I, LOE: B-NR

Smoking Cessation

- Counseling
  - 5 A's – Ask, Advise, Assess, Assist, Arrange
  - AAR – Ask, Advise, Refer
- Resources
  - Rx for Change program
  - 1-800-QUIT-NOW
  - Web-based counseling

Diabetes

- Estimated that each 1% increase in A1c associated with a 28% increased risk of incident PAD
- Perform regular foot exams
- AHA/ACC Guidelines (2016)
  - Management of DM should be coordinated between members of the healthcare team
    - COR: I, LOE: C-EO
  - Glycemic control can be beneficial for patients with chronic limb ischemia to reduce limb-related outcomes
    - COR: IIa, B: NR

Improve Functional Capacity

- Exercise
- Medications
  - Cilostazol
  - Pentoxifylline
- Revascularization

Exercise

- Improves maximal walking time and walking ability
- AHA/ACC Guidelines (2016)
  - In patients with claudication, supervised exercise program is recommended to improve functional status and QOL and to reduce leg symptoms
    - COR: I: LOE: A
  - Structured community- or home-based exercise program with behavioral change techniques can be beneficial to improve walking ability and functional status
    - COR: IIa, LOE: A

Intermittent Claudication – Cilostazol (Pletal)

- Phosphodiesterase type 3 inhibitor
  - Inhibits platelet aggregation and causes vasodilation
- Dosing: 50-100 mg po BID
- Administration: 30 minutes before or 2 hours after meals
- Drug Interactions: CYP3A4 and CYP2C19
- SE: HA, diarrhea, dizziness, palpitations
- Improves maximum walking distance and pain-free walking distance
- Contraindicated in PAD patients with heart failure

Intermittent Claudication

- Cilostazol (Pletal)
  - AHA/ACC Guidelines (2016)
    - Effective therapy to improve symptoms and increase walking distance in patients with claudication
      - COR: I, LOE: A
  - CHEST Guidelines 2012
    - For pts with IC refractory to exercise therapy AND smoking cessation, cilostazol is suggested in addition to other antithrombotic therapies (Grade 2C)

AHA/ACC 2016 PAD Guidelines
CHEST 2012 Guidelines. 9th Edition. e669S-690S.

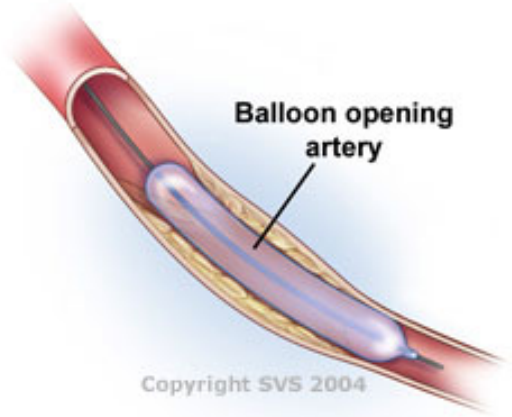
Intermittent Claudication – Pentoxyifylline (Trental)

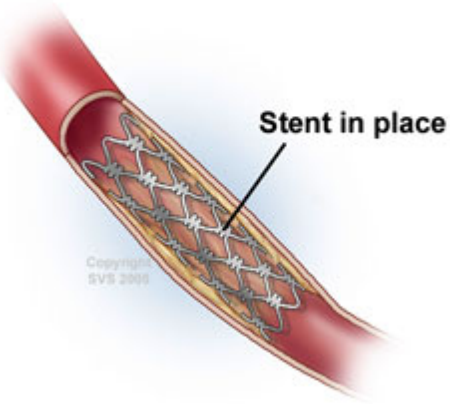
- MOA: Relaxes smooth muscle causing vasodilation
- Dosing: 400mg po TID with meals
- SE: Nausea, vomiting
- Only about 20% of patients benefit
  - Trial of 2-3 months is reasonable
- AHA/ACC Guidelines (2016)
  - Not effective for treatment of claudication
    - COR: III (no benefit), LOE: B-R

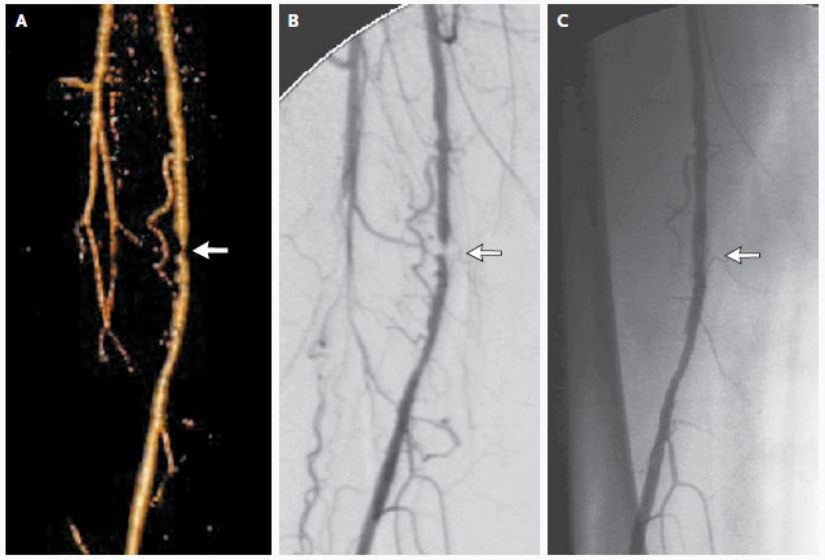
Revascularization

- Angioplasty and Surgery
- Used for patients with:
  - Lifestyle-limiting claudication
  - Chronic limb ischemia (CLI)

Angioplasty and Stenting



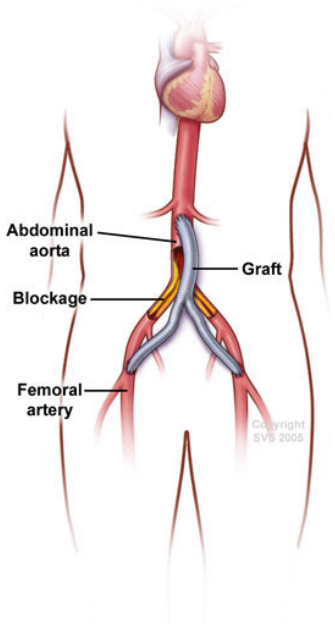


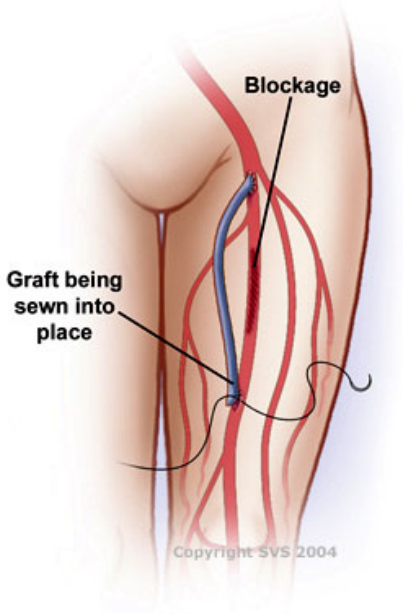


White C. Intermittent claudication. *N Engl J Med*. 2007;356:1241-1250.
Available at http://www.vascularweb.org/vascularhealth/Pages/angioplasty-and-stenting.aspx. Accessed on March 30, 2011.

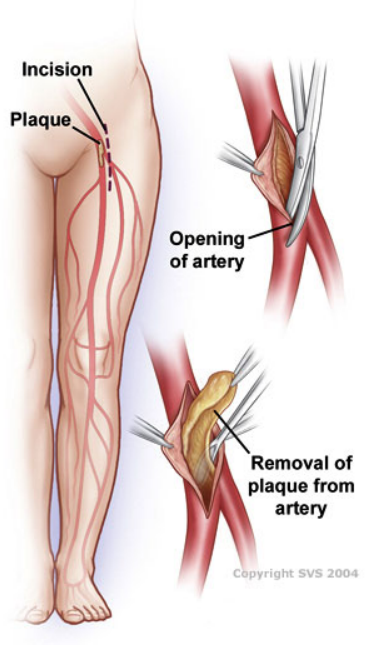
Surgical Procedures

- Bypass Surgery





- Endarterectomy



Available at http://www.vascularweb.org/vascularhealth/Pages/surgical-bypass.aspx. Accessed on March 29, 2011.
Available on http://www.vascularweb.org/vascularhealth/Pages/endarterectomy.aspx. Accessed on March 30, 2011.

Lowering Homocysteine

- Folic Acid
- Vitamin B12 (cyanocobalamin)
- Useful in patients with homocysteine levels greater than 14 mmol/L
- AHA/ACC Guidelines (2016)
  - B-complex vitamin supplementation to lower homocysteine levels for the prevention of CV events is not recommended
    - COR: III (no benefit), LOE: B-R

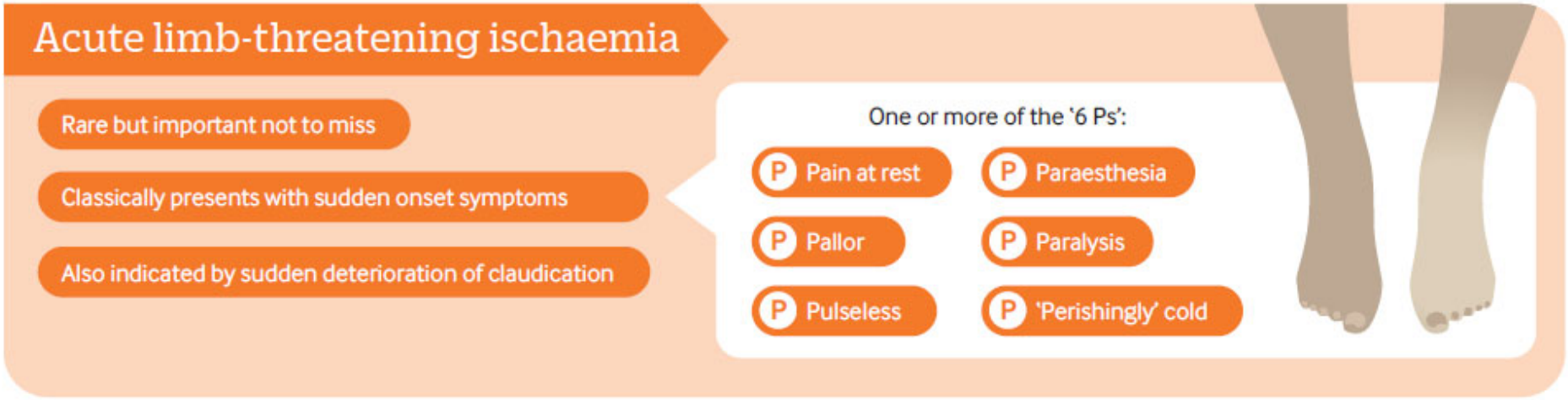
Patient Case

- JM is a 72 yo white female who presents to clinic for her yearly physical exam.
  - PMH: HTN, Type 2 DM x 10 years, dyslipidemia, smokes 1 ppd x 40 years
  - Meds:
    - Lisinopril 10mg po daily
    - Metoprolol 50mg po BID
    - Glipizide 5mg po BID
    - Atorvastatin 20mg po at bedtime
  - SH: 1-2 glasses of wine/day, 1-2 cups of coffee/day, walks 1-2 days/week for 10 minutes
- JM mentions that she has been having leg pain with exercise over the past few months.
  - ABI =0.82 (right), ABI=0.74 (left)
- Vitals: BP: 136/84 mmHg, HR 72 bpm
- Labs: FLP: 205 / 186 / 42 / 126 A1c = 6.6 %

What are your recommendations for JM?

Acute Limb Ischemia

- Symptom duration < 2 weeks
- Medical emergency
- Causes
  - Thrombotic
  - Embolic



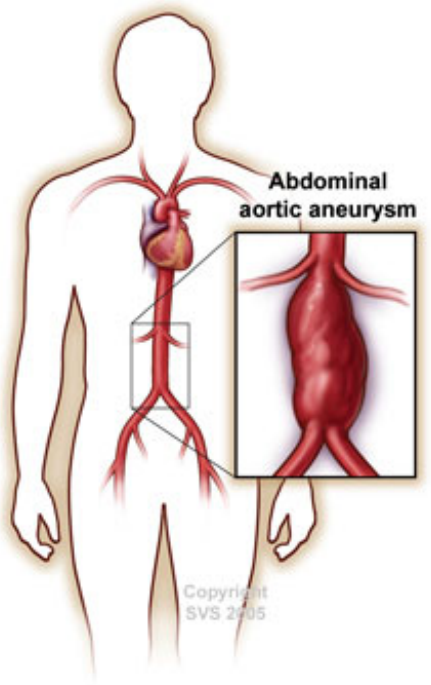
BMJ 2018;360:j5842

Acute Limb Ischemia

- AHA/ACC Guidelines (2016)
  - Systemic anticoagulation with heparin unless contraindicated
    - COR: I, LOE: C-EO
  - Revascularization determined by local resources and patient factors
    - COR: I, LOE: C-LD
  - Cather-based thrombolysis is effective
    - COR: I, LOE: A
  - Amputation if limb is nonsalvageable
    - COR: I, LOE: C-LD
  - Surgical thromboembolectomy can be effective
    - COR: IIa, LOE: C-LD

Aneurysms

- Most common cause is atherosclerosis
- Predisposing factors
  - Hypertension
  - Trauma
  - Infection
  - Inflammatory diseases
- More common in men and with age
- Most are asymptomatic
- Complications related to the site of the aneurysm
  - Rupture
  - Thromboembolic events
  - Compression or erosion of adjacent tissues
- Abdominal aortic aneurysms (AAA)



Questions?

- Don’t hesitate to reach out with any questions or concerns:
  - Andrea Porter – andrea.porter@wisc.edu