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Current Approaches in the Diagnosis and Treatment of Peripheral Arterial Disease

Introduction

Peripheral arterial disease (PAD) is a pathological condition characterized by atherosclerotic occlusion of arterial blood supply to the lower or upper extremities. In a broader sense, it may be defined as a clinical entity that includes a diverse group of disorders that lead to progressive occlusion and/or aneurysmal dilation of the aorta and the noncoronary arteries, including the carotid, upper-extremity, visceral, and lower-extremity arterial branches. From a historical perspective, peripheral vascular disease (PVD), on the other hand, has been used to include all the non-cardiac diseases that affect the circulation, including those conditions that affect not only the arterial tree but also the venous and lymphatic circulation as well. For the purpose of this review, PAD will refer to the arterial disease condition affecting the lower and upper extremities.

Patients with PAD have increased risk of developing cardiovascular and cerebrovascular diseases.[1] Patients with PAD, even in the absence of a history of prior myocardial infarction or ischemic stroke, have similar relative risk of death from cardiovascular death as do patients with a history of coronary or cerebrovascular disease.[2]

Epidemiology

The prevalence of PAD rises with advancing age. In the National Health and Nutrition Examination Survey (NHANES), the prevalence of PAD was 0.9% between the ages of 40-49, 2.5% between the ages of 50-59, 4.7% between the ages of 60-69, and 14.5% older than age 70.[3] The prevalence varies depending on the population studied as well as the type of diagnostic tool, and presence or absence of symptoms. The most common diagnostic tool used for epidemiological studies is the ankle/brachial index (ABI). The ABI is the ratio of the ankle to brachial systolic blood pressure. Using the ABI as the measure of disease, the prevalence of PAD ranges from 3.6% to 29% of the general population.[3-5] There is gender variation in the prevalence of PAD, with men being affected more than women. There is also ethnic variation in the disease distribution of PAD. The prevalence of PAD is greater in blacks than in non-Hispanic whites.[6] Blacks were 1.47 times more likely to develop PAD than non-Hispanic whites, while the odds for Asians of Chinese decent and Hispanics for developing the disease is less than 0.5.[7]

Patients with PAD usually present with intermittent claudication. Intermittent claudication is defined as a reproducible discomfort of a defined group of muscles that is induced by exercise and relieved with rest. Prevalence of intermittent claudication varies depending on the age and gender of the population studied. In general, prevalence of claudication ranges from 1 to 4.5% of population groups 40 years and older.[8,9]

Executive Summary

- Patients with PAD have similar relative risk of CV death to patients with a history of coronary or cerebrovascular disease.
- Prevalence of PAD increases with age and is more common in men. Using ABI as an index of disease, prevalence can be as high as 29% in the general population.
- Risk factors include smoking, diabetes, hypertension, and dyslipidemia.
- The majority of patients with PAD are asymptomatic, as only one-third present with symptoms of intermittent claudication.
- An ABI below 0.9 has 95% sensitivity and nearly 100% specificity in the diagnosis of PAD.
- Estrogen replacement, ginkgo biloba, vitamin E, and chelating therapy have not been found useful in the treatment of PAD.
- Patients who most benefit from surgical and percutaneous interventions are those younger than age 70, non-diabetics, and those with little disease distal to the primary lesion.

Prevalence

Patients with PAD have been shown to have increased prevalence of coronary artery disease and cerebrovascular events.[1]

PAD is a growing problem in developed countries due to the increasing elderly population. The modifiable risk factors that are associated with the development of coronary artery disease (CAD) are similar to those responsible for the development of PAD. Tobacco use, diabetes, dyslipidemia, and hypertension are the main risk factors that contribute to the development of PAD.[10] There is a two- to three-fold increase in risk of developing PAD in patients who smoke.[10] About 90% of patients with intermittent claudication are either active smokers or have a smoking history.[11] There is a dose-dependent correlation of smoking status and the risk of developing PAD in both male and female patients. It has also been shown that this risk of PAD decreases with smoking cessation.[12] Patients with diabetes mellitus have been shown to be at an increased risk of developing PAD compared with their non diabetic counterparts.[13] The risk for diabetic patients can be up to 4 times more than that of non-diabetic patients.[14] In addition, diabetic patients tend to have worse arterial disease and worse outcomes than non-diabetic patients.[15] The Framingham study demonstrated that the odds ratio of developing intermittent claudication was 2.6 for diabetes mellitus, and 1.2 for every 40 mg/dL elevation in the serum cholesterol concentration.[10] Hypertriglyceridemia is positively correlated with the risk of developing PAD.[16] Hypertension also has a positive correlation to developing PAD.[17] There is evidence to suggest that inflammation plays a role in the development of PAD. Inflammation may be the link between the traditional risk factors for atherosclerosis and the pathological processes associated with PAD.[18] Markers of inflammation such as C-reative protein (CRP) and fibrinogen leukocyte adhesion molecules correlate with the development of PAD and future complications.[19,20] There are some emerging new risk factors that are also associated with PAD, such as hyperhomocysteinemia, which have been shown to confer increased risk of developing PAD.[21] (*See Table 1.*)

Clinical Presentation

The majority of patients with PAD are asymptomatic. Approximately one-third of patients with PAD will present with the typical intermittent claudication symptoms. Intermittent claudication refers to pain or discomfort in the lower extremity precipitated by walking or exercise and relieved with rest.[2] The location of the pain depends on the site of occlusion of the artery. The groups of muscles distal to the area of arterial stenosis manifest with ischemic symptoms. Gluteal, hip, or thigh claudication usually points to diseased aorta or iliac arteries. Calf claudication characterizes femoral or popliteal artery occlusion. In general, the most commonly affected muscle group is the gastrocnemius muscle. This is the one muscle that uses the greatest amount of oxygen during exercise. Upper-extremity muscles also can be affected. Subclavian artery disease affects the shoulders, axillary artery disease manifests with symptoms in the biceps, and brachial artery disease causes symptoms in the forearm. Patients with PAD are usually limited by these symptoms and will usually walk shorter distances. (*See Table 2.*)

Intermittent claudication should be distinguished from other mimickers. Symptoms resembling claudication may result from non-atherosclerotic causes of arterial disease. (*See Table 3.*) Lumbosacral radiculopathy can cause pain in the buttock, hip, thigh, or calf with walking. Nerve pain is "electric" and shooting in nature and usually is relieved by sitting down or bending forward. The entire leg may be affected. Patients with chronic venous insufficiency may also report intermittent claudication with exertion. Venous pooling of blood during exercise leads to elevation of venous pressures that also causes an increase in the arterial resistance. This leads to diminished blood flow, leading to tissue ischemia.

Signs and Symptoms

Diagnosis of PAD is based on symptoms. The cardinal symptom of PAD is intermittent claudication. The history obtained from patients reporting claudication should note

Table 1: Risk of Developing PAD Estimated from Epidemiological Studies

Risk Factor	Relative Risk
Smoking	3-4
Diabetes	3-4
Hypercholesterolemia	1-2
Hyperhomocysteinemia	2-3
C-reactive protein	2

Data from: Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg* 2000;31 (1 Pt 2):S1-S196.

Table 2: Classification of PAD Based on Symptoms

Stage	Fontaine Classification of PAD
I	Asymptomatic
II	Intermittent claudication
IIa	Pain-free, claudication walking > 200 m
IIb	Pain-free, claudication walking < 200 m
III	Rest and nocturnal pain
IV	Necrosis and gangrene

the walking distance, speed, and incline that precipitated claudication. This baseline information helps to determine progression or deterioration of symptoms. It is important to distinguish symptoms resulting from other causes that may mimic PAD. Limb pain at rest is suggestive of critical limb ischemia (CLI), a result of total arterial occlusion. This condition must be urgently recognized so that there is no delay in referring the patient for anticoagulation or revascularization therapies in order to salvage the limb. CLI can result from atherosclerosis or thrombo-embolic events. Other conditions that can cause CLI disease include vasospasms, thromboangiitis obliterans, mechanical occlusions of vascular conduits, and traumatic disruption of vessels. From the history, it is important to obtain information about the cluster of conditions that serve as risk factors.

The physical examination should include palpation of pulses and auscultation for bruits. Diminished pulses and bruits are strongly correlated with PAD.[23] The presence of the bruit may indicate the site of arterial occlusion. Elicit for the integrity of the connective tissue and skin. PAD can lead to skin ulcers, muscle atrophy from immobility, brittle nails, and loss of hair on the skin.

Investigations

In patients with suspected PAD, evaluation of the presence and severity of the disease can be done by non-invasive modalities.

The initial screening tool for the presence of PAD is ABI measurements, which involve the measuring pressure using inflatable pneumatic cuffs to suprasystolic levels. The cuffs are then deflated to allow for reflow. Flow of blood distal to the cuffs in the legs is detected with a Doppler probe placed at the dorsalis pedis and posterior tibial arteries.[24] The brachial blood pressure is measured in the usual manner by auscultation of Korotikof sounds. The ratio of the two measurements is taken to calculate the ABI. The highest of the four measurements in the lower extremity is divided into the higher of the two measurements in the upper extremity to obtain the ABI.

The normal ABI is between 1.0 and 1.3. Values above 1.3 indicate that the artery may be calcified and is therefore non-compressible. A value below 0.9 has 95% sensitivity and about 100% specificity for detecting angiogram-positive PAD.[24] ABI also is used to assess the severity of disease. Most patients with intermittent claudication have ABI between 0.5 and 0.8. Values below 0.5 indicate severe critical limb ischemia and will present with resting ischemia.

In cases where the ABI is greater than 1.3 and the arteries are non-compressible, the specially designed toe cuffs can be used to measure the pressure in the toes and the toe-brachial index (TBI) can be calculated.

Treadmill Exercise ABI

Resting ABI may be normal, but this does not preclude presence of obstructive arterial disease. A stenosis of less than 70% does not result in significant flow gradient that would result in abnormal ABI. During exercise, however, there is a reduction in the peripheral resistance and an increase in blood flow, which further creates a pressure gradient across the stenotic segment. This causes a decrease in the ABI because the increase in the blood pressure in the legs is not matched by the increase in the arms. Exercise ABI is a sensitive measure for documenting PAD in subjects with normal resting ABIs.[25]

Measuring the volume of blood flow in the legs assesses disease severity. This is done through the use of segmental volume plethysmography. This done by using pressure pneumatic cuffs, applying some pressure to the segment of the blood vessel of interest, and then measuring the degree of flow distal to the blood vessel using an ultrasound Doppler probe that displays the contour and amplitude of the wave form.

Table 3: Differential Diagnosis of Intermittent Claudication

Characteristic	Intermittent Claudication	Venous Claudication	Nerve Root Pain
Quality	Cramping	Pressure-like	Electric
Onset	Gradual, predictable	Usually gradual	Immediate, unpredictable
Relieved by	Rest	Elevation of the leg	Sitting down/ bending
Location	Localized	Entire leg	Diffuse/whole leg
Limbs affected	Single limb	Single leg	Both legs

Duplex Ultrasound Imaging

Ultrasound imaging provides a direct measurement of flow velocities of blood in the blood vessel. With the addition of color flow imaging, stenotic areas can be localized. Ultrasound has up to 90% sensitivity and about 95% specificity for detecting PAD.[26]

The other testing modalities include magnetic resonance angiography, computer tomography angiography (CTA), magnetic resonance imaging angiography (MRA), and the contrast angiography. MRA and CTA are used in assessing patients for endovascular and surgical intervention.

Contrast angiography is the "gold standard" test for evaluation of PAD. However, it is invasive and has attendant risk. It is still used in defining vascular anatomy, particularly in patients undergoing endovascular repair.

Clinical investigations should also be directed at assessing the global risk factors of the patient. These include assessing for hyperlipidemia, diabetes, hypertension, and renal function, and, in some cases, inflammatory markers such as C-reactive protein.

Management

Management of PAD involves aggressive risk factor and lifestyle modification, exercise rehabilitation, pharmacological therapy, and percutaneous intervention or surgical procedures. Initial treatment should include risk reduction, ASA, statins, exercise, and strict diabetic control. Early evaluation with a vascular/ endovascular surgeon is key for those with positive ABI as well as those with lifestyle-limiting disease.

The goals of treatment of PAD include reduction in the cardiovascular morbidity and mortality, improvement in the quality of life by improving the level of functional status, and decreasing symptoms.

Risk Factor Modification

All patients with PAD should undergo aggressive risk factor and lifestyle modification. The principle factors for the development of PAD are smoking, diabetes, hypertension, and hyperlipidemia, which account for about 69% of patients.[27] Quitting cigarette smoking reduces the progression of disease and lowers the incidence of rest ischemia among patients who quit.[28] Smokers with PAD have a higher mortality rate from myocardial infarction than those who do not smoke. Additionally, PAD patients who quit smoking have twice the five-year survival as those PAD patients who continue to smoke.[11] Lipid-lowering therapies with diet or pharmacotherapy reduce the progression of PAD.[29] In one trial, artovastatin therapy improved pain-free walking distance by 60% compared to placebo.[30] There are limited data on the effect of antidiabetic therapy on the natural history of PAD. However, aggressive control of blood sugar reduces the risk of microvascular complications.[31] Hypertension control reduces the risk of cardiovascular and cerebrovascular events. There are still no data that address the role of antihypertensive medication on the progression of PAD. Hypertension should be treated to reduce cardiovascular and cerebrovascular events. Angiotensin-converting enzymes inhibitors (ACEIs) have been shown to reduce cardiovascular events in patients with atherosclerosis. In the Heart Outcome Prevention Evaluation, PAD patients treated with ramipril reduced cardiovascular events to levels comparable to those in patients without PAD.[32] A target goal of treating hypertension for patients with PAD is less than 140/90 mm Hg for non-diabetics and less than 130/80 mm Hg for patients with diabetes.[33]

Exercise Rehabilitation

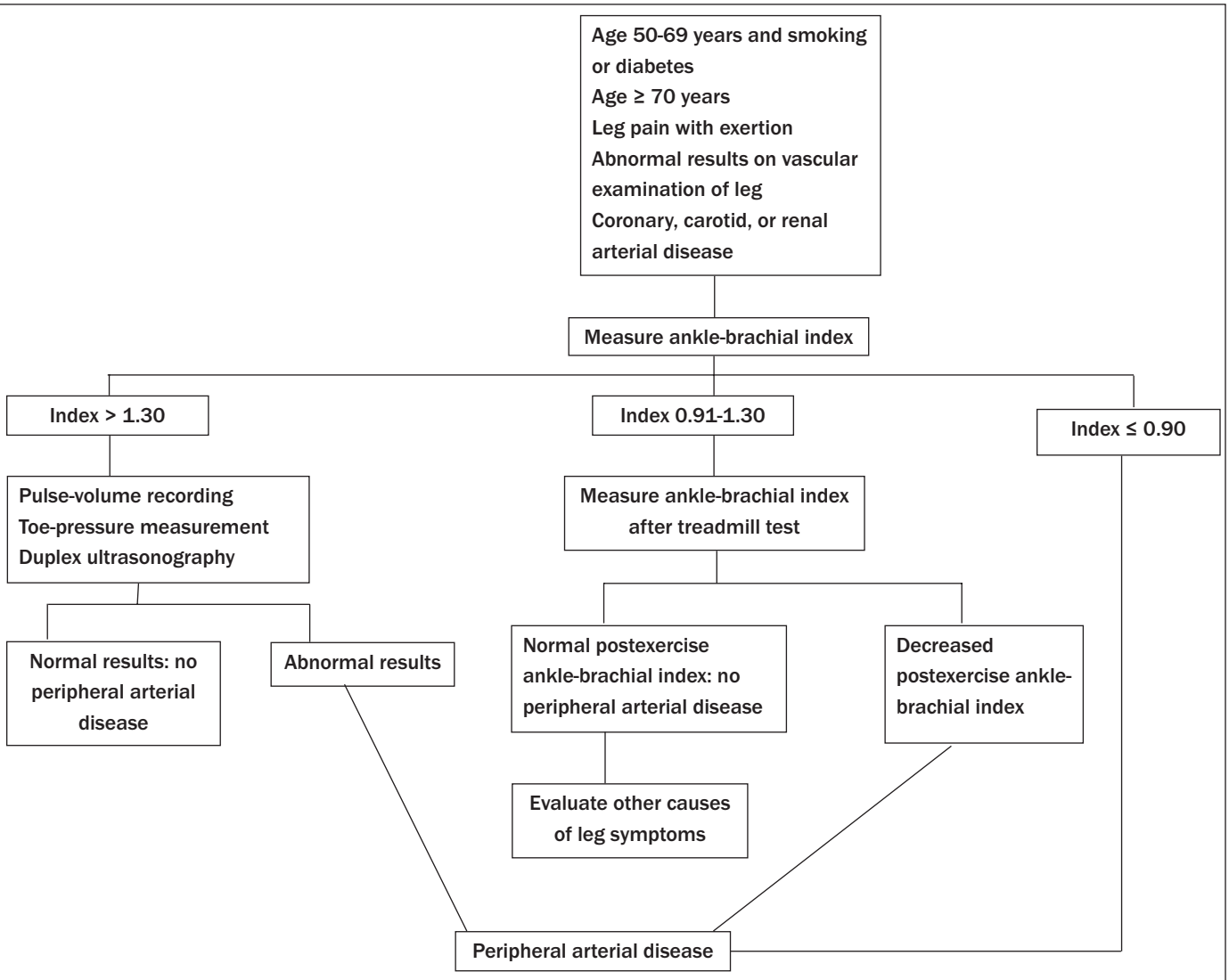
Supervised exercise rehabilitation programs have been shown to increase functional capacity in patients with PAD symptoms. In some studies, exercise programs increased the average distance walked to the onset of claudication by 180%.[34] The greatest benefit comes when patients exercise for 30 minutes three times per week for 6 months. The exercises include an initial warming-up phase, which involves intermittent walking, which is graduated to a few minutes of increased activity. The benefits of the exercise program are thought to be due to formation of collateral blood supply, endothelium-related vasodilatation, muscle metabolism, and improvements in the efficiency of walking.[35] It also has been suggested that exercise decreases red blood cell aggregation and improves the filterability of the blood.[2]

Pharmacotherapy

Besides pharmacological agents that are used to treat risk factors in patients with PAD, there are some pharmacological agents that are used primarily to reduce symptoms and slow the progression of the disease.

Antiplatelet therapy has been shown to reduce the risk of nonfatal myocardial infarction, ischemic stroke, and death from a vascular cause.[36]

Figure 2: Evaluation of Patients in Whom PAD Is Suspected



Reprinted with permission from: Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med* 2001;344:1608-1621.

Aspirin is the most commonly prescribed drug in PAD. Aspirin has been associated with significant reduction in the risk of development of stroke and myocardial infarction.[37] The combination of ASA and dipyridamole (Persantine) was found to increase pain-free walking distance and resting blood flow in patients with PAD.[37] Clopidogrel (Plavix) was found to be more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or vascular death.[38] Cilostazol (Pletal) is a phosphodiesterase inhibitor that can be used in patients with PAD with intermittent claudication. It has both antiplatelet and vasodilator properties. It was shown to be more effective than pentoxifylline in the treatment of intermittent claudication.[39] Cilostazol, like other phosphodiesterase inhibitors, should not be used in patients with heart failure because of an increase in mortality in these patients. Pentoxifylline (Trental) is a rheological modifier used in the treatment of intermittent claudication. Pentoxifylline was found to increase walking distance by 29 meters compared to placebo, although the benefits are less than the benefits derived from a supervised exercise program.[40] There are other classes of drugs that are being considered or are currently under investigation for the treatment of PAD. These include statins, ACE inhibitors, serotonin antagonists, calcium channel blockers, carnitine derivatives, vasodilator prostaglandins, and angiogenic growth factors. ACEIs have been shown to increase the claudication distance.[41] A serotonin antagonist, such as naftidrofuryl, has been shown to be effective in reducing intermittent claudication.[42,43] L-carnitine, which is a co-factor in fatty metabolism, has been shown to improve symptoms in PAD, particularly those patients who have markedly diminished walking distance.[44] Prostaglandin administrations in patients with symptomatic PAD have not shown consistent results.[45-47] Angiogenic growth factors increase collateral blood supply

in animal models but have failed to show improvement in clinical trials.[48] Immune modulators have recently been shown to be effective in the treatment of severely incapacitated patients with short walking distance claudication.[49] Other therapies that have not been shown to be effective include estrogen replacement, ginkgo biloba[50], vitamin E, and chelating therapy.[51-53]

Surgery/Percutaneous Intervention

Peripheral catheter-based interventions for PAD are indicated for patients with severe lifestyle limiting symptoms even after a trial of exercise rehabilitation or pharmacotherapy.[33] Endovascular interventions are also indicated in patients with critical limb ischemia. Long-term success depends on the anatomy of the blood vessel involved. Larger caliber vessels have better long-term outcomes than smaller vessels (aortoiliac disease).

Surgical revascularization is indicated in patients with disabling claudication on maximal medical therapy who are not candidates for percutanous intervention. The surgical risk profile must be favorable and must not outweigh the benefits. Patients who benefit the most are those younger than age 70, non-diabetics, and those with little disease distal to the primary lesion.[54] Early evaluation with a vascular/endovascular surgeon is important for those patients with positive ABIs as well as lifestyle-limiting disease.

Conclusion

Peripheral arterial disease is a prevalent condition that is associated with high morbidity and mortality. Unfortunately, PAD often is under-diagnosed and under-treated. Prevalence will continue to rise because of the increasing segment of the elderly population. Early recognition and diagnosis is key to early adoption of those evidence-based practices that have been shown to improve the quality of life of patients and reduce the adverse outcomes associated with the disease. Initial treatment should include risk reduction, ASA, statins, exercise, and strict diabetic control. Early evaluation with a vascular/endovascular surgeon is key for those with positive ABI as well as those with lifestyle-limiting disease.

The secondary prevention strategies such as aggressive risk factor modifications, exercise programs, and pharmacotherapy should be routinely tailored to patients with PAD, just as much as these measures are employed in patients with CAD. Primary care providers are key in translating the body of knowledge we have on PAD into everyday clinical care of PAD patients.

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Physician CME Questions

21. Which of the following statements concerning PAD is *not true*?
    A. Peripheral vascular disease has similar risk factors as CAD.
    B. Exercise has been shown to improve claudication symptoms.
    C. Vitamin E has been shown to improve claudication symptoms.
    D. ACEIs have been shown to improve symptoms.

22. A 50-year-old man comes for his regular follow-up clinic appointment. He has a history of hyperlipidemia, hypertension, and diabetes, which has been well controlled. On this visit he complains of calf pain that predictably occurs with exertion of a given distance and is relieved with rest. What is the next best recommendation?
    A. Prescribe a supervised exercise program.
    B. Schedule him for ankle–brachial index.
    C. Schedule him for segmental volume plethysomography.
    D. Prescribe some calcium channel blockers.

23. A 60-year-old woman has been referred to your office with newly diagnosed PAD. Her past medical history is significant for

hypertension and hyperlipidemia. Her blood pressure in the office was 145/90 mmHg, which is consistent with one-month blood pressure logs that she has kept. She has been on amlodipine 10 mg daily and simvastatin 40 mg at bedtime. What pharmacotherapeutic recommendations are you going to make?

A. Add an ACEI, ASA.
B. Add beta-blocker therapy to control her hypertension.
C. No adjustment at this time; her blood pressure is not too bad.
D. Increase dosage of amlodipine.

24. Which of the following medications is contraindicated in PAD patients with CHF?

A. cilostazol
B. clopidogrel
C. pentoxifylline
D. ramipril

25. Which of the following diagnostic tests will you recommend for a patient you suspect to have PAD on the basis of symptoms but who had a normal resting ABI?

A. CT angiography
B. exercise ABI test
C. segmental volume plethysomography
D. MR angiography

CME Answer Key

21. C; 22. B; 23. A; 24. A; 25. B

Primary Care Reports

CME Objectives

Upon completion of this activity, participants should be able to:

- summarize recent, significant studies related to the practice of primary care medicine;
- evaluate the credibility of published data and recommendations related to primary care medicine;
- discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

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This CME activity is intended for primary care and family practice physicians. It is in effect for 24 months from the date of the publication.

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By Louis Kuritzky, MD
Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*
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The short-term risks of bariatric surgery

Source: The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium; et al. *N Engl J Med* 2009;361:445-454.

Long-term benefits from bariatric surgery have been definitely established. Nonetheless, perioperative risks associated with bariatric surgery are not insignificant, especially since persons undergoing bariatric surgery often suffer comorbidities of diabetes, hypertension, and dyslipidemia.

The LABS Consortium performed an observational study of short-term outcomes subsequent to bariatric surgery in the United States. From 2005 to 2007, data supplied by 10 different clinical sites (combined total n = 4776 first-time bariatric surgical procedures) provided information on the composite endpoint of 30-day major adverse outcomes (death, DVT, postoperative intervention, and extended hospital stay). Roux-en-Y bypass was performed on approximately 70% of subjects; the majority of the other patients underwent gastric banding.

Death occurred in 0.3% of subjects within 30 days; an additional 4% of subjects experienced at least one adverse event included in the composite primary endpoint. A previous history of DVT was associated with greater likelihood to incur a postoperative adverse event; additionally, the higher the BMI (mean BMI in this report = 46.5 kg/m^2), the greater the frequency of adverse events.

Bariatric surgery has significant associated risks. For most appropriately selected patients, the long-term benefits far outweigh these risks, but patients need to be informed of the potential for serious adverse outcomes. ■

Parsing the death toll of COPD

Source: Zvezdin B, et al. *Chest* 2009; 136:376-380.

Worldwide, COPD is the fourth leading cause of death; unless current trends reverse, the toll will rise. Mortality rates associated with hospitalized acute exacerbations of COPD have been as high as 30%; the mortality in the 1 year after hospitalization is as high as 43%. Some of this mortality is directly attributable to COPD; however, other prominent comorbidities (e.g., CVD, pulmonary embolism) are also responsible. Often, because post-mortem examination is limited, the cause of death can only be opined. To provide greater clarity, Zvezdin et al report on autopsies of 43 patients who died within 24 hours of COPD hospital admission.

The mean age of the study subjects was 70. According to autopsy results, more than half of the deaths were attributed to diagnoses other than COPD: heart failure (in 37%) and pulmonary embolism (in 21%). The authors also separate pneumonia as a "non-COPD" cause of death (occurring in 28%), defining COPD death as those individuals who die of respiratory failure due to COPD progression (14%).

If these results (from a Serbian tertiary care university hospital specializing in pulmonary diseases) are generalizable to U.S. populations, clinicians will need to exercise greater vigilance, enhanced preventive techniques, and intensified intervention for potentially fatal comorbidities when patients are admitted for acute COPD exacerbation. ■

Vardenafil and premature ejaculation

Source: Aversa A, et al. *Int J Impot Res* 2009;21:221-227.

Although clinicians are much more familiar with erectile dysfunction, over the lifespan premature ejaculation (PEJ) is more common. A much smaller percentage of men with PEJ seek help, attributable to factors such as embarrassment, absence of available FDA-approved medications, and lack of public awareness of PEJ as an important sexual health dysfunction.

The technical definition of PEJ is a matter of controversy, although most experts agree that consistent unintended/unwanted ejaculation within 1 min that causes distress is satisfactory for the diagnosis.

The most commonly used metric for measuring PEJ is intravaginal ejaculatory latency time (IELT), or the time after vaginal intromission at which ejaculation occurs. Population studies have suggested that in established heterosexual couples, typical IELT is 6-10 min. Subjects enrolling in PEJ trials typically have an IELT of 30-90 sec, or even ejaculation ante portis (prior to intromission). The above definition would, by construction, seem to exclude gay men or ejaculation involving other orifices/body parts, but the similarities of diagnosis and management of PEJ in gay couples suggest that IELT, while at times anatomically inconsistent, incorporates the broader concepts

of early ejaculation in a variety of sexual settings.

SSRIs have an established role in management of PEJ. Success with SSRIs is greatest when taken on a maintenance schedule; however, patients would generally prefer as-needed administration, all things being equal.

Aversa et al studied men with PEJ (n = 42), all of whom consistently experienced IELT < 1 min. Patients were randomized (double-blind) to placebo or vardenafil 10 mg administered 15-30 min before sexual activity. The primary outcome was change in IELT.

Use of vardenafil provided a significant improvement in IELT (from 36 sec to 4.5 min) compared with placebo (IELT went from 42 sec to 54 sec). The tolerability of vardenafil is well established. Vardenafil appears to be a viable option for PRN treatment of PEJ. ■

Testosterone, depression, and hypogonadal men

Source: Shores MM, et al. *J Clin Psychiatry* 2009;70:1009-1016.

SUBTHRESHOLD DEPRESSION (sDEP), also known as minor depression, occurs in as many as 1 of 4 elderly patients. Although by definition the symptom burden of sDEP is less than major depressive disorder (MDD), it is more common than MDD and is still associated with diverse negative outcomes including decreased quality of life and function, and increased morbidity, mortality, and health care utilization.

Symptoms of hypogonadism include fatigue, decreased libido, and dysphoria, any of which may also be manifestations of depression. Shores et al studied the impact of testosterone replacement in hypogonadal men (total testosterone < 280 ng/dL) meeting DSM-IV criteria for sDEP.

This double-blind trial randomized adult men (n = 33) to testosterone gel 7.5 g/d or placebo for 12 weeks. The primary outcome was change in the HAM-D depression score.

At the end of the trial, testosterone-treated men had a significantly improved HAM-D score compared to placebo, and the percent with remitted sDEP was dramatically different (52.9% vs 18%) favoring testosterone.

No serious testosterone-attributable adverse effects were seen. Testosterone replacement shows benefit for improving sDEP in hypogonadal men. ■

Aspirin after colon cancer diagnosis

Source: Chan AT, et al. *JAMA* 2009; 302:649-658.

MOST COLORECTAL CANCERS OVEREXPRESS cyclo-oxygenase 2 (COX-2). Primary prevention with aspirin (ASA) is associated with reduced risk for colon cancer and colonic adenoma. Secondary prevention with ASA (and celecoxib) is effective in reducing risk of new adenomas in persons who have been previously diagnosed with colonic neoplasia. Because ASA has recognized toxicities, including cerebral hemorrhage and GI bleeding, it is important to determine whether use of ASA in high-risk subjects (persons previously diagnosed with colon cancer) provides net benefit for overall and/or colon cancer-specific mortality.

The Physicians' Health Study and the Nurses' Health Study are observational studies, providing a window of observation for the role of ASA in both primary and secondary prevention. A cohort within both populations took maintenance ASA prior to any diagnosis of colon cancer, and further information about effects of ASA in persons who developed colon cancer and continued with ASA subsequent to the cancer diagnosis (vs subjects who did not take ASA after a diagnosis of colon cancer) is presented here.

Of subjects who developed colon cancer (n = 1279) in these two study populations (combined), there were statistically significant differences in total mortality (35% vs 39%) and colon cancer-related mortality (15% vs 19%) favoring use of ASA. Concordant with current thinking on the putative mechanism of ASA benefit, the risk reduction was greatest in persons whose colon cancer overexpressed COX-2. Despite these favorable results, the authors caution that routine utilization of ASA post colon cancer might be considered premature since these data are observational; placebo-controlled randomized trials are needed for confirmation. ■

The Emperor's new vertebroplasty?

Source: Buchbinder R, et al. *N Engl J Med* 2009;361:557-568.

VERTEBROPLASTY (VERT) HAS RECENTLY enjoyed increased popularity as treatment for painful osteoporotic vertebral fractures. Observational or open-label studies have provided most of the supportive information. Enthusiasm for other previously popular surgical procedures has been dampened when double-blind randomized trials have failed to confirm positive outcomes: Two randomized trials in the last 7 years comparing arthroscopy for knee osteoarthritis found no outcomes difference when compared to placebo.

Buchbinder et al performed a randomized, double-blind, sham procedure-controlled trial of VERT for painful osteoporotic fracture in 78 participants. The primary outcome was pain reduction, which did not differ at weeks 1, 3, or 24 after treatment between intervention and sham intervention.

The Buchbinder study was published immediately preceding another VERT trial in the *New England Journal of Medicine* examining pain and disability at 1 month post intervention, which similarly did not find positive outcomes. These trials call for closer evaluation of the (potential) value of VERT. ■

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WHO Issues Global Alert on Antiviral Use

In this issue: WHO recommendations for antiviral use for H1N1 flu; antibiotic use trends for acute respiratory tract infection; denosumab clears FDA Expert Panel; FDA Actions.

Antiviral Recommendations for H1N1

The World Health Organization (WHO) has issued a global alert and response regarding the use of antivirals for pandemic H1N1 flu, reiterating that antivirals should be used to prevent severe illness and death in children and adults. The neuraminidase inhibitor oseltamivir (Tamiflu®) is recommended for patients who initially present with severe illness or whose condition begins to deteriorate. H1N1 remains sensitive to the neuraminidase inhibitors such as oseltamivir despite isolated reports of resistance earlier this year. The WHO recommends that clinicians in communities where the virus is circulating widely assume that patients with flu-like symptoms have H1N1 and not wait for laboratory confirmation. Most patients with pandemic flu experience typical flu symptoms and recover within a week. These patients do not need antivirals. But in patients with severe illness, studies have shown that early treatment, within the first 48 hours, is associated with better clinical outcomes. WHO also states that if oseltamivir is unavailable zanamivir (Relenza®) may be used in its place. This recommendation applies to all patient groups including children and pregnant women. The WHO statement comes in response to an article in the *British Medical Journal* suggesting neuraminidase inhibitors provide minimal benefit for children with seasonal influenza and have little effect on asthmatic exacerbations or use of antibiotics (Shun-Shin M, et al. *BMJ* 2009;339:b3172). ■

Antibiotic Use Declines Overall, While Use of Broad-Spectrum Increases

Physicians are prescribing fewer antibiotics for acute respiratory tract infections (ARTIs), but if an antibiotic is used, it is more likely to be a broad-spectrum drug. Using data from 1995 to 2006, antibiotic trends were reviewed from a national database for ARTIs, which included otitis media (OM). Children younger than age 5 were seen less frequently for ARTI than in the past, and they were less likely to be prescribed an antibiotic (36% reduction; 95% confidence interval [CI], 26%-45%). Among children age 5 or older, ARTI visit rates remained stable but antibiotic prescription rates decreased by 18% (95% CI, 6%-29%). Excluding otitis media, antibiotic prescription rates decreased by 41% among all age groups. Prescription rates for a penicillin, cephalosporins, and sulfonamide/tetracycline decreased while the rate of prescriptions for azithromycin increased, making it the most commonly prescribed macrolide for ARTI and OM. Among adults, quinolone prescriptions also increased. The authors conclude that overall antibiotic prescription rates for ARTI decreased in the last 10 years; however, prescription rates for

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

broad-spectrum antibiotics increased significantly (Grijalva CG, et al. *JAMA* 2009;302:758-766). This study points out the success of multiple campaigns to decrease antibiotic use for ARTIs, which are primarily caused by viruses. However the increasing use of broad-spectrum antibiotics is concerning. ■

Denosumab Receives Conditional Approval from FDA Expert Panel

Denosumab is a new human monoclonal antibody that suppresses osteoclast function and thus inhibits bone resorption. It is being evaluated by the FDA for treatment of osteoporosis in men and women, and although it has not yet been approved, a recent FDA Expert Panel has given conditional approval paving the way for full FDA approval this fall. Two recently published, industry-sponsored studies suggest the drug is effective in 2 different populations. In the first study, more than 1400 men receiving androgen-deprivation therapy for nonmetastatic prostate cancer were randomly assigned to receive denosumab 60 mg SQ every 6 months or placebo for 2 years. The primary endpoint was change in bone mineral density (BMD) at the lumbar spine, with secondary endpoints of change in BMD in the hip as well as fracture incidence. At 24 months, BMD increased in the lumbar spine with denosumab (5.6% increase vs 1% decrease for placebo; $P < 0.001$). BMD was also increased in the total hip, femoral neck, and distal radius, and the effect was maintained for 36 months. New fracture rate was also decreased with treatment (1.5% vs 3.9% with placebo; $P = 0.006$). Rates of adverse events were similar in both groups (Smith MR, et al. *N Engl J Med* 2009;361:745-755).

In the second study, 7868 postmenopausal women with low BMD were randomized to denosumab 60 mg SQ every 6 months or placebo for 36 months. The primary endpoint was new vertebral fractures. Denosumab was associated with a reduction in vertebral fractures (2.3% vs 7.2% placebo; $P < 0.001$), a reduction in hip fractures (0.7% vs 1.2% placebo; $P = 0.04$), and a smaller reduction in nonvertebral fractures. There was no increase in risk of cancer, infection, cardiovascular disease, delayed fracture healing, hypocalcemia, or osteonecrosis of the jaw in this study (Cummings SR, et al. *N Engl J Med* 2009; 361:756-765).

These last findings are important because the FDA's Expert Panel expressed concerns about infection and cancer data in giving a recommendation to approve denosumab when the FDA votes on the drug in October. If approved, which seem likely, denosumab will be marketed by Amgen under the trade name Prolia™. ■

FDA Actions

The FDA is requiring new boxed warnings on TNF-blockers regarding the risk of lymphoma and other malignancies in children and adolescents who have received the drugs. The new labeling will include warnings regarding cases of leukemia in adults, adolescents, and children, as well as new onset psoriasis. The labeling will also include a revised Medication Guide to reflect the safety information. Products subject to the new boxed warning are infliximab (Remicade®), etanercept (Enbrel®), adalimumab (Humira®), and the recently approved agents certolizumab pegol (Cimzia®) and golimumab (Simponi™). These TNF-blockers are used to treat rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ankylosing spondylitis. The warning is based on reports of nearly 50 cases of various cancers associated with the drugs, of which half were lymphomas.

The FDA has approved a new dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes. Bristol-Myers Squibb and AstraZeneca's saxagliptin (Onglyza™) is the second DPP inhibitor approved after sitagliptin (Januvia®). It is the first drug approved since the FDA changed its standards for diabetes drug approvals, requiring evidence of cardiovascular safety. While saxigliptin has not shown evidence of higher rates of cardiovascular disease, the FDA is requiring post-marketing studies to specifically look at cardiovascular safety in high-risk populations. Saxigliptin is dosed once daily and is approved as monotherapy or in combination with metformin, sulfonylureas, or thiazolidinediones.

The FDA has announced that it is reviewing adverse event reports of liver injury in patients taking the weight-loss drug orlistat, marketed as the prescription drug Xenical® and over the counter as Alli®. The agency has received 32 reports of serious liver injury in patients taking the drug in the last 10 years. Of these, 6 resulted in liver failure. Almost all of the reports are from outside the United States. The FDA is not recommending patients discontinue the drug, but is suggesting that those who have used orlistat should consult a health care professional if they develop jaundice, fever, fatigue, brown urine, or other symptoms of liver injury. ■