
Pharmacotherapy of Peripheral Arterial Disease(PAD)

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Definition

- PAD is the most common form of peripheral vascular disease
 - which is a manifestation of progressive narrowing of arteries due to **atherosclerosis**.
- PAD is associated with elevated risk of CVD morbidity and mortality
- The prevalence of PAD is highly dependent on age,
 - being infrequent in younger individuals and **common in older individuals**

Clinical Spectrum of Atherosclerosis

Cerebro-vascular disease

Coronary artery disease

Renal artery Diseases

Visceral arterial disease

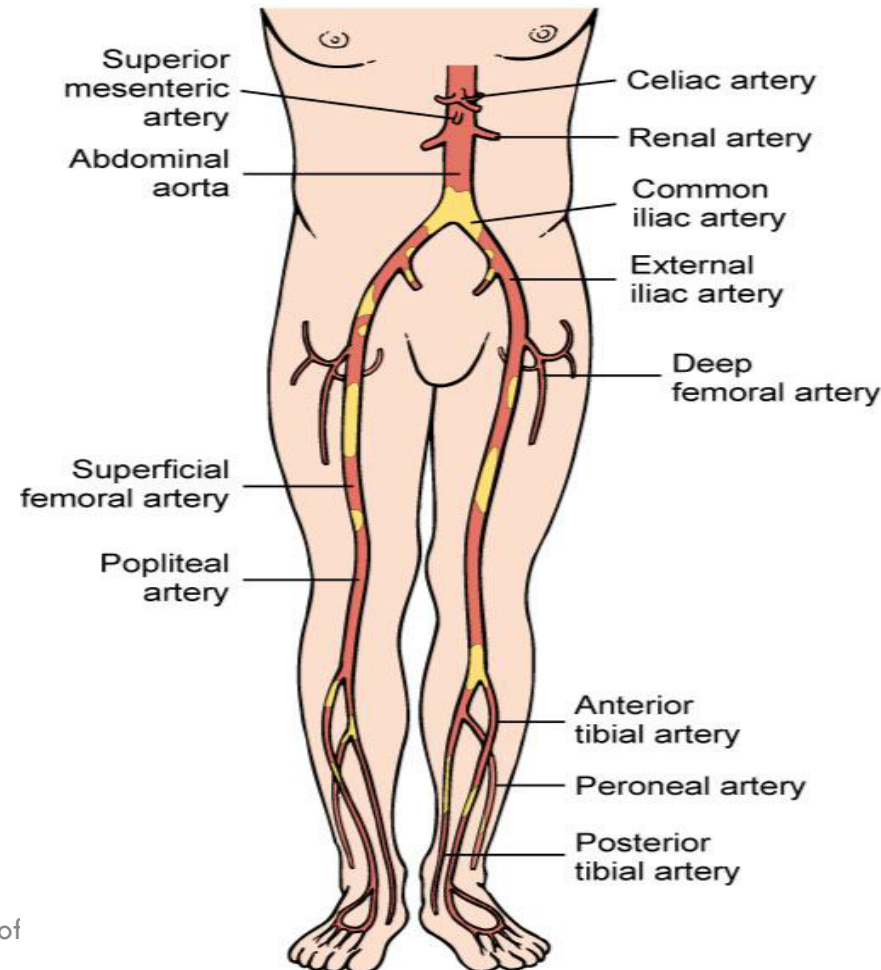
Peripheral arterial disease
Intermittent claudication
Critical limb ischemia
Acute limb ischemia

Pathophysiology

- PAD is most commonly a manifestation of systemic atherosclerosis in which
 - the arterial lumen of the lower extremities becomes progressively occluded by atherosclerotic plaque.
- The major risk factors for the development of atherosclerosis are
 - older age (greater than 40 years)
 - cigarette smoking
 - diabetes mellitus
 - hypercholesterolemia
 - hypertension and
 - hyperhomocysteinemia

Cont...

- The arteries most commonly involved, in order of occurrence, are
 - the femoropopliteal-tibial
 - aortoiliac
 - carotid and vertebral
 - splenic and renal and
 - brachiocephalic



Clinical Presentations

- The clinical presentation of PAD is **variable**, ranging
 - from no symptoms at all (typically early in the disease) to pain and discomfort
- The two most common characteristics of PAD are
 - intermittent claudication (IC) and
 - pain at rest in the lower extremities

Cont...

- **Intermittent Claudication (IC)**
 - is generally regarded as the **primary indicator** of PAD.
 - It is described as reproducible fatigue, discomfort, cramping, pain, or numbness in the affected extremities (typically the buttock, thigh or calf) during exercise and is resolved within a few minutes with rest.
 - Symptoms of IC occur during exercise as the increase in blood flow is limited by occlusive atherosclerotic lesions in the peripheral arteries leading to an inability for oxygen supply to meet the demands of increased metabolic demand by the muscles.

Cont...

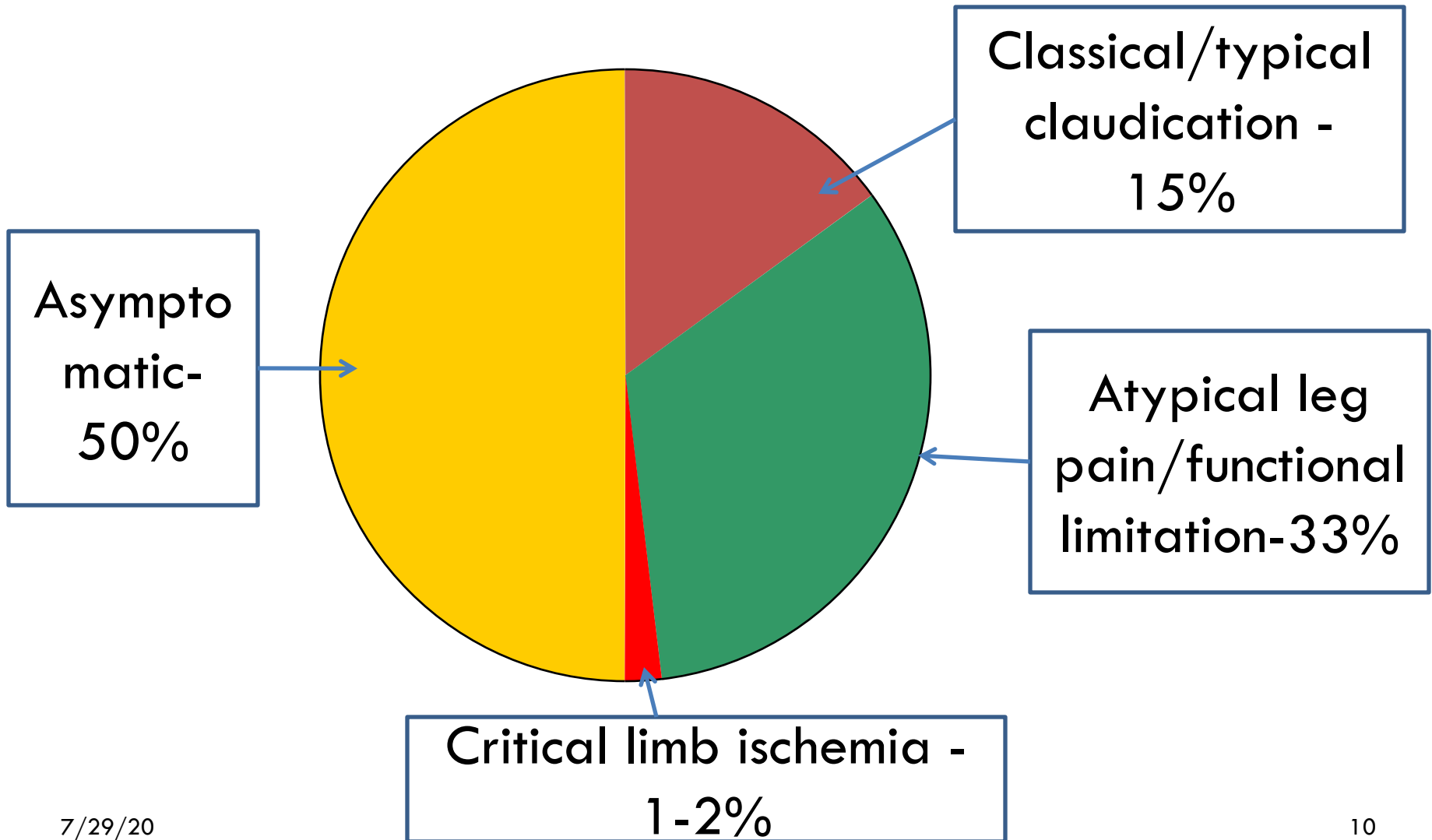
- **Resting Pain**

- typically occurs **later** in the disease when the blood supply is not adequate to perfuse the extremity (**critical limb ischemia**)
- This can be felt most often at **night** in the feet (typically the toes or heel) while the patient is lying in bed.

- Although IC is the primary indicator of PAD, it alone cannot be used to diagnose PAD.

- patients with PAD may not have symptoms of IC because they may have a sedentary lifestyle or some other condition that may be limiting the ability to exercise.

Clinical presentation of PAD



Cont...

TABLE 1 Clinical Presentation of Peripheral Arterial Disease

General

- Patients with PAD are likely to be 40 years of age and older with hypertension, hypercholesterolemia, diabetes, impaired renal function, a history of coronary artery disease or cardiovascular disease, and/or a history of smoking.

Signs and symptoms

- The clinical presentation of PAD is variable and includes symptoms ranging from no symptoms at all (typically early in the disease) to pain and discomfort.
- The two most common characteristics of PAD are intermittent claudication and pain at rest in the lower extremities.
- Intermittent claudication is generally regarded as the primary indicator of PAD. It has been described as fatigue, discomfort, cramping, pain, or numbness in the affected extremities (typically the buttock, thigh, or calf) during exercise and resolves within a few minutes with rest.
- Physical examination may reveal nonspecific signs of decreased blood flow to the extremities (e.g., cool skin temperature, shiny skin, thickened toenails, lack of hair on the calf, feet, and/or toes).

Diagnosis

- A detailed **patient history of symptoms** and atherosclerosis **risk factors** (e.g., smoking, hypertension, hyperlipidemia, and diabetes) can be helpful in the diagnosis of PAD.
- Unfortunately, providers who rely on a history alone will **miss** approximately **85% to 90%** of patients with PAD.
- Therefore, examination of the patient is vital to proper diagnosis.

Cont...

- Requesting that the patient remove socks and shoes may reveal **non specific signs of decreased blood flow** to the extremities e.g.,
 - cool skin temperature
 - shiny skin
 - thickened toenails
 - lack of hair on the calf, feet and/or toes
 - in severe cases, visible sores or ulcers that are slow to heal and may even be black in appearance

Cont...

- An important criterion for the **accurate diagnosis** of PAD is
 - the **exclusion** of other conditions that possess similar signs and symptoms.
- Differential diagnosis should rule out conditions that may mimic PAD like,
 - neurologic conditions (e.g., peripheral neuropathy)
 - inflammatory conditions (e.g., arthritis)
 - vascular conditions (e.g., DVT)

Cont...

- The **ABI (Ankle-Brachial Index)**
 - is a simple, noninvasive, quantitative test that has been proven to be a highly sensitive and specific (90%) tool in the diagnosis of PAD.
 - For measurement of the ABI,
 - the patient lies in the supine position as the SBP is measured at the brachial arteries on both arms and the dorsalis pedis and posterior tibial arteries of the legs with a standard sphygmomanometer and a continuous-wave Doppler device.

Cont...

- The pressures obtained at the dorsalis pedis and posterior tibial arteries are averaged and divided by the mean measurement taken at the left and right brachial arteries.
- An ABI of 1 is considered normal, while a measurement under 0.9 is consistent with PAD.
 - 0.91-0.99= borderline
 - 0.7 - 0.9 = mild PAD
 - 0.4 - 0.7= moderate disease
 - <0.4 =severe PAD

Cont...

- In addition to providing diagnostic information, the ABI measurement has been shown to be a **strong predictor of future cardiovascular events** associated with PAD.
- ABI can **rule out PAD** and suggest alternate diagnosis.
- ABI can be considered as a useful tool in diagnosing both **symptomatic** and **non-symptomatic** patients at high risk of PAD.

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Imaging studies

- **Magnetic resonance angiography (MRA) and Computed Tomographic angiography (CTA)**
 - examine the **presence** and **location** of significant **stenosis** and is a reasonable option for patients who are being considered for surgical **revascularization**.
 - determine the presence of soft tissue diagnostic information that may be associated with PAD (e.g., aneurysms).
- However, as ABI is a sufficient means of diagnosis,
 - **arteriography** is not necessary or encouraged

Desired Outcome

- **Treatment goals for PAD include,**
 - increasing maximal walking distance
 - increasing duration of pain-free walking
 - improving control of comorbid conditions contributing to the morbidity of the condition
 - e.g., hypertension, hyperlipidemia, and diabetes
 - improving overall quality of life and reducing cardiovascular complications and death

Treatment

General Approach

- As with any atherosclerotic condition, several risk factors **play an important role in the morbidity and mortality of PAD.**
- **Many** of these risk factors are **modifiable** with the help of various non-pharmacologic and pharmacologic interventions.

Non-pharmacologic Therapy

- **Smoking Cessation**

- Cigarette smoking not only increases the risk of developing PAD and other cardiovascular disorders, but the quantity smoked and the duration can negatively impact disease progression (e.g., increase the risk of amputation) and increase mortality.
- As a result, providers must advise patients to quit and should offer non-pharmacologic and pharmacologic means to aid the patient in that goal.

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- Individual or group **behavior modification therapy** with or without the addition of certain antidepressants (e.g., **bupropion**), **varenicline**, or **nicotine replacement therapies** (e.g., gum or patches) has been proven effective in numerous studies.
- Reassessment of smoking status and progress encouragement at each encounter can help to re-emphasize to the patient the vital importance of this lifestyle change.

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- **Exercise**

- Walking exercise programs for patients with PAD have been proven to result in
 - an increase in walking duration and distance
 - an increase in pain-free walking and
 - a delayed onset of claudication by **179%**.
- Walking, or any aerobic exercise program conducted under the supervision of a healthcare provider,
 - has the ability to positively impact several of the pathophysiologic abnormalities present in patients with PAD.

Cont...

- Benefits of exercise programs include
 - improving diabetes and lipid management
 - reducing weight
 - improving blood viscosity and flow
 - reducing blood pressure
- **Walking distance** can also be used as a **prognostic tool** for future outcomes for patients with normal and impaired ABIs.
 - walking impairment in conjunction with impaired ABI is associated with higher cardiovascular events, including death.

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- The ACC/AHA Guidelines for the management of PAD recommends supervised exercise training for patients with IC,
 - for a minimum of 30 to 45 minutes
 - to be performed at least 3 times per week
 - for a minimum of duration of 12 weeks.
- PAD patients with higher physical activity have reduced mortality and cardiovascular events
 - compared with those with low physical activity

Cont...

- **Exercise treadmill walking testing** should be repeated at regular intervals (e.g., quarterly to biannually)
 - to assess improvement or decline in walking duration and distance, as well as the time to pain onset while performing this activity.
- The type of aerobic activity recommended, as well as the duration and frequency of the activity, should be individually designed on a patient-to-patient basis.



Cont...

- **Surgical Interventions**
 - Various surgical procedures are available for patients
 - with **severe, debilitating claudication** who have attempted, and failed, other means of non-pharmacologic and pharmacologic therapy.

Cont...

- The Trans Atlantic Inter-Society Consensus (TASC) document on PAD provides clear recommendations for invasive therapy.
 1. there must be a lack of adequate response to exercise therapy and risk factor modification.
 2. the patient must have severe disability from IC resulting in impairment of daily activities
 3. there must be a thorough evaluation of the risks versus benefits of an invasive intervention

Cont...

- **Percutaneous transluminal angioplasty (PTA)**
 - is an example of an invasive treatment for PAD.
 - PTA typically is reserved for patients whose lifestyle and/or job performance are compromised secondary to claudication despite adequate pharmacologic interventions and exercise

Cont...

- **Stent placement**

- The TASC document provides specific recommendations for PTA, with or without stenting, depending on how diffuse the disease process is, the number and size of the lesions, and the location of the lesions.
- For patients with severe IC resulting in critical leg ischemia, physicians may need to discuss alternate surgical interventions including
 - **aorto-femoral bypass**
 - **femoro-popliteal bypass**
 - **amputation**

Treatment

Pharmacologic Therapy

- **Hypertension**

- HTN is a major risk factor for PAD and can lead to AMI, stroke, HF and death.
- Current guidelines recommend the treatment goal for BP in patients with PAD to be **<140/90 mm Hg**.
- No specific class of anti-hypertensive drugs are recommended over another for the treatment of hypertension for patients with PAD.

Cont...

- Therefore, selection of drug therapy for hypertension should be made in accordance with JNC 8 guidelines on the basis of
 - comorbid disease states
 - drug costs and availability
 - drug allergies or
 - other possible limiting factors

Cont...

- For example, patients with concomitant
 - Raynaud phenomenon may benefit from CCBs, while
 - patients with documented CAD may receive a dual benefit by the selection of a BB
 - BBs should be used with caution for patients with critical leg ischemia where acute lowering of BP is contraindicated

Hypertension medication for specific comorbidities

Indication	Medications
• Heart failure	thiazide, beta blocker, ACEI, ARB
• Diabetes	ACEI
• CKD	ACEI, ARB
• Post- MI	beta blocker, ACEI
• Atherosclerosis	ACEI
• Angina	beta blocker
• CVD risk	thiazide, beta blocker, ACEI, ARB

Cont...

- **Dyslipidemia**

- a reduction in lipid levels can reduce the progression of PAD and the severity of claudication
- The ATP III considers PAD to be in the category of highest risk, or a coronary heart disease (CHD) risk equivalent
- LDL goal: maintained at <100 mg/dL (experts now recommend an LDL goal of <70 mg/dL)
- non-high-density lipoprotein levels (TC-HDL) goal: <130 mg/dL.

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- Regardless of the goal LDL chosen, initiation of TLCs
 - reduction in saturated fat
 - weight reduction and
 - increased physical activity are vital to achieving these recommendations.
- Unfortunately, in many cases, TLCs alone will not achieve the desired goals.
- Several options are available for the initiation of drug therapy for **LDL lowering** for patients with PAD.

Cont...

- **Statins, bile acid sequestrants, and nicotinic acid** are all effective treatment options.
- However, in most cases, **statins** are the **preferred** starting agent in this patient population.
 - Found to provide a significant reduction in CV events (e.g., AML, stroke and death).
- If an increase in HDL levels is also necessary,
 - niacin should be considered alone or in combination with a statin without the fear of worsening glucose metabolism

Cont...

- **Diabetes Mellitus**

- Due to the high prevalence of PAD among DM patients,
 - ADA recommends ABI screening for PAD in all diabetics older than 50 years
- Due to the presence of peripheral neuropathy, patients with diabetes may be less likely to experience or report symptoms of PAD,
 - first sign may be as drastic as the appearance of a gangrenous foot ulcer.
- It is widely recommended that all patients with concomitant diabetes and PAD maintain good glycemic control, as evidenced by a HA-1c level of $<7\%$

Treatment

Antiplatelet Drug Therapy

- **Aspirin**

- By far, the most compelling evidence for the use of any pharmacologic agent in PAD can be found for aspirin
- low-dose ASA (75 to 160 mg) and medium-dose ASA (160 to 325 mg/day) lead to a significant reduction in serious vascular events in "high-risk" patients, such as those with PAD.
- the risk of major extracranial bleed is similar between the low-dose and medium-dose regimens.

Cont...

- patients with PAD should use ASA (160 to 325 mg/day) or clopidogrel (75 mg/day) when ASA is not tolerated or contraindicated.
- lifelong ASA (75 to 325 mg/day) is recommended over clopidogrel, ticlopidine and no antithrombotic therapy for patients with PAD.
- Unfortunately, no data are currently available from large, clinical, randomized trials that ASA, or any other antiplatelet therapies, can actually prevent or delay the progression of PAD

Cont...

• Aspirin Plus Dipyridamole Extended Release (Aggrenox)

- In one trial, addition of dipyridamole to aspirin led to an additional reduction in serious vascular events over ASA alone
- however, this reduction was unable to reach statistical significance
- The addition of dipyridamole to ASA may cause an increased risk of bleeding and gastrointestinal side effects when compared with placebo and should not be used with CAD.

Cont...

- **Clopidogrel (Plavix)**

- although clopidogrel was able to reduce serious vascular events, it is significantly less than the reduction seen with ASA
- current recommendations list clopidogrel as a first-line agent, but only in cases where ASA therapy is either not tolerated or contraindicated

TABLE 2 Pharmacotherapy Options for Patients with Peripheral Arterial Disease

Agent	Daily Dose (Oral)	Mechanism of Action	Side Effects	Contraindications	Level of Evidence^b
Aspirin	81–325 mg	Irreversibly inhibits prostaglandin cyclooxygenase in platelets, prevents formation of thromboxane A ₂	Gastrointestinal upset and/or bleeding	Active bleeding; hemophilia; thrombocytopenia	With coronary or cerebrovascular (grade 1A), without (grade 1C+)
Dipyridamole extended-release (Aggrenox)	400 mg (+ aspirin 50 mg)	May act by inhibiting platelet aggregation (complete mechanism of action unknown)	Angina, dyspnea, hypotension, headache, dizziness	Active bleeding; coronary artery disease ("coronary steal syndrome")	Recommendation for use not specified in report
Cilostazol (Pletal) ^a	100 mg bid	Phosphodiesterase inhibitor, suppresses platelet aggregation; direct artery vasodilator	Fever from infection, tachycardia	All congestive heart failure patients (decreased survival)	With intermittent claudication (grade 2A)
Clopidogrel (Plavix)	75 mg	Inhibits binding of ADP analogues to its platelet receptor, causing irreversible inhibition of platelets	Chest pain, purpura generalized pain, rash	Active pathologic bleeding (e.g., peptic ulcer, intracranial hemorrhage)	Recommend clopidogrel over no antiplatelet therapy (grade 1C+)
Pentoxifylline (Trental)	1.2 g	Alters red blood cell flexibility; decreases platelet adhesion; reduces blood viscosity; decreases fibrinogen concentration	Dyspnea, nausea, vomiting, headache, dizziness	Recent retinal or cerebral hemorrhage; active bleeding	Not recommended in patients with intermittent claudication (grade 1B)
Ticlopidine (Ticlid)	500 mg	Inhibits binding of ADP analogues to its platelet receptor, causing irreversible inhibition of platelets	Leukopenia; rash; thrombocytopenia; neutropenia, agranulocytosis; aplastic anemia	Active bleeding, hemophilia; thrombocytopenia	Clopidogrel recommended over ticlopidine (grade 1C+)

^aCilostazol should be used in combination with antiplatelet therapy.^bGrades of recommendation for antithrombotic and thrombolytic therapy are part of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.

Evaluation of Therapeutic Outcomes

- It is vital that the patient be counseled on the evaluation measures that will be used to monitor the outcomes of therapeutic interventions for PAD.
- Various measurements
 - hemoglobin A-1c
 - total cholesterol, LDL, HDL, and non-HDL cholesterol
 - blood pressure checks in the clinic and patient home blood pressure monitoring can assess the effectiveness of antihypertensive therapy.

Cont...

- Repeat exercise treadmill walking testing
- Repeat ABI measurements should be assessed at each patient visit
 - to determine if there has been stabilization or progression of the disease process.
- Most importantly to many patients, simple concern and questioning about improvements to their daily quality of life will aid in an overall picture of the patient's general state of health.

