PERIPHERAL ARTERY DISEASE
Misunderstood, Under-diagnosed, and Ignored

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We all appreciate the dangers of cardiovascular disease (CVD). One third of us will have a CV event in our lifetime, and one quarter will die from it. The underlying process is a combination of atherosclerosis that is compounded and extended by thrombus formation. This process, ***"atherothrombosis",*** can affect the cerebral, coronary, or peripheral vascular circulation.

Hidden Risk for PAD

Peripheral arterial disease (PAD) is a common disease, frequently overlooked, that is associated with a markedly increased risk of CV and cerebrovascular events[1] and mortality[2]. Approximately 8 million people have PAD, but only about 50% are aware of their diagnosis. The other 50% have significant obstruction but are asymptomatic (no claudication) and their PAD is hidden.

PAD is one of the most serious health problems affecting the elderly today.[3] The relationship of PAD to age is striking:

<50 yrs < 1%, <60 yrs < 3%,

> 70 yrs ~ 20% in men and ~13% in women

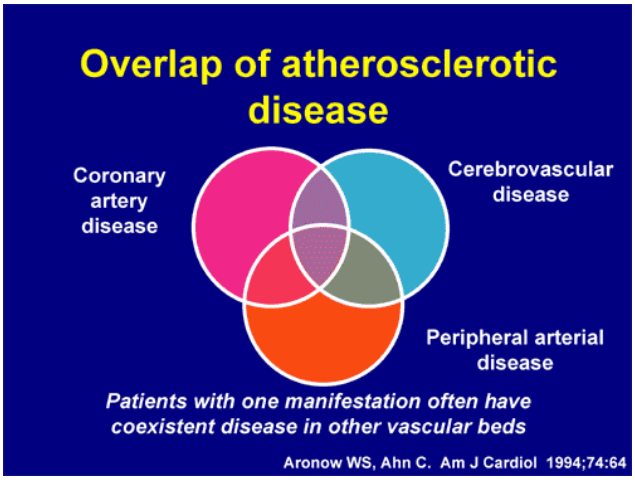
With the proportion of elderly people to the general population growing nationwide, PAD will affect a larger and larger number of people. Unfortunately, patients with PAD are often not diagnosed until the disease is advanced. Additionally, even when PAD is diagnosed early, the CV risks associated with it are often unrecognized and therefore not treated.

1) Individuals seldom die from PAD per se. The mortality from it is relatively small, but that does not lesson its importance.
2) Less than half of patients with significant large-vessel (LV)-PAD have the "classic" intermittent claudication symptoms. This makes the diagnosis difficult; even when present this is only the symptomatic tip of the iceberg.
3) Patients and physicians have difficulty associating leg pain with risk of serious heart disease or stroke.
4) The name itself, *peripheral*, suggests that it is out of sight and unimportant.

The risk of dying from CHD and cerebrovascular disease in patients with PAD is about 2X the risk of dying from other causes. If you diagnose PAD, you are picking up a major marker of CVD that needs to be urgently managed.

Hidden Overlap

PAD overlaps significantly with coronary heart disease (CHD) and cerebrovascular disease[4].



What is interesting is that the overlap is much greater than you might suspect.

The harder you look, the more you find! For instance, in looking for CHD in a patient with PAD, if you do a history, physical and EKG, the incidence would probably be between 20-30%, possibly as high as 40%. If you add a stress myocardial perfusion imaging study, the incidence of CVD in a patient with PAD would jump to over 60%. If you also did coronary angiography, the incidence could jump to greater than 90%.

In patients with PAD, if you look for cerebrovascular disease, you would find the incidence of clinical history of stroke varies from 0.5% to as high as 15%. If you checked for a carotid bruit, the incidence would jump to 45%, and if you did a carotid Doppler, it might go over 50%. *The size of the "hidden" overlap is a function of the intensity of your search.*

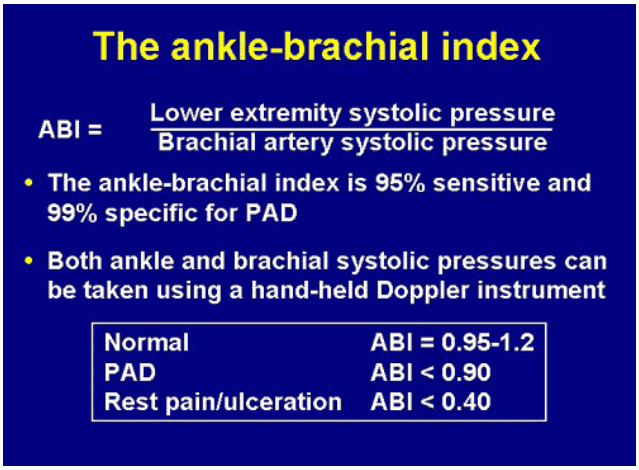
Identification (Diagnosis) of PAD

Identification of PAD provides an important opportunity to introduce therapies that will reduce CV and cerebrovascular events and mortality.

Intermittent claudication, the classic diagnostic symptom for PAD, is usually described as a cramping discomfort or pain in the calf muscles, which occurs reproducibly with exercise and is relieved with rest. The symptoms may occur in the thigh, hip or buttock muscles also. It has also been described as a feeling of aching, tightness, numbness or fatigue. Unfortunately, claudication only develops when demand of the working muscle exceeds supply, and this only occurs in more severe disease, approximately 50% of cases. Furthermore, most physicians familiar with this common symptom are not aware that only about 25% to 33% of all patients with PAD will complain of these symptoms.

The simplest way for the clinician to measure PAD in an accurate way is the ankle-brachial index (ABI).

It is an inexpensive, office-based, non-invasive diagnostic test that is both highly sensitive and specific for PAD. By measuring the systolic pressure ankle to arm ratio using a hand-held Doppler, we can quantitatively stratify PAD severity in nearly all individuals, whether they are symptomatic or asymptomatic. (Normal is > 0.95)



An increase in risk of death from CVD is associated with decreasing ABI levels[5]. Because we cannot rely on the history of claudication (there are too many false positives and negatives), an ABI should be performed in the following groups:

- Patients older than 70 years
- Patients older than 50 years, with two or more risk factors
- Patients with long-standing diabetes (can have false-negative results because of atherosclerosis and subsequent decreased elasticity of vessels—further noninvasive investigation may be necessary)
- Patients with a long history of tobacco dependence
- Patients with classic claudication or other exertional limb pain or discomfort
- Patients with rest pain, a non-healing leg or foot wound (ulcer) or gangrene

Physicians who do not offer objective testing for PAD and subsequent treatment to these patient

groups are potentially liable, since they are permitting undiagnosed PAD and systemic atherothrombosis to progress to more severe and harder to treat stages and possibly even death.

Therapy: Global Ischemic Risk Management and Prevention of Progression

The risk factors for atherothrombosis in PAD are exactly the same as for CHD. These include smoking and diabetes along with hypertension, high cholesterol and sedentary activity. Effective therapy for these risk factors are essential in PAD and can be expected to provide the same degree of risk reduction as seen in CHD patients.

Smoking cessation and tight glycemic control will have the most dramatic effect since these two risk factors are associated with the highest (3-4 x) risk. Antihypertensive and lipid-lowering therapies are also imperative in patients with PAD. (2 x risk)

In addition, there is evidence from two large trials that other strategies should also be used in routine risk management of patients with PAD. These are anti-platelet therapy and angiotensin-converting enzyme (ACE) inhibitor therapy.

In the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events) trial[6], clopidogrel (Plavix) provided a significant reduction in the combined outcome of myocardial infarction (MI), ischemic stroke or vascular death, compared to aspirin 325 mg/d. Anti-platelet treatment with aspirin is generally believed to decrease events by 25%. The benefit of clopidogrel over aspirin, 8.7% in more than 19,000 patients with known atherosclerotic vascular disease, randomized to CAPRIE, was actually somewhat *greater* in the PAD population. *These results make it clear that anti-platelet therapy reduces ischemic events in patients with atherothrombosis, regardless of the vascular bed in which it develops.*

Similarly, the Heart Outcomes Prevention Evaluation (HOPE) trial[7], an extremely powerful study, showed that an ACE inhibitor provides risk-reduction in PAD patients equal to that of others with established CV risk (diabetics, those with prior a coronary event or intervention, or cerebrovascular event). In HOPE, the PAD subgroup along with more than 9,000 patients had a 22% reduction in the combined risk of death, non-fatal MI or stroke on the ACE inhibitor ramipril when compared to placebo.

Exercise is the principal non-pharmacologic treatment for improving symptomatic PAD (claudication) and also helps decrease risk and slow progression of atherothrombosis. *A meta-analysis of 21 published studies found that exercise training increased the distance to onset of claudication by 179%.*[8]

Combining all the risk strategies should reduce progression of atherosclerosis, stabilize atherosclerotic plaque, and reduce the probability of thrombosis, thereby decreasing the risk of MI, stroke and death, regardless of where the lesions first develop.

For further evaluation and interventional treatment for claudication, we refer you to Weitz's recent excellent critical review in *Circulation.*[9]

KEY POINTS

1) PAD, misunderstood, underdiagnosed and ignored, is an important marker of systemic artherothrombosis and significantly increased risk. Almost half of patients with PAD will have significant coronary or cerebrovascular disease upon investigation.
2) PAD detection can be greatly improved by a careful vascular history, physical examination and ABI technique as part of the office routine. This is extremely important because of the increased risk of both fatal and non-fatal CV events in PAD patients.

3) Patients identified with PAD deserve the same "global management of ischemic risk" that is indicated in *all* patients with known CHD or cerebrovascular disease. This would include tobacco cessation, control of diabetes, hypertension, hyperlipidemia and an exercise program. Anti-platelet therapy and ACE-inhibitor therapy are integral parts of the global management of ischemic risk.
4) All patients with PAD should have anti-platelet therapy. The benefits of clopidogrel over aspirin in the CAPRIE trial in patients with PAD were at least as significant (possibly more) as the benefits observed in patients who entered the study with CHD or cerebrovascular disease.
5) All patients with PAD should receive ACE inhibitor treatment based on the definitive HOPE trial data showing a very significant reduction in CV events and mortality.

Global CV Risk Reduction Therapy:

- **Diagnose PAD** (office ABI < 0.9)
- **Smoking Cessation**
- **Diabetes control** (Hgb $A_{1\text{-}C}$ < 7.0%)
  [a biguanide (Glucophage) and / or a glitazone (Actos or Avandia) would be our oral agents of choice]
- **Lipid Control** (statins are our obvious drug of choice, with addition of gemfibrozil or niacin as needed to reach goal)

  Goals:
  LDL cholesterol <100mg/dL
  HDL cholesterol > 45 mg/dL
  Triclycerides < 150 mg/dL
- **Hypertension control** (BP <130/85 mm Hg)
- **Exercise** (30 minutes, 5 x/week, minimum; more is better)
- **Anti-platelet therapy**
  Clopidogrel—1st choice, but costly
  Aspirin—2nd choice (Combination of both should be great, data pending.)
- **ACE-inhibitor therapy** (study dose of ramipril 10 mg or its equivalent of a tissue-specific ACE-inhibitor)
- **Claudication therapy**
  Supervised exercise program
  Pharmocologic treatment:
  cilostanzol (Pletal) —1st choice, or
  pentoxifylline (Trental)
  Interventional therapy
  Peripheral angioplasty or bypass surgery when refractory symptoms persist after all other therapies have been tried.

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