

**2005**  
**CANADIAN CARDIOVASCULAR SOCIETY**  
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**PERIPHERAL ARTERIAL DISEASE**

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## Introduction

**Beth L. Abramson, MD Msc FRCPC**     **Victor Huckell MD FRCPC**  
Assistant Professor of Medicine     Department of Medicine  
University of Toronto     University of British Columbia  
Toronto, Ontario     Vancouver, B. C.

### INTRODUCTION

This Consensus Conference has been supported by the Canadian Cardiovascular Society. The process is dynamic, with intentional structure that requires peer review and feedback from cardiovascular specialists across Canada. The primary writing panel is regionally broad ranging, composed of cardiovascular specialists, cardiologists, internists, and surgeons from coast to coast. The secondary review panel also encompasses a broad range of specialists caring for the patient with peripheral arterial disease. At the outset, the goal in creating this document was to make sure the end product can be effectively applied to practice. As the topic is potentially broad ranging, the scope was focused and clinically driven prior to development of the first iteration. It was felt that given the wide area involved it would not serve our membership/readership to not be focused with a more concise and practical approach. The intent of this document is to be complementary to larger European (TASC) and U.S. documents (AHA/ACC), with a very practical focus of disseminating and implementing knowledge and best practices to our patients. Importantly it is to serve as a guide to the busy clinician. Therefore the current first version of the consensus process will not include: Carotid disease, venous disease, erectile dysfunction, pulmonary arterial disease, or digital disease. We direct our reader to the complex American and European documents in these areas. Although the focus will be on Peripheral Arterial Disease (PAD), in the interest of serving our membership there will be discreet chapters on Thoracic and Abdominal Aortic disease, Renal Arterial Disease and the evidence supporting management. Of course, the CCS consensus process is dynamic, and we hope to expand the focus of this document as it is updated in years ahead.

Peripheral Arterial Disease (PAD) is an often asymptomatic, under-diagnosed, under-recognized and under-treated condition. It is associated with significant morbidity and cardiac mortality. The role of the cardiac specialist has been less defined in the PAD arena than in the patient with coronary disease (CAD). In contrast to the CAD patient, which is cared for ideally with comprehensive care from primary care physicians, specialists, surgeons, and established secondary prevention clinics in concert, there is no such strategy for care with the PAD patient. The PAD patient often is seen by the primary care health provider and when symptomatic, sent for evaluation and possible revascularization to Vascular Surgeons. . Until recently, little attention has focused on the evaluation and treatment of the disease process itself. The delivery of care to the PAD patient is not widely publicized. Although not directly discussed in the following chapters, one of the goals of this consensus process is to stimulate discussion and foster debate as to the most appropriate models for health care delivery in the PAD patient. Implementation strategies are often more critical than dissemination of information itself. Strategies perhaps echoing the care in the CAD patient may at the end of the day benefit the PAD population to a greater extent than important diagnostic and interventional treatments. Ultimately the goal of this process is to ensure better treatment, to reduce both morbidity and mortality in the patient with vascular disease.

#### **QUALITY OF EVIDENCE AND CLASSIFICATION OF RECOMMENDATION**

As with all Canadian Cardiovascular Society Consensus Conferences we use the previously documented levels of evidence and grading of recommendations as follows:

#### **QUALITY OF EVIDENCE**

- I** – Evidence obtained from at least one properly randomized controlled trial or one large epidemiological study.
- II** – Evidence based on at least one non-randomized cohort comparison or multi-centre study, chronological series or extra ordinarily results from large non-randomized studies.
- III** – Opinions of respective authorities, based on clinical experience, descriptive studies or reports of expert committees.

## **CLASSIFICATION AND RECOMMENDATIONS**

- A** – Evidence sufficient for universal use (usually based on randomized clinical trials).
- B** – Evidence acceptable for widespread use, evidence less robust, but based on randomized clinical trials.
- C** – Evidence not based on randomized clinical trials.

## **IN THE COMING CHAPTERS**

The following concepts are discussed in the chapters that ensue:

We discuss the epidemiology of peripheral arterial disease including its prevalence and relationship and overlap with cardiovascular disease and cerebrovascular disease. Management discussions for the patient with atherosclerotic PAD are aided by knowledge of its natural history and prognosis. Therapy directed specifically at PAD will not necessarily improve the patient's life expectancy, which is shortened by coronary and cerebral arterial disease. In a non-diabetic patient with atherosclerotic PAD and no symptoms or only intermittent claudication the outlook for limb survival is favorable – about 5-7% limb loss in five years. The level of the occlusive disease is not predictive of progression to severe ischemia of the limb. When ischemia becomes more severe producing ischemic rest pain, ischemic ulceration, or gangrene limb loss is significantly higher (about 90% loss in one year without therapy ) even in a non-diabetic. The deleterious nature of PAD is compounded by its status as an under diagnosed and under treated disease. Recent data has made us aware of the magnitude of the burden of PAD and its under treatment. There is a large body of evidence supporting non-invasive procedures (for example, the ankle brachial index) as effective diagnostic and risk assessment tools.

This is followed by a discussion on pathophysiology. Atherosclerosis is a generalized disease that affects large – and medium – sized arteries. Atherosclerotic plaques are prone to disruption, thereby triggering the formation of an overlying thrombosis. The term atherothrombosis has been introduced to describe thrombosis complicating atherosclerosis. Peripheral arterial disease

is a distinct atherothrombotic syndrome that is associated with an elevated risk of cardiovascular and cerebrovascular events including death, myocardial infarction and stroke. The prevalence of PAD in Europe and North America varies with age however it is estimated at approximately 27 million people have the disease. Atherothrombosis of all arterial systems is the leading cause of death worldwide and accounts for 28% of all deaths.

We review risk for PAD based on lifestyle modification. Clinical study results show that substantial risk reduction can be achieved by combined non-pharmacologic and pharmacologic intervention in PAD. Tobacco use in patients with intermittent claudication is the most significant independent risk factor for PAD. In patients with symptomatic PAD continued tobacco use is associated with an eleven-fold increase in limb loss as compared to person who discontinued smoking or are non-smokers. Management, thus, must include both non-pharmacologic and pharmacologic strategies.

A discussion of thoracic and abdominal aortic arterial disease including screening techniques and interventional techniques follows. Atherothrombotic disease can affect the renal arteries. This is an emerging subgroup that needs to be dealt with separately. Screening and diagnostic techniques include history and physical examination as well as non-invasive imaging techniques of the renal vasculature are reviewed. Medical management for patients with vascular disease including prevention and risk reduction. This section includes both pharmacologic and non-pharmacologic management strategies. The sections are followed by an introduction to newer percutaneous techniques.

Finally we deal with surgical treatment for claudication including new concepts on the peri-operative risk assessment for patients undergoing major vascular surgery.

## Epidemiology

**Dr Anil Gupta**

Staff Cardiologist

Mississauga, Trillium Health Centre

### INTRODUCTION

Peripheral arterial disease (PAD) is a condition characterized by progressive narrowing of the arteries in the lower extremities. Patients with peripheral artery disease may be asymptomatic or symptomatic. Symptoms range from intermittent claudication to critical limb ischemia.

Intermittent claudication is the most common manifestation of peripheral artery disease. It is characterized by a history of leg pain on exercise that is relieved with rest. Although these symptoms are highly suggestive of PAD, confirmatory examination/investigation is required and other causes of leg pain should be ruled out.

Decreased quality of life and loss of function resulting from intermittent claudication, due to a limited mobility and independence, may rival or even extend beyond that of patients with cardiac disease<sup>(1,2)</sup>. Patients can present with more progressive symptoms such as critical limb ischemia, leading to ulcers and gangrene, necessitating surgical interventions such as angioplasty, stenting, endarterectomy, bypass or amputation.

The prevalence of asymptomatic disease is high and as with symptomatic disease, is associated with up to six fold increase risk of cardiovascular morbidity and mortality<sup>(3)</sup>. Major risk factors for PAD include smoking, diabetes, hypertension and dyslipidemia<sup>(4-11)</sup>. The need for amputation is higher amongst patients with renal dysfunction<sup>(12,13)</sup> and in patients with diabetes<sup>(5)</sup>. Links between peripheral artery disease and inflammatory markers such as C-reactive protein (CRP) have been established<sup>(14,15)</sup>.

The prevalence, natural history and concomitant vascular conditions will be explored further.

## PREVALENCE

Methods at identifying peripheral arterial disease in the population are variable. Using symptoms of claudication as a measure of prevalence is complicated. Many questionnaires have been developed to help define intermittent claudication and to establish prevalence. Additional investigations include clinical examination and noninvasive tests such as ankle brachial index (ABI). The high variability of clinical presentation adds to the problem of accurately defining prevalence. There is a paucity of Canadian data in this area.

The WHO/Rose Questionnaire (see screening chapter) is one of the more widely used questionnaires for identifying intermittent claudication and underlying PAD<sup>(16)</sup>. It has a specificity of 99.8% and sensitivity of 67.5% in detecting claudication<sup>(17)</sup>. When used in a population high prevalence, the sensitivity increases to 92%. The Edinburgh Questionnaire is self-administered and increases the sensitivity to 91% while retaining a specificity of 99%<sup>(18)</sup>. Both questionnaires likely underestimate the true prevalence when used in epidemiological studies amongst the general population.

The prevalence rate of intermittent claudication using the Rose questionnaire varies widely, ranging from 0.4% to 14.4%. In larger studies, a prevalence rate between 3% and 6% amongst patients around the age of 60 years appears to be consistent<sup>(19-23)</sup>.

Peripheral artery disease can also be determined by using a non-invasive test, the ankle-brachial index (ABI). It has sensitivity 95% in detecting angiographically determined disease and a specificity of almost 100% in normal populations. The National Health and Nutrition Examination Survey (NHANES) reports estimates of PAD using ABI less than 0.9 as the definition. In surveying 2174 patients over the age of 40, the prevalence of

PAD was 4.3%, translating to approximately 5 million individuals in the United States. The prevalence rose to 14.5% in those over 70 years of age. No clear gender differences were identified<sup>(24)</sup>.

In the Rotterdam Study, a population based survey of 7715 patients, 16.9% of men and 20.5% women had an ABI less than 0.90, despite only up 4.6 % reporting symptoms of intermittent claudication. This underscores the fact that most patients with PAD are asymptomatic. The Limburg Peripheral Artery Occlusive Study performed a cross sectional survey of 3650 patients and found that asymptomatic patients have a similar risk factor and co-morbidity profile as symptomatic patients<sup>(25)</sup>. Although asymptomatic patients with PAD have fewer complications related to their lower limbs, it is a strong marker of future cardiovascular events.

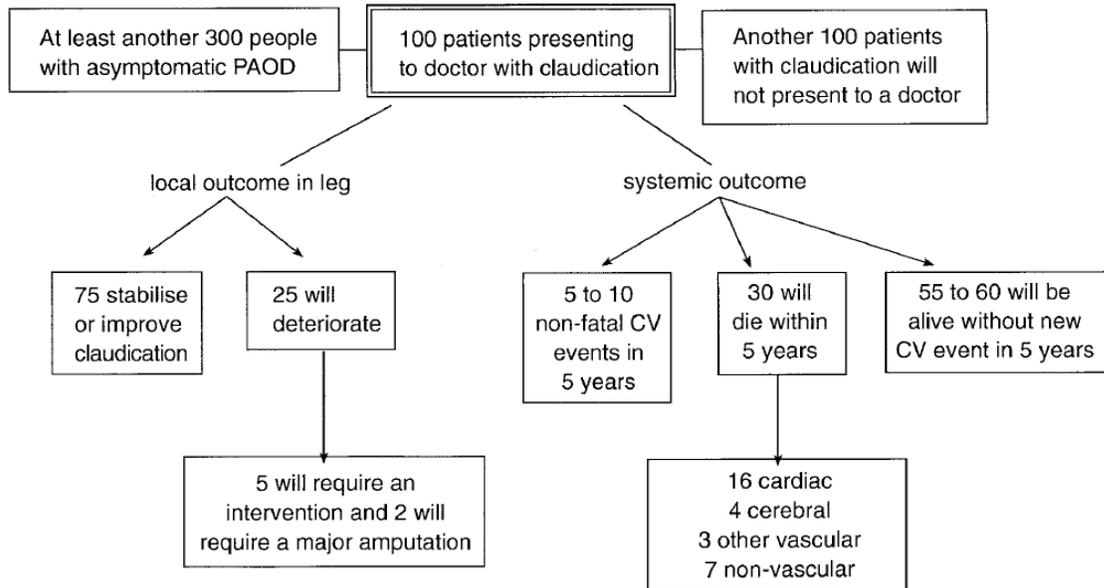
Based on some estimates, 16% of the population in North America and Europe has PAD, correlating to 27 million people. 16.5 million of these patients are asymptomatic.

#### **NATURAL HISTORY**

The progression to clinical local limb deterioration is actually quite low. Data from the classic epidemiological study by Bloor in 1961 demonstrated that 25% of patients presenting with symptoms of intermittent claudication will significantly deteriorate<sup>(26)</sup>. The Basle study from 1979 was an angiographic study, which showed progression of angiographic disease in 63% of patients at 5 years, but 66% of survivors still, had no limiting symptoms<sup>(27)</sup>. A multiple international site study observing patients from a non surgical site provides more recent data showing only 6% of patients had deterioration in their walking distance, over 1 year<sup>(28)</sup>.

There is considerable variability in data indicating the need for surgical intervention, ranging from 3% to 22%<sup>(29,30)</sup>. Studies from Framingham and Balse showed that less than 2% patient presenting with claudication will require amputation<sup>(9,27)</sup>.

The following chart from the TASC document predicts the fate of patients presenting with claudication.



In contrast to the relatively benign progression of local disease, overall mortality is significant, approximately 50%. The San Diego study followed 565 patients for 10 years. It demonstrated a relative risk of death over 10 years in men to be 5.1 and 4.8 in women<sup>(3)</sup>. Amongst these patients who did not have cardiovascular disease at study entry, the relative risk of cardiovascular death was 3.9 for men and 5.7 for women. At 10 years, the survival rate of asymptomatic patients is approximately 50% and for severe symptomatic patients approximately 25%.

The main risk factors which predict the need for revascularization are smoking<sup>(31,32)</sup> and diabetes as well as a low ABI. A recent meta-analysis by Doobay and Anand reviewed 9 studies using an ABI cutoff between 0.8 and 0.9. The sensitivity and specificity of a low ankle-brachial index to predict incident coronary heart diseases were 16.5% and 92.7%, for incident stroke were 16.0% and 92.2%, and for cardiovascular mortality were 41.0% and 87.9%, respectively. The corresponding positive likelihood ratios were 2.53 (95% CI, 1.45 to 4.40) for coronary heart disease, 2.45 (95% CI, 1.76 to 3.41) for stroke, and 5.61 (95% CI, 3.45 to 9.13) for cardiovascular

death. This study demonstrated a high specificity, but low sensitivity for a low ABI to predict future cardiovascular outcomes.

### CONCOMITANT VASCULAR DISEASE

That significant overlap exists in frequency of disease in coronary arteries, cerebrovascular disease and PAD, is well established. Given the similarity in risk factors and pathogenesis of disease, recognizing the overlaps amongst these conditions should be appreciated when investigating and treating PAD. The true overlap is dependant upon the nature of diagnostic criteria employed for each atherosclerotic condition and the sensitivities of the methods used.

Criqui's data used noninvasive tools for diagnosing PAD, but had limited tools for assessing coronary artery disease (CAD) or cerebrovascular disease (CVD). They determined CAD by history of previous myocardial infarction or bypass surgery and defined CVD by previous stroke or stroke related surgery. It was shown that amongst men with PAD, 29.4% had clinical CAD and amongst women, 21.2% had clinical CAD. Among men with CAD, 32.3% had PAD and among women with CAD, 25% had PAD.

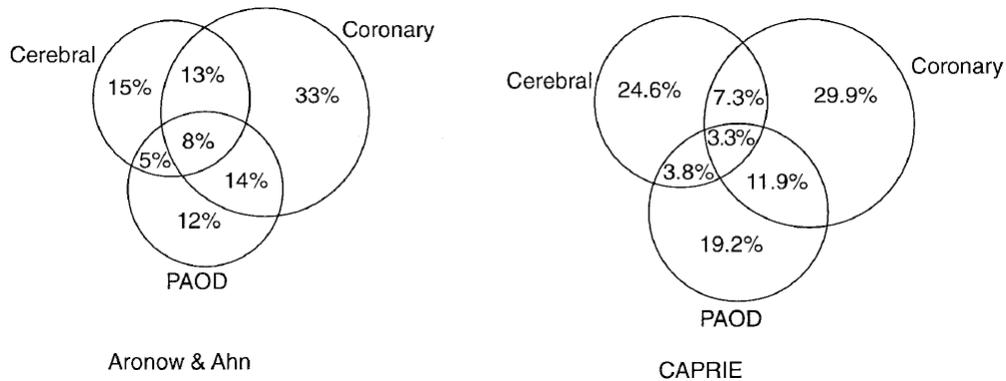
Between 1971 and 1981, all patients presenting to Cleveland Clinic for peripheral arterial disease surgery, underwent cardiac catheterization to determine whether treatment of CAD would improve their survival. 10% of patients had normal coronary arteries.

28% had significant 3-vessel disease. Aronow and Ahn found that 22% of patients with CAD, also had PAD<sup>(34)</sup>.

The correlation between PAD and cerebrovascular disease (CVD) is not as strong, as compared to CAD. Amongst patients with intermittent claudication, 26% have carotid artery disease, by duplex Doppler. Aronow and Ahn found that 33% of patients with CVD also had PAD<sup>(35)</sup>.

There is little data on the co-existence of hemodynamically significant arteriosclerosis in all 3 arterial beds, in the same study. The Aronow and Ahn study prospectively evaluated the incidence and degree of overlap of CAD, PAD and stroke in 1886 patients, 62 years of age or greater, in a

long term facility. The figure shows a significant degree of overlap, with 41% of patients presenting with symptomatic disease in two or more vascular beds. A similar diagram is shown amongst distribution of concomitant disease amongst almost 20, 000 patients from the CAPRIE study<sup>(36)</sup>.



HOPE studied patients aged 55 years or greater and had existing cardiovascular disease (coronary artery disease, previous stroke, peripheral artery disease) or diabetes and an additional risk factor (smoking, hypertension, hypercholesteremia, low HDL or microalbuminuria). 9541 patients were randomized to receive treatment versus placebo. 1715 patients (17.9%) were included on the basis of having symptomatic PAD. 3099 patients (32.4%) had an ABI less than 0.9. Clinical PAD and low ABI (<0.9) without symptoms were strong predictors for cardiovascular morbidity and mortality.

**CONCLUSIONS**

Although there is little contemporary epidemiological data of prevalence of peripheral artery disease in Canada, it likely represents approximately 4% of the population over the age of forty, using ABI less 0.90 as a cut off for definition. Risk factors for peripheral artery disease are similar to those for coronary artery disease. Peripheral artery disease is a powerful indicator of atherothrombotic disease in other arterial beds. Both asymptomatic and symptomatic patients have a high risk of cardiovascular morbidity and mortality. It is an extremely important public health issue affecting a significant portion of the Canadian population.

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## **Pathophysiology of Atherosclerosis**

**Subodh Verma, MD, PhD**  
Division of Cardiac Surgery  
University of Toronto

### **INTRODUCTION**

Atherosclerosis is a systemic and generalized disorder of the arterial tree, which results in localized plaque deposition at selected sites within the vascular bed. Epidemiological studies have revealed a number of risk factors that predispose to pathogenesis of atherosclerosis, although the final expression of the disease appears to be governed by the interaction of a number of genetic and environmental factors, which may exert a different effect on the arterial tree in question. The pathophysiological basis of atherosclerosis is now well accepted to involve a close interplay between endothelial dysfunction and inflammation, which in turn may modify the vascular responses to oxidative stress, and platelet-endothelial interaction. The evolution of atherosclerotic plaques is associated with important anatomic and hemodynamic adaptive responses, and it is when these compensatory mechanisms fail that complications of atherosclerosis such as stenosis, plaque ulceration, embolization and thrombosis appear. This chapter discusses the general pathophysiological features of atherosclerosis, with emphasis on the peripheral arterial system. The chapter is divided into two sections which deal with (a) the pathogenesis of atherosclerosis, including risk factors, endothelial dysfunction and inflammation; (b) the adaptive responses to atherosclerosis, including a discussion of the vessel wall anatomic and hemodynamic compensations to increasing plaque burden. The reader is referred to several excellent reviews on the topic.<sup>(1-6)</sup>

### **PATHOGENESIS OF ATHEROSCLEROSIS: RISK FACTORS, ENDOTHELIAL**

#### **DYSFUNCTION AND INFLAMMATION**

Current views regard atherosclerosis as a dynamic and progressive disease arising from the combination of endothelial dysfunction and inflammation.<sup>(1-9)</sup> The vascular endothelium, located at the interface of blood and tissue, is able to sense changes in hemodynamic forces and

blood-borne signals and react by synthesizing and releasing vasoactive substances. Vascular homeostasis is maintained by a balance between endothelium-derived relaxing and contracting factors. With disruption of this balance, mediated by inflammatory and traditional cardiovascular risk factors, the vasculature becomes susceptible to atheroma formation. Inflammatory mediators appear to play a fundamental role in the initiation, progression and eventual rupture of atherosclerotic plaques.

Endothelial dysfunction is a broad term that implies diminished production or availability of nitric oxide (NO) and/or an imbalance in the relative contribution of endothelium-derived relaxing and contracting factors, such as endothelin-1 (ET-1), angiotensin and oxidants.<sup>(7)</sup> NO, generated by the conversion of the amino acid L-arginine to NO and L-citrulline by the enzyme nitric oxide synthase (NOS), is the key endothelium-derived relaxing factor that plays a pivotal role in the regulation of vascular tone and vasomotor function.<sup>(10)</sup> Impaired endothelium dependent vasodilation in coronary arteries with established atherosclerosis results in paradoxical vasoconstriction, which may result in reduced myocardial perfusion and myocardial ischemia. However, endothelial dysfunction, as assessed in terms of vasomotor dysfunction, can occur well before the structural manifestation of atherosclerosis and thus, can serve as an independent predictor of future cardiovascular events.<sup>(9)</sup>

In addition to its vasodilatory effect, NO also protects against vascular injury, inflammation and thrombosis. NO inhibits leukocyte adhesion to the endothelium, maintains vascular smooth muscle in a nonproliferative state, and limits platelet aggregation.<sup>(11-13)</sup> However, in response to the traditional cardiovascular risk factors, such as hypertension, diabetes and hypercholesterolemia, the endogenous defenses of the vascular endothelium begin to break down. Hypercholesterolemia promotes attachment of blood leukocytes to the endothelium, a cell layer that under ordinary conditions is resistant to firm leukocyte adhesion.<sup>(5)</sup> Oxidized low-density lipoprotein (oxLDL) causes endothelial activation and changes its biological characteristics in part by reducing the intracellular concentration of NO.<sup>(14)</sup> Angiotensin II (AII), a vasoconstrictor associated with hypertension, opposes NO action. AII can elicit the production of reactive oxygen species (ROS), increase the expression of the proinflammatory cytokines interleukin (IL)-6 and monocyte chemoattractant protein-1 (MCP-1), and upregulate vascular cell adhesion molecule-1 (VCAM-1)

on endothelial cells.<sup>(15-17)</sup> Newer risk factors such as elevated C-reactive protein (CRP) levels can also promote endothelial dysfunction by quenching the production of NO and diminishing its bioactivity.<sup>(18)</sup> These endothelial modifications promote inflammation within the vessel wall setting the stage for the initiation and progression of an atherosclerotic lesion.

When endothelial cells undergo inflammatory activation, the increased expression of selectins, VCAM-1 and intercellular adhesion molecule-1 (ICAM-1), promotes the adherence of monocytes. Adhesion molecule expression is induced by proinflammatory cytokines such as IL-1 $\beta$ , tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), C-reactive protein (CRP), protease activated receptor (PAR) signaling, oxLDL, CD40/CD40 ligand (CD40L, CD154) interactions.<sup>(19-23)</sup> Once adherent, the monocytes penetrate into the tunica intima, the innermost layer of the arterial wall, passing between the endothelial cells. This monocyte migration is directed along a concentration gradient of MCP-1, via interaction with the monocyte receptor CCR2.<sup>(24)</sup> Once within the arterial intima, the monocytes develop into macrophages and begin to express scavenger receptors, such as LOX-1, that internalize modified lipoproteins.<sup>(25)</sup> Internalization of these lipoprotein particles gives rise to lipid-laden macrophages or foam cells, which characterize early atherosclerotic lesions. Within the developing atheroma, the foam cells begin to secrete proinflammatory cytokines that maintain a chemotactic stimulus for adherent leukocytes, augment expression of scavenger receptors and promote macrophage replication.<sup>(6)</sup>

However, macrophages are not alone in contributing to atheroma formation. T cells and mast cells are also recruited into atheromatous plaques.<sup>(26)</sup> Binding to adhesion molecules, such as VCAM-1 facilitates T cell entry into the intima. Once within the arterial intima, T cells may become activated by encountering antigens such as ox-LDL and begin to secrete cytokines that can influence macrophage activity. CD40/CD40L engagement between activated T cells and macrophages can result in the expression of tissue factor, matrix metalloproteinases (MMPs) and proinflammatory cytokines that perpetuate the inflammatory response.<sup>(6)</sup> Plaque formation is further promoted by the less abundant mast cells. Upon mast cell degranulation, TNF- $\alpha$ , heparin and serine proteases are released.<sup>(6)</sup> If the risk factors inducing endothelial dysfunction and inflammation remain, the atheroma will progress from a fatty streak to a more complex lesion.

Fatty streak evolution toward a complex lesion is typified by the proliferation of smooth muscle cells (SMCs), their migration toward the intima and their synthesis of collagen. Continued release of cytokines, such as MCP-1, by activated endothelial cells, T cells and foam cells, not only perpetuates inflammation and lipid accumulation within the atheroma, but also influences SMC activity.<sup>(23,27)</sup> Expansion of this lesion within the coronary arteries can result in lumen obstruction, causing a reduction of blood flow, which may present clinically as angina. Neovascularization supports plaque growth and rupture of these newly formed, fragile cells is postulated to result in an acute expansion of the lesion.<sup>(28)</sup> However, lipid core growth, whether progressive or acute, eventually causes destabilization of the plaque.

Proinflammatory cytokines secreted by activated T cells, such as interferon (IFN)- $\gamma$ , can limit the synthesis of new collagen required for fibrous cap preservation.<sup>(6)</sup> Accumulation of oxLDL has toxic effects on macrophages and SMCs, leading to necrotic core formation.<sup>(29)</sup> Implicated with oxLDL toxicity is lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>), an enzyme that when inhibited, reduces macrophage death.<sup>(30)</sup> The death of macrophage foam cells leads to lipid spillage promoting further inflammation while SMC death further reduces collagen synthesis and promotes fibrous cap thinning. The thinning of the fibrous cap is enhanced by the overexpression of MMPs, interstitial collagenases and gelatinases, which degrade supportive collagen.<sup>(31)</sup> MMP overexpression and activation within the plaque are mediated by IL-1 $\beta$ , TNF- $\alpha$ , oxLDL and CD40L. Once the fibrous cap is weakened, the plaque is vulnerable to rupture, precipitating acute thrombotic complications.

Disruption of the vulnerable atherosclerotic plaque, upon exposure to hemodynamic stresses, can trigger thrombosis and plaque ulceration. Erosion of the plaque surface, characterized by areas of endothelial cell desquamation, exposes a prothrombotic surface. An even greater prothrombotic stimulus arises from the rupture of a fibrous cap and the spilling of its contents into the lumen. Subendothelial collagen, tissue factor (TF) and von Willebrand factor (vWF) become accessible to components in the circulation, promoting coagulation and thrombin formation.<sup>(6)</sup> Platelet activation and aggregation ensue, mediated by interactions with thrombin, TF and vWF. TF overexpression by endothelial cells and macrophages is enhanced by the presence of inflammatory mediators within the plaque, namely IL-1, TNF- $\alpha$  and CD40L. In response to this vascular insult,

thrombogenicity is further favoured by the activation of PARs on platelets and in the adjacent tissue.<sup>(32)</sup> Thus, inflammation participates in all steps of atherosclerosis.

The inflammatory biomarker C-reactive protein (CRP) has emerged as a powerful independent predictor of cardiovascular disease. Elevated levels of hsCRP predict cardiovascular risk in a wide variety of clinical settings, including men and women without overt cardiovascular disease<sup>(33,34)</sup>, patients with stable angina or presenting with acute coronary syndromes<sup>(35,36)</sup>, post-myocardial infarction patients<sup>(37)</sup> and those with the metabolic syndrome.<sup>(38)</sup> Furthermore, hsCRP predicts not only incident myocardial infarction and cardiovascular death, but also the risk of ischemic stroke<sup>(39)</sup>, sudden cardiac death<sup>(40)</sup>, incident peripheral artery disease<sup>(41)</sup>, and restenosis after percutaneous coronary intervention.<sup>(42)</sup> In primary prevention, CRP confers additional prognostic value at all levels of Framingham risk and at all levels of the metabolic syndrome and blood pressure.<sup>(43-45)</sup> The circulating level of hsCRP not only effectively predicts cardiovascular risk but it also appears to be specific for cardiovascular death.<sup>(46)</sup> In head to head comparisons with LDL cholesterol, CRP was found to be at least as strong a predictor of incident cardiovascular events.<sup>(43)</sup> The Women's Health Study (WHS) was comprised of 27 939 American women with no history of cardiovascular disease. At the study's onset, participants underwent a Framingham risk assessment, hsCRP evaluation and a full lipid screen. LDL cholesterol and hsCRP were compared at baseline levels for their ability to predict first myocardial infarction, ischemic stroke, coronary revascularization or cardiovascular death. Mean follow-up was 8.3 years. The relative risks for a future vascular event, for increasing quintiles of hsCRP at baseline, were 1.0, 1.8, 2.3, 3.2 and 4.5 ( $P < 0.001$ ). After adjusting for age, smoking status, diabetes, blood pressure and the use of hormone replacement therapy, the relative risk in the top hsCRP quintile was 2.3 (95% CI: 1.6 to 3.4). Risk of a first vascular event increased with increasing quintile for both LDL cholesterol and hsCRP (both  $P < 0.001$ ). Of all the vascular events that occurred in the study population, 46% occurred in participants with baseline LDL-cholesterol levels below current LDL cholesterol goals. Importantly, LDL cholesterol and hsCRP levels correlated poorly ( $r = 0.08$ ), suggesting each of these biomarkers predicted events in different risk groups. Indeed, a combined approach with both LDL cholesterol and hsCRP levels provided an improvement in the prediction of cardiovascular event-free survival. The predictive power of hsCRP remained significant after adjustment for the Framingham Risk Score, a result that has also

been demonstrated in the Physician's Health Study (PHS)<sup>(47)</sup>, the Atherosclerosis Risk in Communities Study (ARIC)<sup>(48)</sup>, the Air Force/Texas Atherosclerosis Prevention Study (AFCAPS/TexCAPS)<sup>(49)</sup>, the Monitoring of Trends and Determinants of Cardiovascular disease (MONICA) study<sup>(50)</sup> and most recently, in the Reykjavik Study.<sup>(51)</sup> The Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) released a series of recommendations regarding the application of hsCRP for the assessment of cardiovascular risk.<sup>(52)</sup> Within their Scientific Statement they recognized that hsCRP retains an independent association with incident coronary events after adjusting for age, total cholesterol, HDL cholesterol, smoking, body mass index, diabetes, hypertension, exercise level and family history of cardiovascular disease and thus adds to the predictive capacity of established risk factors. Similarly, in the setting of secondary prevention, hsCRP is a good predictor for poorer outcomes following acute coronary syndromes, percutaneous transluminal interventions or stroke. Based on the current clinical data available, the AHA/CDC have issued a class IIa recommendation, where the evidence weighs in favour of usefulness or efficacy, for the screening of hsCRP as a routine part of global cardiovascular risk assessment in those patients judged at intermediate risk by global risk assessment (10 to 20% risk of cardiovascular disease per 10 years) and in patients with stable coronary disease or acute coronary syndromes. CRP appears to serve not only as a marker of this pathologic inflammatory process but also as an active partaker in all stages of atherogenesis (see 3 for review)

In addition to CRP, much recent attention has focussed on the role of CD40 and LOX-1, in the pathophysiology of atherosclerosis. Originally identified in B and T lymphocytes as being involved in T-cell dependent B cell activation and differentiation, the CD40/CD40L system has since been implicated in the pathophysiology of severe chronic inflammatory diseases, including atherosclerosis.<sup>(23,53, 54)</sup> CD40, a 50 kDa integral membrane protein of the tumor necrosis factor receptor family, and CD40L, a 39 kDa member of the tumor necrosis factor family, are coexpressed by all of the major cellular players in atherosclerosis, namely activated T lymphocytes, vascular endothelial cells, smooth muscle cells and macrophages.<sup>(23)</sup> Both the receptor and ligand are functional, mediating various proatherogenic processes. Immunohistochemistry studies revealed the presence of the CD40/CD40L signaling dyad within both early and advanced human atherosclerotic plaques.<sup>(54, 55)</sup> The importance for CD40 signaling in atherosclerotic plaque

development and evolution was demonstrated using low-density lipoprotein receptor-deficient mice that were fed a high cholesterol diet.<sup>(56, 57)</sup> By interrupting CD40 signaling in these mice, using a neutralizing anti-CD40L antibody, both the de novo formation and the further progression of established atherosclerotic lesions were drastically reduced. Further evidence suggesting a link between atherosclerosis and the inflammatory properties of CD40/CD40L emerges from studies examining circulating levels of soluble CD40L (sCD40L), which is primarily derived from activated platelets and is considered to possess biological activity.<sup>(58)</sup> Elevated plasma concentrations of sCD40L were observed in patients with unstable angina, and predicted patients with features of high risk atherosclerotic lesions as well as the risk for future cardiovascular events in women.<sup>(59-61)</sup> A recent study examining sCD40L in acute coronary syndromes found that elevated sCD40L levels indicated a significantly increased risk of death or nonfatal myocardial infarction, a risk that was significantly reduced with abciximab.<sup>(62)</sup> Also, a general upregulation of the CD40 system was observed in patients with moderate hypercholesterolemia.<sup>(63)</sup> The clinical associations of the CD40/CD40L proinflammatory system and atherosclerosis suggest CD40 signaling function spans from early atherogenesis to late thrombotic complication.

The initial trigger for CD40/CD40L expression within the atheroma remains uncertain, but a recent study suggests oxLDL may play this role.<sup>(64)</sup> OxLDL induced the expression of CD40 and CD40L in human ECs, SMCs and macrophages, induction that was diminished upon statin administration. Endothelial dysfunction and the subsequent changes in blood flow promote CD40-mediated endothelial activation by decreasing the intracellular expression of a CD40 signaling blocker.<sup>(65)</sup> CD40 signaling in endothelial cells stimulates the production of ROS, which in turn antagonize endothelial NO production, which assists in the perpetuation of a dysfunctional endothelium.<sup>(66)</sup> Endothelium activation and CD40/CD40L then work in concert to initiate atherosclerotic lesion formation. Ligation of CD40 on ECs and SMCs induces the expression of adhesion molecules such as E-selectin, VCAM-1 and ICAM-1, promoting the recruitment of monocytes and lymphocytes to the lesion.<sup>(53)</sup> Leukocyte recruitment is further enhanced by CD40L induced secretion of MCP-1, IL-1, IL-6 and TNF- $\alpha$  by the atheroma-associated cells.<sup>(23)</sup> These cytokines and chemokines amplify the inflammatory effect and serve to foster a proatherogenic environment.

CD40L induced pathways contribute to conditions that favor plaque progression towards instability. The balance between the synthesis and breakdown of collagen, the predominant structural component of the fibrous cap, is shifted towards degradation by CD40 ligation. With the ligation of CD40, human vascular ECs, SMCs and macrophages increase expression of a full complement of MMPs, including the interstitial collagenases MMP-1, MMP-8 and MMP-13.<sup>(23)</sup> Plaque stability and lesional collagen content were actually increased upon interruption of CD40 signaling.<sup>(55, 67)</sup> In addition to making the plaque more fragile, CD40 signaling induces TF expression in both endothelial and smooth muscle cells.<sup>(68, 69)</sup> Elevated levels of TF enhance the thrombogenic potential of the plaque upon rupture by instigating the extrinsic pathway of blood coagulation. Furthermore, CD40L inhibits endothelial cell migration.<sup>(66)</sup> By preventing endothelial cells to migrate, reendothelialization of any plaque erosions is impaired, enhancing the possibility of an acute atherosclerotic event. Thus, the proinflammatory dyad, CD40/CD40L, participates in inducing not only proatherogenic but also prothrombotic conditions.

The endothelial injury, activation and dysfunction caused by oxLDL in the pathogenesis of atherosclerosis are exerted via LOX-1 activation.<sup>(70, 71)</sup> LOX-1, initially identified as the major receptor for oxLDL in endothelial cells, can also be expressed in macrophages and SMCs.<sup>(72-74)</sup> It is a type II membrane protein with a C-type lectin like extracellular domain that can be cleaved, to release the soluble form of LOX-1, by an unknown protease.<sup>(70)</sup> In addition to being the main receptor for oxLDL, LOX-1 has the ability to bind damaged or apoptotic cells, activated platelets, advanced glycation end products, pathogenic organisms and endotoxin.<sup>(75-77)</sup> Once bound, these ligands can be endocytosed or phagocytosed into the cell. Under physiological conditions, LOX-1 may play a role in host defense or serve to scavenge cellular debris.<sup>(70)</sup> However, in pathological states, LOX-1 may be involved in binding proatherogenic materials, such as oxLDL, that activate the endothelium. With its ability to bind products that induce inflammation and endothelial activation, it is not surprising that elevated LOX-1 expression is observed in both initial and advanced atherosclerotic lesions.<sup>(78, 79)</sup>

The stage for atherosclerosis is set once endothelial dysfunction occurs. LOX-1 may play a role in initiating and potentiating this crucial first step. Under conditions of hypercholesterolemia, hypertension and diabetes, disease states that promote vascular injury, LOX-1 is highly expressed in blood vessels.<sup>(71)</sup> Induction of LOX-1 expression is mediated by AII and ET-1, both

antagonists of NO.<sup>(80, 81)</sup> With elevated levels of LOX-1 on the endothelium, increased amounts of oxLDL can be endocytosed, an activity that further enhances LOX-1 expression.<sup>(82)</sup> OxLDL through LOX-1 also increases the expression of angiotensin converting enzyme and reduces the intracellular concentration of NO.<sup>(83, 84)</sup> Thus, LOX-1 activity amplifies the extent of endothelial dysfunction. However, oxLDL uptake by LOX-1 also mediates endothelial cell apoptosis, potentially via NF- $\kappa$ B activation.<sup>(84)</sup> This may result in direct vascular denudation and injury that may trigger or enhance an existing inflammatory reaction.

In addition to setting the stage for atherosclerosis, LOX-1 activation contributes to the initiation and progression of atherogenesis. OxLDL, via upregulation of LOX-1, induces monocyte adhesion to the endothelium via enhanced expression of P-selectin, VCAM-1 and ICAM-1.<sup>(86)</sup> Receptor activation also results in MCP-1 expression, promoting monocyte migration into the intima.<sup>(87)</sup> Enhanced expression of LOX-1 by macrophages within the plaque suggests the receptor may be involved in oxLDL uptake and subsequent transformation into foam cells.<sup>(70)</sup> LOX-1 upregulation in response to cytokines secreted by lymphocytes, such as TNF- $\alpha$ , further enhances lipid accumulation.<sup>(88)</sup> However, LOX-1 activation may also contribute directly to plaque instability.

OxLDL binding to LOX-1 induces increased production of intracellular ROS, apoptosis of vascular smooth muscle cells and modulation of MMP activity, towards conditions favoring fragilization of the fibrous cap.<sup>(89-91)</sup> Upon plaque rupture, activated platelets may interact with the surrounding endothelium via LOX-1.<sup>(92)</sup> In addition to thrombus formation, the activated platelets can further induce endothelial dysfunction in the surrounding tissue. Activated platelet-LOX-1 interaction promotes the release of ET-1 from endothelial cells and stimulates the generation of ROS that inactivate NO.<sup>(77)</sup> Thus, LOX-1 signaling initiates a vicious circle of events that may potentially end in vascular occlusion and ischemic insult.

It is important to note that in addition to the mechanisms and mediators of atherosclerosis discussed above, due to space limitations, the importance of the PPAR system, the cannabannoid receptor system, and myeloperoxidase pathway were not discussed. All of these are important determinants of atherosclerosis.

We conclude this section by highlighting the role of risk factors in the development of atherosclerosis. The two risk factors that correlate most with the development and progression of peripheral atherosclerosis are cigarette smoking and diabetes. As reviewed by Faxon et al. smokers have up to a 5.6 fold increase in the development of peripheral arterial disease, compared to non-smokers.<sup>(93)</sup> A similar heightened risk is seen with diabetes, with rates of intermittent claudication increased by 3.5-fold in men with glycosuria compared to non-diabetic men. Women with glycosuria have a gargantuan 860% increased risk, compared to women without glycosuria. Although dyslipidemia and hypertension remain important risk factors for coronary and cerebral atherosclerosis, they do not feature prominently in the peripheral circulation. It is important to emphasize that genetic factors may contribute up to 50% of the risk, and clearly the multifactorial nature of atherosclerosis, involves cross-talk between a number of susceptible genes, with environmental factors.

#### **ANATOMIC AND HEMODYNAMIC ADAPTATIONS TO ATHEROSCLEROSIS**

The arterial wall undergoes a number of adaptive and compensatory responses to atherosclerotic plaque formation, and complications ensue when these adaptive mechanisms are overwhelmed by disease (reviewed 94).

Intimal thickening with lipid accumulation, along with changes in the wall thickness, atherosclerotic arterial enlargement (Glagov geometric remodeling) and eventual decreases in lumen size, with hemodynamic changes including shear stress, stasis, oscillation, and turbulence are some of the key adaptive mechanisms seen in atherosclerosis.

Intimal thickening has been ascribed to chronically reduced blood flow and/or a compensatory mechanism in the face of increase wall stress. Focal intimal thickening appears to occur at branch points, and although there is no direct evidence that intimal thickening is a precursor for fatty streaks and fibrous plaques, these processes appear to occur in the same arterial territory.

Fatty streaks, believed to represent the precursor lesion of fibrous atherosclerotic plaques, are defined as lipid-laden foam cells within the intima. These lesions may serve as the template for the progressive development of plaques, although they do not usually compromise the lumen nor

ulcerate per se. The classical atherosclerotic lesion is a fibrous plaque in which the subendothelial layer comprises a well-organized layer of smooth muscle and connective tissue fibres called the fibrous cap, which may provide structural support or may function as a barrier, separating the necrotic core from the lumen. The necrotic core, which is found in the deeper and central areas of the plaque, contains both amorphous, crystalline and droplet forms of lipids.

Advanced atherosclerotic lesions are prominently calcified, a feature that can be quite extensive and involve all aspects of the plaque.

Geometric remodeling is a characteristic adaptive mechanism in atherosclerosis. This was described by Glagov several years ago<sup>(95)</sup>, whereby outward displacement of the arterial wall compensates for an enlarging atheroma. Said differently, in the initial stages of atherosclerosis, the lumen dimensions may remain unchanged, yet plaques develop as compensatory arterial enlargement occurs. Once the plaque enlarges to greater than 40% of the vessel area, the artery no longer enlarges, and the lumen decreases as the atherosclerotic lesion increases in size.

In terms of hemodynamic adaptations, it is now well established that atherosclerotic lesions appear predominantly in areas of low shear stress, and indeed plaques form where shear stress is near zero.<sup>(94)</sup> It is believed that low shear stress may serve to limit vascular wall turnover, and inhibit the transport of proinflammatory and proatherosclerotic agents away from the vessel wall.

Likewise, the development of an atherosclerotic lesion is associated with flow stasis and flow separation which promote increased residence time for atherogenic agents. These cellular and inflammatory components of atherosclerosis have greater propensity to adhere and transmigrate into the vessel wall in the face of flow stasis.<sup>(94)</sup>

Oscillation of flow, a change in blood flow velocity as a function of the cardiac cycle, has also been implicated in plaque development. Pulsatile flow favors greater endothelial permeability, whereas unidirectional shear stress tends to favour mechanical endothelial integrity and function. Oscillation modulates endothelial NO bioavailability, and reducing oscillation in blood velocity, by virtue of reducing heart rate, may have an indirect effect on plaque morphology. Another

feature of abnormal vascular biology is turbulent flow; initially believed to play an important role in the development of atherosclerotic lesions, although this is not generally accepted.<sup>(94)</sup>

The lower extremity arteries appear to be preferentially affected by atherosclerosis, with similar caliber blood vessels in the upper extremity being spared. This has been ascribed to a number of factors including greater variations in flow rate, and the greater susceptibility of the smooth muscle of the lower extremity arteries to risk factors. The superficial femoral artery which is the most frequent site of atherosclerotic lesions, where lesions appear to form at the adductor hiatus due to mechanical trauma of the adductor magnus tendon, and the failure of this segment of the vessel to undergo appropriate compensatory geometric remodeling.<sup>(94)</sup>

### **CONCLUSIONS**

Over the past two decades our understanding of the pathophysiology of atherosclerosis has advanced considerably. The systemic nature of this disease appears to have at its root a complex and multifactorial etiology, with inflammation and endothelial dysfunction featuring prominently in the development, progression and complications of atherosclerosis. In addition to these important cellular events, segments of the arterial wall respond to injury with compensatory anatomic and hemodynamic adaptations, including low shear stress, intimal thickening, and early Glagov geometric remodeling. The clinical consequences of progressive atherosclerosis, including stenosis, ulceration, embolization or thrombosis, depend upon the interplay of the aforementioned pathways, superimposed on a poorly understood genetic susceptibility. Although we have gleaned much of our information from coronary arteries, there is an urgent need for focused efforts aimed at better defining the biochemical, cellular, metabolic, anatomic and hemodynamic components of peripheral atherosclerosis, a sentiment echoed in the recent American Heart Association atherosclerotic vascular disease conference 2004.<sup>(93)</sup>

**KEY CONCEPTS**

The key concepts of this section are summarized in the following table.

**TABLE 3A: KEY CONCEPTS FOR THE PATHOPHYSIOLOGY OF ARTEROSCLEROSIS**

#	Concept
1	Atherosclerosis is a systemic and generalized disorder of the arterial tree, which results in localized plaque deposition at selected sites within the vascular bed.
2	The pathophysiological basis of atherosclerosis is now well accepted to involve a close interplay between endothelial dysfunction and inflammation, which in turn may modify the vascular responses to oxidative stress, and platelet-endothelial interaction.
3	The evolution of atherosclerotic plaques is associated with important anatomic and hemodynamic adaptive responses, and it is when these compensatory mechanisms fail that complications of atherosclerosis such as stenosis, plaque ulceration, embolization and thrombosis appear.

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## **Risk Factors For Peripheral Arterial Disease- Traditional and Emerging, Lifestyle Modification and Evidence for Symptom Relief**

**Koon K. Teo, MB, PhD, FRCPC**

Division of Cardiology, Department of Medicine and  
Population Health Research Institute  
McMaster University and Hamilton Health Sciences

### **Address for Correspondence:**

Dr. Koon K. Teo  
Rm 3U4 McMaster University Medical Centre  
1200 Main Street West  
Hamilton  
Ontario  
Canada L8N 3Z5

**Tel:** 905 521 2100 ext 76222

**E-mail:** [teok@mcmaster.ca](mailto:teok@mcmaster.ca)

A risk factor has been defined, in the broadest sense, as a trait associated with an increased risk of disease<sup>(1)</sup>. This definition can be expanded to include the following: that the presence of some risk factors is associated with increased risk of a disease, a causal relationship in the pathway leading to the disease has been established, and that these risk factors can be used to assess disease prognosis. A further corollary is that modification or reduction of these factors, such as in cardiovascular disease, through life-style modification and/or specific therapy, can be undertaken to reduce the risk, and improve the prognosis of disease.

Our knowledge and understanding of the epidemiology of atherosclerotic vascular disease is extensive. Atherosclerosis is a generalized process affecting important parts of the arterial tree, namely the coronary, cerebrovascular, aortic, renal and peripheral (lower extremity) arterial vascular beds. Risk factors for atherosclerotic vascular disease have been identified through many studies from large populations<sup>(2-6)</sup>. While the focus of these studies has been primarily on atherosclerotic coronary heart disease, ***evidence from these studies suggests that the risk factors for coronary and non-coronary atherosclerotic disease are generally similar and independent of the end organ subserved by a given arterial vascular bed***<sup>(2-6)</sup>. Given that much fewer studies have been carried out specifically on risk factors for peripheral arterial disease (PAD), it is fortunate that we can obtain an understanding of risk factors for PAD from extrapolation of information derived from the traditional risk factors for atherosclerotic coronary heart disease.

Risk factors for PAD can be considered from several perspectives<sup>(7)</sup>. One can consider risk factors for specifically predicting the risk of developing symptomatic PAD. More broadly and given that symptomatic PAD is associated with a two to four fold excess risk of mortality, predominantly from cardiovascular disease<sup>(8)</sup>, the presence of established symptomatic and asymptomatic PAD is generally accepted as evidence of wide spread atherosclerotic disease elsewhere and is associated with increased risk in the other end-organs, particularly coronary heart and cerebrovascular diseases. Secondary prevention therapies can be directed at reducing the risk of PAD by modification of the risk factors

common to all atherosclerotic vascular diseases. In doing so, these treatments will reduce the risk of events and outcomes due to atherosclerotic vascular disease in other affected organs.

### **TRADITIONAL RISK FACTORS FOR ATHEROSCLEROTIC VASCULAR DISEASE**

Data from large population studies focusing on coronary heart disease have identified a number of risk factors for atherosclerotic vascular disease. Traditional established risk factors include age, family history, and the modifiable risk factors of elevated lipid levels, cigarette smoking, systolic and diastolic hypertension and diabetes<sup>(2)</sup>. Other risk factors include sedentary life-style, psychosocial factors and obesity<sup>(2,9)</sup>. The recently published case-control study of potentially modifiable risk factors associated with myocardial infarction in 52 countries found that abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, adverse psychosocial factors, decreased consumption of fruits, vegetables, and alcohol and lack of regular physical activity account for most of the risk of myocardial infarction in both sexes and at all ages in all regions of the world<sup>(10)</sup>. These risk factors can also be modified in order to reduce the risk of disease.

In a review of data from 10 prospective cohort studies, three international studies and 28 randomized controlled trials, it is found that long term reductions of total or LDL-cholesterol by 0.6 mmol/L in these populations is associated with a decrease in risk of ischemic heart disease of about 50% at age 40, 40% at age 50, 30% at 60 and 20% at 70-80<sup>(11)</sup>. The proportional decrease in risk decreases with age, but the absolute benefit increases because the disease becomes more common with age. The benefits of total cholesterol and LDL cholesterol lowering have been subsequently confirmed by major clinical trials using “statin” therapy.

Smokers have twice the risk of heart attacks, and two to four times the risk for sudden deaths, compared to non-smokers<sup>(12)</sup>. Smokers with vascular disease who quit smoking for five years have the same risk for cardiovascular disease as non-smokers. Hypertension is a major risk factor for cerebrovascular disease (stroke), coronary heart disease (acute myocardial infarction), congestive heart failure and renal dysfunction. The risk is directly associated

with the blood pressure level and with the presence of target organ involvement and other risk factors<sup>(13)</sup>. The risk of elevated blood glucose levels in cardiovascular disease is well known. People with diabetes have a two-four fold higher risk of coronary, cerebrovascular and peripheral vascular disease compared to non-diabetic people<sup>(14)</sup>. Every 1% increase in HbA1c in type 2 diabetic subjects increases the risk of death by 14%, myocardial infarction by 14% and stroke by 12%. Ongoing studies are evaluating the benefits of long-term intensive control of elevated blood glucose levels on cardiovascular outcomes. Increased physical activities have numerous beneficial health effects including reducing the risks of premature death and dying from heart disease, developing diabetes and hypertension and aiding in the control of these risk factors<sup>(15)</sup>. Increased prevalence of hypertension, lack of physical activity, dyslipidemia and dysglycemia are often found in obese people, thus increasing their risk for cardiovascular disease. Mechanisms by which psychosocial factors may be linked to cardiovascular disease include acting through health-related behaviors such as smoking, diet, alcohol or physical activity or through direct pathophysiological changes modulating the clotting mechanism, increasing cardiac arrhythmia and development of atherosclerosis<sup>(16)</sup>.

#### **CLUSTERING OF COEXISTING RISK FACTORS**

It is well recognized that individuals with combinations of traditional risk factors are at much higher risk for coronary heart and other vascular disease. This has been clearly demonstrated in the Multiple Risk Factor Intervention Trial (MRFIT) Primary Screenees Cohort study on 350,977 individuals examining the outcomes of individuals with various combinations of risk factors including elevated cholesterol levels, smoking, hypertension and diabetes by stratifying the individuals into 20 strata by multiple cross-classifications. It was found that that the range of risk across the 20 strata was more than 13 fold. The 6-year age-adjusted coronary heart disease death rate was 21.4 per 1000 for cigarette smoking hypertensive hypercholesterolemic (>6.4 mmol/L) men compared to a rate of only 1.6 per 1000 for non-smoking normotensive men with a cholesterol level of < 4.74 mmol/L. Most individuals have more than one risk factor and only 10% of the entire cohort were in the lowest risk subgroup and 90% were at higher risk. Absolute excess risk, the difference in risk for a

given group compared to the group at lowest risk, increased progressively and steeply with the various combinations of the other risk factors<sup>(1, 17, 18)</sup>.

### **RISK FACTORS FOR SYMPTOMATIC PAD**

While the risk factors for developing PAD are similar to those for other atherosclerotic vascular disease, a number of studies have specifically examined the association of these traditional risk factors on the risk the development of intermittent claudication, an early form of symptomatic PAD. Several studies suggest that cigarette smoking and diabetes are the strongest risk factors for PAD.<sup>(19, 20)</sup>

### **DIABETES MELLITUS AND IMPAIRED GLUCOSE TOLERANCE**

Diabetic patients have twice as much the risk of developing intermittent claudication as non-diabetic individuals; women have higher relative risk for developing diabetes than men<sup>(20)</sup>. Overall individuals with insulin resistance or impaired glucose tolerance are at increased risk. A clustering of risk factors, including obesity, type 2 diabetes mellitus or impaired glucose tolerance, hyperinsulinemia, hyperlipidemia, hypertension, and hyperuricemia has been reported to be associated with increased risk. This condition has been referred as the metabolic syndrome<sup>(21)</sup>.

### **SMOKING**

Smoking as a risk factor for atherosclerotic vascular disease has been very well established<sup>(22)</sup>. Studies have shown that the association between PAD and smoking is even stronger than that between smoking and coronary heart disease, by as much as two-fold<sup>(8, 18)</sup>. PAD is seen in smokers a decade earlier than non-smokers<sup>(23)</sup>. The severity of PAD tends to increase with the number of cigarettes smoked<sup>(24, 25)</sup>. Heavy smokers of both sexes have been shown to have a four-fold risk of developing intermittent claudication compared to non-smokers<sup>(8)</sup>. While it may seem practical to distinguish “heavy smokers” from “light smokers”, data from INTERHEART suggest that relationship between the number of cigarettes smoked and risk is curvilinear with no minimal number of cigarettes smoked which is not associated with increased risk when compared to that faced by non-smokers<sup>(10)</sup>. A review of 4 prospective

cohort and 13 cross sectional studies shows that smokers had a 2.3 fold increased risk of PAD compared to non-smokers and that a clear dose response relationship was observed<sup>(26)</sup>. In countries in which the prevalence of smoking is approximately 30%, the population attributable risk of smoking on PAD has been reported to be at least 50%<sup>(26)</sup>.

#### **HYPERTENSION**

Data from the Framingham and other studies indicate a strong and convincing relationship between hypertension and PAD<sup>(27)</sup>. The Framingham study reported that hypertensive men had a 2.5 fold and women a 3.9 fold age-adjusted increased risk for PAD compared to controls without hypertension, a finding that has been confirmed in other studies<sup>(18)</sup>. While it is anticipated that blood pressure lowering therapy benefits individuals with and without PAD, a recent report from the HOPE trial on individuals with symptomatic PAD and normal blood pressure or borderline hypertension, demonstrates clearly that reductions in risk of cardiovascular events were obtained in the PAD patients<sup>(28)</sup>.

#### **HYPERLIPIDEMIA**

The relationship between hyperlipidemia and PAD appears firm but findings from studies correlating the lipid-cholesterol subfractions appear less consistent. In one study, a fasting cholesterol level greater than 7 mmol/L was associated with a 2-fold increase in risk of symptomatic PAD<sup>(29)</sup> and the ratio of total to HDL cholesterol appeared to be the best predictor for PAD<sup>(29)</sup>. Hypertriglyceridemia has been shown in one study to be associated with increased risk of PAD<sup>(29)</sup>. Similarly, Lp(a) has been shown to have some predictive value<sup>(30)</sup>. It is likely that while these relationships are reasonable and plausible, the inconsistency of the relationships from various studies could be due to the presence of other risk factors and the focus and design of these studies, which did not primarily address these relationships.

The presence of coexisting risk factors in any individual has an additive effect on the risk of developing PAD. For example, the Basle study reported that in individuals with one, two or three of the risk factors cigarette smoking, diabetes mellitus and systolic hypertension, the

relative risk increased from 2,3, 3.3 and 6.3 respectively<sup>(31)</sup>. The Framingham study also showed that inclusion of cigarette smoking dramatically increases the risk of intermittent claudication when combined with any other risk factors<sup>(32)</sup>. Individuals with the metabolic syndrome, which is characterized by coexisting obesity, type II diabetes mellitus, hyperinsulinemia, hyperlipidemia and hyperuricemia are at particularly high risk of atherosclerotic vascular disease, including PAD<sup>(21)</sup>.

#### **EMERGING RISK FACTORS FOR ATHEROSCLEROTIC VASCULAR DISEASE AND PAD**

Pathophysiological studies on the role of inflammation in atherothrombotic vascular disease have identified several factors that are increasing being recognized as emerging risk factors<sup>(2, 33)</sup>. By monitoring the ongoing inflammatory process by identifying and measuring the markers of inflammation it has been envisaged that these markers can be used as risk factors to predict the risk of atherosclerotic vascular disease. Potential targets for measurement include proinflammatory risk factors such as oxidized low-density lipoproteins, proinflammatory cytokines (e.g. interleukin-1), tumor necrosis factor alpha, adhesion molecules (such as intercellular adhesion molecule-1, selectins), inflammatory stimuli with hepatic effects (e.g. interleukin-6) or the products of hepatic stimulation, such as serum amyloid A, C-reactive protein (CRP) and a host of other acute-phase reactants<sup>(33)</sup>. Other indicators of cellular responses to inflammation, such as elevated leucocyte counts, have also been evaluated. In addressing the relationship between these inflammatory markers and atherosclerotic disease end points, several issues should be considered<sup>(33)</sup>. The first is whether the substance is a risk factor or a risk marker, i.e., whether the substance is related to a step in the causal pathway leading to atherosclerosis or to the disease process itself. Second, the relationship of the markers, which may have a differential relationship to prevalent atherosclerotic disease and to acute or chronic syndromes in the coronary, cerebral or peripheral vascular beds should be considered. Thirdly, whether and to what extent the marker can predict disease endpoints over the timeframe of the events, short versus long term is an important consideration. Finally, whether measurement of the marker can indicate efficacy of therapy or changing prognosis should be considered. In addition, specific criteria are essential to qualify such markers, including consistency of prospective data, strength or

independence of the association, improvement of predictive value, standardization of the measure, low variability, high reproducibility, biologic plausibility and low costs<sup>(2)</sup>.

Novel markers such as lipoprotein(a), apolipoprotein A-1, apolipoprotein B-100, high-sensitivity C-reactive protein (hs-CRP), fibrinogen and homocysteine have been evaluated for potential additive value to traditional risk factors<sup>(2)</sup>. These studies show that the addition of hs-CRP to traditional risk factors substantially improved the prediction of increased risk for cardiac events<sup>(34)</sup>. Several studies have indicated that an increased plasma level of fibrinogen has been associated with PAD<sup>(35)</sup>. The prevalence of hyperhomocysteinemia has been reported to occur in 28% to 30% of patients with premature PAD<sup>(36)</sup>. The INTERHEART Study has shown that the ratio of apolipoprotein B to apolipoprotein A1 to have a high population attributable risk for acute myocardial infarction (odds ratio 3.25 for top vs lowest quintile, 95% confidence interval 2.81 to 3.76)<sup>(10)</sup>. Another study comparing 11 biomarkers associated with the development of PAD in men reported that the ratio of total to HDL cholesterol levels to be the highest lipid predictor of risk and the addition of either CRP or fibrinogen to the lipid screening significantly improved the predictive value<sup>(34)</sup>. The Centers for Disease Control and Prevention and the American Heart Association have jointly indicated that hs-CRP has the analytic and assay characteristics as an independent marker of cardiovascular risk<sup>(33)</sup>. However, the clinical benefits of medical therapies based on elevated hs-CRP are unknown and clinical trial results are needed on which to base decisions about treatment strategies to lower the hs-CRP levels.

#### **APPROACHES TO MANAGEMENT OF PAD**

Individuals with PAD often have, or are at increased risk for coronary artery and cerebrovascular disease and are at high risk for myocardial infarction, stroke or death. They also suffer from poor functioning capacity and lowered quality of life from symptoms due to lower limb ischemia ranging from intermittent claudication to critical limb ischemia, rest pain, skin ulcers and loss of limb viability. Management and therapeutic strategies are directed to modify the risk factors, reduce cardiovascular events and improve functional status and quality of life. In addition to the non-pharmacological approaches outlined below,

specific pharmacological therapies are available. Surgical and angioplasty interventions are primary therapeutic options for the PAD. Please see chapters on management and therapies.

Steps taken to identify and modify risk factors are central to the therapeutic strategies to manage the affected individuals. Both pharmacological and non-pharmacological approaches should be administered simultaneously. Two important non-pharmacological approaches to life style have been shown to effective in reversing symptoms of PAD. These are cessation of smoking and regular exercise.

### **SMOKING CESSATION**

Cigarette smoking is one of the most important risk factors for development and progression of PAD, and cessation of smoking, in addition to reducing the risk of myocardial infarction and death, also reduces the risk of progression to critical limb ischemia and limb loss<sup>(37, 38)</sup>. Smoking cessation has been reported to be associated with a rapid decline in incidence of intermittent claudication and that the risk for former smokers one year after stopping smoking has been reported to be approximately the same as that for non-smokers<sup>(39)</sup>. Another study, however, found that the relative risk of intermittent claudication was 3.7 in smokers compared to 3.0 in former smokers who have discontinued for 5 years or longer<sup>(18)</sup>. The inconsistency in findings may be due to the pre-existing severity of disease in the patients studied. Among individuals with PAD and who quit smoking, significant improvements are seen in graft patency, walking distance and decreases in mortality.

### **EXERCISE TRAINING**

Programs of exercise rehabilitation, particularly walking programs, have been shown to improve functional capacity in patients with intermittent claudication. Meta-analyses of randomized and non-randomized trials of walking programs showed improvements in pain-free walking time by 180% and maximal walking time by 120% to 150% in patients with claudication<sup>(40, 41)</sup>. Walking program sessions lasting 30 minutes or longer three times per week appear most effective in improvement of symptoms.

**CONCLUSIONS**

Risk factors for PAD have to be considered in the broader context of atherosclerotic vascular disease. Modification of these risk factors are important in reducing the risk of PAD and adverse cardiovascular events (Table 1 & Table 2).

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**TABLE 1. CONCLUSIONS**

1.	Risk factors for coronary and non-coronary atherosclerotic disease are generally similar and independent of the end organ subserved by a given arterial vascular bed. Risk factors that are modifiable include elevated lipid levels, cigarette smoking, systolic and diastolic hypertension, diabetes mellitus, sedentary life style, psychosocial factors and obesity.
2	Identification and modification of established risk factors are important in reducing the risk of developing PAD and reducing the risk of adverse cardiovascular events.
3	Promising emerging risk factors or markers are being evaluated for their utility in predicting prognosis and stratifying of risk. There is inadequate information to support routine measurements of these markers.

**TABLE 2. RECOMMENDATIONS**

1	All individuals with symptomatic or asymptomatic PAD should be assessed for all modifiable risk factors.	<b>Grade</b> <b>1A</b>
2	Identified risk factors should be managed appropriately in order to reduce the risk of (a) adverse cardiovascular events, and (b) progression of the PAD.	<b>Grade</b> <b>1A</b> <b>1B</b>
3	Individuals with PAD are recommended to quit smoking and have regular walking programs as non-pharmacological approaches to (a) reducing overall cardiovascular risk, and (b) improving symptoms of the PAD.	<b>Grade</b> <b>1A</b> <b>1B</b>

## **Aortic Aneurysms Incidence, Screening and Indications for Repair**

**Thomas Lindsay MDCM MSc FRCS, FACS**  
Division of Vascular Surgery  
Toronto General Hospital and the University of Toronto

### **INTRODUCTION**

**Aortic aneurysms** are silent killers. They develop in predominantly in patients over the age of 60 and rarely present secondary to symptoms until they rupture. Survival rates for aortic rupture depend upon location of the aneurysm and the population examined. Mortality rates can be as low as 40% in some surgical series; however populations based series that take into account pre hospital deaths demonstrates mortality rates up to 90%. The true mortality rate and incidence of aortic rupture are unknown in North America secondary to the lack of population based autopsy studies of patients who experience sudden death. Elective AAA repair offers the best survival rates and endovascular aneurysm repair (EVAR) is challenging the conventional therapy. This chapter will identify the population at risk for the development of aneurysm, their incidence and distribution. An evidence based guide to intervention considering conventional and newer minimally invasive forms of therapy will be discussed.

### **INCIDENCE AND DISTRIBUTION OF ANEURYSMS**

Aneurysms can occur in every artery in the human body. They are frequently multiple. An aneurysm is defined by a permanent localized dilatation of an artery by 50% above the normal size.<sup>(1)</sup> The most frequent site of aneurysm is the infra renal abdominal aorta (65%) which occurs with an incidence of 4-5% in the general population.<sup>(2)</sup> Ninety percent of abdominal aortic aneurysms (AAA) occur below the renal arteries. Other aneurysms include those which occur in the thoracic aorta (ascending 5%, aortic arch 5%, descending 13%), those in the combined thoracic and abdominal aorta (14%, thoracoabdominal aneurysms, TAA), and iliac aneurysms (isolated 1%, combined abdominal and iliac 13%). Popliteal aneurysms account for

70% of peripheral aneurysms and are more prone to occlusion than rupture precipitating acute limb ischemia.

Aneurysms occur of the visceral arteries including the splenic, superior mesenteric, celiac and its branches (hepatic, gastro duodenal arteries) and renal arteries. These visceral artery aneurysms occur in approximately 2% of the population and may present with abdominal apoplexy (abdominal pain and collapse).

Ruptured AAA is the 15<sup>th</sup> leading cause of death overall and is the 10<sup>th</sup> leading cause of death in men over the age of 55 in the USA. Comparable figures for Canada are not available. In Ontario each year approximately 1526±41 elective AAA repair are carried out as well as 325± 10 ruptured AAA repairs.<sup>(3)</sup> The prevalence of AAAs ( $\geq 3$  cm) is 3-10% for patients over the age of 50.<sup>(4)</sup> Randomized trials looking at screening men have identified an incidence of 4.9-7.6 % in men between 65-74.<sup>(5,6)</sup>

Abdominal aneurysms are considered a degenerative disease of the aorta and are therefore distinct from pure peripheral vascular disease and other manifestations of atherosclerosis. Many occur in association with atherosclerosis/PAD however at least 30% of infrarenal AAA patients do not have evidence of coronary atherosclerosis as determined by coronary angiography.<sup>(7)</sup> Risk factors for the development of aneurysm include male sex (4.5 fold increased risk), smoking (up to 95% of those with AAA are current or former smokers, relative risk is 5.6 vs. non smokers), white race (2 fold risk) and positive family history (2 fold).<sup>(8)</sup>

#### **DETECTION OF AORTIC ANEURYSMS: WHAT IS THE EVIDENCE FOR POPULATION BASED SCREENING?**

A recent meta-analysis of published ruptured abdominal aortic aneurysm (RAAA) papers over a 50 year period suggest only a modest improvement in the survival from this condition.<sup>(9)</sup> Thus, early detection followed by elective repair is a much lower risk and cost alternative.

Several geographical series and recently large randomized trials of screening have demonstrated that screening has merit. The MASS trial of men between 65-74 years of age demonstrated a

53% decrease in aneurysm related deaths in those who were screened compared to the control group.<sup>(10)</sup> Screening did not reduce all cause mortality but did reduce aneurysm related mortality. In regional centers where screening is performed on an annual basis after 9 years of screening a 64% reduction in ruptured AAA was noted.<sup>(11)</sup> In this study screening was found to be cost effective at a cost of \$1137(US\$) for every life year saved.<sup>(12)</sup> Recent evidence from Western Australia suggested that screening may only decrease death rates in targeted populations and communities where levels of elective has not reached expected levels.<sup>(13)</sup> Screening does not seem to be associated with adverse physical or mental health effects.<sup>(14,15)</sup> A consensus statement from The Society for Vascular Surgery surgeons recommended screening for all men aged 60-85, women over 60 with cardiovascular risk factors, and men and women older than age 50 with a positive family history.<sup>(16)</sup> A recent meta-analysis of the randomized trials examining the role of screening undertaken for the US Preventative Services Task force which included over 125,000 men, has recommended screening for men between 65-75.<sup>(12)</sup> The US Preventative Service task force took a much more conservative position. They recommend screening for men age 65-74 who currently or have previously smoked more than 100 cigarettes the their lifetime.<sup>(14)</sup> This is a much more conservative approach to screening for AAAs compared to the consensus statement of the vascular surgeons or the conclusions of the meta-analysis.<sup>(11,12)</sup> Screening recommendations are found in Table 5A.

#### **ANEURYSM SCREENING FOR WOMEN**

Only one randomized trial has specifically included women for screening. In over 3000 women screened a six times lower incidence of aneurysms compared to men was identified. The screening program in women failed to reduce the incidence of rupture leading the authors to conclude that screening of women was not clinically indicated or economically viable.<sup>(18)</sup> The US Preventative Services Task force also concluded that there is no evidence to support screening in women at this time.<sup>(19,20)</sup> (Quality of Evidence I, Classification of Recommendations B) Future research may influence this recommendation.

**WHEN SHOULD ANEURYSMS BE REPAIRED?**

The size at which infra renal abdominal aortic aneurysms should be repaired has been studied in Britain and in the US Veterans Administration System. In the British Small Aneurysm Trial patients with an AAA between 4 and 5.5 cm were randomized to early surgery or observation. If the AAA exceeded 5.5 cm or expanded by more than 1 cm or became symptomatic in the observation group it was repaired. In those randomized to early surgery the mortality of the surgical procedure (5.4%) resulted in an early reduced survival in the surgery group however by 9 years the early surgery group had a weak benefit of early surgery. The ADAM trial in the US Veterans Administration also randomized patients with AAA between 4 and 5.5 cm to early surgery or observation.<sup>(21)</sup> Surgery was performed with a 30 day mortality of 2.1% yet there was no survival benefit to repair of these small aneurysms. In the observation group the incidence of rupture was 0.6% per year. This study had almost exclusively men compared to the British Trial where there were more women (17%). Thus there does not appear to be a benefit of improved survival when infrarenal aortic aneurysms of less than 55 mm in size for men are repaired.

Data from patients enrolled in an aneurysm follow-up program in Kingston, Ontario demonstrated that in aneurysms between 5 and 5.9 cm were associated with a 1% annual risk of rupture compared to 3.9% in women. For aneurysms greater than 6.0 cm the risk of rupture was 14.1% for men vs. 22.3% for women. A US Veterans study followed patients who had been evaluated for elective AAA repair and had been determined to be unfit for surgery. In this patient population the rupture rate of AAAs between 5.5 and 5.9 was 9.4% in 1 year compared to 10.9% for 6-6.9 cm and 32.5% for 7 cm or more.

Currently AAA patients are evaluated for aneurysm size and risk of operative repair. Men whose aneurysm exceeds 5.5 cm and women with aneurysms of 5.0 cm are evaluated for operative therapy. The decision to proceed to surgical repair is a balance between the estimated risk of rupture compared to the expected operative mortality. The predictors of perioperative mortality are elevated serum creatinine, congestive heart failure, EKG evidence of ischemia, pulmonary dysfunction, older age and female gender. Perioperative mortality rates can be as low as 2.1% seen in the ADAM trial for fit individuals with small aneurysms or 4.9% noted in the Canadian

Aneurysm study. In statewide or national series the elective mortality is frequently higher 6.8% in Michigan for men between 1980 and 90 and 10.6% for women in this study. Recent randomized trials comparing EVAR to open repair the mortality of open repair in patients deemed healthy for open repair, the 30 day mortality of open repair has been 4.6% in the DREAM trial and 4.7% in EVAR-1 trial.<sup>(22,23)</sup>

Thus elective aneurysm repair is recommended to men with aneurysms over 5.5 cm and women with aneurysms over 5.0 cm however once their operative risk and aneurysm anatomy is assessed.<sup>(24)</sup> (Quality of Evidence I, Classification of Recommendations A) For patients at low risk with favorable anatomy and a surgeon with low mortality rate, open repair will likely be advised. However when the same surgeon identifies a patient at high risk for open repair then conservative management or EVAR may be selected depending upon anatomical considerations. (Evidence grading for EVAR(Quality of Evidence I, Classification of Recommendations A)

#### **PREDICTING ANEURYSMS RUPTURE: SCIENCE OR PIPE DREAM**

The best predictor of aneurysm rupture has been size, however patients with larger initial diameter, hypertension, COPD and those with rapid expansion rates may be more prone to rupture prior to the 5.5 cm threshold for men. Women's aneurysms rupture at smaller sizes leading to the conclusion that the 5.5 cm threshold is likely too large and 5 cm has been suggested as the appropriate level.<sup>(25)</sup>

Recently peak wall stress has been calculated using finite element analysis.<sup>(26)</sup> Early use of this technique has been able to identify areas in AAA's that have localized areas of increased wall stress at similar blood pressure. Preliminary application to a retrospective cohort of patients has suggested that peak wall stress may be an important predictor of aneurysm rupture.<sup>(27)</sup> This technique awaits larger trials and longer follow-up.

#### **ANEURYSM EXPANSION RATES: IMPLICATIONS FOR FOLLOW-UP INTERVALS**

Two recent publications have examined data from screening programs and proposed intervals of aneurysm follow-up. One screening program invited only men aged 65 for screening and follow-up while the other study analyzed data from the MASS study which contained age groups between

65-74.<sup>(28,29)</sup> Those screened at age 65 had a mean follow-up of 4.5 year vs. 1.9 years in the MASS study and smaller aneurysms were observed over longer periods. While others have suggested that aneurysms less than 3 cm need no further follow-up this can be dependant upon the age at which that aneurysm was identified.<sup>(30)</sup> Screening interval recommendations have not been subjected to cost effective analysis. Suggested intervals for re-evaluation of aneurysm size are noted in Table 5B. Once an aneurysm reaches 45 mm referral to a Vascular Specialist is suggested.<sup>(31)</sup> (Quality of Evidence I, Classification of Recommendations A)

### **ANEURYSM REPAIR IN 2005: METHODS AND RESULTS**

Since the first successful elective AAA repair in 1950, modifications in surgical techniques, better perioperative medical and anesthetic management and patient selection have been the only method to improve 30 day mortality. In 1991 the first reported endovascular aneurysm repair (EVAR) was reported.<sup>(32)</sup> The years that have followed have seen rapid advances in materials, engineering and case series which have demonstrated the usefulness and effectiveness of this therapy. EVAR is a minimally invasive method to repair aneurysms under fluoroscopic control. The concept is to place a device made of fabric and stents inside the aorta that prevents the transmission of blood pressure to the weakened aortic wall preventing rupture. These devices are contained within a sheath that is introduced through the femoral arteries (or through a graft sewn to an artery large enough to accommodate the introducer sheath), carefully positioned under fluoroscopic imaging. Retraction of the sheath allows the self expanding stents and fabric to contact the vessel wall and seal the aneurysm. Assembly of modular components within the aneurysm completes the exclusion of the aneurysm. Anatomic criteria have been published that are associated with high rates of successful aneurysm exclusion. Sufficient proximal neck length, lack of severe angulation and thrombus within the neck are a few of the key elements that when followed lead to high rates of success. The introduction of this technology has resulted in a dramatic change in the practice of aneurysm repair. In New York State there was a dramatic shift in how aneurysms were repaired between 2000 and 2002.<sup>(33)</sup> In 2000 a minority of aneurysms were repaired by EVAR however by 2002 more aneurysms were repaired by EVAR than by the open technique. This study also demonstrated that the in-hospital mortality of EVAR was 0.8% compared to open repair mortality of 4.2% despite the EVAR patients having a greater

number of severe co-morbidities. Previously other authors had failed to demonstrate this improvement in mortality.

During 2004 the first randomized trials comparing open to EVAR in patients medically fit to undergo both procedures were published. The EVAR-1 trial studied 1082 patients with aneurysms over 5.5 cm in patients 60 and older. Open repair had a significantly higher mortality of 4.7% compared to 1.7% for EVAR, however secondary interventions were more common in the EVAR group 9.8 vs. 5.8%.<sup>(34)</sup> In the DREAM study 345 patients were randomized to EVAR or Open repair with respective 30 day mortalities of 1.7 and 4.6%. The combined rate of death or severe complication in the open group was 9.8% compared to 4.6% in the EVAR group.<sup>(35)</sup> Thus EVAR is clearly justified in healthy fit AAA patients who are willing to comply with long term follow-up and understand that they may require a greater number of secondary interventions. (Quality of Evidence I, Classification of Recommendations A) The Canadian Society for Vascular Surgery has also recognized the important benefits of EVAR and published a consensus statement outlining adoption of EVAR as a national standard for intermediate and high risk patients.<sup>(36)</sup> There are data from specific devices that demonstrate excellent longer term performance however the longer term results of the patients in these randomized trials will help to answer the questions of long term durability of EVAR repair. Long term results have been published and demonstrate excellent durability of the EVAR procedure with comparable survival to open repair that was performed on a younger healthier population.<sup>(37)</sup> The benefits of EVAR in medically unfit patients would be expected to be better than open repair however no randomized data has been published however trials are underway comparing conservative therapy and EVAR.

#### **SCREENING FOR THORACIC ANEURYSMS**

No studies have examined this subject in any systematic way. As chest x-rays give way to low dose chest CT scans for the diagnosis of chest pathology new evidence on the incidence and long term outcome of thoracic aneurysms will likely be forthcoming.

**SUMMARY**

Abdominal aortic aneurysms are silent killers. Screening of asymptomatic men over 65 has been proven in randomized trials, with higher yields in those with a smoking history. Referral to a Vascular Specialist should occur when the aorta reached 45 mm. Aneurysm repair thresholds differ between men and women and new minimally invasive lower risk options for aneurysm treatment exist.

A national screening program for AAA should be undertaken for AAA in men in Canada. A familial incidence of aneurysms is well recognized and although it has not been the subject of large randomized studies those with a positive family history of aneurysms or those with significant cardiovascular disease should likely be screened at an earlier age.

**RECOMMENDATIONS**

Recommendations are indicated for aneurysm screening and follow-up according to the quality of evidence and classification of recommendation indicated by the “Grade” shown in the right-hand column of the tables to follow.

**TABLE 5A: RECOMMENDATIONS FOR ANEURYSM SCREENING**

#	Recommendation	Grade
1	Men age 65-74	1A
2	Women aged 65 who have cardiovascular disease and positive family history of AAA	3C
3	Men aged 50 and above with a positive family history	3C

**TABLE 5B: RECOMMENDED AAA FOLLOW-UP BASED ON INITIAL SIZE**

Initial size	Recommendation	Grade
<3.0 cm	Repeat ultrasound follow-up in 3-5 years	1A
3.1-3.4cm	Repeat ultrasound in 3 years	1A
3.5-3.9 cm	Repeat ultrasound in 2 years	1A
4.0-4.5 cm	Repeat ultrasound in 1 year	1A
4.5 cm or >	Referral to Vascular Surgeon and repeat ultrasound every 6 months	1A
If > 1cm growth in 1 year	Referral to Vascular Surgeon for consideration of repair	1A

Compiled from references 28, 29 and 30.

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## Diagnosis and Management of Atherosclerotic Renal Artery Stenosis

**Asad Junaid, M.D., F.R.C.P. (C)**  
Vascular Medicine Program,  
Department of Internal Medicine,  
University of Manitoba

### INTRODUCTION

Renal artery stenosis commonly arises as a result of either atherosclerosis or fibromuscular dysplasia. These guidelines will specifically focus on atherosclerotic renal artery stenosis (ARAS) and are meant to provide information that will hopefully be helpful in clinical decisions regarding: A) who should be investigated for ARAS, B) the utility of various diagnostic tests, and C) the management of ARAS.

ARAS may be discovered by active investigation or as a co-incidental finding during imaging studies such as abdominal ultrasound, MR or CT angiography, aortography or coronary catheterization. The incidence of renal arterial disease is reported to be up to 45% in individuals with acute, severe or refractory hypertension.<sup>(1, 2)</sup> Also the finding of acute renal failure shortly after the initiation of an ACE inhibitor is strongly suggestive of the presence of renal arterial disease.<sup>(3)</sup> Patients with peripheral vascular disease are at high risk of renal artery stenosis.<sup>(4, 5)</sup> However, not all patients in the latter category have significant hypertension or renal dysfunction. Patients with moderate or severe hypertension and otherwise unexplained pulmonary edema that may be recurrent and sudden in onset are much more likely to have either bilateral renal arterial disease or arterial stenosis of a solitary functioning kidney.<sup>(6)</sup> Criteria that suggest the presence of hemodynamically significant renal arterial disease are shown in Table 1.

**TABLE 1: CLINICAL FINDINGS SUGGESTIVE OF ARAS**

Onset of hypertension at age <30 yr or >55 yr

Abrupt onset of hypertension

Acceleration of previously well controlled hypertension

Hypertension refractory to an appropriate three-drug regimen

Accelerated hypertensive retinopathy

Malignant hypertension

Recurrent flash pulmonary edema

An unexplained rapid decline in renal function

Asymmetry in kidney size on imaging studies

Acute kidney failure upon treatment with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker.

**OVERVIEW OF DIAGNOSTIC TESTS FOR RENAL ARTERY STENOSIS:**

The gold standard for the diagnosis of renal arterial disease remains renal arteriography. Less invasive diagnostic modalities include magnetic resonance angiography (MRA), computed tomographic angiography (CTA), duplex Doppler ultrasonography, intravenous pyelography, assays of plasma renin activity and captopril renography and are summarized in Table 2. The greatest pitfall of these less invasive tests, with the possible exception of MRA is their low sensitivity (high rate of falsely negative tests that fail to detect a significant lesion).

*MRA* - This technique is reported to have a sensitivity of 100% and a specificity of 71 - 96%, but is not very good at visualizing accessory arteries that may provide clues to the significance of a primary renal artery lesion.<sup>(7, 8)</sup> Also MRA tends to overestimate the degree of stenosis, however, gadolinium enhanced three-dimensional MR imaging provides a more accurate estimation of the degree of luminal compromise.<sup>(9, 10)</sup> However, the difficulty in distinguishing moderate from severe stenoses remains. In addition, consideration should be given to the contraindications of an implanted cardiac pacemaker, claustrophobia and certain

metallic implants such as middle ear prostheses. Most implanted vascular stents are now not considered to be contraindications to MR imaging.

*CTA* - Contrast enhanced spiral CT scanning has been reported to have a sensitivity and specificity of 98% and 94%, respectively, for detecting renal artery stenoses.<sup>(11)</sup> However these values are reduced to 93% sensitivity and 81% specificity in patients with serum creatinine values above 150  $\mu\text{mol/l}$ . Also the relatively large amount of iodinated radiocontrast material administered during this test makes it hazardous and impractical for patients with a significant degree of renal failure.

*Duplex Doppler ultrasound* - In patients at high risk of renal arterial disease the sensitivity and specificity of this modality have been reported to be as high as 99 % and 97%, respectively.<sup>(12, 13)</sup> Unfortunately this procedure is time consuming, technically difficult and highly operator dependent. Given these limitations, further imaging studies should be pursued despite a negative study if the index of suspicion for renal artery stenosis is high.

*Captopril renography* - In populations at high risk for renal arterial disease the positive and negative predictive values for this test have been reported to be 85 – 90 percent.<sup>(14)</sup> These values are likely to be significantly lower in low risk patients and those with bilateral disease.

Intravenous pyelography and plasma renin activity determinations have largely been replaced by the above tests due to the inferiority of these two techniques in terms of both their sensitivity and specificity.

**TABLE 2. SUMMARY OF NON-INVASIVE TESTING FOR ARAS**

Diagnostic Test	Sensitivity	Specificity	Limitations
MRA	100%	71-96%	Poor visualization of accessory arteries Overestimation of degree of stenosis
CTA	98% (93%)	94% (81%)	( ), if Cr. > 150 $\mu\text{mol}$
DUS	99%	97%	Time consuming Operator dependent
Captopril Renography	85-90% NPV	85-90% NPV	Lower sensitivity in the presence of bilateral disease and renal failure

*MRA*- magnetic resonance angiography, *CTA*-computed tomographic angiography, *DUS*-duplex Doppler ultrasound, *NPV*-negative predictive value, (see text for details).

#### INVESTIGATIONAL STRATEGY FOR THE DETECTION OF ARAS

The main indications for investigation for the presence or renal arterial disease are otherwise unexplained progressive renal dysfunction, recurrent flash pulmonary edema and refractory hypertension. Investigation should only be undertaken if the patient is a candidate for revascularization. In centers where expertise is available *duplex Doppler examination* of the renal arteries is the preferred method. Otherwise, *three-dimensional MRA with gadolinium enhancement* can be used because it is non-invasive and avoids the use of potentially nephrotoxic, iodinated, radiocontrast agents.

A caveat that underlies the decision as to which test(s) to use to diagnose renal arterial disease is the *level of renal function* in a given patient and the *index of suspicion* of the disease. In high-risk individuals (patients with previously stable hypertension and a sudden rise in blood pressure or refractory hypertension) with *normal or near normal* (serum creatinine concentration < 150  $\mu\text{mol/l}$ ) *renal function* and a *high index of suspicion*, intra-arterial digital subtraction angiography is the test of choice.<sup>(15,16)</sup> Spiral CT scanning and MR angiography are non-invasive alternatives that are useful in detecting proximal disease.

If there is an *intermediate index of suspicion* and *normal renal function*, non-invasive tests such as spiral CT scanning or MR angiography can be employed (duplex doppler ultrasound in experienced institutions) initially and results can be confirmed with contrast angiography if an interventional strategy is planned. *Diagnostic testing is not recommended if there is a low index of suspicion.*

The main concerns in patients with *renal insufficiency* are the risk of contrast nephropathy with iodinated contrast agents and the risk of atheroembolic disease with invasive techniques. Clues that may suggest the presence of significant renal arterial disease in this subpopulation are; an unexplained progressive decline in renal function, a bland urinary sediment with or without mild or moderate proteinuria, and a unilateral small kidney on ultrasound evaluation.

#### **EVALUATION OF THE SIGNIFICANCE OF INCIDENTAL RENAL ARTERY STENOSIS**

The incidence of incidental renal artery disease in patients being investigated for peripheral arterial or coronary artery disease is reported to be 10 to 42 percent.<sup>(17, 18)</sup>

When patients with uncontrolled hypertension are excluded from analysis the natural history of incidental ARAS has been shown to be relatively benign.<sup>(19)</sup> Therefore we do not recommend routine revascularization of incidental lesions.

Renal arterial lesions may be considered hemodynamically significant if there is a significant decrease in blood pressure with the institution of an ACE inhibitor.<sup>(20)</sup> Renal vein renin sampling may provide a good estimate of who is to benefit from renal revascularization if the ratio is greater than 1.5 compared to the contralateral kidney.<sup>(21)</sup> However, approximately one half of patients without renal vein renin lateralization may benefit from renal revascularization, thus a positive test is an indication for repair, but a negative test does not exclude candidacy for revascularization, therefore routine use of this test can not be recommended.

A captopril enhanced renal scan may be helpful in that it has been shown to have a positive and negative predictive value of 80 and 90 percent, respectively, in regards to benefit from revascularization.<sup>(22-24)</sup> Therefore in uncertain cases this test may be of utility.

In centers that are experienced with the use of renal resistive indices, an index of greater than 0.8 may indicate an unfavorable response to renal angioplasty with and without stenting.<sup>(25)</sup> However, these results have not been repeated and need verification before resistive index criteria can be used to exclude patients from invasive interventions.

## **MANAGEMENT OF ARAS**

### **MEDICAL MANAGEMENT**

Patients with ARAS generally have diffuse atherosclerosis and should be treated as those with coronary artery, cerebrovascular or peripheral arterial disease. Therefore, independent of a decision in regards to revascularization, the average blood pressure target value should be 130/80 in the absence of renal insufficiency or significant proteinuria. If the serum creatinine is over 140 $\mu$ mol/l or there is greater than one gram of proteinuria per day this target should be lowered to 125/75 as per the 2004 Canadian Hypertension Education Program recommendations ([www.hypertension.ca](http://www.hypertension.ca)). Some caution needs to be exercised as kidneys with hemodynamically significant stenotic arterial lesions may be underperfused at these pressures. ACE inhibitor therapy should be the first line of therapy with the addition of a diuretic if required (this recommendation is based on the evidence for the vascular protective effect of ACE inhibitors in patients with atherosclerosis from recent large scale trials).<sup>(26, 27)</sup> *Level I, Grade A.*

The serum creatinine should be monitored regularly. If there is a greater than 30% increase in this value consideration to raising the blood pressure target or revascularization should be given.

Plasma LDL cholesterol concentration should be targeted to less than 2.5 mmol and less than 1.8 mmol in very high-risk individuals.<sup>(28)</sup> This should primarily be achieved with statin therapy and additional lipid lowering agents as required. In addition, these patients should be maintained on anti-platelet therapy.

As in other atherosclerotic diseases, smoking cessation should be strongly advised and the patient should be referred to a smoking cessation program if resources allow.

### INVASIVE INTERVENTIONAL MANAGEMENT

In patients demonstrated to have > 70% luminal compromise of one or both renal arteries and **uncontrolled hypertension** (BP >140/90) despite the use of 3 antihypertensive medications at maximum dose, revascularization should be attempted with percutaneous balloon angioplasty and stenting. These patients should have relatively preserved renal function (serum creatinine less than 300 µmol/l) and a low likelihood that renal parenchymal disease is a major contributor to the hypertension (at least one normal sized kidney with normal echogenicity). This recommendation is largely based upon the meta-analysis of Nordmann et al of the three published randomized trials addressing this issue.<sup>(29)</sup> *Level I, Grade B.*<sup>(30 - 32)</sup> Patients with impaired renal function should be adequately hydrated prior to the administration of iodinated radiopaque contrast agents.<sup>(33)</sup>

In younger patients (aged < 60 years) with minimal operative risk and in those patients with aortic involvement vascular surgical consultation should be obtained for consideration of surgical repair.<sup>(34)</sup> *Level II, Grade B*

Patients with **recurrent episodes of flash pulmonary edema** and no other readily identifiable cause for this presentation (poor LV systolic function, significant coronary artery lesions, arrhythmias etc.) and greater than 70 percent stenosis of at least one renal artery should undergo attempts at revascularization as indicated for uncontrolled hypertension, see above. This recommendation is based on several case reports and case series.<sup>(35 - 38)</sup>

*Level II, Grade C.*

Revascularization for **preservation of renal function** should only be considered in individuals with either bilateral renal artery stenosis or stenosis of a renal artery supplying a single functioning kidney who have a rapid decline in renal function and a serum creatinine less than 300  $\mu\text{mol/l}$ .<sup>(39, 40)</sup> *Level II, Grade C.*

Patients with more chronic elevations of serum creatinine (greater than 300 $\mu\text{mol/l}$ ) are less likely to benefit, however, this criteria does not absolutely exclude attempts at revascularization for preservation of renal function.<sup>(41 - 43)</sup> It should be recognized that the decision for revascularization in this population has to be balanced against the risk of complications, which may be as high as 20%. In centers experienced in the determination of renal resistive indices a resistive index greater than 0.8 indicates a low likelihood of success with revascularization. An approach for which there is not any evidence, but seems reasonable is to obtain a renal biopsy prior to attempts at revascularization to see if there is a “relative” preservation of renal microarchitecture that may favour renal functional recovery or preservation. The decision for revascularization must be individualized and based upon the characteristics of the patient, the experience of the managing physician and the level of expertise available at the treating institution.

## SUMMARY

Atherosclerotic renal arterial disease remains a challenging problem. The relative contribution of this condition to the propagation of hypertension, progression of renal failure and cardiopulmonary compromise can be difficult to determine. The algorithm shown below is meant to be a simplified guide to the evaluation and management of this condition. The decision as to which test to use obviously depends upon a number of factors including, but not limited to, availability, reliability, local expertise and patient suitability.

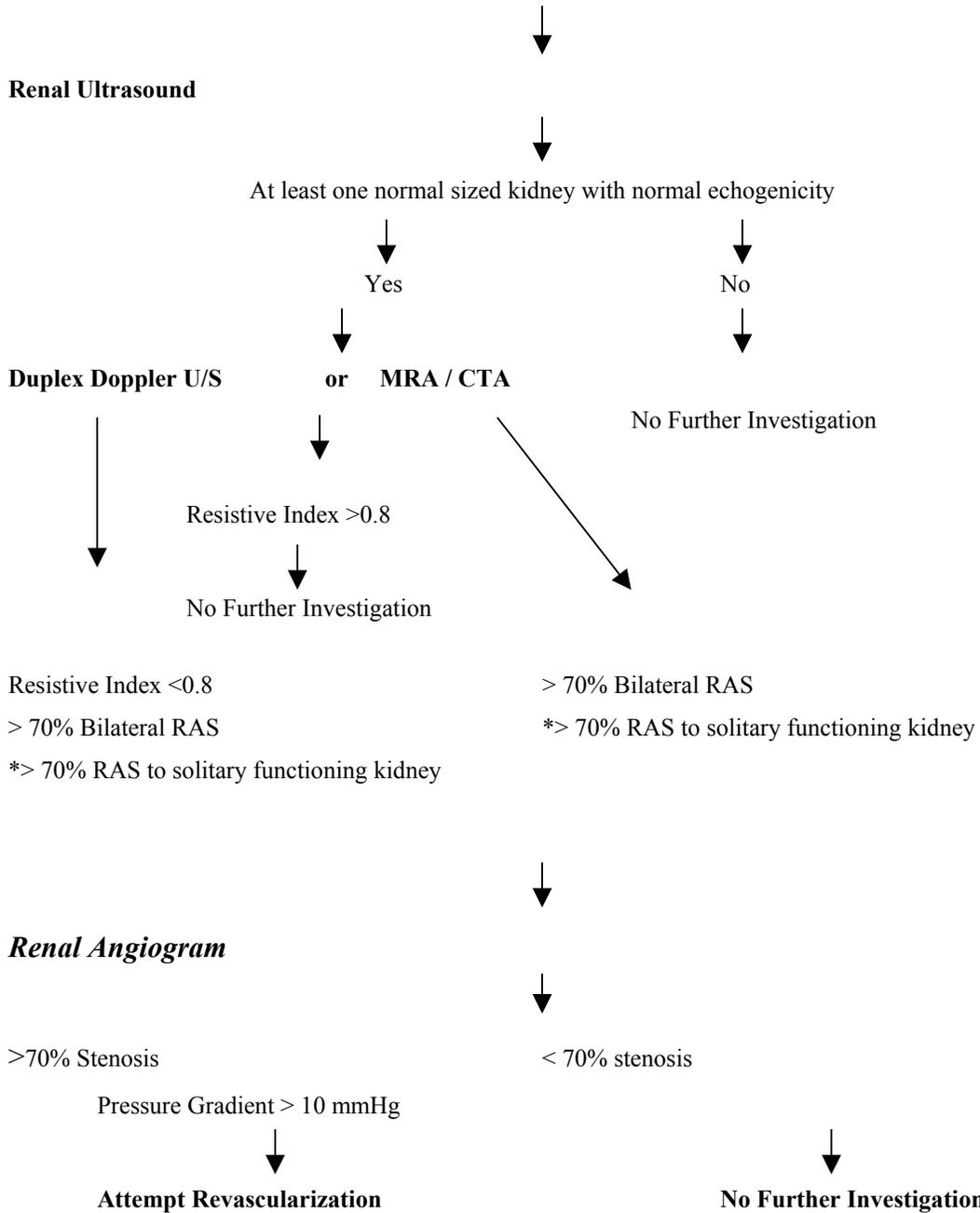
For instance in an individual with a serum creatinine of 200  $\mu\text{mol/l}$  and recurrent flash pulmonary edema in a facility not capable of MR angiography, but able to perform CT angiography it would likely be more prudent to proceed with renal angiography with a view to intra-procedure renal artery angioplasty and stenting if indicated. This would lower the

risk of contrast induced nephropathy (due to a lower volume of contrast dye) and possible exacerbation of pulmonary edema. Clearly the algorithm shown below can not account for all circumstances in which ARAS may be encountered, but hopefully will serve as a general initial approach applicable to most patients and institutions.

**SIMPLIFIED ALGORITHM FOR THE DIAGNOSIS AND MANAGEMENT OF ARAS**

**INDICATION FOR INVESTIGATION FOR ARAS**

1. Uncontrolled Hypertension despite maximum dosing of 3 antihypertensive medications and serum Cr. less than 300  $\mu\text{mol/l}$ .
2. Rapid (within weeks to months) otherwise unexplained decline in renal function and serum Cr. less than 300  $\mu\text{mol/l}$ .
3. Otherwise unexplained recurrent flash pulmonary edema.



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\* may require nuclear renography for verification

**TABLE 3: RAS MANAGEMENT**

		Grade
1	In patients demonstrated to have >70% luminal compromise of one or both renal arteries and <i>uncontrolled hypertension</i> (BP>140/90) despite the use of 3 antihypertensive medications at maximum dose, revascularization should be attempted with percutaneous balloon angioplasty and stenting.	Level I Grade B
2	Patients with <i>recurrent episodes of flash pulmonary edema</i> and no other readily identifiable cause (poor LV systolic function, significant coronary artery lesions, arrhythmias etc.) and greater than 70% stenosis of at least one renal artery should have revascularization attempted with percutaneous balloon angioplasty and stenting.	Level II Grade C
3	Revascularization for <i>preservation of renal function</i> should only be considered in individuals with either bilateral renal artery stenosis or stenosis of a renal artery supplying a single functioning kidney who have a rapid decline in renal function and a serum creatinine less than 300 µmol/l. <sup>(39, 40)</sup>	Level II Grade C

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## **Screening and Diagnostic Techniques for Peripheral Arterial Disease**

**André Roussin, MD, FRCP**  
Associate professor of medicine  
University of Montreal  
Director of the Vascular Laboratory  
Notre-Dame Hospital (CHUM), Montreal

### **GENERAL INTRODUCTION AND SCREENING**

Peripheral arterial disease (PAD) being a manifestation of atherosclerosis, screening for its presence implies simultaneous screening for cerebrovascular disease, coronary artery disease (CAD) as well as for renal vascular disease. The presence of PAD, whether symptomatic or not, markedly augments total mortality<sup>1</sup>. The risk of doubling stroke and myocardial infarction during a follow-up of 5 years in PAD patients persists even after taking into account age, sex, coronary disease and diabetes<sup>2</sup>.

Since PAD confers such an increased risk of vascular morbidity and mortality, screening for PAD by history and physical examination should be part of the health evaluation of men over 40 years of age and women who are postmenopausal or over 50 years of age as well as of patients with a recognized cardiovascular risk factor. (*Recommendation level 1A*)

### **HISTORY AND PHYSICAL EXAMINATION**

#### **HISTORY**

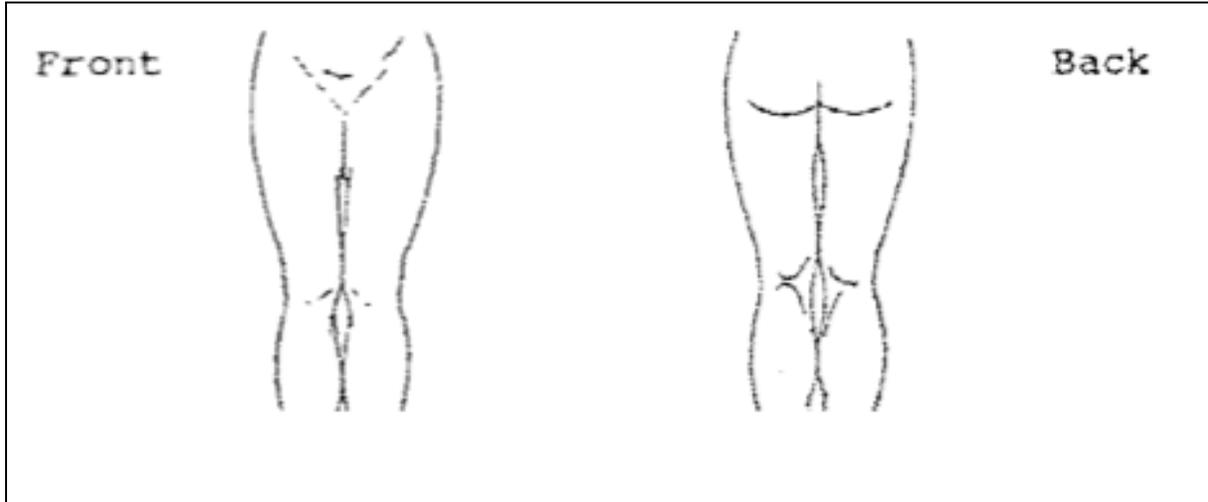
PAD can present with claudication but is frequently asymptomatic in less severe cases. A representative data base from the Limburg PAD Study found that if the cut-off point for ABI was set at < 0.95, the incidence of symptomatic patients was 22% but rose to 47% if the cut-off was 0.75<sup>3</sup>. PAD is thus asymptomatic in up to 78% of patients. In general claudication will appear when the degree of luminal stenosis exceeds 50% in vessel diameter, depending upon the

patient's walking habits<sup>4</sup>. The WHO/ROSE questionnaire was the first successful attempt to detect claudication in a general population<sup>5</sup>.

Subsequently, the Edinburgh Claudication Questionnaire was devised to improve the sensitivity of the WHO/Rose Questionnaire by establishing the relative usefulness of every question asked<sup>6</sup>. This questionnaire (Table 7A), which adds a cartoon to help the patient localize the pain, was shown in a family practice setting to help reproducibly diagnose claudication with a sensitivity of 91.3% (95% CI 88.1% - 94.5%) and retaining a specificity of 99.3% (95% CI 98.9% - 100%).

**Table 7A: The Edinburgh Claudication Questionnaire**

<p><b>The Edinburgh Claudication Questionnaire</b></p> <p>1. Do you get a pain or discomfort in your leg(s) when you walk? YES/ NO/ Unable to walk</p> <p>If you answered "yes" to question 1, please answer the following questions.</p> <p>2. Does this pain ever begin when you are standing still or sitting? NO</p> <p>3. Do you get it when you walk uphill or hurry? YES</p> <p>4. Do you get it when you walk at an ordinary pace on the level? YES</p> <p>5. What happens to it if you stand still?</p> <ul style="list-style-type: none"><li>• Usually continues more than 10 minutes NO</li><li>• Usually disappears in 10 minutes or less YES</li></ul> <p>6. Where do you get this pain or discomfort? Mark the place(s) with "x" on the diagram below</p>
-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------



**Legend:** A positive questionnaire diagnosis of claudication is made only if the “correct” answer is given to all questions.

Other similar questionnaires have been described. Essentially, a leg discomfort appearing specifically only with walking and rapidly subsiding in less than 10 minutes with rest is very suggestive of arterial claudication.

Impotence can result from pelvic atherosclerotic disease, whether from primitive or internal iliac involvement or, more frequently, from internal pudendal artery disease. A difficulty in attaining and maintaining a firm erection with preserved libido and ejaculation should arise the possibility of vascular involvement, especially if there is associated gluteal claudication.

### **PHYSICAL EXAMINATION**

Grading pulses, looking for bruits and examining for potential trophic changes in skin, hair or nails have classically been the hallmark of a basic peripheral vascular examination. Examination of skin temperature, elevation pallor or dependent rubor as well as venous dependent filling time or capillary refill have also been previously proposed as useful. A physical examination would be incomplete without palpation to exclude aneurysms, in particular an aortic abdominal aneurysm. Before grading the relative value of these diverse physical signs, it is important to take into account anatomical variations.

A number of studies collected in a critical review leads to the conclusion that in healthy individuals the dorsalis pedis, posterior tibial and femoral pulses are not palpable 8.1%, 2.9%, and 0% of the time, respectively<sup>7</sup>. However pedal and posterior tibial arteries are both absent at the same time in only 0.7% of normal feet since anatomical dissection reveals that hypoplasia of one of these vessels is usually compensated by prominence of the other<sup>8</sup>. Moreover, the absence of apparent palpable pulses may be often contradicted by the presence of audible arterial flow on further Doppler examination, such that true congenital absence of the dorsalis pedis and posterior tibial artery is seen in only 2% and 0.1% of cases respectively<sup>9,10</sup>.

The presence of a femoral bruit is an easy and interesting sign to look for since its specificity for PAD defined as defined by an ABI < 0.9 is 95% in a large recent study<sup>11</sup>: indeed, even if the sensitivity of this physical sign in PAD appeared low at 29%, finding its presence confers a likelihood ratio of 5.7 for the diagnosis of PAD

Other physical signs of PAD require more experience to interpret correctly and are less reliable than palpating pedal pulses and looking for femoral bruits.

The relative diagnostic value of abnormal physical findings is reported in table 7B<sup>vii</sup>. The performance of the different tests have been selected in accordance with the requisite that PAD is defined as an ABI < 0.9 (disease present) or < 0.5 (severe disease)<sup>viii</sup>

**TABLE 7B: PHYSICAL FINDINGS AND PAD: SENSITIVITY AND SPECIFICITY**  
**ADAPTED FROM MCGEE SR AND BOYCO EJ<sup>7</sup>**

#	Abnormal Finding	ABI	Sensitivity	Specificity	Likelihood ratio +
<b>1</b>	<b>Weak or absent PT and DP pulses</b>	< 0.9	0.63-0.73	0.92-0.99	9.0-44.6
		< 0.5	0.65-0.95	0.73-0.79	3.0-3.8
<b>2</b>	<b>Femoral arterial bruit</b>	< 0.9	0.29	0.95	5.7
		< 0.8	0.20	0.96	4.7
<b>3</b>	<b>Delayed Venous refilling time</b>	< 0.5	0.22-0.25	0.94-0.95	3.6-4.6
<b>4</b>	<b>Unilateral cool skin</b>	< 0.9	0.10	0.98	5.8
		< 0.5	0.65-0.80	0.46-0.47	1.2-1.5
<b>5</b>	<b>Foot discoloration</b>	< 0.9	0.35	0.87	2.8
		< 0.5	0.24-0.32	0.84-0.85	1.6-2.0
<b>6</b>	<b>Atrophic skin and Hair loss</b>	< 0.5	0.43-0.50	0.70-0.71	1.4-1.6

**CONCLUSION.**

**We recommend a directed history for symptoms of PAD.** A validated questionnaire, such as the Edinburgh Questionnaire, can help diagnose arterial claudication in men over 40 years of age and women who are postmenopausal or over 50 years of age as well as of patients with a recognized cardiovascular risk factor. (*Recommendation level 1A*)

*Expert opinion would propose, especially in screening asymptomatic individuals, to focus mainly on questions 1, 2 and 5 of the Edinburgh Questionnaire:*

- a. *Do you get a pain or discomfort in your leg(s) when you walk? YES/ NO/ Unable to walk*
- b. *Does this pain ever begin when you are standing still or sitting? NO*
- c. *What happens to it if you stand still?*

- Usually continues more than 10 minutes **NO**
- Usually disappears in 10 minutes or less **YES**

*Answering “in bold” to these questions should raise the possibility of arterial claudication and lead to a more detailed questionnaire as well as to the appropriate physical examination.*

**We recommend a directed examination focusing on physical findings that have been proven useful to detect PAD as defined as an ABI < 0.9, in men over 40 years of age and women who are postmenopausal or over 50 years of age as well as of patients with a recognized cardiovascular risk factor (*Recommendation level 1A*)**

*Expert opinion would propose that focusing on pedal pulses and femoral bruits achieves reasonable sensitivity and specificity levels without lengthening the duration of the examination and without necessitating specialized training or experience.*

Abdominal aortic aneurysm can easily be missed, especially in obese patients, so that echography is the preferred method of diagnosis in high-risk patients. We refer the reader to the chapter on aortic aneurysms

## **NON-INVASIVE VASCULAR EVALUATION**

### **INTRODUCTION**

Non-invasive evaluation usually includes the measurement of the ankle-brachial index (ABI).

This method is applicable to:

- The basic work-up in **symptomatic** patients with suspected claudication.
- General screening in **asymptomatic** patients with one or more of the following risk factors (see related chapter) for PAD after the age of 40 in men and postmenopausal women as well as after 50 in all women:
  - Definite increased risk:
    - Cigarette smoking
    - Diabetes
  - Increased risk :
    - Family history of PAD, CAD or Stroke
    - Dyslipidemia

- **Systolic and Diastolic Hypertension**

The ABI can be done by a physician or an assistant with appropriate technical training. All other methods described in this chapter should be done in collaboration with a vascular specialist.

## **DOPPLER ULTRASOUND TECHNIQUES**

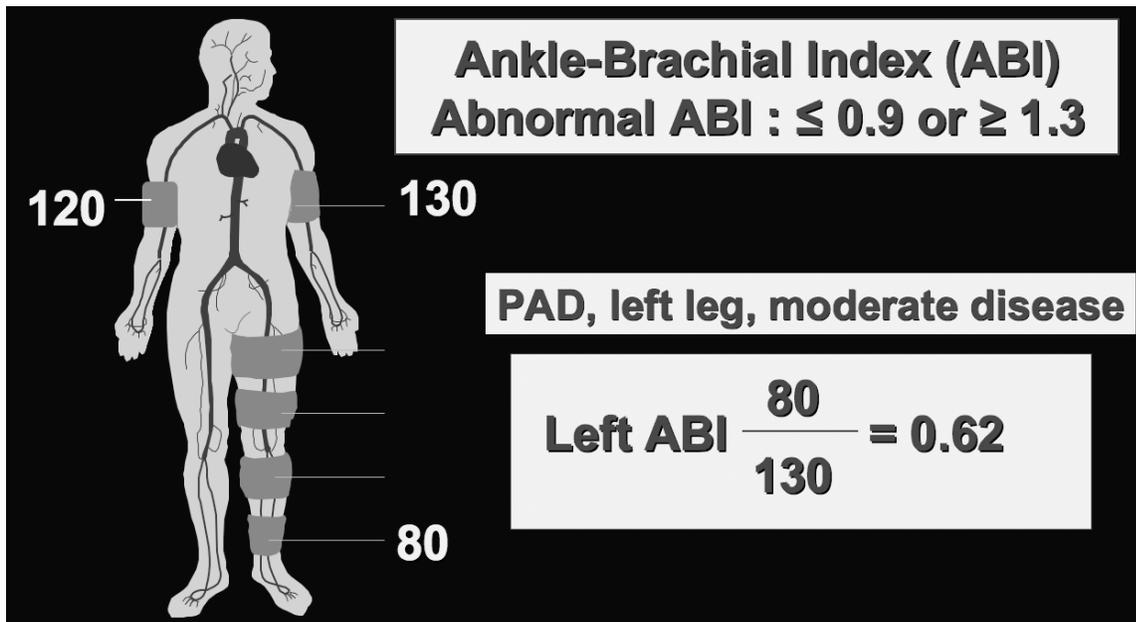
### **ANKLE-BRACHIAL INDEX: ABI**

The simplest method permitting quantitative assessment of the peripheral circulation is the measurement of the systolic blood pressure in the ankle arterial vessels using a blood pressure cuff assisted by an ultrasound Doppler device (instead of a stethoscope) to detect the presence of flow distal to the cuff. In young patients, this pressure is actually slightly higher than the systolic brachial pressure. With aging, the systolic tibial pressures gradually drop to marginally less than the systolic brachial pressure. This has led to using the ratio of the highest tibial pressure in the right leg over the higher of the two brachial pressures as the right ABI<sup>12</sup>. The left ABI is calculated the same way using the highest left tibial pressure over the highest brachial pressure<sup>12</sup>. See Figure 7A.

An ABI is considered normal between 0.9 and 1.3 in most studies. An ABI below 0.9 is diagnostic of PAD and an ABI over 1.3 reflects noncompressible calcified vessels<sup>12</sup>. Both situations are associated with augmented cardiovascular mortality<sup>13</sup>. The ABI has been widely used in epidemiological studies to demonstrate hemodynamic impairment in claudicant patients but also to help detect PAD in the more frequent patients with PAD that do not present with claudication.

The ABI may not accurately reflect the severity of PAD in the presence of bilateral subclavian artery stenosis: indeed, the measured brachial pressure on either side will underestimate the true central aortic pressure and the denominator of the ABI. Thus, the latter may be falsely elevated (and even normal) compared to the true severity of the disease. Thus the ABI should be viewed with circumspection in the presence of symptoms of subclavian steal, upper extremity claudication and bilateral subclavian bruits and alternate tests may be required to confirm the severity of PAD.

FIGURE 7A: ANKLE-BRACHIAL INDEX



#### SEGMENTAL LIMB PRESSURES

Systolic pressures can be obtained at various levels of the arterial tree (Figure 7A) by applying a blood pressure cuff of appropriate width for the size of the limb at that level while assessing the presence of arterial flow at any point distal to the cuff. In most vascular laboratories, a pressure gradient exceeding 20 mmHg between measurements at two adjacent levels would be considered abnormal and indicative of a significant stenosis situated between the two sites of blood pressure cuff location. Although this technique complements simple ABI measurement by adding pressure information at the proximal calf, distal thigh and proximal thigh, the interpretation is hindered by technical considerations caused by inadequate cuffs and anatomical problems such as obesity. In those conditions, alternate diagnostic tests may be needed to provide more reliable data, such as Duplex ultrasound imaging or angiographic techniques.

#### EXERCISE TESTING WITH TREADMILL

Similarly to patients with a typical history of angina who presents with a normal rest ECG, some patients with a classical history of intermittent claudication present a normal pulse examination and ABI values within the normal range. PAD can be demonstrated by reproducing the symptoms during an exercise stress test on a treadmill: this is most commonly done at a constant

speed of 2 mph with a 12% grade. The exercise is stopped either because of symptoms or after having walked a total of 5 minutes. The time to the onset of symptoms (initial claudication time) or to the end of walking because of severe pain (terminal claudication time) are recorded. ABI are first measured at rest. Immediately upon cessation of walking because of symptoms, the ABI is remeasured: a decrease of ABI below the cut-off value of 0.9 linked to occurrence of classical claudication symptoms with exercise is indicative of PAD.

### **ARTERIAL WAVEFORM DOPPLER ANALYSIS**

Useful information can be derived from the analysis of the arterial flow pattern. A normal arterial velocity tracing typically presents a normal triphasic configuration, with a main forward systolic component followed by a short early diastolic reversal and a late diastolic small forward component depending on the distal vascular resistance. With the development of progressive stenosis, the flow distal to the obstruction will gradually lose the diastolic components: the tracing will become biphasic, then monophasic. As the stenosis becomes severe or critical, the remaining systolic phase eventually becomes blunted before disappearing with total occlusion. The arterial waveform pattern can be qualitatively assessed by listening to the audio display of a handheld Doppler ultrasound unit. Alternatively, with more sophisticated ultrasound systems using pulsed wave Doppler, the arterial flow velocity waveform pattern may be visually displayed on a strip chart recorder or monitor where peak flow velocities may be measured<sup>14</sup>.

### **DUPLEX ULTRASOUND IMAGING**

Two-dimensional ultrasound imaging, also known as B-mode ultrasound, provides a direct tomographic view of anatomical structures including blood vessels. Duplex ultrasound imaging refers to the combination of B-mode imaging with flow velocity imaging by color and pulsed wave Doppler: the resulting duplex scan provides not only direct images of the vessel under study, but also yields hemodynamic information about blood flow velocity at various points within its lumen. In several vascular laboratories, this has become the next step in non-invasive vascular evaluation after ABI measurement. In a recent study, the sensitivity of color flow duplex sonography, prospectively compared to conventional arteriography ranged from 89% for hemodynamically significant iliac stenosis (> 50%) to 68% for popliteal and 90% for tibial

stenoses<sup>15</sup>. Specificity in that study was at least 97% for supra-popliteal lesions and 93% for infra-popliteal lesions<sup>16</sup>.

Duplex ultrasound imaging is at this time the most widely accessible and used technique in the complete diagnosis of arterial disease, short of using angiography. It also yields useful structural and hemodynamic information to the data provided by ABI measurements and segmental pressure recordings. While it may be time-consuming, has some limitations in imaging collateral vessels and may be hampered by the presence of calcifications in the vessel wall, it may still help orient clinical decisions about ordering invasive testing or planning a revascularisation by percutaneous or surgical techniques.

#### ***LASER DOPPLER***

Laser Doppler uses the movement of red cells to qualitatively evaluate circulation. Its use is restricted by the mere fact it reflects cutaneous microcirculation and adds very little to all other techniques.

#### **PLETHYSMOGRAPHY**

##### ***PULSE VOLUME RECORDING: PVR***

Doppler measurements measure velocities and help measure pressures. Volume measurements, i.e. plethysmography, reflect the pulse wave transmitted by tissues. Pulse volume recording (PVR) is done by applying cuffs at different level on both legs and measuring the volume variations<sup>17</sup>. The readings, which resemble an intra-arterial pressure recording, help detect hemodynamic lesions along the arterial tree. The qualitative aspect of PVR rarely makes it an interesting source of additional information to the quantitative pressure data obtained by Doppler. Clinical situations where PVR is superior to Doppler are calcified vessels and digital or toe measurements. PVR is usually done by air plethysmography.

#### **PHOTOPLETHYSMOGRAPHY**

Photoplethysmography is a technique using infrared detection of moving blood cells to permit calculation of toe pressures. In fact, it does not measure volume at all.

## CONCLUSION

### RECOMMENDATION:

We recommend ordering an **ABI** to help diagnose arterial claudication in patients suspected of claudication. An ABI below 0.9 is diagnostic of PAD with values below 0.4 associated with severe disease. An ABI over 1.3 is abnormal but cannot be used to diagnose occlusive PAD: it only reflects non-compliant non-compressible vessels. However, it is also associated with increased vascular morbidity and mortality. *Recommendation level IA.*

### RECOMMENDATION:

We recommend ordering an **ABI** to diagnose PAD in asymptomatic patients with arterial bruits or diminished pulses.

*Recommendation level IA.*

### RECOMMENDATION:

We suggest ordering an **ABI** to diagnose PAD in **asymptomatic** patients with one or more of the following risk factors (see related chapter) for PAD after the age of 40 in men and postmenopausal women as well as after 50 in all women:

- Definite increased risk:
  - Cigarette smoking
  - Diabetes (definite increased risk)
- Increased risk:
  - Family history of PAD, CAD or Stroke
  - Dyslipidemia
  - Systolic and Diastolic Hypertension

While femoral bruits are specific for PAD and reduced peripheral pulses are relatively sensitive (about 70%) and specific for PAD, measurement of ABI still detects PAD in a fair number of patients with an apparently normal physical examination.

*Recommendation level IB.*

**RECOMMENDATION:**

The measurement of segmental limb pressures to help diagnose the anatomical level(s) of arterial stenoses in patients with claudication is rarely helpful and should be left to the discretion of a vascular specialist. Clinical correlation is warranted, as adequate knowledge of the symptoms history and physical findings is essential in the proper interpretation of the test results.

***Recommendation level IIC.***

We suggest considering a **Duplex scanning** study to help diagnose level of arterial disease in patients with claudication and to help planning of an intervention. Interpretation of Duplex scanning is operator dependant but can be useful in expert hands, especially in the follow-up of arterial bypasses and angioplasties.

***Recommendation level IIC.***

**RECOMMENDATION:**

We suggest considering a Treadmill study to help diagnose arterial disease in patients with uncertain diagnosis of claudication and to help quantify claudication if deemed useful. This method is time consuming, carries a small but definite risk and should be ordered and supervised by a vascular specialist.

***Recommendation level IIC.***

**ANGIOGRAPHY**

**DIGITAL SUBTRACTION ANGIOGRAPHY: DSA**

DSA is the gold standard against which non-invasive vascular diagnosis is compared and still remains the standard of comparison for magnetic resonance angiography and multi-row detector computed angiography. The drawbacks of this technique are well known and include local trauma from the arterial puncture, arterial embolism due to catheter insertion, allergy to the contrast material as well as renal toxicity especially in chronic renal failure and in diabetic patients with proteinuria.

Angiography in a patient with intermittent claudication is usually indicated when a decision has been made to proceed with either percutaneous or surgical revascularization, should a suitable lesion be identified

**MAGNETIC RESONANCE ANGIOGRAPHY: (MRA, OR MR ANGIO)**

Advances in magnetic resonance imaging (MRI) has enabled imaging of the arterial tree using an intravenous bolus injection of Gadolinium, a MR contrast agent. Thus, in comparison to DSA, it is considered a non-invasive mode of angiography and presents a significant lower risk of puncture site complication and radiocontrast media nephrotoxicity and adverse reactions. Excellent correlation with conventional angiography has been reported in the detection of occlusion and stenosis of proximal arteries (aorto-iliac and femoropopliteal). Sensitivity and specificity for detection of stenosis greater than 50% varying respectively between 90-99 % (median 95%) and 93-99% (median 96%) have been reported<sup>1819202122</sup>. Excellent sensitivity values of 87-92% (median 92%) have also been reported for detection of infra-popliteal stenosis or occlusion. Lower values of specificity have been reported for grading infra-popliteal disease (64-99%) (median 84%).

A drawback of MRA is a trend toward an overestimation of the lesions<sup>2023</sup>. However, no patients would have been discarded from useful treatment based on MRA findings<sup>20</sup>. The consensus is now that MRA can safely replace catheter angiography for the diagnosis of PAD. Furthermore it improves the evaluation of infra-popliteal over catheter angiography in cases of severe proximal disease.

Based on the above studies and assuming further improvement of these results from recent technical developments, the following can be said about MRA:

- A diagnostic examination can be achieved in 95 % of the cases
- Sensitivity and specificities values of 95% can be obtained for the detection of suprapopliteal stenosis
- Sensitivity greater of 90 % and specificity of 85 % can be obtained for the detection of infra-popliteal stenosis
- The rate of false negative examinations is very low (no more than 2%).

- Improved evaluation of infra-popliteal vessels is observed when compared with DSA especially in cases of critical limb ischemia.
- A trend toward overestimation of lesions can lead to indication of peripheral angioplasty in patients without significant stenosis requiring unnecessary DSA examinations in 5 to 10 % of the cases.

The main advantage of MRA over DSA is the fact that it is completely non-invasive with minimal adverse reactions linked to contrast agents and minimal nephrotoxicity. However, we have to take into consideration the relatively frequent clinical contraindications to MRA such as the presence of a pacemaker or defibrillator and claustrophobia. Another limitation of MRA is imaging of stented arteries because of metallic artifact that impair visualization of the lumen<sup>2425</sup>.

#### **COMPUTED TOMOGRAPHY ANGIOGRAPHY: CTA**

The most recent technical breakthrough in CT is the introduction of multi-row detector CT that may allow CT vascular imaging with intravenous contrast enhancement to become the initial imaging modality for PAD.

Excellent correlation with DSA has been reported for detecting aorto-iliac and femoropopliteal lesions, with a sensitivity ranging from 90 to 98 % (median 95%), and a specificity ranging from 70 to 100 % (median 95%)<sup>2627282930</sup>. Quantification of stenosis involving infra-popliteal arteries is generally accurate but may at times be inadequate, as differentiation between calcification, opacified lumen and plaque is more problematic in small vessels<sup>28</sup>. Sensitivity values of 90-100% (median 96%) and specificity values of 74-100% (median 85%) have been reported for detection of infra-popliteal stenosis or occlusion.

As it was also the case for MRA, more patent arterial segments are detected in the calves using CTA when compared with DSA. These findings legitimate the questioning of DSA as the gold standard for the diagnosis and evaluation of PAD<sup>28</sup>. While these results were obtained with older 4-detectors MDCT, newer available 16, 32, 64 and 128 detector MDCT have even more higher spatial resolution and faster data acquisition rate which will probably yield better quantification of occlusive disease especially in the infrapopliteal lesions. The rate of technical failure (non-

diagnostic examination) is generally low with CTA (2-3%)<sup>26,30</sup>, but it can rise to 14% in infra-popliteal arteries<sup>27</sup>.

Based on previous studies and assuming some improvement of these results based on recent technical development the following can be assumed concerning CT Angio:

A diagnostic examination can be achieved in 95 % of examinations

Sensitivity and specificity values greater than 90% are obtained for the detection of suprapopliteal stenosis Sensitivity above 90% and specificity around 85 % are observed for the grading of infra-popliteal stenosis. The diagnostic performance of MDCTA in critical limb ischemia could be lower than that in claudication because of calcifications in smaller vessels.

The main advantage of CTA over DSA is that it does not require a catheter-based intra-arterial puncture with its inherent risk of local complication. However, it still requires exposure to possibly nephrotoxic or allergic radiocontrast media as well as to ionizing radiations.

There is currently no data yet in the literature directly comparing MRA vs CTA, while studies evaluating patient outcomes after screening by MRA or CTA are scarce. The current cost of a CTA examination in Canada is \$350 while the cost of a MRA examination is around \$750, a little less than DSA

## **CONCLUSION**

In patients with claudication and PAD, since MRA and CTA both show an excellent correlation with DSA for treatment planning of PAD, most authors agree that diagnostic DSA is no longer necessarily required. We thus recommend that, where facilities exist, MRA or CTA be considered rather than DSA. CTA is less expensive than MRA but requires injection of an iodinated contrast agent. **Recommendation level IA.**

In patients where an angiography is necessary, we recommend MRA rather than CTA or DSA if there is a history of severe allergy to iodinated contrast or if the patient suffers from chronic renal failure or is a diabetic with proteinuria. **Recommendation level IIIC**

**TABLE 7C: OVERALL RECOMMENDATIONS**

#	Recommendation	Grade
1	Taking a directed <b>history</b> for symptoms of PAD. A validated questionnaire, such as the Edinburgh Questionnaire, can help diagnose arterial claudication in patients suspected of suffering from PAD.	1A
2	Performing a directed <b>examination</b> focusing on physical findings that have been proven useful to detect PAD as defined as an ABI < 0.9	1A
3	Ordering an <b>ABI</b> to help diagnose arterial claudication in patients suspected of claudication. An ABI below 0.9 is diagnostic of PAD with values below 0.4 associated with severe disease.	1A
4	Ordering an <b>ABI</b> to diagnose PAD in asymptomatic patients with arterial bruits or diminished pulses	1A
5	Considering an <b>ABI</b> to diagnose PAD in patients with a high cardiovascular risk, particularly patients over the age of 40 with smoking or diabetes. Femoral bruits are specific (95%) for PAD and reduced pulses are quite sensitive ( $\pm 70\%$ ) for PAD but the ABI will still detect PAD in a fair number of patients with a normal physical exam	1B
6	Considering <b>Segmental pressures, Duplex scanning</b> and <b>Treadmill testing</b> in conjunction with a vascular specialist	3C
7	Considering, where facilities exist, <b>MRA</b> or <b>CTA</b> rather than DSA in patients with incapacitating claudication. Since MRA and CTA both show an excellent correlation with DSA, diagnostic DSA is no longer necessarily required to plan an intervention. CTA is less expensive than MRA but requires injection of an iodinated contrast agent	1A
8	Considering, in patients where an angiography is necessary, <b>MRA</b> rather than CTA or DSA if there is a history of severe allergy to iodinated contrast or if the patient suffers from chronic renal failure or is a diabetic with proteinuria	3C

PAD is one of the clinical manifestations of the spectrum of atherosclerosis, which results in at least a doubling of the incidence of MI, Stroke and Mortality.

Basic screening for PAD should thus be part of the health evaluation of men over 40 years of age and women who are over 50 years of age as well as of patients with a recognized cardiovascular risk factor.

**Basic screening for PAD** includes a directed history done by asking a few key questions that are highly specific for claudication and a physical examination focusing on femoral bruits and pedal pulses. A majority of patients with PAD are asymptomatic but still carry an important cardiovascular burden, such that history should always be complemented by physical examination.

**Non-invasive evaluation** for suspected PAD should include an ABI in most cases. An ABI  $\leq 0.9$  is diagnostic for PAD.

**Non-invasive evaluation** using the ABI should be considered in **asymptomatic** patients with one or more of the following risk factors (see related chapter) for PAD after the age of 40 in men and postmenopausal women as well as after 50 in all women:

- Definite increased risk:
  - Cigarette smoking
  - Diabetes (definite increased risk)
- Increased risk:
  - Family history of PAD, CAD or Stroke
  - Dyslipidemia
  - Systolic and Diastolic Hypertension

**Further non-invasive testing** should be done in collaboration with a vascular specialist. Imaging by Duplex echography and treadmill are techniques useful in specific circumstances when interpreted by experts.

**Digital subtraction angiography** is being gradually replaced, where available, by CT angiography and MR angiography. Both techniques are valuable aids to patient management when ordered by vascular specialists in the global clinical context.

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## THE MEDICAL TREATMENT OF PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

**Sonia S. Anand MD, PhD, FRCPC**    **A.G.G. Turpie MD FRCP, FRCPC\***  
Department of Medicine                      Department of Medicine  
Population Health Research Institute      McMaster University  
McMaster University                          Hamilton ON Canada

Dr. Anand is a recipient of  
Canadian Institutes of Health Research  
Clinician-Scientist Phase 2 Award.

### INTRODUCTION

Peripheral arterial disease (PAD) of the lower extremity arises when there is significant narrowing of arteries distal to the arch of the aorta. Narrowing can arise from atheroma, arteritis, local thrombus formation, or embolisation from the heart or more central arteries. PAD may be asymptomatic or symptomatic manifested by intermittent claudication, leg ulceration, and gangrene. PAD is more common in people over the age of 50 years than in young people, and is more common in men than women. The prevalence of PAD of the lower extremity (assessed by non-invasive tests) is about 3% in people under the age of 60 years, but rises to over 20% in people over 75 years<sup>(1)</sup>. PAD usually presents as intermittent claudication. The annual rate of a new diagnosis of claudication is 1.5-2.6/1000 men per year and 1.2-3.6/1000 women per year<sup>(2)</sup>. The presence of asymptomatic or symptomatic PAD is an ominous sign that widespread atherosclerosis is present and patients with this condition suffer a 3 to 6 fold increase in myocardial infarction (MI), stroke, and cardiovascular (CV) death (3-6). Therefore, risk factor modification and use of proven medical therapies should be aggressively promoted among these high risk patients.

## RISK FACTOR MODIFICATION

Factors associated with the development of PAD include age, sex, tobacco exposure, diabetes mellitus, hypertension, hyperlipidemia, obesity, elevated homocysteine, and physical inactivity. The strongest association is with smoking (RR 2.0 - 4.0) and diabetes (RR 2.0 - 3.0) <sup>(7-11)</sup>.

## TOBACCO

Tobacco exposure is a strong determinant of atherosclerosis and cardiovascular disease (CVD) <sup>(7,8)</sup>. While there are no randomized trials which demonstrate the precise risk reduction of CV events associated with smoking cessation in people with vascular disease, observational epidemiology indicates that the relationship between tobacco exposure and CV events is continuous, and people with vascular disease who stop smoking attain the same risk of CV disease as do non-smokers in five years <sup>(8,9)</sup>. A recent systematic review by Willigendael et al incorporated data from 4 prospective cohort and 13 cross sectional studies and assessed the association between smoking and PAD. The risk of having PAD was increased 2.3 fold among smokers compared to non-smokers, and a clear dose-response relationship was observed (i.e. increasing risk with increasing number of cigarettes). Further the authors estimated that in countries in which the prevalence of smoking is approximately 30%, the population attributable risk of smoking on PAD is at least 50% <sup>(9)</sup>.

In addition to the association between tobacco and CV events, among patients with PAD, cigarette smokers have an increased progression of claudication symptoms, poor prognosis after bypass surgery, and higher rates of amputation and need for reconstructive surgery <sup>(11)</sup>. On the other hand, smoking cessation leads to significant improvements in graft patency, walking distance, and reduces the risk of CV events among patients with PAD. <sup>(12)</sup> Thus it is reasonable to accept that for patients who smoke, successful cessation is probably more effective at preventing cardiovascular morbidity and mortality than any drug therapy <sup>(13,14)</sup>. Smoking prevention and cessation should be vigorously promoted by physicians at all clinical encounters, and patients should be aided as much as possible by health care professionals by providing advice and smoking cessation programs to increase the chances that patients will quit. <sup>(15-17)</sup>. Quit rates may be improved by the use of nicotine replacement and bupropion (Zyban);

therapies which appear to be safe and somewhat effective for use among people with vascular disease who are motivated to quit smoking <sup>(17)</sup>.

### **MEDICAL THERAPIES TO REDUCE CV EVENTS**

Medical therapies that have been evaluated for the prevention of cardiovascular events in the PAD population can generally be grouped into three categories: Thrombosis-directed therapies, cholesterol lowering therapies, and blood pressure lowering therapies. In recent years, a number of large randomized controlled trials have helped clarify the role of these strategies in patients with PAD, and this information will be summarized below. In addition, the role of tight-glucose control and the special properties of individual classes of pharmacologic agents including ACE inhibitors and Statins will be highlighted.

### **THROMBOSIS-DIRECTED THERAPIES**

Thrombosis is common to all the clinical manifestations of atherosclerotic vascular disease including the pathogenesis of atherosclerosis and acute vascular occlusion <sup>(18)</sup>. Thrombosis occurs as a result of two interrelated processes: activation of platelets and activation of blood coagulation <sup>(19)</sup>. Thrombin, a product of activation of blood coagulation is the principal mediator of thrombus formation at the site of vascular injury, and has a number of important actions that promote and accelerate atherothrombosis <sup>(18,20)</sup>. Platelets also play a key role in the pathogenesis of thrombosis. When endothelium is injured and exposed to flowing blood, platelets become activated, adhere to collagen, aggregate thereby initiating the process that leads to thrombus formation. When platelets have adhered to subendothelial collagen, they undergo a number of changes collectively known as platelet activation. The stimuli to activation include tissue components such as collagen and other subendothelial fibres, physical forces including shear stress, hormones such as epinephrine and a variety of local mediators including thrombin, adenosine diphosphate, serotonin, and thromboxane A<sub>2</sub>, the latter released by platelets themselves. <sup>(19)</sup> The key role of platelets in the pathogenesis of the acute manifestations and the long-term progression of atherothrombosis is the basis for the use of antiplatelet drugs in the management of patients with PAD.

### ANTIPLATELET THERAPY

The role of platelets in the pathogenesis of atherosclerosis and the demonstrated efficacy of antiplatelet drug in ischemic heart disease and cerebrovascular disease provide a strong rationale for the use of antiplatelet drugs in patients at risk of vascular disease. The evidence for the use of antiplatelet drugs in patients with PAD derives largely from the overview of the studies evaluating antiplatelet therapy that demonstrate a benefit in the reduction in myocardial infarction and stroke such in patients. <sup>(21)</sup> The main antiplatelet drugs include aspirin, the thienopyridines: ticlopidine and clopidogrel, and the cyclic AMP inhibitor dipyridamole. Cilostazol is also believed to have antiplatelet actions and is an effective therapy to improve walking distance among claudicants <sup>(22,23)</sup>.

### ASPIRIN

Aspirin is the most widely prescribed antiplatelet agent <sup>(24-27)</sup>. The major mechanism for the antithrombotic effect of aspirin is mediated through its ability to irreversibly suppress the synthesis of platelet thromboxane A<sub>2</sub>, a potent agonist of platelet aggregation. The lowest effective dose of aspirin is 75-100 mg/day <sup>(21)</sup>. The side effects of aspirin are mainly gastrointestinal and are dose related. Short-term aspirin use has been shown to produce gastric erosions and gastric hemorrhage, while long-term use can produce gastric ulcers, anemia, and gastrointestinal hemorrhage. The inhibition by aspirin of the synthesis of prostaglandins in the gastric mucosa, where they play a major role in protecting the mucosa, has been proposed as an important mechanism by which aspirin-induced gastric injury occurs. Therefore, the lowest effective dose of aspirin should be used to reduce the risk of gastrointestinal bleeding. The combination of aspirin with a proton pump inhibitor (PPI) in patients with a history of gastrointestinal bleeding with aspirin exposure results in a low and acceptable rate of recurrent bleeding. <sup>(28)</sup> In general, aspirin does not cause a generalized bleeding abnormality unless it is given to patients with an underlying hemostatic defect, such as hemophilia, uremia or that induced by anticoagulant therapy <sup>(19)</sup>.

**THIENOPYRIDINES:**

Thienopyridine derivatives inhibit platelet aggregation by selective inhibition of adenosine diphosphate activity<sup>(29,30)</sup>. Adenosine diphosphate is one of the agonists that induce platelet aggregation by stimulating both arachidonic acid release and glycoprotein IIb/IIIa activation also involved in both platelet adhesion and aggregation. There are two approved drugs in this class: ticlopidine and clopidogrel. The recommended daily dosage of ticlopidine is 250 mg twice daily<sup>(29)</sup>. However ticlopidine has a number of side effects, the most common of which are diarrhea and skin rash, and the most serious is neutropenia, which occurs in about 2% of the patients. The recommended daily dose of clopidogrel is 75 mg/day.<sup>(30)</sup> Clopidogrel is preferred to ticlopidine because of its faster onset of action and improved safety profile. In addition it is more convenient to use (once versus twice a day) and has stronger clinical trial data demonstrating its benefit.

The largest single study of antiplatelet drugs in patients with PAD is the CAPRIE trial that compared clopidogrel with aspirin in over 19,000 at risk of vascular ischemic events<sup>(30)</sup>. Patients with recent MI, recent stroke or PAD were recruited into the study, the primary outcome was the composite of MI, stroke or vascular death, and patients were followed for 1 – 3 years. The results demonstrated that long-term administration of clopidogrel 75 mg/day in patients with atherosclerotic vascular disease was more slightly more effective than aspirin (325 mg twice daily) in reducing the combined outcome of myocardial infarction, ischemic stroke or vascular death (8.7% relative risk reduction) with a similar safety profile. About one-third of the patients recruited to the CAPRIE trial had PAD. In this subgroup, there was a highly significant reduction in major vascular outcomes of clopidogrel over aspirin (22% relative risk reduction).

**DIPYRIDAMOLE**

Dipyridamole inhibits platelet phosphodiesterase resulting in an increase in an increase in local concentrations of adenosine that acts on platelet A<sub>2</sub> receptors stimulating adenolyte cyclase increasing cyclic AMP levels<sup>(31)</sup>. This results in inhibition of platelet aggregation by various stimuli such as platelet-aggregating factor, collagen and adenosine diphosphate. Dipyridamole is actively absorbed from the gastrointestinal tract and metabolized in the liver primarily by

conjugation with nucleonic acid. The standard dose of dipyridamole for antiplatelet activity is 400 mg per day in divided doses usually four times per day may have a role in patients with prior TIA/stroke but this is untested in patients with PAD.

### **CILOSTAZOL**

Cilostazol is a clinilone derivative that inhibits phosphodiesterase-3, and believed to suppress cyclic AMP degradation within platelets and blood vessels leading to inhibition of platelet aggregation and vasodilatation<sup>(22,23)</sup>. Cilostazol reversibly inhibits platelet aggregation induced by a variety of stimuli including thrombin, ADP, collagen, arachidonic acid, epinephrine and sheer stress. Cilostazol is also a vasodilator. It is absorbed from gastrointestinal tract and metabolized by hepatic cytochrome P450 enzymes. The metabolites are largely excreted in the urine. Cilostazol has only minimal antiplatelet activity and should not be used as a sole antiplatelet drug in the management of vascular disease. There is limited data on cilostazol in the management of vascular disease. More information regarding the effectiveness of cilostazol to improve walking distance is provided below.

### **SUMMARY**

The Antithrombotic Trialists' Collaboration<sup>(21)</sup> analyzed the effect of antiplatelet agents for the prevention of vascular events in a meta-analysis of over 135,000 patients who had taken these agents for longer than 30 days. All of the patients were at risk of atherosclerotic vascular events, due to a history of unstable angina, MI, transient ischemic attack, stroke, PAD and other vascular illnesses. Antiplatelet agents reduced the overall risk of non-fatal stroke by 25%, non-fatal MI by about 34% and vascular mortality by 17%. The overall risk reduction for the combined outcome MI, stroke, or vascular death in secondary prevention was about 27%. In addition, the authors concluded that low doses of aspirin (75 – 150 mg) were as effective for long-term use as higher doses, and reduced the risk of the composite endpoint outcomes by 25%. They also concluded that the addition of a second antiplatelet agent such as clopidogrel to aspirin may produce additional benefits in some clinical circumstances.

The data in the Antithrombotic Trialists' Collaboration indicating the effectiveness of antiplatelet drugs in the management of atherothrombosis were largely obtained from aspirin studies, but there was no evidence that the other antiplatelet drugs were not at least equally effective. The benefit of antiplatelet agents occurred not only in patients with unstable angina, acute myocardial infarction, stroke or TIAs, but also in patients with PAD. The Antithrombotic Trialists' Collaboration overview included 42 trials involving 9,706 patients who had PAD demonstrated a 23% ( $2P < 0.009$ ) reduction in vascular death, MI or stroke in patients treated with antiplatelet therapy (5.8%, 280/4844) compared to control (7.1%, 347/4862). The results of this overview form the basis for the recommendation for antiplatelet therapy in patients with PAD which should be given irrespective of the initial presentation. These recommendations are consistent with the recent review of antiplatelet therapy by the American College of Chest Physicians in their most recent conference on antithrombotic therapy. <sup>(32)</sup>

#### **ORAL ANTICOAGULANTS IN PAD**

In patients with CAD there is strong evidence that high intensity oral anticoagulants (OAC) (International Normalizing Ratio (INR)  $> 2.8$ ) significantly reduce the recurrence of MI, ischemic stroke and death, but also increase the risk of major bleeding <sup>(33)</sup>. On the other hand there is no apparent benefit of low intensity OAC (INR  $< 2$ ) in patients with CAD <sup>(33)</sup>. The evidence using a moderate intensity anticoagulation (INR 2-3) in the presence of aspirin, suggests that combining OAC and antiplatelet therapy significantly reduces recurrent CV events, but increases the risk of major bleeding <sup>(33)</sup>. Nine clinical trials involving 4,889 patients have tested the effectiveness of OAC in PAD patients <sup>(34)</sup>. However, the individual trial results were conflicting perhaps because they were small. Many of these studies focused on peripheral artery patency after vascular reconstruction, and were not designed to assess the potential benefit of OAC to reduce CV outcomes, and ongoing trials seek to clarify this further. <sup>(34)</sup>

#### **CHOLESTEROL LOWERING USING LIPID ALTERING MEDICATIONS**

There is strong evidence to support of cholesterol lowering with HMG CoA reductase inhibitors (known as statins) in patients with PAD <sup>(35)</sup>. The Heart Protection Study randomized 20,536 patients with vascular disease or diabetes, to treatment with simvastatin 40 mg daily or placebo

for a mean follow-up time of 5 years. Approximately one-third of patients included had PAD, and these patients had the highest placebo event rate of the 4 main inclusion groups (32.7% after 5 years), compared to patients with prior stroke (29.8%), coronary artery disease (27.5%), or diabetes mellitus (25.1%). Overall, treatment with simvastatin was associated with a significant 24% relative risk reduction and a 5.5% absolute reduction in the risk of major vascular events<sup>(35)</sup>, and similar relative and absolute risk reductions were observed in PAD patients. These effects were observed irrespective of the baseline LDL cholesterol. In addition recent clinical trials indicate that statins improve symptoms of intermittent claudication and improve treadmill walk times. **These will be reviewed in the section on Vascular Protection on page # 8-10.**

Other lipid-lowering agents such as fibrates are used primarily among patients with a classic “diabetic dyslipidemia” characterized by elevated triglycerides and low HDL cholesterol. Bezafibrate was recently studied in a randomized trial of 1568 men with PAD<sup>(36)</sup> and was observed to improve lipids, reduce serum fibrinogen, improve claudication severity but did not reduce coronary events or stroke (RR 0.96; 95% CI 0.76-1.21). Fibrate trials in patients with coronary artery disease have also revealed conflicting results<sup>(38,39)</sup>. Therefore, given the strong evidence in support of Statins reducing CV events, these agents should be used preferentially over fibrates in the treatment of patients with PAD.

### **BLOOD PRESSURE LOWERING**

Hypertension is highly prevalent among patients with PAD and is associated with a worsened prognosis<sup>(40)</sup>. Blood pressure shares a continuous relationship with the development of vascular disease including PAD. In the Framingham Study, a 2.5 to four-fold increased risk of developing PAD was observed in men and women with hypertension<sup>(41)</sup>. While the benefits of BP lowering observed in the elderly and in patients with coronary or cerebrovascular disease are assumed to exist among patients with PAD given the significant co-existence of these conditions, until recently, there was little direct evidence of the benefit of blood pressure lowering in patients with PAD. Recently, a subgroup analysis of patients with PAD from the HOPE trial was published<sup>(42)</sup>. Of the 9,541 patients randomized into the study, 1,715 had symptomatic PAD and 2,118 had asymptomatic PAD (defined as an ABI<0.9 in the absence of symptoms). In

patients with symptomatic PAD, ramipril 10 mg/day reduced the risk of a cardiovascular event by 25% and by 27% in patients with asymptomatic PAD after 4.5 years of treatment. The mean blood pressure at entry in patients with clinical or silent PAD was 143/79, implying that ACE inhibitors are likely to benefit many PAD patients with borderline or normal blood pressure. These data are supported by a subgroup analysis of normotensive patients (mean BP 136/84) included in the Appropriate Blood Pressure Control in Diabetes trial<sup>(43)</sup>, which enrolled normotensive or hypertensive patients with diabetes mellitus and randomly assigned them to moderate or intensive antihypertensive therapy (with nisoldipine or enalapril). Among patients with PAD (n=53), 13.6% on intensive treatment suffered a cardiovascular event compared to 38.7% who received moderate treatment (P=0.05). Little is known about the effects of other classes of anti-hypertensive drugs in the presence of PAD. A recent Cochrane review by Lip and colleagues was designed to determine the effects of anti-hypertensive drugs on the cardiovascular events and death in patients with hypertension and PAD; symptoms of claudication and critical leg ischemia; progression of PAD, and revascularisation, and amputations. However only 2 randomised trials were found. Due to the limited data, evidence for various anti-hypertensive drug classes in PAD is poor, so that it is unknown whether significant benefit or risk accrues from their use<sup>(44)</sup>. The evidence of the effectiveness of BP lowering in other vascular subgroups such as CHD and stroke, taken together with the emerging data of its effectiveness in PAD patients allows us to advocate for aggressive BP lowering in this high-risk subgroup. Furthermore given the accumulating evidence in support of ACE inhibitors prevention of recurrent events in vascular patients, these agents should be considered for all patients with PAD irrespective of baseline blood pressure unless contraindications exist.

## GLUCOSE

Patients with diabetes mellitus have a two to four-fold increased risk of coronary, cerebrovascular and PAD compared to non-diabetic people<sup>(45)</sup>. There is increasing evidence that glucose shares a continuous relationship with atherosclerosis and CVD, and like total cholesterol or BP, the level of blood glucose appears to be a continuous risk factor for CVD. Observational data suggest that CV events rise by about 10-30% for every 1% increase in HbA1c<sup>(46,47)</sup>. In the UKPDS study, every 1% increase in HbA1c in subjects with type 2 diabetes increased the risk of

death by 14%, MI by 14% and stroke by 12%<sup>(48)</sup>. While to our knowledge there have been no randomized trials of tight glucose control among PAD patients, the above data suggest, but do not confirm, that lowering glucose levels into the normal range will prevent recurrent CV events in PAD patients. Therefore, while randomized trials to date suggest that intensive glucose control reduces CV events, on-going trials are needed to confirm these observations. Reduction in glucose concentration can be brought about by medication, weight reduction and regular exercise are effective methods of improving glucose control, and can decrease medication requirements among established diabetics. This provides additional evidence to advocate for these lifestyle changes among patients with PAD.

## **VASCULAR PROTECTION**

### **STATINS**

While there is strong evidence in support of cholesterol lowering with HMG CoA reductase inhibitors (statins) as a therapy to reduce vascular events, the actions of statins turn out to be more elaborate than originally anticipated. Statins pleiotropic effects include anti-inflammatory properties, improved endothelial dependent vasodilation of peripheral arteries, and angiogenesis promotion. Statins have been demonstrated in small studies and a post-hoc analysis to improve walking distance in patients with symptomatic PAD<sup>(49)</sup>, as well as improve perioperative outcomes in high risk patients, and among those undergoing vascular surgery<sup>(50)</sup>. Therefore given the conclusive evidence in support of statins ability to prevent CV events in high risk patients, their additional benefits on vascular function make this class of drugs the obvious first choice among lipid-lowering agents.

### **BETA-BLOCKERS**

Beta-blockers act by multiple mechanisms including blood pressure lowering, improved balance of oxygen demand and supply and decreased ventricular irritability. Several randomized controlled trials have found benefits associated with the use of beta-blockers post-MI, and a large systematic overview of over 24,000 people reported that beta-blockers improved survival in patients with prior MI by 23%, reduced the risk of sudden death by 30%, and reduced the risk of non-fatal reinfarction by 25%<sup>(51)</sup>. Patients with high baseline risk such as those with large

infarcts, early heart failure symptoms and hypertension are likely to derive the most benefit. Controversy regarding the use of beta blockade in patients with PAD has led many physicians to avoid using them because of a fear that intermittent claudication will be worsened. However a systematic review of 11 randomized trials involving 127 patients with stable intermittent claudication in which beta-blockers were used from > 6 months duration found no significant differences in initial claudication distance or absolute claudication distance on an exercise treadmill was observed<sup>(52)</sup>. This is supported by a subsequent small randomized trial of 49 stable claudicants which showed that atenolol did not significantly reduce the initial claudication distance or absolute claudication distance compared to placebo<sup>(53)</sup>. While the studies to date have been relatively small, there is no compelling evidence to support the avoidance of beta-blockers in order to minimize intermittent claudication. There is strong evidence for protection of vascular events during and after vascular surgery with beta blockers, and therefore they should be considered for use in the perioperative setting.

### ACE INHIBITORS

Recently in the HOPE trial the ACE inhibitor ramipril (10 mg/day) was shown to reduce the composite primary outcome of cardiovascular death, stroke, or MI over an average of 4.7 years by 22%, (95% CI:14-30%),  $P < 0.00001$  compared to placebo<sup>(54)</sup>. Further, ramipril's effect appears to be greater than that accounted for by blood pressure lowering. Ramipril also prevented the progression of atherosclerosis<sup>(55)</sup>, and patients who were allocated to ramipril had a lower incidence of type 2 diabetes at the end of the trial<sup>(56)</sup>. As mentioned above, in HOPE there were 1,715 with symptomatic PAD and 2,118 had asymptomatic PAD. In symptomatic PAD patients, ramipril reduced the risk of a cardiovascular event in follow-up by 25% and by 27% among people with asymptomatic PAD after 4.5 years of treatment. Furthermore, the PROGRESS trial recently demonstrated that among individuals who have suffered a prior TIA or stroke, treatment with an ACE inhibitor perindopril alone, or together with the diuretic indapamide, reduced the risk of recurrent stroke by 28% (20-38%) regardless of whether the patients were hypertensive or normotensive at entry<sup>(57)</sup>. Therefore, ACE inhibitors should be considered for use in all patients with established vascular disease, whether or not blood pressure lowering is required. Other blood pressure lowering agents may be necessary to use when ACE

inhibitors cannot be tolerated, or when an additional blood pressure lowering agent is required (58).

### **MEDICAL TREATMENT FOR PAD SYMPTOMS**

The symptoms of intermittent claudication can resolve spontaneously, remain stable over many years, or progress rapidly to critical limb ischemia. Approximately 15 to 20% of patients with intermittent claudication will eventually develop critical leg ischemia which endangers the viability of the lower extremity and requires surgical revascularization or limb amputation<sup>(59)</sup>. Of this group, 26% of patients have progressive vascular disease and undergo at least one repeat ipsilateral revascularization procedure<sup>(60,61)</sup>. Therefore, although intermittent claudication is debilitating for patients, most patients do not have progressive leg symptoms and only 20% will require surgical intervention. Despite these figures the number one concern of patients with PAD does not appear to be their risk of future CV death, rather it is their limitation to walk and do their activities of daily living. Thus practitioners must be aware of the “treatment options” to improve walking distance among patients with PAD. The mainstay of therapy is regular walking. Regular walking does not have to be supervised but may be difficult to achieve outside of a supervised program. For patients with intermittent claudication who continue to have symptoms despite regular walking, some pharmacologic options do exist.

### **EXERCISE**

Patients with claudication have considerable difficulty in carrying out routine daily activities<sup>(62,63)</sup>. Many affected patients are so deconditioned from lack of exercise that they become housebound or dependent. Systematic reviews provide evidence that regular, supervised exercise three times a week for 30 minute sessions significantly improves the limitation of walking induced by claudication. The first systematic review found that exercise programmes (at least 30 min walking as far as claudication permits, at least 3 times weekly, for 3 to 6 months) versus no exercise increased both the initial claudication distance by 139 meters (4 RCTs; 94 people) and the absolute claudication distance by 179 meters (5 RCTs; 115 people)<sup>(62)</sup>. The

second systematic review (10 RCTs, including all those in the first review) found that exercise versus no exercise increased maximal exercise time by 6.5 minutes. (3 RCTs; 53 people)<sup>(63)</sup>. All the RCTs in the systematic reviews involved walking exercise. One subsequent RCT (67 included people with moderate to severe intermittent claudication, and compared arm versus leg exercise of similar intensity<sup>(64)</sup>. After 6 weeks, both training groups had similar improvements in initial claudication distance (122% with arm exercise v 93% with leg exercise) and absolute claudication distance (47% with arm exercise v 50% with leg exercise).

### **CILOSTAZOL**

As mentioned above Cilostazol is a phosphodiesterase inhibitor which is believed to have antiplatelet effects. Four RCTs have been conducted and demonstrate that cilostazol versus placebo reduced the risk of being rated as unchanged, worsened, or unsure at the end of each trial (4 RCTs; 1091 people; relative risk = 0.71, 95% CI 0.63 to 0.81), and significantly improved the initial claudication distance (by 38 to 80 m) and the absolute claudication distance (by 28 to 84m)<sup>(10)</sup>. None of the trials evaluated cilostazol beyond 24 weeks. Side effects of cilostazol include headache, diarrhoea, abnormal stools, palpitations, and dizziness. RCTs have found that other phosphodiesterase inhibitors (milrinone, vesnarinone) are associated with increased mortality in people with heart failure. Therefore the presence of LV dysfunction or previous CHF is a relative contraindication to cilostazol. Cilostazol is not available in Canada but is available in the United States (Pletal<sup>TM</sup>).

### **PENTOXIFYLLINE**

Pentoxifylline is a xanthine derivative and its precise mechanism of action is not known. It is thought to act by relaxing smooth muscle including those of the peripheral vessels thereby causing vasodilation or preventing spasm, and also has effects on the red blood cells and may promote deaggregation of platelets. Systematic reviews of many small RCTs have found that Pentoxifylline versus placebo increases the walking distance in people with intermittent claudication. Side effects of Pentoxifylline include sore throat, dyspepsia, nausea, diarrhea and vomiting<sup>(11)</sup>. A systematic review of 29 RCTs among people with Fontaine's classification

stage II or III intermittent claudication<sup>(65)</sup> in which pentoxifylline 600 to 1800 mg daily was used for 2 to 26 weeks found that Pentoxifylline significantly increased the absolute claudication distance by 48 meters, and these results were supported by a second systematic review in which the absolute claudication distance was reported to increase by 43 meters although this did not reach statistical significance<sup>(62)</sup>. Furthermore, a recently published RCT found no convincing increase in the absolute claudication distance with Pentoxifylline compared to placebo in people with intermittent claudication<sup>(23)</sup>. Therefore the available evidence is not good enough to clearly define the effects of Pentoxifylline, and its use is not encouraged.

### STATINS FOR SYMPTOMS

Two randomized trials also suggest improvements in walking performance in patients with PAD treated with statins<sup>(66-67)</sup>. In the largest study, by Mohler et al, 354 patients with PAD were randomized to receive placebo, atorvastatin 10 mg vs atorvastatin 80 mg per day. Atorvastatin 80 mg increased the initial claudication walking time by 81 sec vs placebo after an average 12 months treatment period<sup>(67)</sup>. The atorvastatin group also demonstrated a striking 84% reduction in vascular events (P=0.003). These data further support the use of statins to prevent cardiovascular events as well as having the potential to increase walking time among patients who suffer from intermittent claudication.

### CONCLUSIONS AND RECOMMENDATIONS

Given the strong evidence from randomized trials that aspirin, ACE-inhibitors, and Statins clearly reduce the risk of future vascular events by approximately a quarter each, and that their benefits appear to be largely independent, it is plausible to expect that, when used together with lifestyle changes, the cumulative risk reduction of future vascular events approaches 75%<sup>(68,69)</sup>. Given the high baseline risk of this population and the effectiveness of these interventions, a combination of multiple drug therapies, in concert with aggressive lifestyles changes (smoking cessation and regular walking) should be emphasized for all patients with PAD.

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**TABLE 8A: EXERCISE PRESCRIPTION FOR PATIENTS WITH INTERMITTENT CLAUDICATION**

#	Element
1	Clinicians should recognize that there are no data to support the efficacy of the informal "go home and walk" advice
2	A supervised hospital- or clinic-based program, which ensures that patients are receiving a standardized exercise stimulus in a safe environment, is effective.
3	Exercise training for claudication follows a pattern of short periods of walking that induce discomfort of moderate intensity, interspersed with short rest periods.
4	Clinical benefits can be observed as early as four weeks after the initiation of exercise and may continue after six months of participation. Improvements in walking ability continue beyond 6 months of supervised exercise.
5	Improvements in walking distance are sustained when patients continued to participate in an exercise maintenance program for an additional 12 months.

**TABLE 8B: SUMMARY OF RECOMMENDATIONS FOR ANTITHROMBOTIC THERAPIES**

#	Agent	Recommendation	Grade
1	Aspirin or Clopidogrel	Lifelong antiplatelet therapy with aspirin (75 to 325 mg/d) or clopidogrel (75 mg/day) in patients with or without clinically manifest coronary or cerebrovascular disease.	1A
2	Ticlopidine	Aspirin or Clopidogrel recommended over ticlopidine	1B
4	Cilostazol	Recommended for patients with disabling intermittent claudication who do not respond to conservative measures (risk factor modification and exercise therapy) and who are not candidates for surgical or catheter-based intervention.	1B
5	Pentoxifylline	Pentoxifylline is not recommended.	2B
6	Vitamin K Antagonists	Anticoagulant therapy is not recommended	2B

**TABLE 8C: SUMMARY OF EVIDENCE SUPPORTING MEDICAL THERAPIES TO REDUCE CARDIOVASCULAR EVENTS IN PAD**

<b>Grade</b>	<b>#</b>	<b>Class of Agents</b>
1A	1	Statins
1A	2	ACE Inhibitors
2B	3	Oral Hypoglycemics or Insulin in diabetics
1A	4	Antiplatelet Therapy (see table above)

There is evidence that ACE inhibitors may be effective irrespective of their blood pressure lowering effect, and therefore this class of drugs is a reasonable first choice if blood pressure lowering is required.

## **Percutaneous Endovascular Interventions for Peripheral Arterial Diseases**

**Dr Jacqueline Saw**

Clinical Assistant Professor of Medicine, UBC  
Vancouver General Hospital

Address for Correspondence:

Jacqueline Saw

Assistant Professor of Medicine,

University of British

Interventional Cardiology

Vancouver General Hospital

865 West 10<sup>th</sup> Ave

Vancouver, BC, V5Z 1L7

Tel: (604) 875-5547, Fax: (604) 875-5563

[jsaw@interchange.ubc.ca](mailto:jsaw@interchange.ubc.ca)

## INTRODUCTION

Percutaneous endovascular interventions (PEI) of lower extremity peripheral arterial disease (PAD) was first described by Dotter and Judkins in 1964<sup>(1)</sup>. Over the past few decades, dramatic evolutions of vascular imaging, interventional equipments and techniques have improved technical success and long-term patency. The two landmark milestones were the development of polyvinyl chloride balloon catheters by Gruentzig in 1974<sup>(2)</sup>, and the advent of stents in the 1980s. Other important advancements include hydrophilic wires, self-expanding stents, and larger diameter sheaths and catheters. Such developments, along with the incline in PAD prevalence, and progressive substitution of surgery with PEI for increasingly complex lesions, have led to a continual rise in PEI case volumes. The 2004 estimated prevalence of 27 million PAD patients in North America and Europe is projected to roughly double by year 2050<sup>(3)</sup>.

The indications for PEI are more liberal than surgical indications for PAD, predominantly due to the substantially less invasiveness, low peri-procedural complications, and shorter recovery time. Currently accepted indications for PEI include severe claudication that interferes with work or lifestyle despite pharmacologic and exercise therapies, chronic critical limb ischemia (rest pain, non-healing ulcer, or gangrene), and emergency treatment of acute limb ischemia. The TransAtlantic Inter-Society Consensus (TASC) Working Group recommends that type A iliac and femoropopliteal lesions are eligible for PEI, whereas type D lesions are most suitable for traditional surgery<sup>(4)</sup>. There are inadequate data for firm treatment recommendations of type B and C lesions, although the PEI approach is increasingly replacing surgery for initial revascularization of more complex lesions (including selected type D lesions). Although the TASC recommendations are internationally accepted, these were published in 2000 and are now relatively outdated with respect to PEI indications. Our consensus recommendations have expanded the role of PEI, taking into consideration recent improved outcomes (Tables 1 & 2). Readers should be mindful that the presence of patient medical comorbidities, operator skill and experience, and availability of laboratory peripheral equipments could affect PEI decision-making. Overall, PEI is a low-risk procedure and should be considered the first-line treatment strategy for suitable lesions. Moreover, PEI usually does not preclude future vascular surgery, and allows preservation of venous conduits for future cardiac or peripheral bypass grafting. Our

recommendations focus on patients with chronic severe intermittent claudication; the role of PEI in the setting of acute or chronic critical limb ischemia with the threat of limb loss has to be individualized.

Indications for Percutaneous Interventions of PAD (where technically feasible\*):

1. *Severe intermittent claudication that interferes with work or lifestyle despite pharmacologic and exercise therapies (Grade C, Level II)*
2. *Chronic critical limb ischemia (rest pain, non-healing ulcer, gangrene) (Grade C, Level II)*

Note: \*Technical feasibility depends upon lesion anatomy, operator experience, and equipment availability. Please refer to tables 1 & 2 for TASC classification of lesion anatomy and revascularization recommendations. Surgery is indicated if the lesion is unsuitable for or failed PEI. For interventions of infrapopliteal lesions, **please see section on Infrapopliteal Artery Intervention**

### **BALLOON ANGIOPLASTY & STENT**

Accepted conventional PEI of PAD includes the use of percutaneous transluminal angioplasty (PTA), stents, and thrombolysis for suitable lesions. As the focus of this document is predominantly on patients with intermittent claudication, the use of thrombolytic therapy for acute thrombotic lesions will not be discussed. Grading of recommendations for PTA and stents of PAD will be discussed according to anatomic arterial segments: iliac, femoropopliteal, and infrapopliteal. A brief discussion of novel devices will follow; however, because of relatively limited experience with these devices, definitive recommendations are not pursued.

### **ILIAC ARTERY INTERVENTION**

PEI of the iliac artery is associated with higher patency compared with more distal lower-extremity interventions. Success and long-term patency are dependent upon lesion types, locations, and symptom presentations. Non-occluded lesions tend to have better technical success and long-term patency. Claudicants tend to have greater patency than patients with

chronic critical ischemia. In addition, external iliac lesions have lower patency than common iliac lesions. Most of the studies that evaluated PTA alone<sup>(5-9)</sup> or stenting<sup>(10-26)</sup> were small, and non-randomized. The advantages of stent utilization following iliac PTA include improvement of immediate hemodynamic results, treatment of flow-limiting dissections, and provision of radial support for management of elastic recoil.

Procedural success for iliac PEI is over 95% for non-occluded lesions, and over 80% for occluded lesions. The 1-year primary patency ranges from 78% to 95% for iliac stenting, and from 59% to 94% for iliac PTA alone; occluded vessels are associated with lower patency. The overall 5-year primary patency is 64-76% with iliac stenting (weighted average 72%), and 56-78% with iliac PTA (weighted average 61%)<sup>(4)</sup>. The secondary patency is highly acceptable at 5 years, 78-95% with iliac stenting, and 61-85% with iliac PTA<sup>(4)</sup>.

Most operators currently favor routine iliac stenting as opposed to provisional stenting, although this is still somewhat controversial. Two randomized controlled trials have compared iliac PTA versus stenting. Richter et al showed superiority of Palmaz balloon-expandable stents compared to PTA in 185 patients, with 4-year patency of 94% and 69%, respectively<sup>(27)</sup>. In contrast, the Dutch Iliac Stent trial, which enrolled 279 patients, showed no benefit of routine stenting over PTA with provisional stenting (57% did not require stent). The initial hemodynamic success (ABI increment by >0.1), cumulative patency rates (70% vs. 71%), and 2-yr clinical success (77% vs. 78%) were similar<sup>(28)</sup>. However, in the meta-analysis by Bosch et al, which included over 2,100 patients in 14 studies (6 PTA, 8 stent studies), iliac stenting was associated with better long-term patency, without increasing complications. Technical success was non-significantly better with stenting (96% vs. 91%). Among patients with intermittent claudication, the 4-yr primary patency with PTA was 65% for stenosis and 54% for occlusions, and with iliac stenting was 77% for stenosis and 61% for occlusions. Overall long-term failure was reduced by 39% with stent placement<sup>(29)</sup>.

**RECOMMENDATIONS FOR ILIAC ARTERY PEI:**

1. *Provisional iliac stenting (either balloon-expandable or self-expanding) should be performed following suboptimal PTA results (flow-limiting dissection, residual stenosis >30%, residual mean pressure gradient >5mmHg, treatment of chronic total occlusions, restenosis of previous PTA) (Grade A, Level I)*
2. *More data is required before routine iliac stenting is recommended*

**FEMOROPOPLITEAL ARTERY INTERVENTION**

PAD involving the femoropopliteal arteries tends to be diffuse, involves multiple segments, and is frequently occlusive. Furthermore, the femoral artery is a superficial vessel and is prone to stress forces of torsion, compression, flexion and extension. These adverse characteristics, as well as the smaller luminal diameter compared with iliac arteries, result in less favorable outcomes of femoropopliteal PEI. Moreover, femoropopliteal PAD is often complicated by poor distal run-off (0 to 1-vessel arterial supply to the feet), creating a high-resistance and low-flow state that also dramatically reduces long-term results. Both early and late patencies are progressively worse with the diminution of patent distal vessels. In a retrospective case-series of 310 patients who received Palmaz stents, the 6-month restenosis rates were 0.5% for iliac artery, 11% for superficial femoral artery (SFA), and 20% for popliteal artery. The corresponding 4-year primary patencies were 86%, 65%, and 50%, respectively <sup>(30)</sup>.

The technical success rates are over 90% for PTA of femoropopliteal stenoses, and over 80% for long occlusions <sup>(31-33)</sup>. The Achilles heel, however, is the suboptimal long-term patency, with 5-yr primary patency between 40-60% for PTA <sup>(32,34-38)</sup>. Earlier studies have suggested that favorable characteristics include stenotic lesions (not occluded), intermittent claudication, nondiabetics, short-lesions, and good distal run-off (2-3 vessel) <sup>(32,38,39)</sup>. However, with the improved success in crossing chronic total occlusions (CTO), more recent data suggest that the most important predictive factor for long-term outcome is distal run-off <sup>(4,33,38)</sup>.

The use of stents for femoropopliteal interventions remains very controversial, as the long-term patency is not clearly superior to PTA. Cejna et al randomized 141 patients to PTA versus Palmaz stents for femoropopliteal occlusions. The initial technical success was superior with stenting (99% vs. 84%,  $p=0.009$ ), but there was no difference in primary or secondary patency rates at 1 or 2 years<sup>(40)</sup>. In a meta-analysis of 19 studies (~1,400 PTA or stent procedures) by Muradin et al, femoropopliteal PTA resulted in 3-yr primary patency of 30%, 48%, and 61% for occlusions with critical ischemia, occlusions with claudication, and stenoses with claudication, respectively. The use of femoropopliteal stents resulted in 3-yr primary patency of 63-66%, irrespective of lesion types and indications<sup>(41)</sup>. Most of the earlier studies included the use of balloon-expandable stents, which were limited by significant intimal hyperplasia, restenosis, external compressions and fractures (due to the superficial location of SFA).

Contemporary femoropopliteal interventions are now performed with self-expanding stents, which are more flexible and non-compressible, particularly relevant with the stress forces exerted on the SFA and popliteal artery. Recent small studies show promising results with these stents, 1-yr primary patency of ~85%<sup>(42,43)</sup>, and 3-yr primary patency of ~70%<sup>(44-46)</sup>. In fact, in a recent retrospective analysis comparing stainless steel balloon-expandable stents ( $n=123$ ) to nitinol (nickel-titanium) self-expanding stents ( $n=104$ ), primary patencies at 6-month, 1-yr, and 2-yr were 85%, 75%, 69% for nitinol stents, and 78%, 54%, 34% for stainless steel stents. Propensity-adjusted multivariable analysis showed that nitinol stents reduced restenosis with a hazard ratio of 0.44 ( $p=0.014$ ) compared with stainless steel stents<sup>(47)</sup>. Although these data are promising for self-expanding stents in the femoropopliteal arteries, randomized trials in comparison to PTA are not available to assess long-term outcomes. Therefore, most operators still favor a provisional stent approach when PTA results are suboptimal (residual stenosis >30%, flow-limiting dissection, or restenosis), particularly in this era of healthcare budget constraints.

With the growing use of stents in the femoropopliteal arteries, the phenomenon of stent fractures are increasingly recognized. In a recent study by Scheinert et al, a systematic

follow-up X-ray of 93 patients who underwent femoropopliteal stenting was performed<sup>(48)</sup>. At a mean follow-up of 10.7 months, stent fractures were identified in 37.2% (47/121) of treated legs, with a mean stent length of 15.7mm. More than 50% incidence of stent fracture was noted in patients with >16mm length of stents, or who have  $\geq 3$  stents placed. The primary patency rate at 12 months was significantly lower amongst patients with stent fractures (41.1% vs. 84.3%,  $p < 0.0001$ ). Thus, interventionalists should avoid excessively long stents if possible.

#### **RECOMMENDATIONS FOR FEMOROPOPLITEAL PEI:**

1. *Femoropopliteal stents should be deployed in the setting of suboptimal PTA results (residual stenosis >30%, flow-limiting dissection, mean pressure gradient >5mmHg, restenosis) (Grade B, Level I)*

#### **INFRAPOPLITEAL ARTERY INTERVENTION**

Percutaneous interventions of infrapopliteal arteries (anterior tibial, posterior tibial, and peroneal arteries) are usually reserved for acute or chronic critical limb ischemia. Unfortunately, infrapopliteal disease tends to be diffuse and occlusive, involving all 3 vessels, such that only 20-30% have suitable anatomy for PEI<sup>(49,50)</sup>. The reluctance to revascularize these distal vessels also stems from higher restenosis rates and procedural complications (e.g. dissections, embolization). Although restenosis rates can be up to 30-40% at 6-10 months<sup>(51,52)</sup>, limb salvage (preventing amputation) may be highly successful with infrapopliteal interventions (72-91%)<sup>(49,53,54)</sup>. Achieving at least 1-vessel run-off is often adequate for limb salvage<sup>(55)</sup>. These interventions improve tissue oxygenation for repair of non-healing ulcers or gangrene. Once healing occurs, even if long-term patency is not maintained, collateral flow may be sufficient to maintain tissue integrity. Another indication for infrapopliteal intervention is to improve distal run-off (and thus, long-term patency) in patients with multi-segmental PAD, who had or will be undergoing femoropopliteal percutaneous or surgical interventions for intermittent claudication. The use of stents in these smaller distal vessels in preventing restenosis is likely more important than iliac or femoropopliteal vessels. In a small randomized (n=32) study by Rand et al, the Carbostent™

(Sorin, Saluggia, Italy) had higher 6-month patency compared with PTA (81% vs. 51%) for infrapopliteal stenoses up to 3cm in length <sup>(56)</sup>.

#### **RECOMMENDATIONS FOR INFRAPOPLITEAL PEI:**

1. *Limb salvage of acute or chronic critical limb ischemia (Grade C, Level II)*
2. *To improve long-term patency of femoropopliteal interventions by improving distal run-off (Grade C, Level III)*

#### **NOVEL INTERVENTIONAL DEVICES**

The complexity of PAD percutaneous interventions with frequent long occlusions, diffuse multi-segmental arterial disease, and relatively high restenosis with femoropopliteal lesions, have prompted developments of novel devices to improve technical success and long-term patency.

#### **BRACHYTHERAPY**

Despite the initial popularity of brachytherapy for treatment of coronary artery disease in the 1990's, this modality has lost favor since the availability of drug-eluting stents. In fact, two commercial systems were removed from the market in 2004, leaving only the BetaCath system (Novoste Corporation, Norcross, GA) available for clinical coronary use. However, this system is not approved for peripheral arterial indications, and is not useful for large peripheral arteries as the beta particle penetrates vessels >4mm very poorly. The majority of brachytherapy trials for PAD utilized the gamma system, but this is also no longer available for clinical use. Therefore, even though studies have demonstrated effectiveness of gamma-brachytherapy for both de novo and restenotic femoropopliteal lesions <sup>(57-63)</sup>, they are irrelevant to current management of PAD. Brachytherapy is unlikely to be revived for clinical use, particularly with its many limitations: relatively cumbersome, requires precautionary radiation shielding, costly equipments, associated with early and late thrombotic complications.

## DRUG-ELUTING STENTS

Although the use of drug-eluting stents is widely accepted for percutaneous coronary interventions, its use for PAD interventions remains unproven. In the SIROCCO-1 trial, 36 patients with SFA disease were randomized to sirolimus-coated SMART® versus bare-metal SMART® stents. The restenosis rate at 6 months was only 6% in the sirolimus group, and in-stent mean luminal diameter was larger than the bare-metal stent group<sup>(64)</sup>. At 18 months, there was 0% restenosis in the slow-release sirolimus group, which prompted the randomized SIROCCO-2 study (n=57) evaluating the slow-release sirolimus SMART® stents. However, there were no significant difference in the 6-month angiographic or 9-month ultrasound restenosis rates<sup>(65)</sup>. Another peripheral self-expanding stent being evaluated prospectively for femoropopliteal artery in the United States is the Zilver® PTX paclitaxel-eluting stent (Cook Incorporated, Bloomington, IN). Until further data is available, the use of drug-eluting stents for lower-extremity PAD is not recommended.

## SUBINTIMAL ANGIOPLASTY

PEI of CTO are challenging for PAD, with frequently long segments of occlusion consisting of hard fibrotic and calcified atherosclerotic plaques. Wiring into subintimal planes are often unavoidable despite the best of efforts. Over the past 2 decades, intentional subintimal angioplasty had gained popularity, since long occlusions can be tackled and procedural time can be markedly shortened. In this approach, the subintimal space is intentionally entered with the guidewire, and the dissection is extended throughout the length of the occlusion. Beyond the occlusion, the operator then attempts to reenter the true lumen. Failure of reentry into the true lumen (up to 25%) is the predominant cause of technical failure of subintimal angioplasty<sup>(66)</sup>. This step may be facilitated by special catheters to localize the true lumen, such as the intravascular ultrasound-guided CrossPoint™ TransAccess catheter (Medtronic, Minneapolis, MN)<sup>(66)</sup>, which may be used for various vascular beds, e.g. iliac, SFA, popliteal, subclavian arteries. This device is equipped with a 24-gauge needle to puncture and allow entry of a 0.014" guidewire into the true lumen with ultrasound-guidance. Following reentry, stents are then deployed at both the entrance and exit sites, and often throughout the length of the occlusion. The most experience with subintimal angioplasty is with

femoropopliteal occlusions, with overall procedural success reported at 74-92%, 1-yr primary patency 22-92%, and 2-3 yr primary assisted patency 19-58%<sup>(67-70)</sup>. There is a learning curve associated with subintimal angioplasty<sup>(68)</sup>, and this technique is usually limited to poor surgical candidates with critical limb ischemia<sup>(71)</sup>. However, more recent data is promising, with subintimal angioplasty achieving similar short term primary patency results as bypass surgery<sup>(72,73)</sup>. Randomized trial data is still required before this technique receives widespread acceptance as the treatment for long occlusive lesions.

### **ATHERECTOMY DEVICES**

Atherectomy devices have also been utilized in the peripheral arteries for excision of atherosclerotic plaques. Initial data showed technical success of 93% in 17 patients with infra-genicular stenoses, however, long-term data is not available<sup>(74)</sup>. Currently, only the SilverHawk™ atherectomy device (FoxHollow Technologies, Redwood City, CA), which uses carbide blade, is approved for PAD in the United States. This device will not be available in Canada till at least mid-2005. Randomized trials comparing atherectomy to stenting is necessary to evaluate long-term efficacy.

### **THROMBECTOMY DEVICES**

Treatment of acute critical limb ischemia with thrombotic lesions may theoretically be facilitated with thrombectomy devices. The AngioJet® Xpedior® (Possis Medical, Minneapolis, MN) which is approved for peripheral indication, uses the Venturi effect to suction in and fragment surrounding thrombus. The KPS Rinspiration™ System (Kerberos Proximal Solution, Mountain View, CA), on the other hand, is a hand-activated mechanical device that simultaneously aspirate and irrigate the treatment site. This device is currently available for peripheral indication in the United States, but not in Canada. Both these devices are not useful for chronic thrombotic lesions. In a retrospective study of 99 patients with lower-extremity acute thrombosis (within 14 days of symptom onset), the AngioJet® device was successful in thrombus removal in 71% of patients, with 30-day amputation rate of 4%<sup>(75)</sup>.

## CRYOPLASTY

Cryoplasty is an experimental technique that utilizes cooling of the injured arterial wall to induce apoptosis of smooth muscle cells, theoretically reducing neointimal proliferation. The PolarCath™ system (CryoVascular Systems, Los Gatos, CA) has an angioplasty balloon filled with nitrous oxide to lower the inflating balloon temperature to  $-10^{\circ}\text{C}$ . The ongoing PVD-CHILL study, which is a 102-patient registry using this device, had preliminary promising results with 85% of lesions remaining patent at 1 year (presented at the 2003 Society of Interventional Radiology Meeting).

## DEVICES TO CROSS CHRONIC TOTAL OCCLUSIONS

Several other devices have been developed to improve the success of guidewire crossing of CTO, and are approved for use in the peripheral arteries. The Safe-Cross™ guidewire and support catheter (IntraLuminal Therapeutics, San Diego, CA) uses optical coherence reflectometry and radiofrequency microablation through the guidewire, to enable navigation through and cross total occlusions. This system is available for both coronary and peripheral use in the United States, but not in Canada. The Frontrunner™ system (LuMend Corporation, Redwood City, CA) utilizes the controlled blunt dissection technique to separate atherosclerotic plaque, creating a channel to enable guidewire to cross total occlusions. This device is available for coronary use in the United States, but not for PAD in North America. Laser angioplasty of PAD was initially abandoned in the 1980s because of higher complications. With improvements in the laser technology, interests have been renewed for use in CTO. The excimer laser produces pulsed bursts of ultraviolet light energy that penetrates  $\sim 50\mu\text{m}$  and ablates tissues. The Excimer Laser CLiRpath® catheters and CVX-300® system (Spectranetics Corporation, Colorado Springs, CO) are available for use for total occlusions of infrainguinal PAD that cannot be crossed with standard guidewires. In Canada, this device is available for coronary use, but not for PAD. In a study by Scheinert, the reported success rate was 90% for crossing 411 CTO of the SFA (mean occlusion length 19.4cm) with this device<sup>(76)</sup>. Importantly, all these above devices are to be used in conjunction with PTA with or without stenting. Although technical success may be higher

with these niche devices, long-term patency has not been shown to be better than conventional PTA.

### **COVERED STENTS**

There was some initial enthusiasm regarding the use of covered self-expanding stents (e.g. with polytetrafluoroethylene) for lower-extremity PAD, with hopes that they may reduce distal embolization and restenosis. However, recent studies had shown unfavorable patency rates, particularly for stent-grafts >10cm in length<sup>(77)</sup>. Intimal hyperplasia was particularly problematic at the proximal and distal edge of the stent-graft. Furthermore, stent-graft occlusion occurred in over 70% of this small series of 17 femoropopliteal interventions<sup>(77)</sup>. Thus, covered stents are not routinely used for lower-extremity PEI.

### **COMPLICATIONS WITH PAD PEI**

The rate of complications associated with PEI is dependent on several factors, such as operator skill and experience, case complexity, and devices used. With respect to PTA alone, reported complications range from 3 to 33%, with the majority of these being minor. In a review by Becker et al, the incidence of major complications (prolonged hospitalization, permanent adverse sequelae, or death) involving 4662 PTA procedures was 5.6% (2.5% required surgery, 0.2% suffered limb loss, and 0.2% died)<sup>(78)</sup>. More recently, Matsi et al found a 5% major complication rate among 410 lower extremity PTA, with 2% requiring surgery<sup>(79)</sup>. In a more contemporary single-center retrospective series (n=550) by Papavassiliou et al, incidence of peripheral embolization was 4.5%, perforation 4.0%, and only 0.5% of patients required surgery<sup>(80)</sup>.

### **FINAL SUMMARY**

The field of percutaneous endovascular intervention of PAD has made dramatic strides over the past four decades. These technological advances improved procedural success and long-term patency. Furthermore, the percutaneous approach is less invasive, has low complication rate, and allows shorter hospital stay and recovery time. Therefore, percutaneous interventions are increasingly chosen as the initial treatment of more complex lesions, which

used to be exclusively tackled by surgery. Adjunctive to the use of conventional balloon angioplasty and stents (both balloon-expandable and self-expanding), novel devices targeted at reducing restenosis and treatment of chronic total occlusions are projected to further improve immediate and long-term outcomes. Many such devices are still considered experimental, and randomized trial data are eagerly anticipated.

**FINAL RECOMMENDATIONS**

<b>CCS Consensus Recommendations</b>	<b>Level of Evidence</b>
<b>1. Clinical Indications for percutaneous interventions of PAD</b> (where technically feasible*)	
a. Severe intermittent claudication that interferes with work or lifestyle despite pharmacologic and exercise therapies	Grade C, Level II
b. Chronic critical limb ischemia (rest pain, non-healing ulcer, gangrene)	Grade C, Level II
Note: *Technical feasibility depends upon lesion anatomy, operator experience, and equipment availability. See tables 1 & 2 for revascularization recommendations based on lesion anatomy classification. Surgery is indicated if the lesion is unsuitable for or failed PEI. Please see recommendation 4 for infrapopliteal lesions.	
<b>2. Recommendations for iliac artery interventions</b>	
a. Provisional iliac stenting (either balloon-expandable or self-expanding) should be performed following suboptimal PTA results (flow-limiting dissection, residual stenosis >30%, residual mean pressure gradient >5mmHg, treatment of chronic total occlusions, restenosis of previous PTA)	Grade A, Level I
<b>3. Recommendations for femoropopliteal interventions</b>	
a. Femoropopliteal stents should be deployed in the setting of suboptimal PTA (residual stenosis >30%, flow-limiting dissection, mean pressure gradient >5mmHg, or restenosis)	Grade B, Level I
<b>4. Recommendations for infrapopliteal interventions</b>	
a. Limb salvage of acute or chronic critical limb ischemia	Grade C, Level II
b. To improve long-term patency of femoropopliteal interventions by improving distal run-off	Grade C, Level III

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**TABLE 1. CCS RECOMMENDATION OF MANAGEMENT OF ILIAC ARTERY LESIONS**

<b>Lesion</b>	<b>Description</b>	<b>Recommendation</b>
Type A	- Single stenosis <3cm of the CIA or EIA	PEI first-line treatment
Type B	- Single stenosis 3-10cm, not extending into CFA - Total of 2 stenoses <5cm in the CIA and/or EIA, not extending into CFA - Unilateral CIA occlusion	PEI first-line treatment
Type C	- Bilateral 5-10cm stenosis of CIA and/or EIA, not extending into CFA - Unilateral EIA occlusion, not extending into CFA - Unilateral EIA stenosis extending into CFA - Bilateral CIA occlusion	PEI may be attempted for patients at high-risk for surgery
Type D	- Diffuse, multiple unilateral stenoses involving the CIA, EIA, and CFA (>10cm) - Unilateral occlusion involving both CIA and EIA - Bilateral EIA occlusions - Diffuse disease in the aorta and both iliac arteries - Iliac stenosis in patients with abdominal aortic aneurysm or lesion requiring aortic or iliac surgery	Surgery preferred

Based on TASC classification (4). CIA, common iliac artery; CFA, common femoral artery; EIA, external iliac artery; PEI, percutaneous endovascular intervention; TASC, TransAtlantic Inter-Society Consensus.

**TABLE 2. CCS RECOMMENDATION OF MANAGEMENT OF FEMOROPOPLITEAL ARTERY LESIONS**

<b>Lesion</b>	<b>Description</b>	<b>Recommendation</b>
Type A	- Single stenosis <3cm	PEI first-line treatment
Type B	- Single stenosis 3-10cm not involving distal popliteal - Heavily calcified stenoses up to 3cm - Multiple lesions, each <3cm (stenosis/occlusion) - Single or multiple lesions in the absence of continuous tibial run-off to improve inflow for distal surgical bypass	PEI first-line treatment
Type C	- Single stenosis or occlusion >5cm (or >10cm) - Multiple stenoses or occlusions, each 3-5cm, with or without heavy calcification	PEI may be attempted for patients at high-risk for surgery
Type D	- Complete CFA or SFA occlusion, or complete popliteal and proximal trifurcation occlusions	Surgery preferred

Based on TASC classification (4). CFA, common femoral artery; PEI, percutaneous endovascular intervention; SFA, superficial femoral artery; TASC, TransAtlantic Inter-Society Consensus.

## **Non-Medical Management of Chronic Limb Ischemia**

**Thomas L. Forbes, MD**  
Division of Vascular Surgery  
London Health Sciences Centre &  
The University of Western Ontario  
London, ON

**Kenneth A. Harris, MD**  
Division of Vascular Surgery  
London Health Sciences Centre &  
The University of Western Ontario  
London, ON

### **INTRODUCTION**

The choice of treatment for a patient presenting with chronic limb ischemia must be based on a thorough knowledge of the natural history of the presenting signs and symptoms, the anatomic details of the causative lesion, the short and long term durability of the proposed intervention and the patient's comorbidities.

Patients with claudication have a more benign natural history with respect to the limb. The 5-year survival is 70% and it is 50% at 10 years <sup>(1)</sup>. The risk of limb loss is only 5% at 5 years with only 20% of patients requiring operative intervention for limb salvage. Despite the progressive nature of the atherosclerotic disease process these figures have been demonstrated by many natural history trials. Randomized control trials have demonstrated that across a population of patients the introduction of an exercise program and risk factor management provides a durable improvement in symptoms.

It is recommended that intervention in patients presenting with intermittent claudication is therefore discretionary and used mainly for patients who are unable to work, or have a very poor quality of life because of symptoms and have failed conservative management.

Those patients with a more advanced atherosclerosis (i.e. Critical Limb Ischemia) present with a constellation of signs and symptoms that suggest a more aggressive type of atherosclerosis

putting the limb at higher risk. Pain in the foot or toes at night (night pain) or pain at all times in the distal extremity (rest pain) have critical limb ischemia. They may also present with small ulcers, gangrenous changes, or diabetic infections in the toes or foot. There have been no recent natural history studies because it is accepted that these patients deserve intervention for limb salvage. Studies performed on patients who are deemed too high risk to undergo intervention suggest that the risk of limb loss is as high as 40% at 1 year. These patients have a higher 5-year mortality rate of 50% at 5 years, again largely cardiac in nature. Most would consider the presence of chronic critical limb ischemia an indication for intervention for limb salvage.

## INTERVENTIONS

A functional classification of available non-medical interventions for arterial occlusive disease follows:

- Inflow – diseases affecting the aortoiliac segment (vast majority in infra renal aortoiliac segment)
  - Anatomic intervention or reconstruction
    - Dilate ± stent
    - Endarterectomy
    - Bypass
  - Extra anatomic Bypass
- Outflow – diseases of the common femoral artery and beyond
  - Dilate ± stent
  - Bypass

As atherosclerosis is a generalized disease many patients will present with multilevel disease. The proximal lesions should be addressed initially and if the hemodynamic significance is questioned then pressure measurements may be made across them before and after vasodilatation.

## INFLOW RECONSTRUCTION

To assist in the decision on the most appropriate intervention for inflow disease a number of classifications have been introduced. The most useful is that of the TASC conference<sup>(1, 2)</sup>:

**TABLE 10A: TASC RECOMMENDATION:  
 MORPHOLOGICAL STRATIFICATION OF ILIAC LESIONS**

<b><i>TASC Type iliac lesions</i></b>	<b><i>Morphological stratification</i></b>
<b>Type A</b>	- single stenosis <3cm of the CIA or EIA (unilateral/bilateral)
<b>Type B</b>	- single stenosis 3-10cm in length, not extending into CFA - total of two stenoses <5cm long in the CIA and/or EIA and not extending into the CFA - unilateral CIA occlusion
<b>Type C</b>	- bilateral 5-10cm long stenoses of the CIA and/or EIA, not extending into the CFA - unilateral EIA occlusion not extending into the CFA - unilateral EIA stenosis extending into the CFA - bilateral CIA occlusion
<b>Type D</b>	- diffuse, multiple unilateral stenoses involving the CIA, EIA, and CFA (usually >10cm) - unilateral occlusion involving both the CIA and EIA - bilateral EIA occlusions - diffuse disease involving the aorta and both iliac arteries iliac stenoses in a patient with an abdominal aortic aneurysm or other lesion requiring aortic or iliac surgery

**Abbreviations:** CIA=common iliac artery, EIA=external iliac artery, CFA=common femoral artery.

For TASC type A lesions endoluminal therapy is indicated and for type D lesions surgical therapy is indicated. For Types B & C lesions evaluation needs to be made on an individual basis on comorbidities, estimated durability and other patient factors <sup>(2)</sup>.

**SURGICAL INTERVENTION**

In performing a bypass operation the major technical considerations involve:

- a. selecting an “inflow” artery with uncompromised flow from the heart
- b. selection of an “outflow” vessel that must be capable of carrying blood to the affected ischemic tissue and permit sufficient flow to prevent graft thrombosis
- c. selection of an appropriate conduit must. Either Dacron or ePTFE may be chosen in the aortoiliac segment.

### ***ENDARTERECTOMY***

Recently interest has been rekindled in the procedure of endarterectomy whereby the occluding atherosclerotic plaque is removed in a semi-blind fashion from the affected arteries. The procedure is technically more demanding than bypass although results in the appropriate hands are adequate. Many lesions that might be considered as appropriate for endarterectomy may be treated as well with endoluminal therapy. Endarterectomy results in a 5 year patency of 60 – 90%.

### **ANATOMIC BYPASS (ABF)**

A bypass graft placed in a configuration and course that follows the usually arteries is referred to as an anatomic bypass. The incidence of bilaterality of aortoiliac disease suggests that if there is an indication to bypass one iliac artery then a bilateral procedure should usually be carried out. The gold standard procedure is the aortobifemoral bypass whereby a synthetic graft is placed from the infrarenal abdominal aorta to both common femoral arteries. The proximal anastomosis may be done in an end-to-end or end-to-side fashion. The indications for end-to-end anastomosis are the association of aneurysmal disease and aortic occlusion. In the presence of superficial femoral artery occlusions the grafts may be extended down the profunda femoris arteries if there is a stenotic process at the origin. The reporting of patency on a bilateral procedure is divided into limb based and patient based and is as follows:

**TABLE 10B: PATENCY AT 5 AND 10 YEARS AFTER AORTOBIFEMORAL BYPASS<sup>3</sup>**

Indication	5 year (% patency)		10 year (%patency)	
	Claudication	CLI	Claudication	CLI
Limb Based	91.0	87.5	86.8	81.8
Patient Based	85.8	80.4	79.4	72.1

In the presence of multi-level disease it has been estimated that 21 – 25% of patients will eventually require additional distal bypass grafting for limb salvage but only 4% require simultaneous proximal and distal grafts. <sup>(4)</sup>

#### **EXTRA ANATOMIC BYPASS**

At times the abdominal aorta is not accessible as an inflow artery due to infection, previous intraabdominal procedures (the hostile abdomen), or major comorbidities. In such cases the axillary artery may provide an inflow site from the infraclavicular portion. The graft may be configured as an axillofemoral or an axillobifemoral bypass depending upon the need for flow to one or both legs. These secondary procedures are usually recommended for limb salvage only.

In cases of truly unilateral disease a major intraabdominal procedure may be avoided by using the normal iliac or femoral artery as a donor artery for the contralateral affected leg. The graft may be tunneled subcutaneously or deep to the rectus muscles. In high risk patients needing operation for limb salvage this may occasionally be accompanied by dilatation of a stenosis in the donor iliac artery.

**TABLE 10C: PATENCY RATES AT 5 YEARS (STUDIES WITH >50% OF PATIENTS WITH CLI)<sup>5</sup>**

<i>Procedure</i>	<i>5 year % patency</i>
Axillo uni femoral bypass	44-79
Axillo bi femoral bypass	50-76
Femoral femoral bypass	55-92

Other inflow arteries such as the ascending and descending thoracic aorta have been used but reports have been largely anecdotal.

Complications reported after aortoiliac reconstruction are documented in the following table <sup>(1,2)</sup>.

**TABLE 10D: COMPLICATIONS REPORTED AFTER AORTOILIAC RECONSTRUCTION**

<i>Complication</i>	<i>Incidence (%)</i>
Myocardial infarction	0.8-5.2
Mortality	0-3.3
Bowel ischemia	1.1
Renal failure	0-4.6
Ureteral injury	1.6
Spinal cord ischemia	0.25
Graft infection	0.1-1.3
Aortoenteric fistula	0.1-0.5
Lymph fistula	1.5-3.5
False aneurysm	3-5
Altered sexual function	20

## **OUTFLOW RECONSTRUCTION**

Following confirmation of adequate lower extremity arterial inflow, or achievement of such via an inflow procedure, outflow procedures or infrainguinal revascularization procedures can be considered. However along with reviewing patients' comorbidities it is essential to determine their presenting complaints and symptoms when considering infrainguinal revascularization.

## **FUNCTIONAL LOWER LIMB ISCHEMIA (CLAUDICATION)**

With a nondiseased aortoiliac segment the most common lesion resulting in claudication is that of the superficial femoral artery. Historically, many bypass operations have been performed for this lesion and indication. The most common operation being a synthetic bypass from the common femoral artery to the above knee popliteal artery. More recently there has been much debate regarding the choice of conduit in this position, with many surgeons favoring autogenous vein over synthetic material with such bypasses to the above knee popliteal artery.

Corresponding five year patencies have been reported between 78 – 87% for venous conduits and 67 – 83% for PTFE <sup>(6, 7)</sup>.

Although these bypass procedures are successful in eliminating claudication symptoms and can have reasonable mid term patency rates, they do not change the underlying progression of atherosclerotic disease. This is a major concern as thrombosis of these grafts inevitably results in acute limb threatening ischemia with significant risks of limb loss and mortality.

As a result, the current approach to claudicants with isolated superficial femoral artery disease is to employ risk factor modification and best medical management that includes an exercise program and smoking cessation. In such a situation, treatment of the systemic atherosclerosis is more important than that of the isolated superficial femoral artery lesion as the five year mortality risk (30%) greatly outweighs that of limb loss (5%) <sup>(1)</sup>. As a result bypasses to the above knee popliteal artery for claudication are presently performed rarely and should only be considered in the rare patient who is truly unable to meet his/her daily work responsibilities or has a very poor health related quality of life.

### **CRITICAL LOWER LIMB ISCHEMIA (LIMB THREATENING)**

Anatomically chronic limb threatening ischemia most commonly presents with disease of the superficial femoral artery and the tibial and peroneal vessels. This is especially common in diabetics with their propensity for tibial-peroneal atherosclerotic involvement, along with small pedal vessel disease. Clinically these patients present with pedal rest pain, non-healing sores or ulcers, gangrenous changes, and/or diabetic foot infections. As limb loss can occur in up to half of these patients without intervention, these symptoms should result in prompt referral for consideration of revascularization.

Given this risk of limb loss most patients with acceptable medical comorbidities are candidates for revascularization procedures for limb salvage. With the often more diffuse nature of this disease, as opposed to those with solely claudication, it is necessary to construct bypasses utilizing the infrapopliteal arteries (anterior and posterior tibial arteries and peroneal artery) as outflow vessels.

Differing from the above knee popliteal artery there is little controversy surrounding the preferred conduit in such infrapopliteal bypass procedures. Numerous studies have confirmed superior patency with autogenous venous conduits compared to synthetic conduits. A meta-analysis reported a five year patency of autogenous bypasses for critical limb ischemia of 66% compared with only 33% for infrapopliteal PTFE bypasses<sup>(8)</sup>. Most frequently the ipsilateral greater saphenous vein is utilized in either a reversed or in situ configuration. If this vein is unavailable other venous alternatives include contralateral greater saphenous vein, short saphenous vein, and arm vein.

Infrapopliteal synthetic bypasses for critical limb ischemia should never be performed primarily, but are used when venous alternatives are exhausted. Recognizing the poor patency rates of such procedures, several investigators have described adjunctive surgical procedures including the creation of distal arteriovenous fistulae and various configurations of distal anastomotic vein patches or cuffs. Although studies have been inconclusive regarding the benefit of these

adjunctive procedures, they are widely employed in such synthetic bypasses that are often seen as a last effort to avoid limb loss.

Complications of infrainguinal bypass procedures are reported in the following table <sup>(1, 2)</sup>:

**TABLE 10E: COMPLICATIONS OF INFRAINGUINAL BYPASS PROCEDURES**

<i>Complication</i>	<i>Incidence (%)</i>
Mortality	1.3-6
Myocardial infarction	1.9-3.4
Wound:	
-vein	10-30
-prosthetic	18
-exposure/blowout	9.5/1.6
Infection:	
-vein	1.36
-prosthetic	3.56
Leg edema	50-100
Lymph leak	0.5-1.8
Acute limb ischemia	1-2

**ENDOLUMINAL INTERVENTIONS**

Recently the use of endovascular procedures has been increasingly reported in the infrainguinal arterial segment <sup>(9)</sup>. Such procedures include subintimal angioplasty and standard angioplasty with or without stent insertion. Excellent primary technical success rates have been reported. However mid and long term patency and limb salvage rates have often been absent, or at best conflicting. These techniques are further discussed in an accompanying chapter.

At present, although these less invasive procedures are attractive and promising, there is insufficient data to support liberal utilization. Currently their use in situations of critical limb

ischemia can be supported either as a primary procedure or as an adjunct to a bypass based on the high risk of limb loss. However in the absence of longer term follow up and data regarding restenosis rates these procedures should not be routinely used in claudicants. This may change as experience with such techniques as subintimal angioplasty increases.

#### **ADJUNCTIVE MEDICAL TREATMENT**

Following infrainguinal revascularization procedures medical management should be employed as a risk reduction strategy for coronary and cerebrovascular events, as well as optimizing graft patency and limb salvage rates.

Antiplatelet therapy via low dose aspirin is extensively used in risk reduction and all patients who have undergone lower extremity revascularization procedures, or those with claudication for that matter, should be on some form of antiplatelet therapy. The role of aspirin versus warfarin anticoagulation in infrainguinal graft patency has been recently reviewed in a randomized study<sup>10</sup>. Although more bleeding complications occurred in patients treated with warfarin, oral anticoagulation offered improved patencies with autogenous venous bypasses while aspirin alone was better for the prevention of synthetic graft thrombosis.

Of particular note from this Dutch study was the target level of anticoagulation (INR: 3.0-4.5). With the significant risk of bleeding complications with such a level of anticoagulation close observation and monitoring is essential. These results may not be reproducible in clinical practice as such control may not be possible outside of a study situation.

Presently we recommend postoperative warfarin anticoagulation (target INR: 2-3) with synthetic infrapopliteal bypasses, redo bypasses in the face of previous graft thrombosis, and in situations where the inflow artery, the outflow vessels, or the venous conduit is of dubious quality.

#### **POSTOPERATIVE SURVEILLANCE**

In order to maintain optimal patency rates following infrainguinal revascularization procedures, patients should undergo surveillance consisting of ankle-brachial indices and duplex studies.

Following autogenous venous conduits ankle-brachial indices and duplex studies of the inflow and outflow arteries, anastomoses and the vein graft itself should be performed to identify any intraluminal lesions which may limit long term patency. With identification of such lesions secondary procedures can then be performed.

Following synthetic bypasses ankle-brachial indices should be performed solely, as duplex imaging has limited benefit and ability to identify intraluminal synthetic graft lesions.

### **OTHER TREATMENTS**

A number of other therapies have been suggested throughout the years to treat critical limb ischemia. For those at risk of limb loss the ideal treatment is surgical or interventional revascularization but at times this is not possible.

In some studies from the last decade there has been a suggestion that prostinoids such as PGE<sub>1</sub> may have some benefit and that iloprost may lead to improved healing. Prediction of which patient will benefit from this type of therapy is difficult and in North America it has largely fallen out of favor.

Some drugs have been shown not to be effective in reducing the risk of limb loss in patients with critical limb ischemia. These include: vasodilating drugs, antiplatelet agents, anticoagulants, and defibrinating agents. Results with low molecular weight heparin are inconclusive. Similarly results for naftidrofuryl and pentoxifylline are mixed and neither should be used as first line therapy for critical limb ischemia.

Cochrane reviews suggest that spinal cord stimulation may reduce the risk of amputation in those patients with critical limb ischemia and no possibility of revascularization. Hyperbaric oxygen therapy may have some benefit in patients with diabetic foot ulcers. Chelation therapy is no more effective than placebo in the treatment of critical limb ischemia. Gene therapy, although having some initial promising reports, has not progressed sufficiently to be recommended <sup>(11)</sup>.

In conclusion there is poor evidence to support treating patients with critical limb ischemia with spinal cord stimulation and only a limited proportion of patients will respond to prostinoids. The results of other pharmacotherapies are less than ideal <sup>(12)</sup>.

#### **SUMMARY**

When considering non-medical management options, it is essential to determine the severity of the chronic limb ischemia and differentiate between functional and limb threatening chronic limb ischemia or critical limb ischemia.

The vast majority of patients with functional lower extremity ischemia, or claudication, are best treated with such conservative measures as smoking cessation, walking programs, risk factor modification and medical management. These measures are discussed more extensively in other chapters. Surgical or interventional approaches should be considered in the few patients whose claudication prevents them from meeting their work and everyday responsibilities and contributes to a very poor quality of life.

Those with limb threatening ischemia suffer from such symptom complexes as rest pain, gangrene, non-healing ulcers or sores, and diabetic foot infections. These patients should be urgently referred for consideration of revascularization procedures. The choice of surgical versus interventional revascularization options will depend on the anatomy of the occlusive disease and patient comorbidities.

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## RECOMMENDATIONS

Recommendations are summarized in the following table.

**TABLE 10F: RECOMMENDATIONS**

#	Recommendation	Grade
1	The majority of claudicants should undergo risk factor modification, medical management and a walking program rather than revascularization procedures	1B
2	Only those claudicants who suffer from severely limiting claudication should be considered for revascularization procedures	1B
3	Patients with critical limb ischemia should be considered for revascularization procedures	1A
4	An aortobifemoral bypass grafting offers superior long term patency compared to extraanatomic bypasses as an inflow procedure	2B
5	Infrainguinal bypasses to the tibial vessels should be performed with autogenous conduits as they offer superior patency to synthetic conduits	1A
6	Antiplatelet therapy and, in select instances, warfarin anticoagulation is recommended following lower extremity revascularization	1B
7	Noninvasive imaging and graft surveillance is recommended following infrainguinal revascularizations to identify failing grafts, and to allow for possible reintervention	2B
8	Life long atherosclerotic related risk factor modification and medical therapy is recommended following lower extremity revascularization	1A

## **Perioperative Risk Assessment of Patients Undergoing Major Non-Cardiac Vascular Surgery**

**Finlay A. McAlister, MD MSc FRCPC**

Division of General Internal Medicine  
University of Alberta Hospital  
Edmonton, AB

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## INTRODUCTION

Each year in Canada, nearly 500,000 patients undergo non-cardiac surgery- assuming that the distribution of surgeries are similar in Canada and the United States, approximately 40,000 of these operations are for peripheral arterial disease (PAD).<sup>(1)</sup> As the risk factors for PAD are the same as those for coronary disease, it is not surprising that up to 60% of patients presenting for PAD surgery have significant stenoses (i.e. >70%) in at least one coronary artery- importantly, in almost two thirds of these patients, their coronary disease was clinically silent.<sup>(1,2)</sup> As vascular surgical procedures are often associated with substantial fluid volume shifts and fluctuations in systemic blood pressure, it is also not surprising that perioperative cardiac complications occur in 4% to 15% of patients who undergo major non-cardiac vascular surgery (a category which includes all forms of PAD surgery except carotid endarterectomy).<sup>(3-10)</sup> It should be recognized that the complication rates after infrainguinal surgery are just as high, and in some studies higher, than for aortic surgery.<sup>(9,10)</sup>

General internists and cardiologists are frequently asked to perform preoperative assessments on patients who are scheduled to undergo major vascular surgery. The purpose of these assessments should not be to “clear” someone for surgery, but rather to evaluate the severity and stability of a surgical candidate’s medical conditions and, where necessary and possible, to optimize their management before surgery. The preoperative assessment should be seen as a venue for the provision of risk estimates to the surgeon, patient, and anaesthetist which can be used to inform decision making about the proposed surgery. This task is particularly challenging since the standard models of cardiac risk assessment developed for general surgery patients<sup>(11-13)</sup> were derived in populations in whom the prevalence of coronary disease is substantially lower than in PAD patients and thus these risk prediction equations underestimate risk in those undergoing vascular surgery.<sup>(14)</sup>

In developing the recommendations in this chapter, we used the 2002 American College of Cardiology/American Heart Association guidelines<sup>(15)</sup> as a starting point since they (i) are comprehensive, (ii) provide a consensus of expert opinion for the many aspects of perioperative assessment for which there is little high quality evidence, and (iii) have been

independently validated and shown to accurately predict adverse cardiac events in patients undergoing vascular surgery.<sup>(16-19)</sup> As outlined below, where appropriate, the ACC/AHA guidelines have been modified to reflect new evidence identified by a systematic literature review. In brief, we carried out literature searches in MEDLINE, the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register, and Clinical Evidence which were limited to English language studies published between 1990 and 2004 with adult human subjects. We used the search terms “preoperative evaluation”, “preoperative assessment”, “perioperative risk”, “postoperative risk”, “cardiac risk”, “pulmonary risk”, “perioperative cardiac morbidity”, “perioperative pulmonary morbidity”, “perioperative outcome predictors”, “vascular surgery”, “peripheral arterial disease”, and “risk stratification”. Additional references were obtained from the reference lists of identified papers, review papers on perioperative assessment (including the 2002 ACC/AHA guidelines), and contact with experts in the field.

Although any type of surgery, including PAD surgery, can have several potential adverse outcomes, we have focused on cardiac complications (and specifically myocardial infarctions and/or cardiac death) in this document as they are the most serious complications after non-cardiac vascular surgery. While we acknowledge that the preoperative assessment also represents an opportunity to address the long term management of atherosclerotic risk factors and other medical co-morbidities in patients with PAD, this is not the focus of this manuscript and readers are referred to the relevant guidelines of the Canadian Hypertension Education Program, the Canadian Working Group on Lipid Disorders, and the Canadian Diabetes Association. Further, we recognize that PAD patients are at risk for other complications after surgery (including, but not restricted to, arrhythmias, heart failure, infection, bleeding, and venous thromboembolic disease) but a full discussion of all potential postoperative events is beyond the scope of this chapter.

## **PERIOPERATIVE CARDIOVASCULAR RISK EVALUATION**

### **RECOMMENDATIONS**

Our recommended approach to the preoperative assessment of a patient scheduled for non-cardiac major vascular surgery (i.e. all types of vascular surgery except carotid endarterectomy) is outlined in Figure 11A (Level III evidence). Three principles are paramount in applying this algorithm:

- i. The approach to the preoperative evaluation should be appropriate to the situation – if the patient presents with a surgical emergency then clearly the preoperative evaluation should be tailored to address any pressing issues with a more complete evaluation deferred until after the operation.
- ii. Preoperative coronary revascularization should not be done to try to reduce surgical risk but rather should only be considered in patients who would warrant revascularization for medical reasons independent of the proposed operation- for example, poorly controlled angina despite maximal medical therapy, 3 vessel coronary disease with involvement of the proximal left anterior descending, left main disease, or 2 vessel disease with left ventricular systolic dysfunction. Indeed, prophylactic CABG leads to more harm than good if employed solely to reduce perioperative risk (since the risk of mortality peri-CABG is approximately 5% and the periprocedural risks in patients with PAD were as high as 12% in the Bypass Angioplasty Revascularization Investigation registry).<sup>(20-22)</sup>
- iii. The preoperative approach should be tempered by the patient's overall health status. In other words, if the patient would not be a candidate for coronary revascularization irrespective of their angiographic findings, there is no reason to proceed to coronary angiography.

As can be seen in Figure 11A, we are only recommending non-invasive testing in selected patients scheduled for elective vascular surgery (Level II evidence). This is consistent with the 2002 ACC/AHA guidelines and the evidence reviewed later in this chapter. Our recommendations for the choice of non-invasive test are outlined in Figure 11B.

**BACKGROUND**

At the outset, it should be acknowledged that the pathophysiology of perioperative myocardial infarctions (MI) is incompletely understood.<sup>(23)</sup> While autopsy studies have shown that most patients suffering a fatal perioperative MI had significant left main or 3 vessel coronary disease but without plaque fissuring or acute thromboses (suggesting that the MIs were due to imbalances between the supply and demand of oxygen to the myocardium),<sup>(23)</sup> a large prospective coronary angiography study demonstrated that many events were due to acute coronary thromboses or plaque fissuring in arteries without high grade stenoses.<sup>(24)</sup> Further research is needed to clearly elucidate the pathways leading to perioperative MIs.

Although a complete history and physical examination is the cornerstone of perioperative risk assessment for any type of surgery (including vascular), the preoperative evaluation should particularly focus on searching for those conditions which have been shown to increase the risk of cardiovascular events after vascular surgery: coronary artery disease, congestive heart failure, previous stroke, diabetes mellitus (particularly insulin dependent), renal insufficiency, older age, and uncontrolled system hypertension (i.e.  $\geq 180/110$  mmHg).<sup>(3,4,7,11,25,26)</sup> In estimating risk, greater weight should be placed on those conditions which are active (rather than those which are dormant or have been corrected) and/or those which cause substantial functional impairment in that patient.

***PREOPERATIVE CARDIAC RISK INDICES***

A number of indices have been developed which incorporate the results of the clinical evaluation to derive estimates of postoperative cardiovascular risk.<sup>(4,7,11-13,15,25,26)</sup> Although all of these risk indices predict postoperative events better than chance,<sup>(27)</sup> their recommendations are not always concordant<sup>(28)</sup> and the area under the receiver operating characteristic curve for the Revised Cardiac risk index is superior to the other cardiac risk indices in general surgery patients, making it the currently favoured index for preoperative evaluation in patients undergoing a mix of surgical procedures (especially orthopedic and general surgical).<sup>(7,20)</sup> The Revised Cardiac Index is a six variable risk prediction score

derived and validated in 4,315 patients over the age of 50 years undergoing elective major noncardiac procedures (898 of whom underwent vascular surgery).<sup>(11)</sup>

However, as outlined in the Introduction to this chapter, risk prediction models derived in general surgical populations underestimate risk in vascular surgery populations and thus we chose to base our recommendations for patients undergoing PAD surgery on the 2002 American College of Cardiology/American Heart Association guidelines<sup>(15)</sup> since they (i) are comprehensive, (ii) provide a consensus of expert opinion for the many aspects of perioperative assessment for which there is little high quality evidence, (iii) present a step-wise approach with primary consideration of clinical variables and judicious use of non-invasive testing in only some patients, and (iv) have been independently validated and shown to accurately predict adverse cardiac events in patients undergoing vascular surgery.<sup>(16-19)</sup>

While some may question the wisdom of recommending any perioperative risk assessment strategy given the paucity of high quality evidence in this area, we elected to do so for two reasons. First, use of the ACC/AHA guidelines has been shown to reduce the frequency of preoperative testing and improve the appropriateness of any testing which is done compared to clinical judgement.<sup>(29)</sup> Second, a survey of Canadian general internists who perform a high volume of preoperative consultations demonstrated wide variability in their judgements of perioperative risk in standardized patients and the communication of these risks to the patients and their surgeons- indeed, these physicians' perception of what constituted "low risk for perioperative events" ranged from <1% to 20% and their perceptions of "high risk" varied from 2% to >50%.<sup>(30)</sup>

The value of using the ACC/AHA guidelines to help standardize risk estimates and better inform surgeons and patients about the risks of planned surgery is perhaps best illustrated by considering an example. In a cohort of 1351 patients undergoing major vascular surgery, those without any intermediate clinical risk predictors had a 1% incidence of cardiac complications within 30 days after surgery; those with 1 or 2 intermediate predictors had a 3% incidence of cardiac complications within 30 days after surgery; the incidence was 6% in those with 3 or more intermediate clinical risk predictors and a negative non-invasive stress

test (dobutamine stress echocardiography in that study); and 33% of those with 3 or more risk predictors and a positive non-invasive test suffered a cardiac complication in the first 30 postoperative days.<sup>(3)</sup>

Of the six factors in the Revised Cardiac Risk Index (high risk type of surgery, ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin requiring diabetes mellitus, and preoperative serum creatinine greater than 180 umol/L),<sup>(11)</sup> all but renal failure and diabetes mellitus were also found to be associated with postoperative cardiac outcomes in a cohort of 1,351 patients who underwent major vascular surgery.<sup>(3)</sup> Of note, in both the Revised Cardiac Risk Index and the DECREASE study cohort<sup>(3)</sup>, history of cerebrovascular disease was associated with the highest odds ratios in the multivariate analyses. While another study of 1,081 vascular surgery patients confirmed that older age, diabetes mellitus, ischemic heart disease, and congestive heart failure were associated with increased risk of postoperative cardiac events, that study did not include prior cerebrovascular disease in the baseline assessment.<sup>(4)</sup> On the basis of the Revised Cardiac Risk Index and the DECREASE study (Level II evidence), we have modified the clinical predictors outlined in the ACC/AHA guidelines to include history of cerebrovascular disease.

#### **TIMING OF ELECTIVE OPERATIONS IN PATIENTS AFTER MYOCARDIAL INFARCTION**

Although there is a paucity of evidence examining perioperative risks over time after myocardial infarction in the thrombolytic era (the 3 and 6 month distinction widely cited in the past arose from cohort studies in the 1970's),<sup>(3)</sup> the consensus of the 2002 ACC/AHA cardiovascular committee was that elective surgery should be delayed for at least 6 weeks after myocardial infarction (Level III evidence- expert opinion).<sup>(15)</sup> While we concur with this recommendation for patients with small uncomplicated infarcts or with larger infarcts but successful percutaneous coronary revascularization, we believe that in those patients who have suffered a large infarct with residual complications (particularly reduced left ventricular ejection fraction [LVEF] or residual ischemia) a delay of 3 months to optimize therapy and maximize function is more appropriate (Level III evidence- expert opinion).

**TIMING OF ELECTIVE OPERATIONS IN PATIENTS AFTER PERCUTANEOUS ANGIOPLASTY**

Based on concerns over arterial recoil and/or acute thrombosis after balloon angioplasty, we concur with the 2002 ACC/AHA recommendation to wait at least 7 days after angioplasty before proceeding with elective surgery (Level III evidence- expert opinion). This recommendation is consistent with the evidence from 5 retrospective cohort studies which demonstrated lower rates of postoperative cardiac events in high risk patients who had undergone percutaneous angioplasty a median of 9-11 days preoperatively (Level II evidence).<sup>(32-36)</sup> For example, a retrospective cohort study of 2980 patients who underwent noncardiac surgery a median of 1 year after successful PTCA suggested that the PTCA-treated patients were much less likely to suffer an adverse cardiac outcome within 30 days of surgery than age/sex matched controls with coronary disease who had not undergone PTCA (19% vs. 32%, OR 0.50, 95% CI 0.38-0.65).<sup>(36)</sup> While this study reported that patients who had noncardiac surgery within 90 days of PTCA did not seem to derive the same benefits, this sub-analysis was based on very small numbers (37 events in 142 patients) and awaits further verification.

**TIMING OF ELECTIVE OPERATIONS IN PATIENTS AFTER CORONARY STENTING**

Three retrospective cohort studies have reported very high mortality rates when noncardiac surgery was performed soon after coronary stent placement: 32% when surgery was within 2 weeks<sup>(37)</sup>, 26% when surgery was within 3 weeks,<sup>(38)</sup> and 5% when surgery was within 6 weeks.<sup>(39)</sup> Thus, we concur with the 2002 ACC/AHA recommendation that elective surgery be delayed for 6 weeks after coronary artery stenting if possible (Level II evidence). There is a paucity of evidence about perioperative risks in patients with drug eluting stents and, given the delays in endothelialization with these types of stents, it is not inconceivable that the risk of stent thrombosis may remain elevated even after 6 weeks (particularly given a recent case series reporting late thrombosis in drug eluting stents after antiplatelet therapy was stopped one year after the procedures).<sup>(40)</sup> There is an urgent need for research to determine when antiplatelet therapy can be safely stopped for elective surgery after a drug eluting stent is implanted, or indeed whether it is safer to proceed to elective surgery without stopping the antiplatelet therapy in patients with drug eluting stents.

**TIMING OF ELECTIVE OPERATIONS IN PATIENTS AFTER CORONARY ARTERY BYPASS SURGERY**

While the 2002 ACC/AHA guidelines state that successful coronary revascularization within 5 years mitigates the need for further evaluation in patients who have remained asymptomatic, we believe this issue remains open to debate. The ACC/AHA guideline was based largely on a secondary analysis of the Coronary Artery Surgery Study registry data which demonstrated that patients with prior CABG had lower rates of death and/or MI after noncardiac surgery in the subsequent 6 years than patients managed medically (a finding supported by other, smaller, cohort studies).<sup>(41-45)</sup> However, other cohort studies (including one in 6895 patients who underwent infra-inguinal vascular surgery) have suggested that the 5-year protection afforded by CABG is not absolute.<sup>(10,46,47)</sup> Although rates of cardiac death are relatively low (in the range of 1% to 2% per year) in the first 5 years after CABG in patients who are not subjected to surgical stress,<sup>(48)</sup> analysis of a cohort of 873 asymptomatic patients after CABG demonstrated that 5 clinical factors were associated with increased risk of MI or death in the first few years after CABG: age older than 65 years, diabetes mellitus, hypertension, heart failure, or poor exercise capacity.<sup>(49)</sup>

While there is clearly a need for better evidence in this area, we base our reluctance to accept “CABG within 5 years” as a modifier to the preoperative assessment for all patients on the basis of our concern that it is difficult without objective assessments of myocardial perfusion to differentiate between those asymptomatic patients with a “successful” CABG and those with graft occlusions, particularly in patients with PAD who are often unable to exercise sufficiently to induce angina pectoris due to their intermittent claudication. While it is currently estimated that coronary graft occlusion rates are 10% to 15% within the first year after CABG (and 25% by 5 years), patency rates after CABG are affected by many factors: some of these (gender, Body Mass Index, use of antithrombotic and/or statin therapy) are readily apparent to the clinician at the time of preoperative assessment, but some (experience of the CABG surgeon, harvesting and grafting techniques, vessel diameters, off-pump vs. on-pump surgery, and saphenous vein grafts vs. left internal thoracic artery or radial artery grafts) are unlikely to be apparent at the time of the preoperative assessment.<sup>(50-57)</sup>

As a result, we recommend that patients with clinical factors shown to be associated with a risk of early occlusion post-CABG (aged 65 years or older, diabetes mellitus, hypertension, heart failure, and/or poor functional capacity) should have further cardiac evaluation even if they are asymptomatic if the CABG was more than 2 years ago; in other patients without these risk factors and who are asymptomatic, then CABG within 5 years would mitigate the need for further testing.

#### **UTILITY OF FUNCTIONAL CAPACITY ASSESSMENTS**

We maintained the ACC/AHA emphasis on assessment of functional capacity in patients with minor cardiac risk predictors on the basis of small observational cohort studies demonstrating that reduced exercise capacity is associated with perioperative cardiopulmonary outcomes (level II evidence).<sup>(58,59)</sup>

#### **NON-INVASIVE TESTING FOR MYOCARDIAL ISCHEMIA**

In our recommended preoperative evaluation algorithm (Figure 11A), it is assumed that a standard 12-lead ECG has been obtained in all patients at the time of the initial clinical assessment (since certain abnormalities on the 12-lead ECG- LVH, LBBB, and ST/T abnormalities- have been shown to be associated with an increased risk of perioperative cardiac events).<sup>(60)</sup>

The evidence supporting each of the recommended non-invasive tests is outlined below and in Table 11A. As can be seen, none of the tests is perfect- all have reasonably good negative likelihood ratios but moderate positive likelihood ratios. Thus, while a “negative” non-invasive test would be helpful in identifying patients at low risk for perioperative cardiac events, patients with a “positive” test would require further testing to fully stratify risk. Given the likelihood ratios associated with each of the non-invasive tests it is clear that they are less useful in patients with major risk predictors (in whom perioperative risks are sufficiently high that non-invasive test results will not contribute meaningful information) or in patients with no clinical risk predictors (in whom the pretest probability of perioperative events is sufficiently low that even a positive non-invasive test will not shift the post-test probability of perioperative event sufficiently to change monitoring or treatment

recommendations). However, non-invasive tests are most beneficial in patients with intermediate clinical risk predictors. For example, Eagle et al reported that perioperative cardiac event rates in patients undergoing vascular surgery were 3% in patients without clinical risk predictors, 50% in patients with 3 or more clinical risk predictors, and 16% of patients who had 1 or 2 clinical risk predictors; however, stress thallium imaging refined the risk stratification in this last subgroup of patients at intermediate risk by 10-fold (those without reversible defects had a 3% perioperative event rate versus 30% in those with reversible perfusion defects).<sup>(25)</sup>

Although a meta-analysis of 58 studies (8119 patients all of whom were scheduled for major vascular surgery) suggested that dobutamine stress echocardiography was superior to myocardial perfusion scintigraphy (see Table 11A for comparison of diagnostic test characteristics),<sup>(61)</sup> comparisons between studies is fraught with potential problems given the different selection criteria and thus varying prevalence of underlying CAD (some studies enrolled consecutive patients while some restricted enrollment to patients deemed as high or intermediate risk on clinical criteria). In addition, the evidence base supporting all of the tests is relatively weak given the small number of cardiac events in these studies and the fact that virtually all of the studies were retrospective and did not blind test or outcome assessors to the results of the pre-test clinical assessments. Thus, we recommend that local expertise and availability, and consideration of patient-specific features (such as presence of left bundle branch block) or contraindications (such as bronchospastic airways disease), should continue to dictate the choice of non-exercise non-invasive test (Level III evidence- expert opinion).

### **IS NON-INVASIVE TESTING NECESSARY?**

While some authors have advocated that non-invasive tests should not be done and that all eligible vascular surgery patients should merely be prescribed perioperative beta-blockade,<sup>(20)</sup> we believe this strategy needs to be rigorously evaluated before it is accepted given the conflicting and limited evidence for/against either strategy. In support of the approach outlined in Figure 11A, several studies have shown that the clinical risk factors we outlined do accurately identify patients at elevated risk of postoperative cardiac events,<sup>(16-19)</sup> a

retrospective cohort study reported that one year mortality was lower in patients who had undergone preoperative testing before their major vascular surgery compared to those who had not (5% vs. 15%,  $p=0.02$ ),<sup>(10)</sup> and a before/after study found that the application of a stepwise evaluation akin to that in our Figure 11A did significantly reduce postoperative cardiac complications (from 11% to 5%,  $p < 0.01$ ).<sup>(62)</sup>

On the other hand, a very small randomized trial (only 4 events occurred in the 99 patients) did not find any significant difference in postoperative cardiac complications between patients who did compared to those who did not have preoperative non-invasive testing (2% vs. 6%,  $p=0.62$ ).<sup>(63)</sup> Furthermore, the Coronary Artery Revascularization Prophylaxis Trial demonstrated that, in patients with stable cardiac symptoms, delaying elective major vascular surgery by an average of 5 weeks to perform coronary revascularization did not reduce perioperative myocardial infarctions (12% vs. 14%,  $p=0.37$ ) or improve mortality (either perioperatively [3.1% vs. 3.4%,  $p=0.87$ ] or over a median follow-up of 2.7 years [22% vs. 23%,  $p=0.92$ ]) compared to a policy of merely proceeding with surgery.<sup>(64)</sup> However, it should be noted that medical management in both arms of this trial was excellent (with 85% of patients on beta-blockers, 73% on aspirin, and 54% on statins) and patients with unstable angina, aortic stenosis, or high risk angiographic findings ( $\geq 50\%$  stenoses in the left main coronary or  $LVEF < 0.20$ ) were excluded- as a result, there were only 15 deaths and 60 myocardial infarctions within 30 days of vascular surgery. As a result, while the CARP trial does establish that preoperative coronary revascularization does not improve outcomes after vascular surgery in patients with stable cardiac symptoms, it does not directly answer the question of whether non-invasive testing should or should not be part of the preoperative assessment of patients undergoing major non-cardiac vascular surgery.

Finally, although small trials have suggested a substantial benefit with perioperative beta-blockade,<sup>(65,66)</sup> more recent trials have reported no benefits to beta-blockade in over 1500 patients<sup>(67-69)</sup> - thus, the PeriOperative Ischemic Evaluation (POISE) Trial remains ongoing at this time.<sup>(70)</sup> Until the results of POISE are known, we believe it is premature to recommend beta-blockade in lieu of preoperative non-invasive testing in patients presenting for elective vascular surgery with clinical features suggesting elevated cardiac risk.

## **NON-INVASIVE TESTING- THE TESTS**

### **A) RESTING LEFT VENTRICULAR EJECTION FRACTION**

Although a low ejection fraction preoperatively is associated with poorer long-term cardiac outcome<sup>(71,72)</sup> and the occurrence of postoperative heart failure<sup>(73-75)</sup>, a systematic review of 22 observational studies (3096 patients prior to vascular surgery) revealed that resting LVEF was not a consistent predictor of perioperative cardiac events.<sup>(76)</sup> Indeed, it adds sufficiently little additional prognostic information that we recommend that it should not be done routinely, although it may be considered for patients with specific indications such as those with symptoms of heart failure and no prior objective assessments of LVEF (Level II evidence).<sup>(76)</sup>

### **B) EXERCISE STRESS TEST**

The risk of perioperative cardiac events is significantly increased in patients undergoing vascular surgery who have an abnormal exercise ECG at low workloads (12 observational studies, 2221 patients scheduled for major vascular surgery- Level II evidence).<sup>(15,61)</sup> In addition, the exercise stress test provides an estimate of functional capacity and does not expose the patient to radioactivity or potential reactions to pharmacologic agents. Thus, we concur with the 2002 ACC/AHA guidelines that this should be the non-invasive test of choice in patients scheduled for vascular surgery who have intermediate clinical risk predictors.

However, an exercise stress test is often not feasible in patients with peripheral arterial disease due to intermittent claudication or baseline abnormalities on the resting ECG. Thus, tests which rely on pharmacological stresses (either by increasing myocardial oxygen demand with dobutamine or by reducing myocardial oxygen supply with the peripheral vasodilator dipyridamole) may be necessary to evaluate myocardial perfusion in this setting.

### **C) MYOCARDIAL PERFUSION SCINTIGRAPHY**

Myocardial perfusion imaging with thallium-201 or technetium-99m has been shown, in patients with intermediate clinical risk predictors awaiting vascular surgery, to provide prognostic information (23 observational studies, 3119 patients scheduled for major vascular

surgery- Level II evidence).<sup>(61)</sup> While fixed defects predict long-term cardiac events, reversible perfusion defects have been shown to predict perioperative cardiac events (Table 3)<sup>(15)</sup> - while the sensitivity of this test is high (meaning that normal test results help to rule out disease), the specificity is low and false positive results are not uncommon. As the magnitude of risk correlates with the extent of the perfusion defect, it is not surprising that the inclusion of semi quantitative analysis (as opposed to dichotomizing results as positive or negative) improves diagnostic accuracy.<sup>(77)</sup> For example, in patients undergoing vascular surgery with “positive” dipyridamole myocardial stress perfusion scans, the probability of perioperative cardiac complications ranges from 11% in those with reversible defects in 20% to 29% of myocardial segments up to a 45% risk of perioperative cardiac complications in those with reversible defects in at least 50% of myocardial segments.<sup>(77)</sup>

Dipyridamole should be avoided in patients on chronic theophylline therapy or with a history of bronchospasm.<sup>(15,78)</sup>

#### ***d) Dobutamine Stress Echocardiography***

Dobutamine stress echocardiography, in experienced hands, has been shown to accurately risk stratify patients before vascular surgery (8 observational studies, 1877 patients scheduled for major vascular surgery- Level II evidence)<sup>(61)</sup>, and has been shown to provide additional prognostic information to clinical risk scores in patients with intermediate clinical risk predictors.<sup>(3)</sup>

The stimulus provided by dobutamine mimics the adrenergic flux seen perioperatively and thus this test is contraindicated in patients with a history of serious arrhythmias, uncontrolled hypertension, or hypotension at rest. This test relies on direct visualization of left ventricular regional wall motion for abnormalities (particularly those induced at low ischemic thresholds) and thus in patients with left bundle branch block or poor echocardiographic windows this test would not be the best choice.

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**SUMMARY OF RECOMMENDATIONS:**

The recommended approach to the preoperative assessment of a patient scheduled for non-cardiac vascular surgery (except carotid endarterectomy) is outlined in Figure 11A (Level III evidence- expert opinion only). Key principles include:

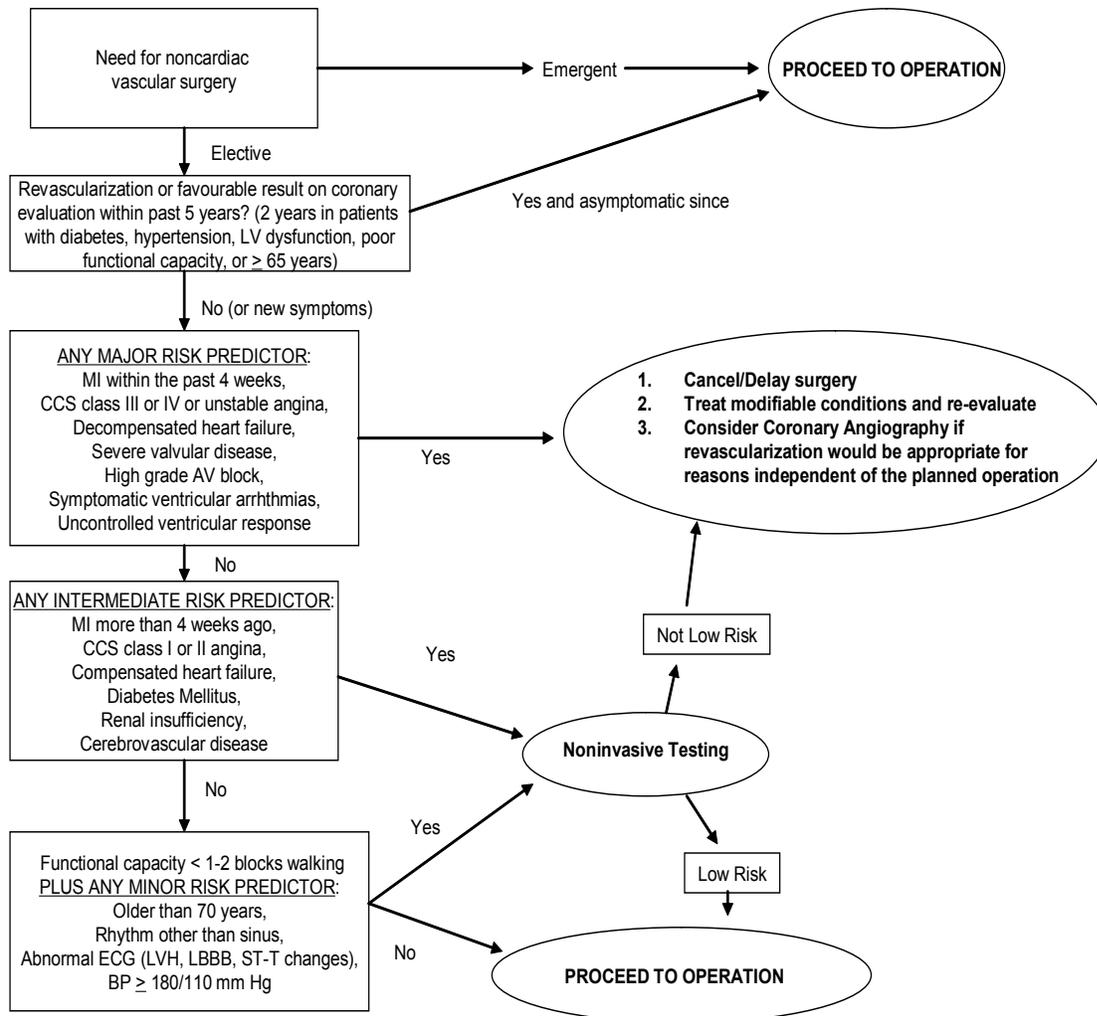
- i. The approach to the preoperative evaluation should be appropriate to the situation (elective versus emergent surgery) and should be tempered by the patient's overall health status.
- ii. Preoperative coronary revascularization does not reduce risk in patients with stable cardiac symptoms and thus should only be considered in patients who would warrant revascularization for medical reasons independent of the proposed operation.
- iii. Non-invasive testing is recommended only for selected patients scheduled for elective vascular surgery (see Figure 11A).
- iv. In patients who can ambulate, the exercise stress test is the non-invasive test of choice (Level II evidence). In patients who are unable to exercise, the choice of non-exercise non-invasive test should be dictated by availability, local expertise, and consideration of contraindications (Level III evidence).

**TABLE 11A: SUMMARY OF DIAGNOSTIC TEST CHARACTERISTICS FOR NON-INVASIVE TESTS APPLIED IN MAJOR VASCULAR SURGERY PATIENTS (ADAPTED FROM REFERENCE 61)**

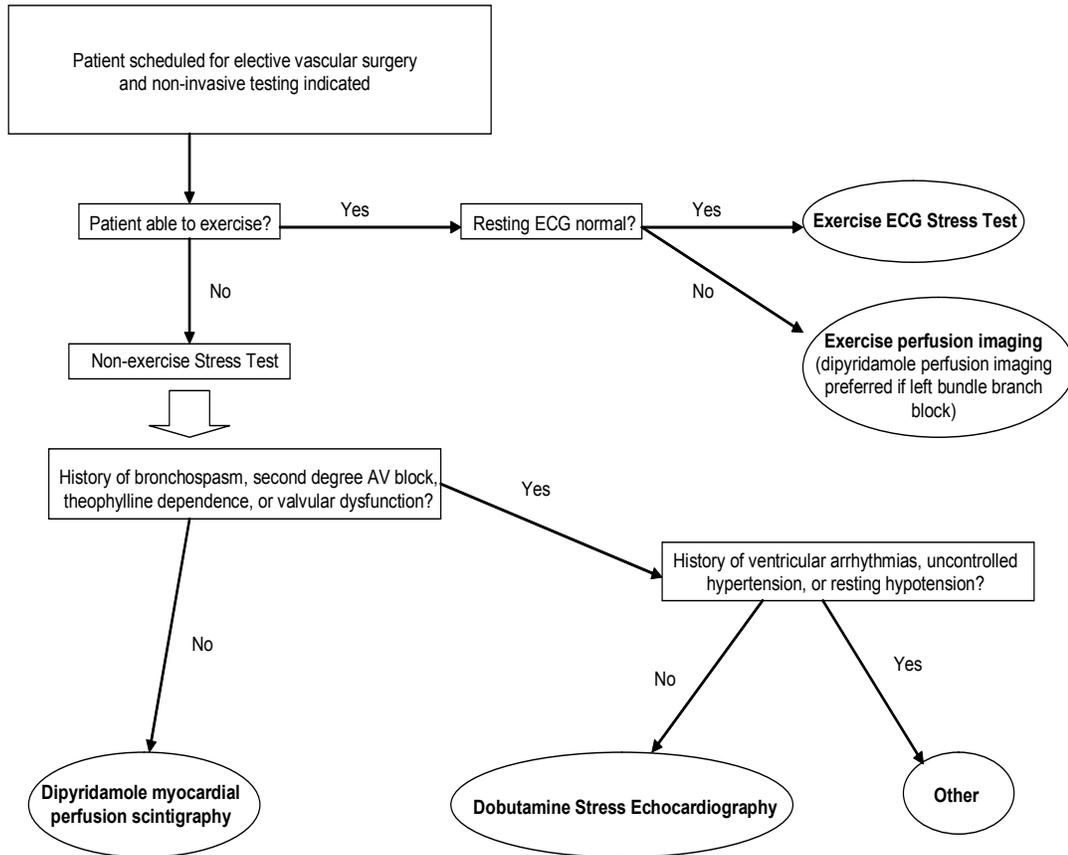
<i>Test</i>	<i>Number of Studies (total number of patients)</i>	<i>Sensitivity (95% CI)</i>	<i>Specificity (95% CI)</i>	<i>Positive Likelihood Ratio</i>	<i>Negative Likelihood Ratio</i>
Radionuclide ventriculography	8 (532)	50 (32 to 69)	91 (87 to 96)	5.6	0.55
Exercise ECG Stress Test	7 (685)	74 (60 to 88)	69 (60 to 78)	2.4	0.38
Myocardial perfusion scintigraphy	23 (3119)	83 (77 to 89)	49 (41 to 57)	1.6	0.50
Dobutamine stress echocardiography	8 (1877)	85 (74 to 97)	70 (62 to 79)	2.8	0.21

See Figure 11A on next page.

**FIGURE 11A: ALGORITHM FOR PREOPERATIVE EVALUATION FOR CARDIAC RISK IN PATIENTS UNDERGOING MAJOR NON-CARDIAC VASCULAR SURGERY**



**FIGURE 11B: ALGORITHM FOR CHOOSING NON-INVASIVE TESTING STRATEGY**



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