

# Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)

L. Norgren,<sup>a</sup> W.R. Hiatt,<sup>b</sup> J.A. Dormandy, M.R. Nehler, K.A. Harris, and F.G.R. Fowkes on behalf of the TASC II Working Group, Örebro, Sweden and Denver, Colorado

## INTRODUCTION

The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC) was published in January 2000<sup>1-3</sup> as a result of cooperation between fourteen medical and surgical vascular, cardiovascular, vascular radiology and cardiology societies in Europe and North America. This comprehensive document had a major impact on vascular care amongst specialists. In subsequent years, the field has progressed with the publication of the CoCaLis document<sup>4</sup> and the American College of Cardiology/American Heart Association Guidelines for the Management of Peripheral Arterial Disease.<sup>5</sup> Aiming to continue to reach a readership of vascular specialists, but also physicians in primary health care who see patients with peripheral arterial disease (PAD), another consensus process was initiated during 2004. This new consensus document has been developed with a broader international representation, including Europe, North America, Asia, Africa and Australia, and with a much larger distribution and dissemination of the information. The goals of this new consensus are to provide an abbreviated document (compared with the publication in 2000), to focus on key aspects of diagnosis and management, and to update the information based on new publications and the newer guidelines, but not to add an extensive list of references. Unreferenced statements are, therefore, to be found, provided they are recognized as common practice by the authors, with existing evidence. The recommendations are graded according to levels of evidence. It should also be emphasized that good practice is based on a combination of the scientific evidence described below, patients' preferences, and local availability of facilities and trained professionals. Good practice also includes appropriate specialist referral.

## Process

Representatives of sixteen societies from Europe, North America, Australia, South Africa and Japan were elected from their respective society and were called together in 2004 to form the new Working Group. Specialists in health economics, health outcomes and evidence-based medicine were also included to elaborate on the text for the following sections: history, epidemiology and risk factors; management of risk factors; intermittent claudication; critical limb ischemia; acute limb ischemia; and technologies (intervention/revascularization and imaging).

The Working Group reviewed the literature and, after extensive correspondence and meetings, proposed a series of draft documents with clear recommendations for the diagnosis and treatment of PAD. Each participating society reviewed and commented on these draft consensus documents. The liaison member from each society then took these views back to the Working Group, where all of the amendments, additions and alterations suggested by each participating society were discussed, and the final Consensus Document was agreed upon.

The participating societies were then again invited to review the final document and endorse it if they agreed with its contents. If an individual participating society did not accept any specific recommendation, this is clearly indicated in the final document. Therefore, except where such specific exclusions are indicated, this Consensus Document represents the views of all of the participating societies.

Compared with the original TASC, more emphasis has been put on diabetes and PAD. The text is presented in such a way that vascular specialists will still find most of the information they require, while general practitioners and primary health physicians will easily find guidance for diagnosis and diagnostic procedures, referral of patients and expected outcome of various treatment options.

## Grading of recommendations

Recommendations and selected statements are rated according to guidance issued by the former US Agency for Health Care Policy and Research,<sup>6</sup> now renamed the Agency for Healthcare Research and Quality:

From the Department of Surgery, University Hospital,<sup>a</sup> and University of Colorado School of Medicine and Colorado Prevention Center.<sup>b</sup>

Correspondence: L. Norgren, Department of Surgery, University Hospital, Örebro, Sweden (e-mail: lars.norgren@orebroll.se) and W.R. Hiatt, University of Colorado School of Medicine, Denver, CO (e-mail: will.hiatt@uchsc.edu).

0741-5214/\$32.00

Copyright © 2007 by The Society for Vascular Surgery.

doi:10.1016/j.jvs.2006.12.037

Grade	Recommendation
A	Based on the criterion of at least one randomized, controlled clinical trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B	Based on well-conducted clinical studies but no good quality randomized clinical trials on the topic of recommendation
C	Based on evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities (i.e. no applicable studies of good quality)

Note that the grade of recommendation is based on the level of available evidence and does not necessarily relate to the clinical importance.

### Acknowledgements

The development of this document was supported by an unrestricted educational grant from sanofi-aventis. Additional support for publication of the document was also provided by Bristol-Myers Squibb.\* The sponsors did not participate in any of the discussions or provide recommendations as to the preparation of these guidelines. The TASC Steering Committee acknowledges the administrative and logistic assistance from Medicus International, with great appreciation of the work performed by Dr Barbara Byth.

## SECTION A – EPIDEMIOLOGY OF PERIPHERAL ARTERIAL DISEASE

### A1 EPIDEMIOLOGY

The management of the patient with peripheral arterial disease (PAD) has to be planned in the context of the epidemiology of the disease, its natural history and, in particular, the modifiable risk factors for the systemic disease as well as those that predict deterioration of the circulation to the limb.

#### A1.1 Incidence and prevalence of asymptomatic peripheral arterial disease

Total disease prevalence based on objective testing has been evaluated in several epidemiologic studies and is in the range of 3% to 10%, increasing to 15% to 20% in persons over 70 years.<sup>7-9</sup> The prevalence of asymptomatic PAD in the leg can only be estimated by using non-invasive measurements in a general population. The most widely used test is the measurement of the ankle-brachial systolic pressure index (ABI). (For detailed discussion of the ABI, see Section C2.1.) A resting ABI of  $\leq 0.90$  is caused by hemodynamically-significant arterial stenosis and is most often used as a hemodynamic definition of PAD. In symptomatic individuals, an ABI  $\leq 0.90$  is approximately 95% sensitive in detecting arteriogram-positive PAD and almost 100% specific in identifying healthy individuals. Using this criterion, several studies have looked at symptomatic and asymptomatic PAD patients in the same population. The ratio of the two is independent of age and is usually in the range of 1:3

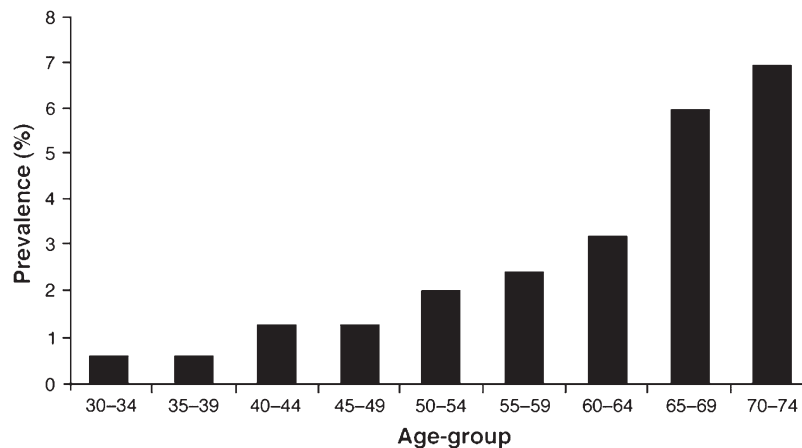
to 1:4. The Edinburgh Artery Study found that, using duplex scanning, a third of the patients with asymptomatic PAD had a complete occlusion of a major artery to the leg.<sup>10</sup> The PARTNERS (PAD Awareness, Risk, and Treatment: New Resources for Survival) study screened 6979 subjects for PAD using the ABI (with PAD defined as an ABI of  $\leq 0.90$  or a prior history of lower extremity revascularization). Subjects were evaluated if they were aged  $\geq 70$  years or aged 50–69 years with a risk factor for vascular disease (smoking, diabetes) in 320 primary care practices in the United States.<sup>11</sup> PAD was detected in 1865 patients which was 29% of the total population. Classic claudication was present in 5.5% of the newly diagnosed patients with PAD and 12.6% of the patients with a prior diagnosis of PAD had claudication. The National Health and Nutritional Examination Survey recently reported on an unselected population of 2174 subjects aged  $\geq 40$  years.<sup>9</sup> The prevalence of PAD, as defined by an ABI of  $\leq 0.90$ , ranged from 2.5% in the age group 50–59 years to 14.5% in subjects  $>70$  years (there was no information about the proportion of subjects with an ABI of  $\leq 0.90$  who had symptoms in the legs). In autopsies of unselected adults, 15% of men and 5% of women who were asymptomatic, had a 50% or greater stenosis of an artery to the leg. It is interesting to compare this with the finding that 20% to 30% of subjects with complete occlusion of at least one coronary artery on autopsy are asymptomatic. Some of the apparent inconsistency regarding data on the prevalence of symptomatic PAD is due to methodology, but in summary it can be concluded that for every patient with symptomatic PAD there are another three to four subjects with PAD who do not meet the clinical criteria for intermittent claudication.

#### A1.2 Incidence and prevalence of symptomatic peripheral arterial disease

Intermittent claudication (IC) (see section C1.1 for definition) is usually diagnosed by a history of muscular leg pain on exercise that is relieved by a short rest. Several questionnaires have been developed for epidemiological use. In looking at methods for identifying IC in the population, it must be remembered that while it is the main symptom of PAD, the measurement of this symptom does not always predict the presence or absence of PAD. A patient with quite severe PAD may not have the symptom of IC because some other condition limits exercise or they are sedentary. In contrast, some patients with what seems to be IC may not have PAD (for example, spinal stenosis can produce symptoms like IC in the absence of vascular disease). Likewise, patients with very mild PAD may develop symptoms of IC only when they become very physically active.

The annual incidence of IC is more difficult to measure and probably less important than its prevalence (unlike the case of the relatively very much smaller number of patients with critical limb ischemia [CLI]). The prevalence of IC would appear to increase from about 3% in patients aged 40 to 6% in patients aged 60 years. Several large popula-

\*The TASC Working Group also acknowledges Otsuka Pharmaceuticals for defraying some travel costs and, together with Mitsubishi Pharma, supplying additional support for the future dissemination of these guidelines.



**Fig. A1.** Weighted mean prevalence of intermittent claudication (symptomatic PAD) in large population-based studies.

tion studies have looked at the prevalence of IC and Fig. A1 shows a calculated mean prevalence weighted by study sample size. In the relatively younger age groups, claudication is more common in men but at older ages there is little difference between men and women. A surprising finding in population screening studies is that between 10% and 50% of patients with IC have never consulted a doctor about their symptoms.

### A1.3 Epidemiology of peripheral arterial disease in different ethnic groups

Non-white ethnicity is a risk factor for PAD. Black ethnicity increases the risk of PAD by over two-fold, and this risk is not explained by higher levels of other risk factors such as diabetes, hypertension or obesity.<sup>12</sup> A high prevalence of arteritis affecting the distal arteries of young black South Africans has also been described.

## A2 RISK FACTORS FOR PERIPHERAL ARTERIAL DISEASE

Although the various factors described in this section are usually referred to as risk factors, in most cases the evidence is only for an association. The criteria used to support a risk factor require a prospective, controlled study showing that altering the factor alters the development or course of the PAD, such as has been shown for smoking cessation or treatment of dyslipidemia. Risk may be conferred by other metabolic or circulatory abnormalities associated with diabetes.

### A2.1 Race

The National Health and Nutrition Examination Survey in the United States found that an ABI  $\leq 0.90$  was more common in non-Hispanic Blacks (7.8%) than in Whites (4.4%). Such a difference in the prevalence of PAD was confirmed by the recent GENOA (Genetic Epidemiology Network of Arteriopathy) study,<sup>13</sup> which also showed that the difference was not explained by a difference in classical risk factors for atherosclerosis.

### A2.2 Gender

The prevalence of PAD, symptomatic or asymptomatic, is slightly greater in men than women, particularly in the younger age groups. In patients with IC, the ratio of men to women is between 1:1 and 2:1. This ratio increases in some studies to at least 3:1 in more severe stages of the disease, such as chronic CLI. Other studies have, however, shown a more equal distribution of PAD between genders and even a predominance of women with CLI.

### A2.3 Age

The striking increase in both the incidence and prevalence of PAD with increasing age is apparent from the earlier discussion of epidemiology (Fig. A1).

### A2.4 Smoking

The relationship between smoking and PAD has been recognized since 1911, when Erb reported that IC was three-times more common among smokers than among non-smokers. Interventions to decrease or eliminate cigarette smoking have, therefore, long been advocated for patients with IC. It has been suggested that the association between smoking and PAD may be even stronger than that between smoking and coronary artery disease (CAD). Furthermore, a diagnosis of PAD is made approximately a decade earlier in smokers than in non-smokers. The severity of PAD tends to increase with the number of cigarettes smoked. Heavy smokers have a four-fold higher risk of developing IC compared with non-smokers. Smoking cessation is associated with a decline in the incidence of IC. Results from the Edinburgh Artery Study<sup>10</sup> found that the relative risk of IC was 3.7 in smokers compared with 3.0 in ex-smokers (who had discontinued smoking for less than 5 years).

### A2.5 Diabetes mellitus

Many studies have shown an association between diabetes mellitus and the development of PAD. Overall, IC is

about twice as common among diabetic patients than among non-diabetic patients. In patients with diabetes, for every 1% increase in hemoglobin A1c there is a corresponding 26% increased risk of PAD.<sup>14</sup> Over the last decade, mounting evidence has suggested that insulin resistance plays a key role in a clustering of cardiometabolic risk factors which include hyperglycemia, dyslipidemia, hypertension and obesity. Insulin resistance is a risk factor for PAD even in subjects without diabetes, raising the risk approximately 40% to 50%.<sup>15</sup> PAD in patients with diabetes is more aggressive compared to non-diabetics, with early large vessel involvement coupled with distal symmetrical neuropathy. The need for a major amputation is five- to ten-times higher in diabetics than non-diabetics. This is contributed to by sensory neuropathy and decreased resistance to infection. Based on these observations, a consensus statement from the American Diabetes Association recommends PAD screening with an ABI every 5 years in patients with diabetes.<sup>16</sup>

### A2.6 Hypertension

Hypertension is associated with all forms of cardiovascular disease, including PAD. However, the relative risk for developing PAD is less for hypertension than diabetes or smoking.

### A2.7 Dyslipidemia

In the Framingham study, a fasting cholesterol level greater than 7 mmol/L (270 mg/dL) was associated with a doubling of the incidence of IC but the ratio of total to high-density lipoprotein (HDL) cholesterol was the best predictor of occurrence of PAD. In another study, patients with PAD had significantly higher levels of serum triglycerides, very low-density lipoprotein (VLDL) cholesterol, VLDL triglycerides, VLDL proteins, intermediate density lipoprotein (IDL) cholesterol, and IDL triglycerides and lower levels of HDL than controls.<sup>17</sup> Although some studies have also shown that total cholesterol is a powerful independent risk factor for PAD, others have failed to confirm this association. It has been suggested that cigarette smoking may enhance the effect of hypercholesterolemia. There is evidence that treatment of hyperlipidemia reduces both the progression of PAD and the incidence of IC. An association between PAD and hypertriglyceridemia has also been reported and has been shown to be associated with the progression and systemic complications of PAD. Lipoprotein(a) is a significant independent risk factor for PAD.

### A2.8 Inflammatory markers

Some recent studies have shown that C-reactive protein (CRP) was raised in asymptomatic subjects who in the subsequent five years developed PAD compared to an age-matched control group who remained asymptomatic. The risk of developing PAD in the highest quartile of baseline CRP was more than twice that in the lowest quartile.<sup>18</sup>

### A2.9 Hyperviscosity and hypercoagulable states

Raised hematocrit levels and hyperviscosity have been reported in patients with PAD, possibly as a consequence of smoking. Increased plasma levels of fibrinogen, which is also a risk factor for thrombosis, have been associated with PAD in several studies. Both hyperviscosity and hypercoagulability have also been shown to be markers or risk factors for a poor prognosis.

### A2.10 Hyperhomocysteinemia

The prevalence of hyperhomocysteinemia is high in the vascular disease population, compared with 1% in the general population. It is reported that hyperhomocysteinemia is detected in about 30% of young patients with PAD. The suggestion that hyperhomocysteinemia may be an independent risk factor for atherosclerosis has now been substantiated by several studies. It may be a stronger risk factor for PAD than for CAD.

### A2.11 Chronic renal insufficiency

There is an association of renal insufficiency with PAD, with some recent evidence suggesting it may be causal. In the HERS study (Heart and Estrogen/Progestin Replacement Study), renal insufficiency was independently associated with future PAD events in postmenopausal women.<sup>19</sup>

### A2.12 Summary

Fig. A2 summarizes graphically the approximate influence or association between some of the above factors and PAD, taking a global view of the existing evidence.

## A3 FATE OF THE LEG

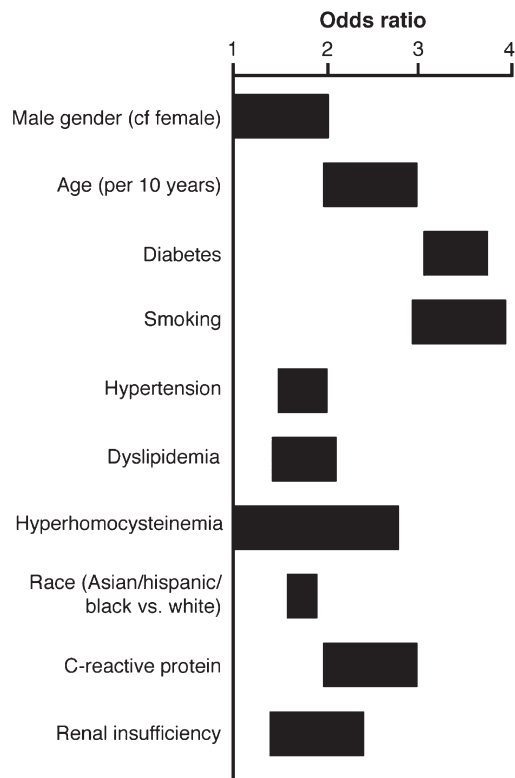
### A3.1 Asymptomatic

Evidence suggests that the progression of the underlying PAD is identical whether or not the subject has symptoms in the leg. There is nothing to suggest that the risk of local deterioration, with progression to CLI, is dependent on the presence or absence of symptoms of intermittent claudication. Whether symptoms develop or not depends largely on the level of activity of the subject. This is one of the reasons why some patients' initial presentation is with CLI, in the absence of any earlier IC. For example, a patient who has a reduction in their ABI just above the ischemic rest pain level but who is too sedentary to claudicate, may develop CLI because of wounds resulting from relatively minor (often self-inflicted) trauma that can not heal at this level of perfusion. It is important to detect this subgroup of patients at a time when protective foot care and risk factor control have their greatest potential to ameliorate outcomes. Functional decline over two years is related to baseline ABI and the nature of the presenting limb symptoms.<sup>20</sup> A lower ABI was associated with a more rapid decline in, for example, 6-minute walk distance.

### A3.2 Intermittent claudication

Although PAD is progressive in the pathological sense, its clinical course as far as the leg is concerned is surprisingly





**Fig. A2.** Approximate range of odds ratios for risk factors for symptomatic peripheral arterial disease. Treatment of risk factors and the effect on the outcomes of PAD are described in Chapter B.

stable in most cases. However, the symptomatic PAD patient continues to have significant functional disability. Large population studies provide the most reliable figures. All of the evidence over the last 40 years since the classic study by Bloor has not materially altered the impression that only about a quarter of patients with IC will ever significantly deteriorate. This symptomatic stabilization may be due to the development of collaterals, metabolic adaptation of ischemic muscle, or the patient altering his or her gait to favor non-ischemic muscle groups. The remaining 25% of patients with IC deteriorate in terms of clinical stage; this is most frequent during the first year after diagnosis (7%–9%) compared with 2% to 3% per year thereafter. This clinical stability is relevant to the patient's perception of their severity of claudication. When these patients have a comprehensive assessment of their actual functional status, measured walking distance does progressively deteriorate over time.<sup>20</sup>

More recent reviews also highlight that major amputation is a relatively rare outcome of claudication, with only 1% to 3.3% of patients with IC needing major amputation over a 5-year period. The Basle and Framingham studies,<sup>21,22</sup> which are the two large-scale studies that have looked at unselected patients, found that less than 2% of PAD patients required major amputation. Although amputation is the major fear of patients told that they have

circulatory disease of the legs, they can be assured that this is an unlikely outcome, except in diabetes patients (Fig. A3).

It is difficult to predict the risk of deterioration in a recent claudicant. The various risk factors mentioned in section A2 (above) probably all contribute to the progression of PAD. A changing ABI is possibly the best individual predictor, because if a patient's ABI rapidly deteriorates it is most likely to continue to do so in the absence of successful treatment. It has been shown that in patients with IC, the best predictor of deterioration of PAD (e.g. need for arterial surgery or major amputation), is an ABI of <0.50 with a hazard ratio of more than 2 compared to patients with an ABI >0.50. Studies have also indicated that in those patients with IC in the lowest strata of ankle pressure (i.e. 40–60 mmHg), the risk of progression to severe ischemia or actual limb loss is 8.5% per year.

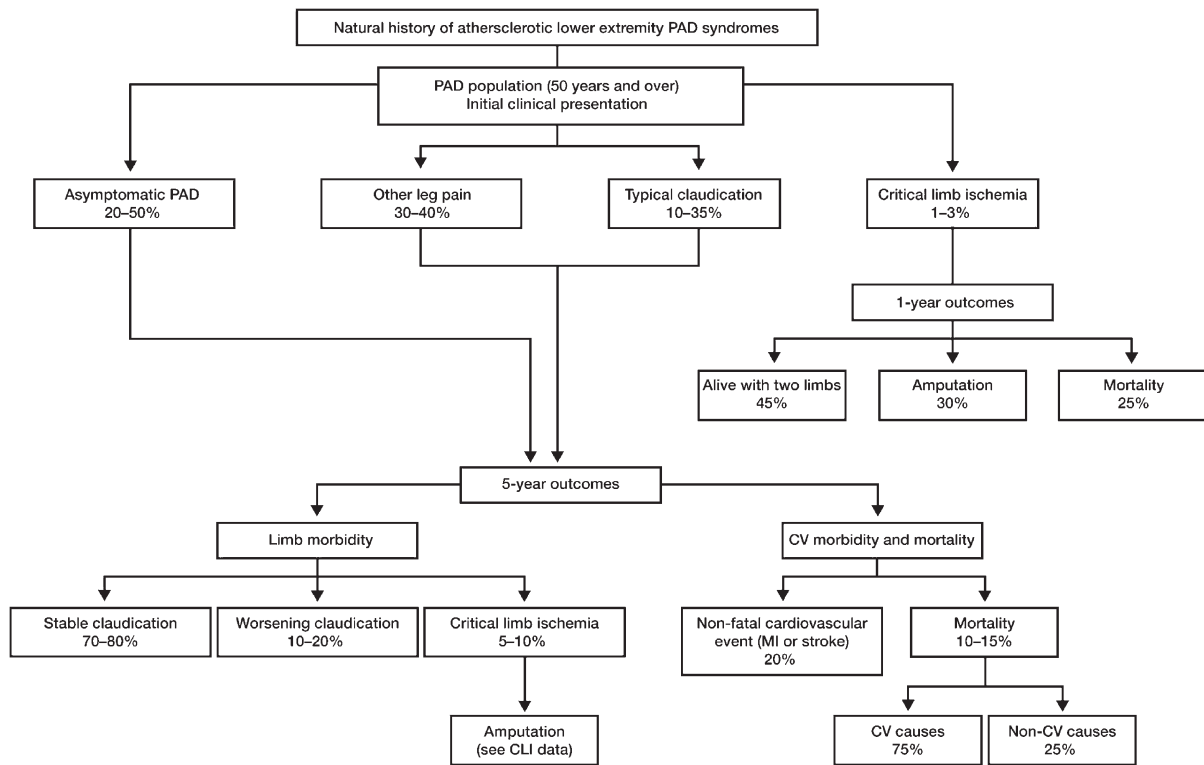
### A3.3 Critical limb ischemia

The only reliable large prospective population studies on the incidence of CLI showed a figure of 220 new cases every year per million population.<sup>23</sup> However, there is indirect evidence from studies looking at the progression of IC, population surveys on prevalence and assumptions based on the major amputation rates. Surprisingly, the incidence calculated using these different methodologies is very similar. There will be approximately between 500 and 1000 new cases of CLI every year in a European or North American population of 1 million.

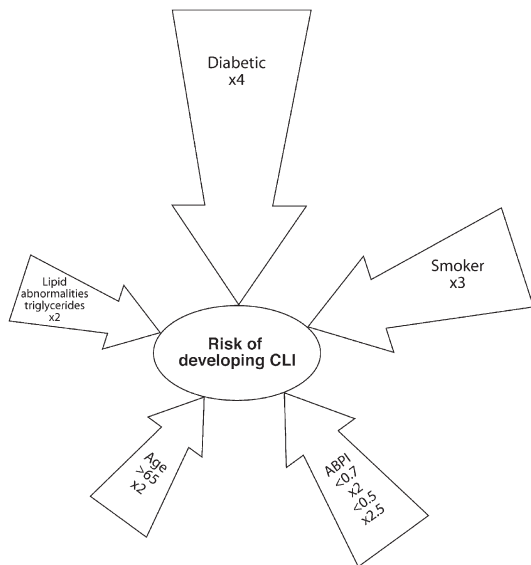
A number of studies have allowed an analysis of the risk factors that seem to be associated with the development of CLI. These are summarized in Fig. A4. These factors appear to be independent and are, therefore, probably additive.

It is no longer possible to describe the natural history of patients with CLI because the majority of these patients now receive some form of active treatment. Treatment very much depends on the center to which the patient is referred. Large surveys suggest that approximately half the patients with CLI will undergo some type of revascularization, although in some, particularly active, interventional centers an attempt at reconstruction is reported in as many as 90% of CLI patients. Fig. A5 provides an estimate of the primary treatment of these patients globally and their status a year later.

There are some good-quality data from multicenter, closely monitored trials of pharmacotherapy for CLI. These only relate to a subgroup of patients who are unreconstructable or in whom attempts at reconstruction have failed. (It is only such patients who are entered into randomized, placebo-controlled, clinical pharmacotherapy trials.) The results for this subgroup reveal the appalling prospect that approximately 40% will lose their leg within 6 months, and up to 20% will die (note that these data refer to 6 months' follow-up and cannot be directly compared with the 1-year data in Fig. A5).



**Fig. A3.** Fate of the claudicant over 5 years (adapted from ACC/AHA guidelines<sup>5</sup>). PAD – peripheral arterial disease; CLI – critical limb ischemia; CV – cardiovascular; MI – myocardial infarction. Adapted with permission from Hirsch AT et al. *J Am Coll Cardiol* 2006;**47**:1239–1312.



**Fig. A4.** Approximate magnitude of the effect of risk factors on the development of critical limb ischemia in patients with peripheral arterial disease. CLI – critical limb ischemia.

**A3.4 Acute leg ischemia**

Acute limb ischemia denotes a quickly developing or sudden decrease in limb perfusion, usually producing new or worsening symptoms and signs, and often threatening limb viability. Progression of PAD from claudication to rest pain to ischemic ulcers or gangrene may be gradual or progress rapidly reflecting sudden worsening of limb perfusion. Acute limb ischemia may also occur as the result of an embolic event or a local thrombosis in a previously asymptomatic patient.

There is little information on the incidence of acute leg ischemia, but a few national registries and regional surveys suggest that the incidence is around 140/million/year. Acute leg ischemia due to emboli has decreased over the years, possibly as a consequence of less cardiac valvular disease from rheumatic fever and also better monitoring and anticoagulant management of atrial fibrillation. Meanwhile the incidence of thrombotic acute leg ischemia has increased. Even with the extensive use of newer endovascular techniques including thrombolysis, most published series report a 10% to 30% 30-day amputation rate.

**A3.5 Amputation**

There is an ongoing controversy, often fuelled by unverified retrospective audit data from large and changing populations, as to whether there is a significant reduction in

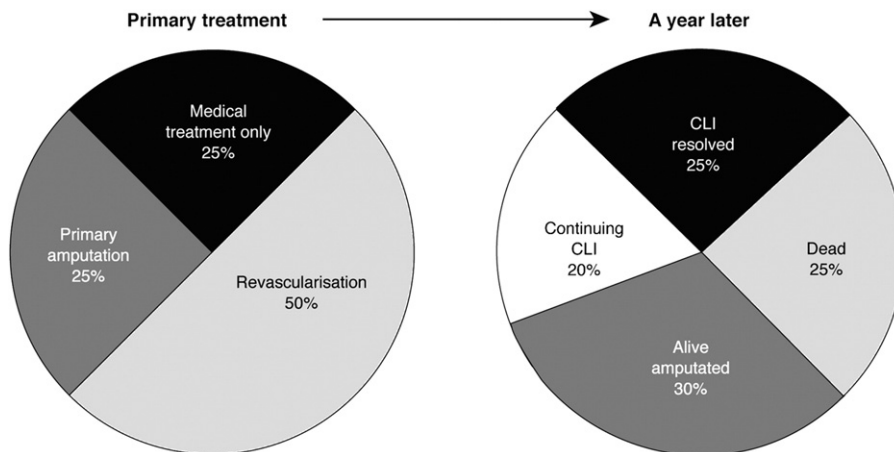


Fig. A5. Fate of the patients presenting with chronic critical leg ischemia. CLI – critical limb ischemia.

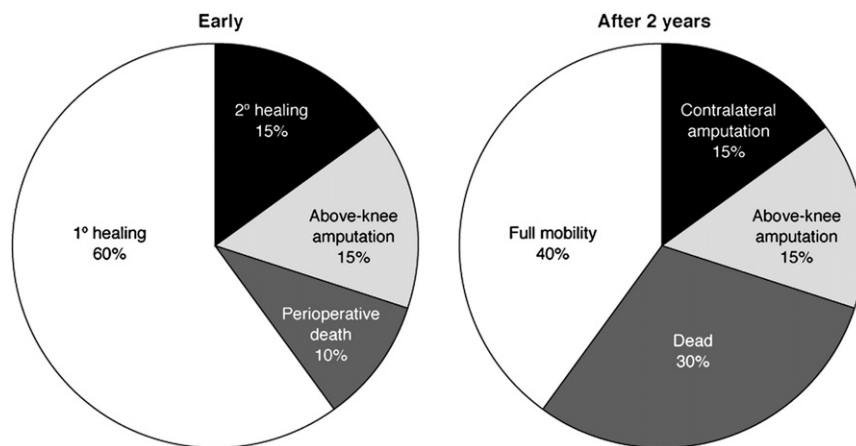


Fig. A6. Fate of the patient with below-knee amputation.

amputations as a result of more revascularization procedures in patients with CLI. Careful, independent studies from Sweden, Denmark and Finland all suggest that increased availability and use of endovascular and surgical interventions have resulted in a significant decrease in amputation for CLI. In the United Kingdom, the number of major amputations has reached a plateau, possibly reflecting increasingly successful limb salvage, but older studies in the United States have not shown benefit of revascularization on amputation rates.<sup>24</sup>

The concept that all patients who require an amputation have steadily progressed through increasingly severe claudication to rest pain, ulcers and, ultimately, amputation, is incorrect. It has been shown that more than half of patients having a below-knee major amputation for ischemic disease had no symptoms of leg ischemia whatsoever as recently as 6 months previously.<sup>25</sup> The incidence of major amputations from large population or nation-wide data varies from 120 to 500/million/year. The ratio of below-knee to above-knee amputations in large surveys is

around 1:1. Only about 60% of below-knee amputations heal by primary intention, 15% heal after secondary procedures and 15% need to be converted to an above-knee level. 10% die in the peri-operative period. The dismal 1- to 2-year prognosis is summarized in Fig. A6.

#### A4 CO-EXISTING VASCULAR DISEASE

Because PAD, CAD and cerebral artery disease are all manifestations of atherosclerosis, it is not surprising that the three conditions commonly occur together.

##### A4.1 Coronary

Studies on the prevalence of cardiovascular disease in patients with PAD show that the history, clinical examination and electrocardiogram identify a prevalence of CAD and cerebral artery disease in 40% to 60% of such patients. In the PARTNERS study, 13% of subjects screened had an ABI of  $\leq 0.90$  and no symptomatic CAD or cerebral artery disease, 16% had both PAD and symptomatic CAD or cerebral artery disease, and 24% had symptomatic CAD and

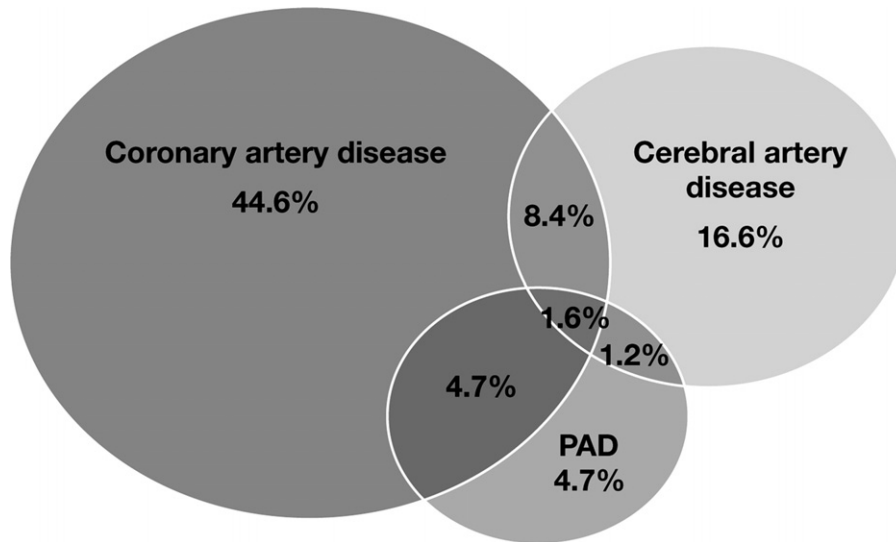


Fig. A7. Typical overlap in vascular disease affecting different territories.<sup>26</sup> Based on REACH data. PAD – peripheral arterial disease.

cerebral artery disease and a normal ABI.<sup>11</sup> As with asymptomatic PAD, the diagnosis of CAD depends on the sensitivity of the methods used. In the primary care setting, approximately half of those patients diagnosed with PAD also have CAD and cerebral artery disease; in PAD patients referred to hospital, the prevalence of CAD is likely to be higher. The extent of the CAD, both by angiography and by computed tomography (CT) measured coronary calcium, correlates with the ABI. Not surprisingly, patients with documented CAD are more likely to have PAD. The prevalence of PAD in patients with ischemic heart disease varies in different series from around 10% to 30%. Autopsy studies have shown that patients who die from a myocardial infarction are twice as likely to have a significant stenosis in the iliac and carotid arteries as compared to patients dying from other causes.

#### A4.2 Cerebral artery disease

The link between PAD and cerebral artery disease seems to be weaker than that with CAD. By duplex examination, carotid artery disease occurs in 26% to 50% of patients with IC, but only about 5% of patients with PAD will have a history of any cerebrovascular event. There is also a good correlation between carotid intimal thickness and the ABI. There is a range of overlap in disease in the cerebral, coronary and peripheral circulations reported in the literature, represented semi-quantitatively in Fig. A7. In the REACH (Reduction of Atherothrombosis for Continued Health) survey<sup>26</sup> of those patients identified with symptomatic PAD, 4.7% had concomitant CAD, 1.2% had concomitant cerebral artery disease and 1.6% had both. Thus in this survey, about 65% of patients with PAD had clinical evidence of other vascular disease. However, in one prospective study of 1886 patients aged 62 or over only

37% of subjects had no evidence of disease in any of the three territories.<sup>27</sup>

#### A4.3 Renal

Studies have also looked at the prevalence of renal artery stenosis in patients with PAD. The prevalence of renal artery stenosis of 50% or over ranges from 23% to 42% (compare this to the prevalence of renal artery stenosis in the hypertensive general population, which is around 3%). Although it has not been studied specifically it is very likely that renal artery stenosis is also a partly independent risk factor for mortality in patients with PAD since renal artery stenosis of 50% or over is associated with a 3.3-fold higher mortality rate than in the general population.

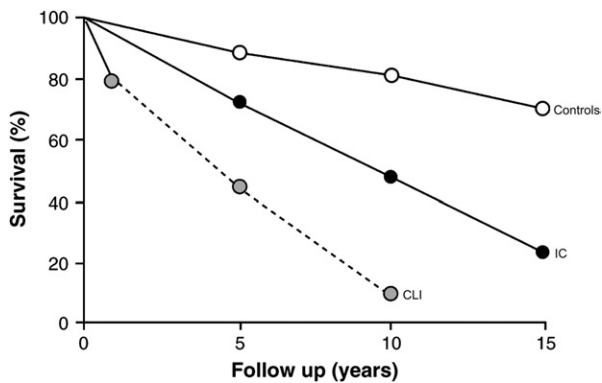
### A5 FATE OF THE PATIENT

#### A5.1 Asymptomatic and claudicating peripheral arterial disease patients

The increased risk of cardiovascular events in patients with PAD is related to the severity of the disease in the legs as defined by an ABI measurement. The annual overall major cardiovascular event rate (myocardial infarction, ischemic stroke and vascular death) is approximately 5%–7%.

Excluding those with CLI, patients with PAD have a 2% to 3% annual incidence of non-fatal myocardial infarction and their risk of angina is about two- to three- times higher than that of an age-matched population. The 5-, 10- and 15-year morbidity and mortality rates from all causes are approximately 30%, 50% and 70%, respectively (Fig. A3). CAD is by far the most common cause of death among patients with PAD (40%–60%), with cerebral artery disease accounting for 10% to 20% of deaths. Other vascular





**Fig. A8.** Survival of patients with peripheral arterial disease. IC – intermittent claudication; CLI – critical limb ischemia.

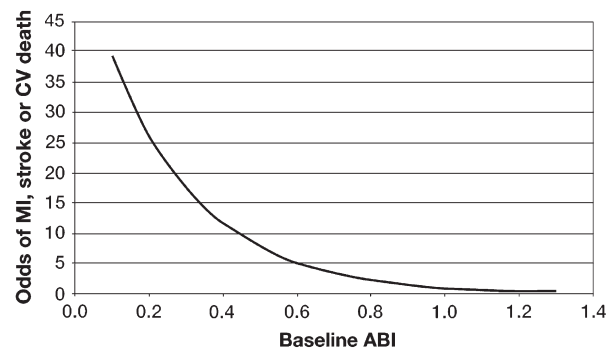
events, mostly ruptured aortic aneurysm, cause approximately 10% of deaths. Thus, only 20% to 30% of patients with PAD die of non-cardiovascular causes.

Of particular interest are the studies in which the difference in mortality rates between patients with IC and an age-matched control population was largely unchanged despite the adjustment for risk factors such as smoking, hyperlipidemia and hypertension. These surprising, but consistent, results suggest that the presence of PAD indicates an extensive and severe degree of systemic atherosclerosis that is responsible for mortality, independent of the presence of risk factors. Fig. A8 summarizes the results from all studies comparing mortality rates of claudicating patients with those of an age-matched control population. As expected, the two lines diverge, indicating that, on average, the mortality rate of claudicant patients is 2.5-times higher than that of non-claudicant patients.

#### A5.2 Severity of peripheral arterial disease and survival

Patients with chronic CLI have a 20% mortality in the first year after presentation, and the little long-term data that exists suggests that mortality continues at the same rate (Fig. A8). The short-term mortality of patients presenting with acute ischemia is 15% to 20%. Once they have survived the acute episode, their pattern of mortality will follow that of the claudicant or patient with chronic CLI, depending on the outcome of the acute episode.

There is a strong correlation between ABI, as a measure of the severity of the PAD, and mortality. A number of studies, using different ABI ‘cut-off’ points have demonstrated this relationship. For instance, in a study of nearly 2000 claudicants, patients with an ABI <0.50 had twice the mortality of claudicants with an entry ABI of >0.50.<sup>28</sup> The Edinburgh Artery Study<sup>10</sup> has also shown that the ABI is a good predictor of non-fatal and fatal cardiovascular events as well as total mortality, in an unselected general population. It has



**Fig. A9.** Adjusted odds of a cardiovascular event by ankle-brachial index.<sup>29</sup> Data from the placebo arm of the Appropriate Blood Pressure Control in Diabetes study<sup>29</sup> show an inverse correlation between ABI and odds of a major cardiovascular event. ABI – ankle-brachial index; CV – cardiovascular; MI – myocardial infarction. Reproduced with permission from Mehler PS *et al. Circulation* 2003;107:753–756.

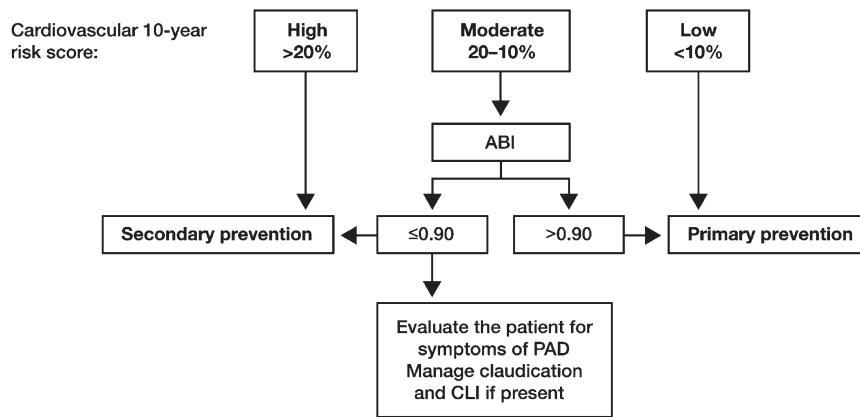
also been suggested that there is an almost linear relationship between ABI and fatal and non-fatal cardiovascular events; each decrease in ABI of 0.10 being associated with a 10% increase in relative risk for a major vascular event. In a study of patients with type 2 diabetes (Fig. A9), the lower the ABI the higher the 5-year risk of a cardiovascular event.<sup>29</sup>

### SECTION B – MANAGEMENT OF CARDIOVASCULAR RISK FACTORS AND CO-EXISTING DISEASE

#### B1 RISK FACTORS

##### B1.1 Identifying the peripheral arterial disease patient in the population

Patients with peripheral arterial disease (PAD) have multiple atherosclerosis risk factors and extensive atherosclerotic disease, which puts them at markedly increased risk for cardiovascular events, similar to patients with established coronary artery disease (CAD).<sup>30</sup> A reduced blood pressure in the ankle relative to the arm pressure indicates the presence of peripheral atherosclerosis, and is an independent risk factor for cardiovascular events. This has been most recently studied in a meta-analysis of 15 population studies and showed that an ankle-brachial index (ABI)  $\leq 0.90$  was strongly correlated with all-cause mortality independent of the Framingham Risk Score.<sup>31</sup> Thus, current recommendations from numerous consensus documents, including the recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines on PAD, identify patients with PAD as a high-risk population who require intensive risk factor modification and need antithrombotic therapy.<sup>5</sup> This section will discuss an approach to identification of PAD as a means to define a high-risk population and the management of each of the



**Fig. B1.** Algorithm for use of the ABI in the assessment of systemic risk in the population. Primary prevention: No antiplatelet therapy; LDL (low density lipoprotein) <3.37 mmol/L (<130 mg/dL) except in patients with diabetes where the LDL goal is <2.59 mmol/L (<100 mg/dL) even in the absence of CVD (cardiovascular disease); appropriate blood pressure (<140/90 mmHg and <130/80 mmHg in diabetes/renal insufficiency). Secondary prevention: Prescribe antiplatelet therapy; LDL <2.59 mmol/L (<100 mg/dL) (<1.81 mmol/L [ $<70$  mg/dL] in high risk); appropriate blood pressure (<140/90 mmHg and <130/80 mmHg in diabetes/renal insufficiency). See section B1.2 and surrounding text for references. In patients with diabetes, HbA1c <7.0%. See text for references. ABI – ankle-brachial index; PAD – peripheral arterial disease; CLI – critical limb ischemia.

major risk factors to reduce the incidence of cardiovascular events.

Over two-thirds of the patients with PAD are asymptomatic or have atypical leg symptoms and thus may not be recognized as having a systemic cardiovascular disease. Also, approximately half of the patients with PAD have not yet suffered a major cardiovascular event. Therefore, many patients with PAD are not identified, resulting in inadequate identification and treatment of their atherosclerosis risk factors.<sup>11</sup>

The initial clinical assessment for PAD is a history and physical examination. A history of intermittent claudication is useful in raising the suspicion of PAD, but significantly underestimates the true prevalence of PAD. In contrast, palpable pedal pulses on examination have a negative predictive value of over 90% that may rule out the diagnosis in many cases. In contrast, a pulse abnormality (absent or diminished) significantly overestimates the true prevalence of PAD. Thus, objective testing is warranted in all patients suspected of having PAD. The primary non-invasive screening test for PAD is the ABI (see section C2 for further discussion of the ABI and ABI screening criteria). In the context of identifying a high-risk population, persons who should be considered for ABI screening in the primary care or community setting include: (1) subjects with exertional leg symptoms, (2) subjects aged 50–69 years who also have cardiovascular risk factors and all patients over the age of 70 years,<sup>11</sup> and (3) subjects with a 10-year risk of a cardiovascular event between 10% and 20% in whom further risk stratification is warranted. Cardiovascular risk calculators are readily available in the public domain, such as the SCORE for use in Europe ([www.escardio.org](http://www.escardio.org)) and the Framingham for the US ([www.nhlbi.nih.gov/guidelines/cholesterol](http://www.nhlbi.nih.gov/guidelines/cholesterol)).

Patients with PAD, defined as an ABI  $\leq 0.90$ , are known to be at high risk for cardiovascular events (Fig. B1). As discussed in section A, mortality rates in patients with PAD average 2% per year and the rates of non-fatal myocardial infarction, stroke and vascular death are 5% to 7% per year.<sup>32,33</sup> In addition, the lower the ABI, the higher the risk of cardiovascular events, as shown in Fig. B2.<sup>34</sup> A similar increased mortality risk has also been observed in patients with an increased ABI as shown in Fig. B2. Therefore, an abnormal ABI identifies a high-risk population that needs aggressive risk factor modification and antiplatelet therapy.

### B1.2 Modification of atherosclerotic risk factors

As highlighted above, patients with PAD typically have multiple cardiovascular risk factors, which puts them at markedly increased risk for cardiovascular events. This section will discuss an approach to each of the major risk factors of this disorder.

**B1.2.1 Smoking cessation.** Smoking is associated with a marked increased risk for peripheral atherosclerosis. The number of pack years is associated with disease severity, an increased risk of amputation, peripheral graft occlusion and mortality. Given these associations, smoking cessation has been a cornerstone of the management of PAD as is the case for CAD.<sup>35</sup> Other drugs for smoking cessation are becoming available.

In middle-aged smokers with reduced pulmonary function, physician advice to stop smoking, coupled with a formal cessation program and nicotine replacement is associated with a 22% cessation rate at 5 years compared with only a 5% cessation rate in the usual care group.<sup>36</sup> By 14 years, the intervention group had a significant survival advantage. A number of randomized studies

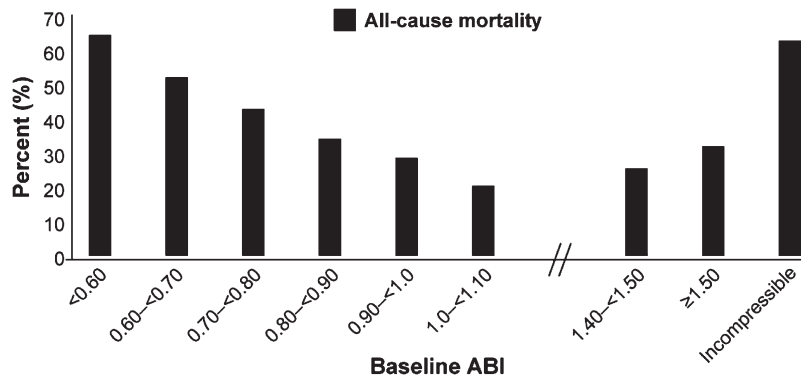


Fig. B2. All cause mortality as a function of baseline ABI. Excess mortality was observed at ABI values <1.00 and >1.40.<sup>34</sup> ABI – ankle-brachial index. Reproduced with permission from Resnick HE *et al. Circulation* 2004;109(6): 733–739.

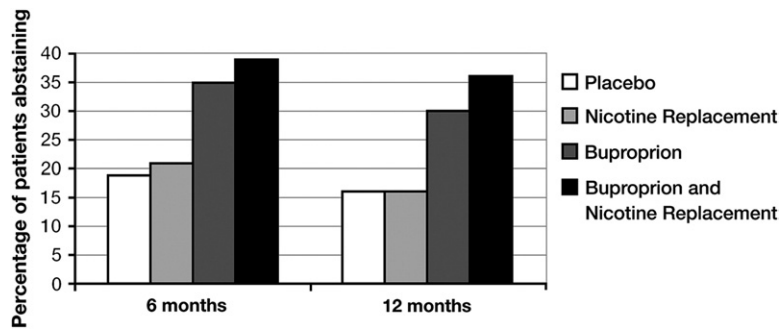


Fig. B3. Percent abstinence for bupropion SR, nicotine replacement, or both, versus placebo.<sup>38</sup> Reproduced with permission from Jorenby DE *et al. N Engl J Med* 1999;340(9):685–691.

have supported the use of bupropion in patients with cardiovascular disease, with 3-, 6- and 12-month abstinence rates of 34%, 27% and 22%, respectively, compared with 15%, 11% and 9%, respectively, with placebo treatment.<sup>37</sup> Combining bupropion and nicotine replacement therapy has been shown to be more effective than either therapy alone (Fig. B3).<sup>38</sup> Thus, a practical approach would be to encourage physician advice at every patient visit, combined with behavior modification, nicotine replacement therapy and the antidepressant bupropion to achieve the best cessation rates.

The role of smoking cessation in treating the symptoms of claudication is not as clear; studies have shown that smoking cessation is associated with improved walking distance in some, but not all patients. Therefore, patients should be encouraged to stop smoking primarily to reduce their risk of cardiovascular events, as well as their risk of progression to amputation and progression of disease, but should not be promised improved symptoms immediately upon cessation. Recent studies have shown a three-fold increased risk of graft failure after bypass surgery with continued smoking with a reduction in that risk to that of non-smokers with smoking cessation.<sup>39</sup>

### Recommendation 1

#### Smoking cessation in peripheral arterial disease

- All patients who smoke should be strongly and repeatedly advised to stop smoking [B].
- All patients who smoke should receive a program of physician advice, group counseling sessions, and nicotine replacement [A].
- Cessation rates can be enhanced by the addition of antidepressant drug therapy (bupropion) and nicotine replacement [A].

**B1.2.2 Weight reduction.** Patients who are overweight (body mass index [BMI] 25–30) or who are obese (BMI>30) should receive counseling for weight reduction by inducing negative caloric balance with reduction of calorie intake, carbohydrate restriction and increased exercise.

**B1.2.3 Hyperlipidemia.** Independent risk factors for PAD include elevated levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and lipoprotein(a). Factors that are protective for the development of PAD are elevated high-density lipoprotein (HDL) cholesterol and apolipoprotein (a-1) levels.

Direct evidence supporting the use of statins to lower LDL cholesterol levels in PAD comes from the Heart Protection Study (HPS).<sup>33</sup> The HPS enrolled over 20,500 subjects at high risk for cardiovascular events including 6748 patients with PAD, many of whom had no prior history of heart disease or stroke. Patients were randomized to simvastatin 40 mg, antioxidant vitamins, a combination of treatments, or placebo using a 2×2 factorial design, with a 5-year follow up. Simvastatin 40 mg was associated with a 12% reduction in total mortality, 17% reduction in vascular mortality, 24% reduction in coronary heart disease events, 27% reduction in all strokes and a 16% reduction in non-coronary revascularizations. Similar results were obtained in the PAD subgroup, whether they had evidence of coronary disease at baseline or not. Furthermore, there was no threshold cholesterol value below which statin therapy was not associated with benefit. Thus, the HPS demonstrated that in patients with PAD (even in the absence of a prior myocardial infarction or stroke), aggressive LDL lowering was associated with a marked reduction in cardiovascular events (myocardial infarction, stroke and vascular death). A limitation of the HPS was that the evidence in PAD was derived from a subgroup analysis in patients with symptomatic PAD. Despite these limitations, all patients with PAD should have their LDL cholesterol levels lowered to <2.59 mmol/L (<100 mg/dL). To achieve these lipid levels, diet modification should be the initial approach, however, in most cases, diet alone will be unable to decrease the lipids levels to the values mentioned above; therefore, pharmacological treatment will be necessary.

A more recent meta-analysis of statin therapy concluded that in a broad spectrum of patients, a 1 mmol/L (38.6 mg/dL) reduction in LDL cholesterol level was associated with a 20% decrease in the risk of major cardiovascular events.<sup>40</sup> This benefit was not dependent on the initial lipid levels (even patients with lipids in the “normal” range responded), but did depend on the baseline assessment of cardiovascular risk. Since patients with PAD are at high risk, and were included as a subgroup in this meta analysis, the majority of these patients would be considered candidates for statin therapy.

Current recommendations for the management of lipid disorders in PAD are to achieve an LDL cholesterol level of <2.59 mmol/L (<100 mg/dL) and to treat the increased triglyceride and low HDL pattern.<sup>41,42</sup> The recent ACC/AHA guidelines recommend as a general treatment goal achieving an LDL cholesterol level <2.59 mmol/L (<100 mg/dL) in all patients with PAD and in those at high risk (defined as patients with vascular disease in multiple beds) the goal should be an LDL cholesterol level <1.81 mmol/L (<70 mg/dL).<sup>5</sup> In patients with PAD who have elevated triglyceride levels where the LDL cholesterol cannot be accurately calculated, the recommendation is to achieve a non-HDL-cholesterol level <3.36 mmol/L (<130 mg/dL),<sup>43</sup> and in the highest risk patients (with vascular disease in multiple beds) the non-HDL-cholesterol goal should be <2.56 mmol/L (<100 mg/dL).

Patients with PAD commonly have disorders of HDL cholesterol and triglyceride metabolism. The use of fibrates in patients with coronary artery disease who had an HDL cho-

lesterol level <1.04 mmol/L (<40 mg/dL) and an LDL cholesterol level <3.63 mmol/L (>140 mg/dL) was associated with a reduction in the risk of non-fatal myocardial infarction and cardiovascular death.<sup>44</sup> Niacin is a potent drug used to increase HDL cholesterol levels, with the extended-release formulation providing the lowest risk of flushing and liver toxicity. In patients with PAD, niacin has been associated with regression of femoral atherosclerosis and reduced progression of coronary atherosclerosis.<sup>45,46</sup> Whether fibrates and/or niacin will reduce the progression of peripheral atherosclerosis or reduce the risk of systemic cardiovascular events in patients with PAD is not yet known.

### Recommendation 2

Lipid control in patients with peripheral arterial disease (PAD)

- All symptomatic PAD patients should have their low-density lipoprotein (LDL)-cholesterol lowered to <2.59 mmol/L (<100 mg/dL) [A].
- In patients with PAD and a history of vascular disease in other beds (e.g. coronary artery disease) it is reasonable to lower LDL cholesterol levels to <1.81 mmol/L (<70 mg/dL) [B].
- All asymptomatic patients with PAD and no other clinical evidence of cardiovascular disease should also have their LDL-cholesterol level lowered to <2.59 mmol/L (<100 mg/dL) [C].
- In patients with elevated triglyceride levels where the LDL cannot be accurately calculated, the LDL level should be directly measured and treated to values listed above. Alternatively, the non-HDL (high-density lipoprotein) cholesterol level can be calculated with a goal of <3.36 mmol/L (<130 mg/dL), and in high-risk patients the level should be <2.59 mmol/L (<100 mg/dL).
- Dietary modification should be the initial intervention to control abnormal lipid levels [B].
- In symptomatic PAD patients, statins should be the primary agents to lower LDL cholesterol levels to reduce the risk of cardiovascular events [A].
- Fibrates and/or niacin to raise HDL-cholesterol levels and lower triglyceride levels should be considered in patients with PAD who have abnormalities of those lipid fractions [B].

**B1.2.4 Hypertension.** Hypertension is associated with a two- to three-fold increased risk for PAD. Hypertension guidelines support the aggressive treatment of blood pressure in patients with atherosclerosis, indicating PAD. In this high-risk group the current recommendation is a goal of <140/90 mmHg, and <130/80 mmHg if the patient also has diabetes or renal insufficiency.<sup>47,48</sup>

Regarding drug choice, all drugs that lower blood pressure are effective at reducing the risk of cardiovascular events. Thiazide diuretics are first-line agents, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers

should be used in patients with diabetic renal disease or in congestive heart failure, and calcium channel blockers for difficult to control hypertension. Most patients will require multiple agents to achieve desired blood pressure goals. The ACE inhibitor drugs have also shown benefit in PAD, possibly beyond blood-pressure lowering in high-risk groups. This was documented by specific results from the HOPE (Heart Outcomes Prevention Evaluation) study in 4046 patients with PAD.<sup>49</sup> In this subgroup, there was a 22% risk reduction in patients randomized to ramipril compared with placebo, which was independent of lowering of blood pressure. Based on this finding, the United States Federal Drug Administration has now approved ramipril for its cardioprotective benefits in patients at high risk, including those with PAD. Thus, in terms of a drug class, the ACE inhibitors would be recommended in patients with PAD.

Beta-adrenergic blocking drugs have previously been discouraged in PAD because of the possibility of worsening claudication symptoms. However, this concern has not been borne out by randomized trials; therefore, beta-adrenergic-blocking drugs can be safely utilized in patients with claudication.<sup>50</sup> In particular, patients with PAD who also have concomitant coronary disease may have additional cardioprotection with beta-adrenergic-blocking agents. Therefore, beta-adrenergic-blocking agents may be considered when treating hypertension in patients with PAD.

#### Recommendation 3

Control of hypertension in peripheral arterial disease (PAD) patients

- All patients with hypertension should have blood pressure controlled to <140/90 mmHg or <130/80 mmHg if they also have diabetes or renal insufficiency [A].
- JNC VII and European guidelines for the management of hypertension in PAD should be followed [A].
- Thiazides and ACE inhibitors should be considered as initial blood-pressure lowering drugs in PAD to reduce the risk of cardiovascular events [B].
- Beta-adrenergic-blocking drugs are not contraindicated in PAD [A].

**B1.2.5 Diabetes [see also section D2.4].** Diabetes increases the risk of PAD approximately three- to four-fold, and the risk of claudication two-fold. Most patients with diabetes have other cardiovascular risk factors (smoking, hypertension and dyslipidemia) that contribute to the development of PAD. Diabetes is also associated with peripheral neuropathy and decreased resistance to infection, which leads to an increased risk of foot ulcers and foot infections.

Several studies of both type 1 and type 2 diabetes have shown that aggressive blood-glucose lowering can prevent microvascular complications (particularly retinopathy and nephropathy); this has not been demonstrated for PAD, primarily because the studies conducted to date examining glycemic control in diabetes were neither designed nor

powered to examine PAD endpoints.<sup>51,52</sup> The current American Diabetes Association guidance recommends hemoglobin A1C of <7.0% as the goal for treatment of diabetes “in general”, but points out that for “the individual patient,” the A1C should be “as close to normal (<6%) as possible without significant hypoglycemia.” However, it is unclear whether achieving this goal will effectively protect the peripheral circulation or prevent amputation.<sup>53</sup> A single study in patients with type 2 diabetes and a history of cardiovascular disease did not show a benefit of lowering blood glucose levels with the insulin-sensitizing agent pioglitazone on the primary endpoint of the study (cardiovascular morbidity and mortality) but did show a reduction in the risk of a secondary endpoint of myocardial infarction, stroke and vascular death.<sup>51,54</sup> Additional studies will be necessary to define the role of insulin sensitizing agents in the management of cardiovascular complication of diabetes in patients with PAD.

#### Recommendation 4

Control of diabetes in peripheral arterial disease (PAD)

- Patients with diabetes and PAD should have aggressive control of blood glucose levels with a hemoglobin A1c goal of <7.0% or as close to 6% as possible [C].

**B1.2.6 Homocysteine.** An elevated plasma homocysteine level is an independent risk factor for PAD. While supplement with B-vitamins and/or folate can lower homocysteine levels, high-level evidence for the benefits in terms of preventing cardiovascular events is lacking. Two studies of supplemental B vitamins and folic acid in patients with CAD demonstrated no benefit and even a suggestion of harm, so this therapy cannot be recommended.<sup>55,56</sup>

#### Recommendation 5

Use of folate supplementation in peripheral arterial disease (PAD)

- Patients with PAD and other evidence of cardiovascular disease should not be given folate supplements to reduce their risk of cardiovascular events [B].

**B1.2.7 Inflammation.** Markers of inflammation have been associated with the development of atherosclerosis and cardiovascular events. In particular, C-reactive protein is independently associated with PAD.

**B1.2.8 Antiplatelet drug therapy.** Aspirin/acetylsalicylic acid (ASA) is a well-recognized antiplatelet drug for secondary prevention that has clear benefits in patients with cardiovascular diseases. Numerous publications from the Antithrombotic Trialists' Collaboration have concluded that patients with cardiovascular disease will realize a 25% odds reduction in subsequent cardiovascular events with the use of aspirin/ASA.<sup>57</sup> These findings particularly apply to patients with coronary artery and cerebral artery diseases.



This most recent meta-analysis has also clearly demonstrated that low-dose aspirin/ASA (75–160 mg) is protective, and probably safer in terms of gastrointestinal bleeding than higher doses of aspirin/ASA. Thus, current recommendations would strongly favor the use of low-dose aspirin/ASA in patients with cardiovascular diseases. However, the initial Antithrombotic Trialists' Collaboration meta-analysis did not find a statistically significant reduction in cardiovascular events in PAD patients treated with aspirin/ASA who did not have other evidence of vascular disease in other territories.<sup>58</sup> However, in the more recent meta-analysis, when the PAD data were combined from trials using not only aspirin/ASA but also clopidogrel, ticlopidine, dipyridamole and picotamide, there was a significant 23% odds reduction in ischemic events in all subgroups of patients with PAD. Antiplatelet drugs are clearly indicated in the overall management of PAD, although the efficacy of aspirin/ASA is uniformly shown only when PAD and cardiovascular disease coexist.<sup>59</sup>

Picotamide is an antiplatelet drug that inhibits platelet thromboxane A<sub>2</sub> synthase and antagonizes thromboxane receptors that has a mortality benefit in the subgroup of patients with PAD who also have diabetes.<sup>60</sup> In that study, the drug significantly reduced 2-year, all-cause mortality, but not the incidence of non-fatal cardiovascular events. Based on these data, further study is warranted before a recommendation can be made in regards to picotamide.

In addition to aspirin/ASA, the thienopyridines are a class of antiplatelet agents that have been studied in patients with cardiovascular disease. Ticlopidine has been evaluated in several trials in patients with PAD, and has been reported to reduce the risk of myocardial infarction, stroke and vascular death.<sup>61</sup> However, the clinical usefulness of ticlopidine is limited by side effects such as neutropenia and thrombocytopenia. Clopidogrel was studied in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial and shown to be effective in the symptomatic PAD population to reduce the risk of myocardial infarction, stroke and vascular death. The overall benefit in this particular group was a 24% relative risk reduction over the use of aspirin/ASA.<sup>32</sup> This represents a number needed to treat with clopidogrel compared with aspirin/ASA of 87 patients to prevent an event. Clopidogrel has a safety profile similar to aspirin/ASA, with only rare reports of thrombocytopenia. Patients undergoing surgical procedures are at increased risk of bleeding when taking anti-thrombotics including heparins, aspirin/ASA or clopidogrel. Thus, temporary cessation of these drugs should be individualized based on the type of surgery and/or endovascular intervention/revascularization to reduce bleeding risks.

Recent publications in patients with acute coronary syndromes suggest that combination therapy with aspirin/ASA and clopidogrel is more effective than with aspirin/ASA alone, but at a higher risk of major bleeding.<sup>62</sup> A recent study of clopidogrel combined with aspirin/ASA (versus aspirin/ASA alone) was performed in a high-risk population consisting of patients with

established cardiovascular disease (including PAD) and patients without a history of cardiovascular disease but who had multiple risk factors. This study showed no overall benefit of the combination of antiplatelet drugs as compared with aspirin/ASA alone on the outcome of myocardial infarction, stroke and vascular death.<sup>63</sup> Thus, combination therapy cannot be recommended in patients with stable PAD, and if clopidogrel is considered it should be used as monotherapy.

#### **Recommendation 6**

Antiplatelet therapy in peripheral arterial disease (PAD)

- All symptomatic patients with or without a history of other cardiovascular disease should be prescribed an antiplatelet drug long term to reduce the risk of cardiovascular morbidity and mortality [A].
- Aspirin/ASA is effective in patients with PAD who also have clinical evidence of other forms of cardiovascular disease (coronary or carotid) [A].
- The use of aspirin/ASA in patients with PAD who do not have clinical evidence of other forms of cardiovascular disease can be considered [C].
- Clopidogrel is effective in reducing cardiovascular events in a subgroup of patients with symptomatic PAD, with or without other clinical evidence of cardiovascular disease [B].

## **B2 HEALTH ECONOMICS OF RISK-FACTOR MANAGEMENT**

For all cardiovascular risk factors, including smoking cessation, the most effective and cost-effective interventions are those that combine a government-led action with individual prevention interventions. In other words, laws that reduce the amount of added salt in processed foods and that increase taxes on tobacco are more cost effective than individual prevention alone, but a combination of both is best.<sup>64</sup>

The issue in dealing with risk factors is the overall budgetary impact of enforcing compliance to published guidelines. This is due to the large size of the population at risk and the difficulty of organizing the follow up of chronic patients treated by numerous health professionals. An additional difficulty for payers is that the health and economic benefits are delayed while resources for treatment have to be expended at once. Studies on dyslipidemia, diabetes and hypertension have shown that compliance with guidelines is usually cost effective, within the range of \$20–30,000 per added year of life. This holds true when several risk factors are associated.<sup>65,66</sup>

The effectiveness and cost-effectiveness of a number of lifestyle interventions, including smoking cessation, exercise and diet, have been assessed by the Cochrane Collaboration.

### **B2.1 Cost-effectiveness of smoking cessation interventions**

For smoking cessation, the performance of professionals in detection and interventions (including follow-up appointments, self-help materials and nicotine gum) is improved by training, although the overall effect on quit rates is modest. However, “training can be expensive, and simply providing programs for health care professionals, without addressing the constraints imposed by the conditions in which they practice, is unlikely to be a wise use of health care resources”.<sup>67</sup> Advising patients to use the telephone services is an effective strategy.<sup>67</sup>

The unit cost of advice alone is estimated \$5 per patient, while counseling costs \$51 per patient. Adding pharmacologic agents to counseling increases the quit rate and is cost effective: assuming that a long-term quitter increases his life expectancy by an average 2 years, the cost-effectiveness ratio of added pharmacological intervention ranges from \$1 to \$3,000 per life-year gained.<sup>68</sup>

### **B2.2 Cost-effectiveness of exercise interventions**

Exercise interventions are heterogenic, including one-to-one counseling/advice or group counseling/advice; self-directed or prescribed physical activity; supervised or unsupervised physical activity; home-based or facility-based physical activity; ongoing face-to-face support; telephone support; written education/motivation material; and self monitoring. The intervention can be delivered by one or a number of practitioners including physicians, nurses, health educators, counselors, exercise leaders, and peers. Interventions “have a positive moderate sized effect on increasing self-reported physical activity and measured cardio-respiratory fitness, at least in the short to mid-term”.<sup>69</sup> Assuming an adherence of 50% in the first year and 30% in subsequent years, the cost-effectiveness ratio of unsupervised exercise is less than \$12,000 per life year gained. Supervised exercise has a cost-effectiveness ratio ranging from \$20,000–\$40,000 per life year gained (the strategies are more efficient in elderly males with multiple risk factors).<sup>70</sup>

### **B2.3 Cost-effectiveness of pharmacologic interventions**

It is difficult to recommend one drug over another for risk factor modification on cost-effectiveness considerations because drug prices are subject to variations between countries and over time. Although this is true for all interventions, the case of a newer drug used in prevention of cardiac risk factors is particular in that the medical benefits of one treatment over another are usually small and, therefore, the cost-effectiveness ratio is highly dependent on drug prices. The global cost-effectiveness analysis on the reduction of cardiovascular disease risk<sup>63</sup> found that treatment by a combination of statin, beta blocker, diuretic and aspirin was most efficient in avoiding death and disability. When oral anti-platelet agents are considered, assuming a threshold of up to £20,000–40,000 per additional quality-adjusted life year (QALY), clopidogrel would be consid-

ered cost effective for treatment duration of 2 years in patients with peripheral arterial disease. For a lifetime treatment duration, clopidogrel would be considered more cost effective than aspirin as long as treatment effects on non-vascular deaths are not considered.<sup>71</sup>

Because recent studies have often failed to demonstrate a benefit on mortality, the efficiency of drug treatments has been measured in ‘cost per major event averted’ and is, therefore, not comparable to ‘cost per life year gained’, although there is a relationship between the two. For example, the cost effectiveness of 40 mg/day simvastatin in high-risk patients is £4,500 (95% CI: 2,300–7,400) per major vascular event averted, but the result is highly sensitive to the statin cost. In this context, it is likely that the use of an off-patent statin would prove more efficient.<sup>72</sup> For patients with high cardiovascular risk, the use of ACE inhibitors appears very cost effective in most countries, as shown by the results of the HOPE study: less than \$10,000 per event averted in the various developed countries where the economic analyses were undertaken.<sup>73</sup>

In conclusion, the risk-management strategy chosen may differ depending on whether the individual or population perspectives are considered. In a population perspective with an objective of sustainability and access, public interventions to reduce smoking, salt and fat intake, combined with the prescription of cheap and off-patent drugs, are preferred. If the individual perspective is considered, however, newer and more expensive drugs offer additional health benefits at reasonable cost-effectiveness ratios.

## **B3 FUTURE ASPECTS OF CONTROLLING ISCHEMIC RISK FACTORS**

It is clear that decreasing the level of any risk factor, such as blood pressure and LDL cholesterol, can help improve prognosis. However, it is not clear what the optimal values are in the general population and in individual disease states. Future studies are also needed to define guidelines for different clinical presentations: should blood pressure be lowered to 140/90 mmHg in patients with PAD, or should it be lower? Should these values also be usable in critical leg ischemia? Is there a J-shaped curve (an increased risk at very low blood pressure values)?

Modifying several risk factors is at least as beneficial as changing only one. Combination therapy with several drugs will become inevitable. However, what is the compliance of the patients who are faced with such combination therapy? Future studies should clarify whether the ‘polypill’ (several drugs in one pill) could help in achieving the goals of improved risk factor modification. Calculations should be made on the costs of such combination therapy versus the change in long-term prognosis.

Diabetes sharply increases total cardiovascular risk; are the current goals for blood pressure and lipids strict enough to control this risk? Studies are needed to show whether the

choice of antihypertensive drugs should be guided by their influence on insulin resistance or other metabolic parameters.

It is becoming evident that inflammatory processes play an important role in the atherosclerotic process. It is not yet clear if drugs that target chronic inflammation (e.g. antibiotics) would add to usual risk factor management in controlling the progress of the atherosclerotic process.

#### **B4 CO-EXISTING CORONARY ARTERY DISEASE**

The prevalence of CAD in patients with PAD is high, which strongly increases the risk for cardiac mortality and morbidity in these patients (see section A4.1).<sup>4,26</sup> Therefore, all PAD patients should be considered at high risk for clinically significant CAD, for which several guidelines exist.<sup>74,75</sup> Patients should be evaluated for evidence of CAD.

Treatment decisions for coexisting CAD should be based on current practice standards, and patients who have unstable symptoms (acute coronary syndrome, decompensated heart failure) should be referred to a cardiovascular physician for appropriate diagnosis and treatment. For patients with stable CAD, management should be guided by the severity of the symptoms and co-morbid conditions. Most patients with severe cardiac symptoms will require coronary angiography to determine the appropriate means for revascularization. All patients should be given appropriate medical therapy to treat symptoms and atherosclerotic risk factors (see section B1).

Cardiac assessment scores may be useful in the context of patients being considered for peripheral revascularization.<sup>76</sup> In patients with a high cardiac risk assessment score, current guidelines recommend further evaluation of the patient for possible coronary revascularization.<sup>76</sup> However in the recent Coronary Artery Revascularization Prophylaxis (CARP) trial of patients with peripheral vascular disease who were considered high risk for perioperative complications and had significant CAD, coronary revascularization did not reduce overall mortality or perioperative myocardial infarction.<sup>77</sup> In addition, patients who underwent coronary revascularization had a significantly longer time to vascular surgery compared with patients who did not. Therefore, this strategy of a pre-emptive coronary revascularization prior to peripheral vascular surgery should not normally be pursued.

In most patients, perioperative use of beta-adrenergic blocking agents is associated with reduced cardiovascular risks of surgery. Recent studies have shown that beta-adrenergic blockade with bisoprolol significantly decreased the risk for cardiovascular events during vascular surgery and afterwards.<sup>78,79</sup> Besides controlling symptoms of

myocardial ischemia, treatment with beta-blocking agents also has the benefit of favorably influencing prognosis in these patients.<sup>80</sup>

#### **Recommendation 7**

Management of coronary artery disease (CAD) in peripheral arterial disease patients

- Patients with clinical evidence of CAD (angina, ischemic congestive heart failure) should be evaluated and managed according to current guidelines [C].
- Patients with PAD considered for vascular surgery may undergo further risk stratification and those found to be at very high risk managed according to current guidelines for coronary revascularization [C].
- Routine coronary revascularization in preparation for vascular surgery is not recommended [A].

#### **Recommendation 8**

Use of beta-blocking agents before vascular surgery

- When there are no contraindications, beta-adrenergic blockers should be given perioperatively to patients with peripheral arterial disease undergoing vascular surgery in order to decrease cardiac morbidity and mortality [A].

#### **B5 CO-EXISTING CAROTID ARTERY DISEASE**

The prevalence of carotid artery disease in PAD patients is also high (see section A4.2); and patients with PAD are at an increased risk for cerebrovascular events. Evaluation of the carotid circulation should be based on a history of transient ischemic attack or stroke. Further evaluation and consideration for revascularization should be based on current guidelines.<sup>81,82</sup>

#### **Recommendation 9**

Management of carotid artery disease in peripheral arterial disease (PAD) patients

- The management of symptomatic carotid artery disease in patients with PAD should be based on current guidelines [C].

#### **B6 CO-EXISTING RENAL ARTERY DISEASE**

Patients with PAD are at an increased risk for renovascular hypertension. The management of patients with PAD and atherosclerotic renal artery disease is focused on control of hypertension and preservation of renal function. In such cases, evaluation and treatment should be based on current guidelines.<sup>5,83,84</sup>

These patients should be referred to an appropriate cardiovascular physician.

### **Recommendation 10**

Management of renal artery disease in peripheral arterial disease (PAD) patients

- When renal artery disease is suspected in PAD patients, as evidenced by poorly controlled hypertension or renal insufficiency, patients should be treated according to current guidelines and consider referral to a cardiovascular physician [C].

## SECTION C – INTERMITTENT CLAUDICATION

### C1 CHARACTERIZATION OF PATIENTS

#### C1.1 Definition of intermittent claudication and limb symptoms in peripheral arterial disease

The majority of patients with peripheral arterial disease (PAD) have limited exercise performance and walking ability. As a consequence, PAD is associated with reduced physical functioning and quality of life. In patients with PAD, the classical symptom is intermittent claudication (which means to limp), which is muscle discomfort in the lower limb reproducibly produced by exercise and relieved by rest within 10 minutes. Patients may describe muscle fatigue, aching or cramping on exertion that is relieved by rest. The symptoms are most commonly localized to the calf, but may also affect the thigh or buttocks. Typical claudication occurs in up to one-third of all patients with PAD. Importantly, patients without classical claudication also have walking limitations that may be associated with atypical or no limb symptoms.<sup>85</sup> Typical claudication symptoms may not occur in patients who have co-morbidities that prevent sufficient activity to produce limb symptoms (i.e. congestive heart failure, severe pulmonary disease, musculoskeletal disease) or in patients who are so deconditioned that exercise is not performed. Therefore, patients suspected of having PAD should be questioned about any limitations they experience during exercise of the lower extremities that limits their walking ability.

PAD is caused by atherosclerosis that leads to arterial stenosis and occlusions in the major vessels supplying the lower extremities. Patients with intermittent claudication have normal blood flow at rest (and, therefore, have no limb symptoms at rest). With exercise, occlusive lesions in the arterial supply of the leg muscles limits the increase in blood flow, resulting in a mismatch between oxygen supply and muscle metabolic demand that is associated with the symptom of claudication. Acquired metabolic abnormalities in the muscle of the lower extremity also contribute to the reduced exercise performance in PAD.

#### C1.2 Differential diagnosis

Table C1 shows the differential diagnosis of intermittent claudication (IC); Table C2 shows potential causes of occlusive arterial lesions in the lower extremity arteries potentially causing claudication.

#### C1.3 Physical examination

The physical examination should assess the circulatory system as a whole. Key components of the general examination include measurement of blood pressure in both arms, assessment of cardiac murmurs, gallops or arrhythmias, and palpation for an abdominal aortic aneurysm (does not exclude the presence of an aneurysm). Less specific aspects of the physical examination for PAD include changes in color and temperature of the skin of the feet, muscle atrophy from inability to exercise, decreased hair growth and hypertrophied, slow-growing nails. The presence of a bruit in the region of the carotid, aorta or femoral arteries may arise from turbulence and suggest significant arterial disease. However, the absence of a bruit does not exclude arterial disease.

The specific peripheral vascular examination requires palpation of the radial, ulnar, brachial, carotid, femoral, popliteal, dorsalis pedis and posterior tibial artery pulses. The posterior tibial artery is palpated at the medial malleolus. In a small number of healthy adults, the dorsalis pedis pulse on the dorsum of the foot may be absent due to branching of the anterior tibial artery at the level of the ankle. In this situation, the distal aspect of the anterior tibial artery may be detected and assessed at the ankle. Also, a terminal branch of the peroneal artery may be palpated at the lateral malleolus. For simplicity, pulses may be graded from 0 (absent), 1 (diminished) and 2 (normal). An especially prominent pulse at the femoral and/or popliteal location should raise the suspicion of an aneurysm. A diminished or absent femoral pulse suggests aorto-iliac artery occlusive disease, which reduces inflow to the limb. In contrast, a normal femoral, but absent pedal, pulse suggests significant arterial disease in the leg with preserved inflow. Pulses should be assessed in both legs and pulse abnormalities correlated with leg symptoms to determine the lateralization of the disease.

Patients with an isolated occlusion of an internal iliac (hypogastric) artery may have normal femoral and pedal pulses at rest and after exercise, but buttocks claudication (and impotence in males). Similar symptoms may occur in patients with stenosis of the common or external iliac artery. These patients may also have normal pulses at rest, but loss of the pedal pulses after exercise. The loss of the pedal pulse is coincident with a drop in ankle pressure due to the inability of the large vessels (in the presence of occlusive disease) to provide sufficient flow to maintain distal pressure with muscle vasodilation during exercise.

Despite the utility of the pulse examination, the finding of absent pedal pulses tends to over-diagnose PAD, whereas if the symptom of classic claudication is used to identify PAD, it will lead to a significant under-diagnosis of PAD.<sup>86</sup> Thus, PAD must be confirmed in suspected patients with non-invasive testing using the ankle-brachial index, or other hemodynamic or imaging studies described below.



**Table C1.** Differential diagnosis of intermittent claudication (IC)

<i>Condition</i>	<i>Location</i>	<i>Prevalence</i>	<i>Characteristic</i>	<i>Effect of exercise</i>	<i>Effect of rest</i>	<i>Effect of position</i>	<i>Other characteristics</i>
Calf IC	Calf muscles	3–5% of adult population	Cramping, aching discomfort	Reproducible onset	Quickly relieved	None	May have atypical limb symptoms on exercise
Thigh and buttock IC	Buttocks, hip, thigh	Rare	Cramping, aching discomfort	Reproducible onset	Quickly relieved	None	Impotence May have normal pedal pulses with isolated iliac artery disease
Foot IC	Foot arch	Rare	Severe pain on exercise	Reproducible onset	Quickly relieved	None	Also may present as numbness
Chronic compartment syndrome	Calf muscles	Rare	Tight, bursting pain	After much exercise (jogging)	Subsides very slowly	Relief with elevation	Typically heavy muscled athletes
Venous claudication	Entire leg, worse in calf	Rare	Tight, bursting pain	After walking	Subsides slowly	Relief speeded by elevation	History of iliofemoral deep vein thrombosis, signs of venous congestion, edema
Nerve root compression	Radiates down leg	Common	Sharp lancinating pain	Induced by sitting, standing or walking	Often present at rest	Improved by change in position	History of back problems Worse with sitting Relief when supine or sitting
Symptomatic Bakers cyst	Behind knee, down calf	Rare	Swelling, tenderness	With exercise	Present at rest	None	Not intermittent
Hip arthritis	Lateral hip, thigh,	Common	Aching discomfort	After variable degree of exercise	Not quickly relieved	Improved when not weight bearing	Symptoms variable History of degenerative arthritis
Spinal stenosis	Often bilateral buttocks, posterior leg	Common	Pain and weakness	May mimic IC	Variable relief but can take a long time to recover	Relief by lumbar spine flexion	Worse with standing and extending spine
Foot/ankle arthritis	Ankle, foot, arch	Common	Aching pain	After variable degree of exercise	Not quickly relieved	May be relieved by not bearing weight	Variable, may relate to activity level and present at rest

IC – intermittent claudication.

**Table C2.** Causes of occlusive arterial lesions in lower extremity arteries potentially causing claudication

Atherosclerosis (PAD)
Arteritis
Congenital and acquired coarctation of aorta
Endofibrosis of the external iliac artery (iliac artery syndrome in cyclists)
Fibromuscular dysplasia
Peripheral emboli
Popliteal aneurysm (with secondary thromboembolism)
Adventitial cyst of the popliteal artery
Popliteal entrapment
Primary vascular tumors
Pseudoxanthoma elasticum
Remote trauma or irradiation injury
Takayasu's disease
Thromboangiitis obliterans (Buerger's disease)
Thrombosis of a persistent sciatic artery

**Recommendation 11**

History and physical examination in suspected peripheral arterial disease (PAD)

- Individuals with risk factors for PAD, limb symptoms on exertion or reduced limb function should undergo a vascular history to evaluate for symptoms of claudication or other limb symptoms that limit walking ability [B].
- Patients at risk for PAD or patients with reduced limb function should also have a vascular examination evaluating peripheral pulses [B].
- Patients with a history or examination suggestive of PAD should proceed to objective testing including an ankle-brachial index [B].



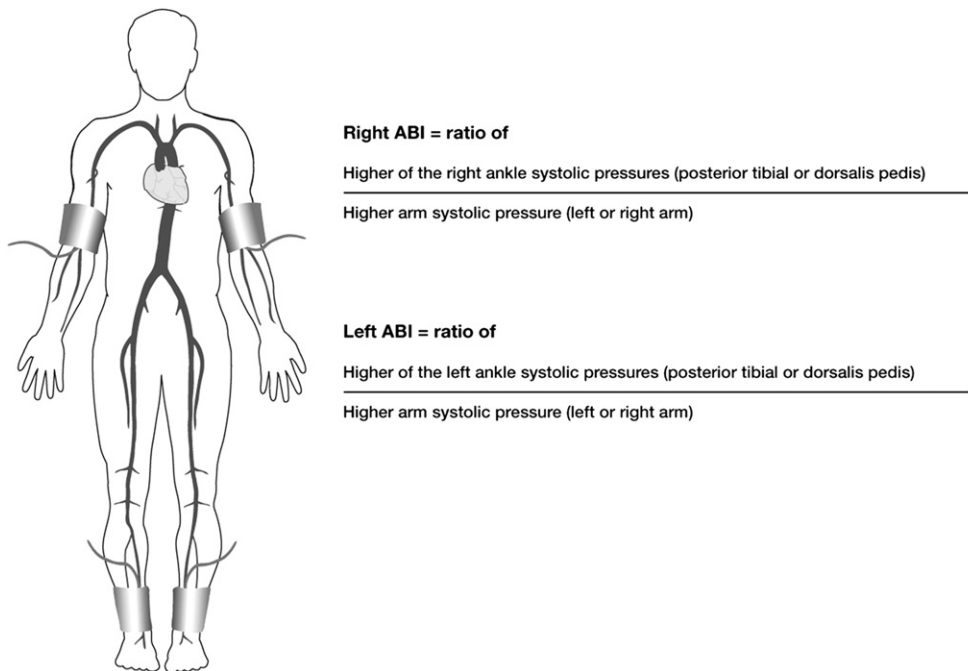


Fig. C1. Measurement of the ABI. ABI – ankle-brachial index.

## C2 DIAGNOSTIC EVALUATION OF PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

### C2.1 Ankle pressure measurements (ankle-brachial index)

Measuring the pressure in the ankle arteries has become a standard part of the initial evaluation of patients with suspected PAD. A common method of measurement uses a 10–12 cm sphygmomanometer cuff placed just above the ankle and a Doppler instrument used to measure the systolic pressure of the posterior tibial and dorsalis pedis arteries of each leg (Fig. C1). These pressures are then normalized to the higher brachial pressure of either arm to form the ankle-brachial index (ABI). The index leg is often defined as the leg with the lower ABI.

The ABI provides considerable information. A reduced ABI in symptomatic patients confirms the existence of hemodynamically significant occlusive disease between the heart and the ankle, with a lower ABI indicating a greater hemodynamic severity of occlusive disease. The ABI can serve as an aid in differential diagnosis, in that patients with exercise-related leg pain of non-vascular causes will have a normal ankle pressure at rest and after exercise. In patients with PAD who do not have classic claudication (are either asymptomatic or have atypical symptoms) a reduced ABI is highly associated with reduced limb function. This is defined as reduced walking speed and/or a shortened walking distance during a timed 6-minute walk. From a systemic perspective, a reduced ABI is a potent predictor of the risk of future cardiovascular events, as discussed in section B1.1. This risk is related to the degree of reduction of the ABI (lower ABI predicts higher risk) and is independent of

other standard risk factors. The ABI thus has the potential to provide additional risk stratification in patients with Framingham risk between 10% and 20% in 10 years, in that an abnormal ABI in this intermediate-risk group would move the patient to high risk in need of secondary prevention whereas a normal ABI would lower the estimate of risk indicating the need for primary prevention strategies (see Fig. B1).

The ABI should become a routine measurement in the primary care practice of medicine. When used in this context, screening of patients aged 50–69 years who also had diabetes or a smoking history, or screening all persons over the age of 70 resulted in a prevalence of PAD of 29%.<sup>11</sup> The reproducibility of the ABI varies in the literature, but it is significant enough that reporting standards require a change of 0.15 in an isolated measurement for it to be considered clinically relevant, or >0.10 if associated with a change in clinical status. The typical cut-off point for diagnosing PAD is  $\leq 0.90$  at rest.

The value of a reduced ABI is summarized as follows:

- Confirms the diagnosis of PAD
- Detects significant PAD in (sedentary) asymptomatic patients
- Used in the differential diagnosis of leg symptoms to identify a vascular etiology
- Identifies patients with reduced limb function (inability to walk defined distances or at usual walking speed)
- Provides key information on long-term prognosis, with an ABI  $\leq 0.90$  associated with a 3–6-fold increased risk of cardiovascular mortality

- Provides further risk stratification, with a lower ABI indicating worse prognosis
- Highly associated with coronary and cerebral artery disease
- Can be used for further risk stratification in patients with a Framingham risk score between 10%–20%.

In some patients with diabetes, renal insufficiency, or other diseases that cause vascular calcification, the tibial vessels at the ankle become non-compressible. This leads to a false elevation of the ankle pressure. These patients typically have an ABI >1.40 and, in some of these patients, the Doppler signal at the ankle cannot be obliterated even at cuff pressures of 300 mmHg. In these patients additional non-invasive diagnostic testing should be performed to evaluate the patient for PAD (discussed in section G1.3). Alternative tests include toe systolic pressures, pulse volume recordings, transcutaneous oxygen measurements or vascular imaging (most commonly with duplex ultrasound). When any of these tests is abnormal, a diagnosis of PAD can be reliably made.

#### Recommendation 12

Recommendations for ankle-brachial index (ABI) screening to detect peripheral arterial disease in the individual patient.

An ABI should be measured in:

- All patients who have exertional leg symptoms [B].
- All patients between the age of 50–69 and who have a cardiovascular risk factor (particularly diabetes or smoking) [B].
- All patients age  $\geq 70$  years regardless of risk-factor status [B].
- All patients with a Framingham risk score 10%–20% [C].

### C2.2 Exercise testing to establish the diagnosis of peripheral arterial disease

As discussed above, patients with claudication who have an isolated iliac stenosis may have no pressure decrease across the stenosis at rest and, therefore, a normal ABI at rest. However, with exercise the increase inflow velocity will make such lesions hemodynamically significant. Under these conditions, exercise will induce a decrease in the ABI that can be detected in the immediate recovery period and thus establish the diagnosis of PAD. The procedure requires an initial measurement of the ABI at rest. The patient is then asked to walk (typically on a treadmill at 3.2 km/h (2 mph), 10%–12% grade) until claudication pain occurs (or a maximum of 5 minutes), following which the ankle pressure is again measured. A decrease in ABI of 15%–20% would be diagnostic of PAD. If a treadmill is not available then walking exercise may be performed by climbing stairs or in the hallway.

### C2.3 Alternative stress tests for patients who cannot perform treadmill exercise

Certain patient populations should not be asked to undergo treadmill testing as previously described, including those who have severe aortic stenosis, uncontrolled hypertension or patients with other exercise-limiting comorbidities, including advanced congestive heart failure or chronic obstructive pulmonary disease.<sup>87</sup>

Patients who cannot perform treadmill exercise can be tested with active pedal plantar flexion. Active pedal plantar flexion has demonstrated excellent correlation with treadmill testing, and should be considered an appropriate alternative to treadmill testing. A second alternative is to inflate a thigh cuff well above systolic pressure for 3 to 5 minutes, producing a similar degree of “reactive” hyperemia. The decrease in ankle pressure 30 seconds after cuff deflation is roughly equivalent to that observed 1 minute after walking to the point of claudication on a treadmill. Unfortunately, many patients do not tolerate the discomfort associated with this degree and duration of cuff inflation and, in modern vascular laboratories, this is rarely performed.

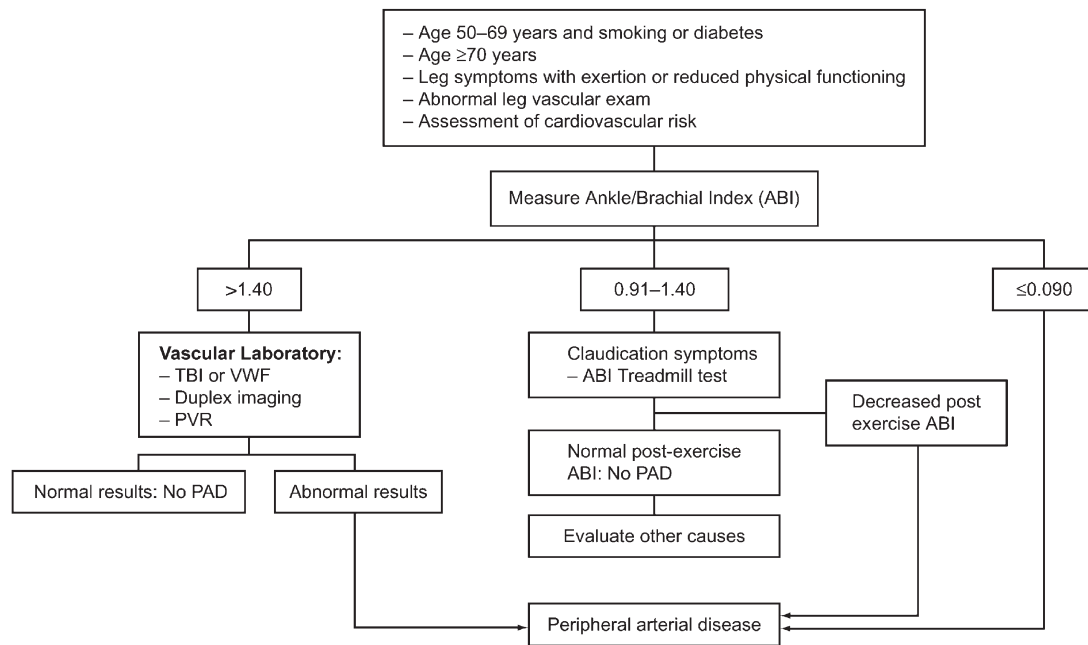
Discussion of additional diagnostic tests to establish the diagnosis of PAD can be found in section G.

Fig. C2 shows an algorithm for the diagnosis of PAD.

### C3 OUTCOME ASSESSMENT OF INTERMITTENT CLAUDICATION IN CLINICAL PRACTICE

Intermittent claudication is a symptom of peripheral arterial disease that profoundly limits the patient’s ability to walk and as a result is associated with a reduced exercise performance. This reduction in exercise performance can be easily quantified with a graded treadmill test where the time of onset of claudication pain (claudication onset time) and peak walking time can be determined at baseline. The treadmill test will also allow the clinician to determine if the patient experiences typical claudication pain with exercise, or other symptoms that limit exercise. This assessment will help guide therapy because if claudication is not the major symptom limiting exercise then specific claudication therapies may not be indicated.

Once claudication is established as the major symptom limiting exercise, then the primary goal of claudication therapy is to relieve the symptoms during walking and improve exercise performance and community activities. Appropriate treatment of the claudicant must address both the specific lower-extremity disability and the systemic impact of the disease. Ideally, treatment will result in an improvement in both the vascular status of the lower extremity and reduce the patient’s subsequent risk of fatal and non-fatal cardiovascular events. In clinical trials of claudication therapy, the primary endpoint is usually a treadmill test of the peak walking time or distance as well as the time or distance for the onset of claudication.<sup>88</sup> The same parameters can be assessed to determine the clinical benefit of any claudication therapy in an individual patient. In addition, changes in the physical domains of the Medical Out-



**Fig. C2.** Algorithm for diagnosis of peripheral arterial disease. TBI – toe brachial index; VWF – velocity wave form; PVR – pulse volume recording. Reproduced with permission from Hiatt WR. *N Engl J Med* 2001;**344**:1608–1621.

comes Short Form 36 (SF-36) or the Walking Impairment Questionnaire (WIQ) serve as patient-based measures of treatment effect. The complete assessment of the outcomes of treatment of the claudicant, therefore, requires the use of both clinical and patient-based parameters.

### Recommendation 13

Determining success of treatment for intermittent claudication.

Patient-based outcome assessment (including a focused history of change in symptoms) is the most important measure; however, if quantitative measurements are required the following may be used:

1. Objective measures include an increase in peak exercise performance on a treadmill [B].
2. Patient-based measures would include an improvement on a validated, disease-specific health status questionnaire; or the physical functioning domain on a validated generic health status questionnaire [B].

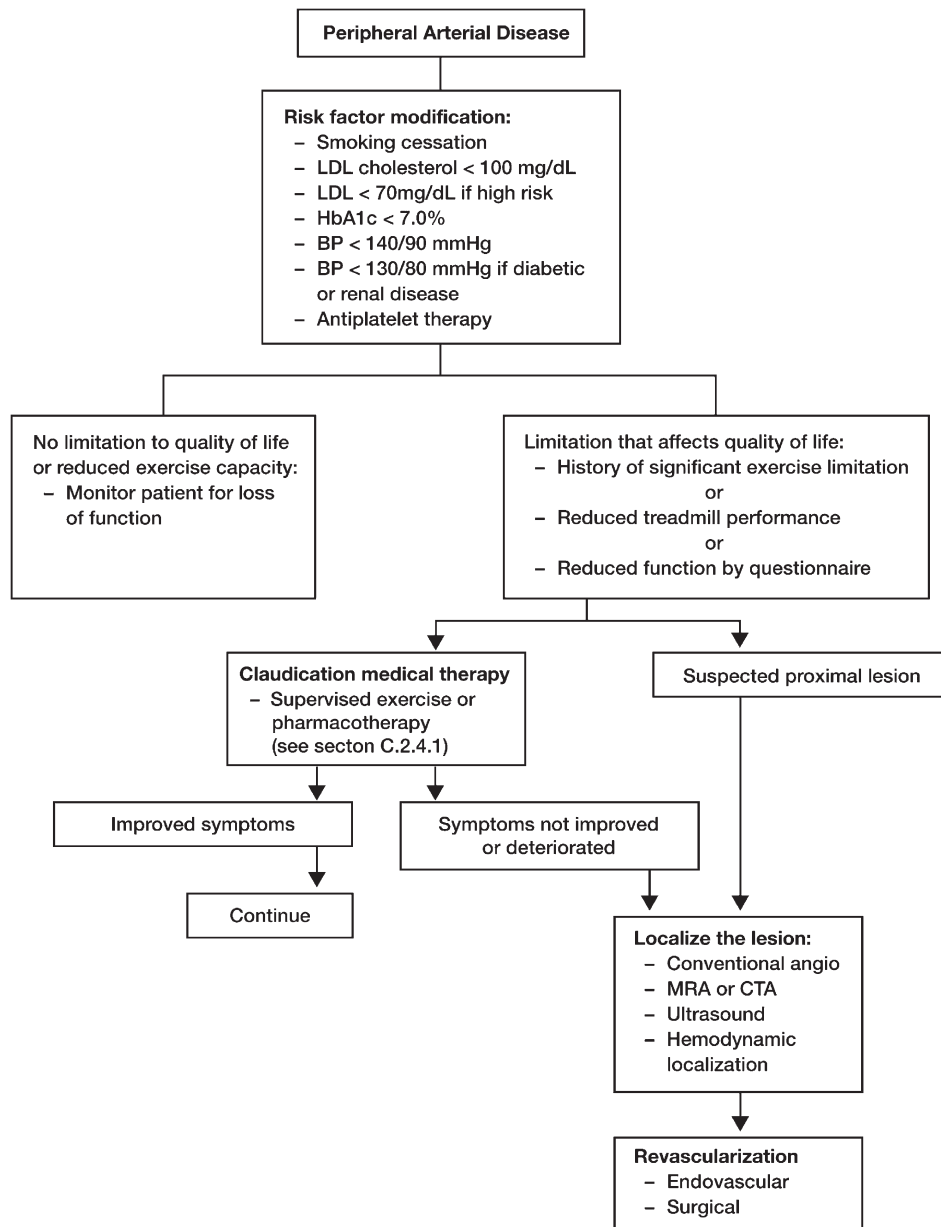
## C4 TREATMENT OF INTERMITTENT CLAUDICATION

### C4.1 Overall strategy and basic treatment for intermittent claudication

**C4.1.1 Overall strategy.** Patients with claudication experience reversible muscle ischemia during walking that is characterized by cramping and aching in the affected muscle. These symptoms result in a severe limitation in exercise performance and walking ability. The exercise lim-

itation is associated with marked impairments in walking distance, walking speed and overall function. Patients with claudication are physically impaired and, therefore, the treatment goals are to relieve symptoms, improve exercise performance and daily functional abilities. The initial approach to the treatment of limb symptoms should focus on structured exercise and, in selected patients, pharmacotherapy to treat the exercise limitation of claudication (risk factor modification and antiplatelet therapies are indicated to decrease the risk of cardiovascular events and improve survival). Failure to respond to exercise and/or drug therapy would lead to the next level of decision making, which is to consider limb revascularization. However, in patients in whom a proximal lesion is suspected (findings of buttocks claudication, reduced or absent femoral pulse) the patient could be considered for revascularization without initially undergoing extensive medical therapy. The overall strategy is summarized in Fig. C3.

**C4.1.2 Exercise rehabilitation.** In patients with claudication, there is a considerable body of evidence to support the clinical benefits of a supervised exercise program in improving exercise performance and community-based walking ability. This intervention has been thoroughly reviewed, both in terms of mechanism of the training effect, as well as practical guidelines for the exercise program.<sup>89,90</sup> Several studies have suggested that some level of supervision is necessary to achieve optimal results (general, unstructured recommendations to exercise by the physician do not result in any clinical benefit). In prospective studies of supervised exercise conducted for 3 months or longer, there are clear increases in treadmill exercise performance



**Fig. C3.** Overall treatment strategy for peripheral arterial disease. BP – blood pressure; HbA1c – hemoglobin A1c; LDL – low density lipoprotein; MRA – magnetic resonance angiography; CTA – computed tomographic angiography. Reproduced with permission from Hiatt WR. *N Engl J Med* 2001;**344**:1608–1621.

and a lessening of claudication pain severity during exercise.<sup>91</sup>

The predictors of response to the training program include achieving a high level of claudication pain during the training sessions and 6 months or longer of formal training and walking exercise (versus other training modalities). Training on a treadmill has been shown to be more effective than strength training or combinations of training modalities. However, different modes of exercise training have been applied including upper extremity cycle ergome-

ter exercise that is associated with a training response. The mechanisms of response to exercise training have been reviewed previously and include improvements in walking efficiency, endothelial function and metabolic adaptations in skeletal muscle.<sup>90</sup>

The exercise prescription should be based on exercise sessions that are held three times a week, beginning with 30 minutes of training but then increasing to approximately 1 hour per session. During the exercise session, treadmill exercise is performed at a speed and grade that will

induce claudication within 3–5 minutes. The patient should stop walking when claudication pain is considered moderate (a less optimal training response will occur when the patient stops at the onset of claudication). The patient will then rest until claudication has abated, after which the patient should resume walking until moderate claudication discomfort recurs. This cycle of exercise and rest should be at least 35 minutes at the start of the program and increase to 50 minutes as the patient becomes comfortable with the exercise sessions (but always avoiding excessive fatigue or leg discomfort). In subsequent visits, the speed or grade of the treadmill is increased if the patient is able to walk for 10 minutes or longer at the lower workload without reaching moderate claudication pain. Either speed or grade can be increased, but an increased grade is recommended if the patient can already walk at 2 mph (3.2 km/h). An additional goal of the program is to increase patient walking speed up to the normal 3.0 mph (4.8 km/h) from the average PAD patient walking speed of 1.5–2.0 mph (approximately 2.4–3.2 km/h).

Many patients may have contraindications for exercise (e.g. severe CAD, musculoskeletal limitations or neurological impairments). Other patients may be unwilling to participate in supervised sessions if they have long distances to travel to the exercise facility, if an appropriate rehabilitation program is not available in their area, or if the expenses incurred are too great. The prevalence of contraindications to an exercise program ranges from 9%–34% depending on the population studied. The major limitation of exercise rehabilitation is the lack of availability of a supervised setting to refer patients. Though exercise therapy is of proven effectiveness, some patients are simply not willing to persist with an exercise program in order to maintain the benefit. In addition, a claudication exercise program in a patient with diabetes who has severe distal neuropathy may precipitate foot lesions in the absence of proper footwear.

#### **Recommendation 14**

Exercise therapy in intermittent claudication

- Supervised exercise should be made available as part of the initial treatment for all patients with peripheral arterial disease [A].
- The most effective programs employ treadmill or track walking that is of sufficient intensity to bring on claudication, followed by rest, over the course of a 30–60 minute session. Exercise sessions are typically conducted three times a week for 3 months [A].

#### **C4.2 Pharmacotherapy for intermittent claudication**

Patients with IC should all receive drug and lifestyle treatment for their cardiovascular risk factors and coexisting diseases to prevent cardiovascular events (myocardial infarction, stroke and death) associated with atherosclerosis. However, this approach will typically not provide a significant reduction or elimination of

symptoms of claudication. Thus, claudication drug therapy for relief of symptoms typically involves different drugs than those that would be used for risk reduction (an exception may be lipid-lowering therapy). However, a number of types of drugs have been promoted for symptom relief, with varying levels of evidence to support their use. Not all the drugs presented in this section are universally available, so access to certain agents may be limited in certain countries. Finally, current drug therapy options do not provide the same degree of benefit as does a supervised exercise program or successful revascularization.

##### **C4.2.1 Drugs with evidence of clinical utility in claudication**

*Note that not all these drugs are available in every country*

**Cilostazol** Cilostazol is a phosphodiesterase III inhibitor with vasodilator, metabolic and antiplatelet activity. The benefits of this drug have been described in a meta-analysis of six randomized, controlled trials involving 1751 patients, including 740 on placebo, 281 on cilostazol 50 mg twice-daily (BID), 730 on cilostazol 100 mg BID. The 73 on cilostazol 150 mg BID and 232 on pentoxifylline 400 mg thrice-daily (TID) were excluded from the analysis.<sup>92</sup> This analysis demonstrated that the net benefit of cilostazol over placebo in the primary endpoint of peak treadmill performance ranged from 50–70 meters depending on the type of treadmill test performed. Cilostazol treatment also resulted in a significant overall improvement in the quality of life measures from the WIQ and SF-36. In a study comparing cilostazol to pentoxifylline, cilostazol was more effective.<sup>93</sup> Side effects included headache, diarrhea, and palpitations. An overall safety analysis of 2702 patients revealed that the rates of serious cardiovascular events, and all-cause and cardiovascular mortality was similar between drug and placebo groups.<sup>94</sup> However, since the drug is in the phosphodiesterase III inhibitor class of drugs, it should not be given to patients with any evidence of congestive heart failure because of a theoretical concern for increased risk of mortality. This drug has the best overall evidence for treatment benefit in patients with claudication.

**Naftidrofuryl** Naftidrofuryl has been available for treating intermittent claudication for over 20 years in several European countries. It is a 5-hydroxytryptamine type 2 antagonist and may improve muscle metabolism, and reduce erythrocyte and platelet aggregation. In a meta-analysis of five studies involving a total of 888 patients with intermittent claudication, naftidrofuryl increased pain-free walking distance by 26% compared with placebo ( $p=0.003$ ).<sup>95</sup> Similar results showing benefits on treadmill performance and quality of life were confirmed in three recent studies of over 1100 patients followed for 6–12 months.<sup>96–98</sup> In all three studies the same dose of 600 mg/day was administered. Side effects were minor and not different to placebo; most frequently occurring complaints in the different studies were mild gastrointestinal disorders.



#### C4.2.2 Drugs with supporting evidence of clinical utility in claudication

**Carnitine and Propionyl-L-Carnitine** Patients with peripheral arterial disease develop metabolic abnormalities in the skeletal muscles of the lower extremity. Thus, claudication is not simply the result of reduced blood flow, and alterations in skeletal muscle metabolism are part of the pathophysiology of the disease. L-carnitine and propionyl-L-carnitine interact with skeletal muscle oxidative metabolism, and these drugs are associated with improved treadmill performance. Propionyl-L-carnitine (an acyl form of carnitine) was more effective than L-carnitine in improving treadmill walking distance. In two multicenter trials of a total of 730 patients, initial and maximal treadmill walking distance improved more with propionyl-L-carnitine than placebo.<sup>99,100</sup> The drug also improved quality of life and had minimal side effects as compared with placebo. Additional trials in the broad population of patients with claudication will be necessary to establish the overall efficacy and clinical benefit of these drugs.

**Lipid lowering drugs** Patients with PAD have endothelial and metabolic abnormalities secondary to their atherosclerosis, which may be improved with statin therapy. There are several promising studies evaluating the effects of statin drugs on exercise performance. While the results are preliminary, several positive trials suggest that further study is warranted.<sup>101,102</sup> Further studies are ongoing to determine the clinical benefits of these observations, including prevention of disease progression in addition to symptom relief.

#### C4.2.3 Drugs with insufficient evidence of clinical utility in claudication

**Pentoxifylline** Pentoxifylline lowers fibrinogen levels, improves red cell and white cell deformability and thus lowers blood viscosity. While early trials were positive on the endpoint of improvement in treadmill exercise performance, later studies demonstrated that pentoxifylline was no more effective than placebo on improving treadmill walking distance or functional status assessed by questionnaires. Several meta-analyses have concluded that the drug is associated with modest increases in treadmill walking distance over placebo, but the overall clinical benefits were questionable.<sup>103–105</sup> The clinical benefits of pentoxifylline in improving patient-assessed quality of life have not been extensively evaluated. While tolerability of the drug is acceptable, pentoxifylline does not have an extensive safety database.

**Isovolemic hemodilution** Isovolemic hemodilution has been advocated for the treatment of claudication, presumably by lowering viscosity of whole blood, but it is still uncertain whether the increase in blood flow compensates for the decrease in oxygen-carrying capacity of the blood. There are insufficient trials to support this therapy and it is only of historical interest.

**Antithrombotic agents** Aspirin/ASA and other antiplatelet agents (clopidogrel) are important in the long-term treatment of patients with PAD to reduce their risk of cardiovascular events with well established efficacy. How-

ever, no studies have shown a benefit of antiplatelet or anticoagulant drugs in the treatment of claudication.<sup>106</sup>

**Vasodilators** Arteriolar vasodilators were the first class of agents used to treat claudication. Examples include drugs that inhibit the sympathetic nervous system (alpha blockers), direct-acting vasodilators (papaverine), beta2-adrenergic agonists (nylidrin), calcium channel blockers (nifedipine) and angiotensin-converting enzyme inhibitors. These drugs have not been shown to have clinical efficacy in randomized, controlled trials.<sup>107</sup> There are several theoretical reasons why vasodilators may not be effective, including the possibility that vasodilator drugs may create a steal phenomenon by dilating vessels in normally perfused tissues thus shifting the distribution of blood flow away from muscles supplied by obstructed arteries.

**L-Arginine** L-arginine has the ability to enhance endothelium-derived nitric oxide and, thus, improve endothelial function. One study of nutritional supplementation with L-arginine improved pain-free but not peak walking time.<sup>108</sup> However, a recent study of L-arginine treatment in acute myocardial infarction showed no clinical benefit and excess mortality.<sup>108</sup> Further studies would be needed to determine if this treatment would have benefit and no unacceptable risk.

**Acyl coenzyme A-cholesterol acyltransferase inhibitors** Drugs in this class may reduce cholesterol accumulation in arterial plaque, thus affecting the natural history of atherosclerosis. A study with avasimibe in claudication demonstrated no clear evidence of efficacy and possible adverse effects on low-density lipoprotein cholesterol levels.<sup>109</sup>

**5-Hydroxytryptamine antagonists** Ketanserin is a selective serotonin (5<sub>2</sub>) antagonist that lowers blood viscosity and also has vasodilator and antiplatelet properties. Controlled trials of this drug have shown it not to be effective in treating claudication.<sup>110</sup> Importantly, the drug has been associated with increased risk of mortality in a subgroup of patients treated with potassium-wasting diuretics, precluding its role for any indication.<sup>111</sup>

AT-1015 is a selective 5-hydroxytryptamine antagonist that was studied in multiple doses in claudication. The drug was ineffective, and there were toxicity concerns at the highest dose.<sup>112</sup> Therefore, this drug cannot be recommended at this time.

Sarpogrelate showed promising results in 364 patients followed for 32 weeks, without safety concerns.<sup>113</sup> Additional trials will be necessary to determine the overall benefits and safety of drugs in this class.

**Prostaglandins** Prostaglandins have been used in several studies in patients with critical leg ischemia with some success in wound healing and limb preservation. In patients with claudication, prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) has been best studied. Intravenous administration of a prodrug of PGE<sub>1</sub> showed positive effects on treadmill performance.<sup>114</sup> Several studies have been performed with oral beraprost. While there was a positive trial in Europe, there have been negative trials in the USA.<sup>115,116</sup> While intravenous administration of PGE<sub>1</sub> may have modest benefits, the overall evi-

dence does not support the use of this drug class for claudication.

**Buflomedil** Buflomedil has an alpha-1 and -2 adrenergic effects that result in vasodilatation. This drug has antiplatelet effects, results in improvements in red cell deformability and weakly antagonizes calcium channels. Two relatively small studies have shown marginally positive effects on treadmill performance.<sup>117,118</sup> However, concerns have been raised about publication bias of only positive trials. Therefore, evidence is insufficient to support the use of this agent at this time.

**Defibrotide** Defibrotide is a polydeoxyribonucleotide drug with antithrombotic and hemorheological properties. Several small studies suggest a clinical benefit, but larger trials would be necessary to better understand the clinical benefits and any risks of therapy.<sup>119-121</sup>

**Other agents** Several studies have evaluated the role of Vitamin E, chelation therapy, omega-3 fatty acids, ginkgo biloba and lowering of homocysteine levels in the treatment of claudication. None of these therapies have proven effective.

#### Recommendation 15

Pharmacotherapy for symptoms of intermittent claudication

- A 3- to 6-month course of cilostazol should be first-line pharmacotherapy for the relief of claudication symptoms, as evidence shows both an improvement in treadmill exercise performance and in quality of life [A].
- Naftidrofuryl can also be considered for treatment of claudication symptoms [A].

### C5 FUTURE TREATMENTS FOR CLAUDICATION

#### Angiogenic growth factors

Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are mitogenic agents that stimulate the development of new vessels. When bFGF protein was given intra-arterially, patients with claudication had an improvement in exercise performance.<sup>122</sup> Newer applications deliver the agent as gene therapy in a viral vector given intra-muscularly. Unfortunately, initial studies have not been positive with VEGF.<sup>123</sup> Therefore, more studies will be needed to address the overall efficacy and modes and frequency of administration of angiogenic factors in the treatment of claudication.

### SECTION D – CHRONIC CRITICAL LIMB ISCHEMIA

#### D1 NOMENCLATURE AND DEFINITIONS

Critical limb ischemia (CLI) is a manifestation of peripheral arterial disease (PAD) that describes patients with typical chronic ischemic rest pain (see Table D1, Fontaine and Rutherford classifications, respectively) or patients with

**Table D1.** Classification of peripheral arterial disease: Fontaine's stages and Rutherford's categories

Stage	Fontaine		Rutherford		
	Clinical	Grade	Category	Clinical	
I	Asymptomatic	0	0	Asymptomatic	
IIa	Mild claudication	I	1	Mild claudication	
IIb	Moderate to severe claudication	I	2	Moderate claudication	
		I	3	Severe claudication	
III	Ischemic rest pain	II	4	Ischemic rest pain	
IV	Ulceration or gangrene	III	5	Minor tissue loss	
		III	6	Major tissue loss	

ischemic skin lesions, either ulcers or gangrene. The term CLI should only be used in relation to patients with chronic ischemic disease, defined as the presence of symptoms for more than 2 weeks. It is important to note in this section that there are limited data available compared with the other sections. CLI populations are difficult to study, with large numbers of patients lost to follow-up or dying in longitudinal studies, leading to incomplete data sets.

The diagnosis of CLI should be confirmed by the ankle-brachial index (ABI), toe systolic pressure or transcutaneous oxygen tension. Ischemic rest pain most commonly occurs below an ankle pressure of 50 mmHg or a toe pressure less than 30 mmHg. Other causes of pain at rest should, therefore, be considered in a patient with an ankle pressure above 50 mmHg, although CLI could be the cause.

Some ulcers are entirely ischemic in etiology; others initially have other causes (e.g. traumatic, venous, or neuropathic) but will not heal because of the severity of the underlying PAD. Healing requires an inflammatory response and additional perfusion above that required for supporting intact skin and underlying tissues. The ankle and toe pressure levels needed for healing are, therefore, higher than the pressures found in ischemic rest pain. For patients with ulcers or gangrene, the presence of CLI is suggested by an ankle pressure less than 70 mmHg or a toe systolic pressure less than 50 mmHg. (It is important to understand that there is not complete consensus regarding the vascular hemodynamic parameters required to make the diagnosis of CLI.)

#### Recommendation 16

Clinical definition of critical limb ischemia (CLI)

- The term critical limb ischemia should be used for all patients with chronic ischemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease. The term CLI implies chronicity and is to be distinguished from acute limb ischemia [C].

**D1.1 Patients presumed at risk for critical limb ischemia**

A subgroup of PAD patients fall outside the definition of either claudication or CLI. These patients have severe PAD with low perfusion pressures and low ankle systolic pressures, but are asymptomatic. They are usually sedentary and, therefore, do not claudicate, or they may have diabetes with neuropathy and reduced pain perception. These patients are presumed vulnerable to develop clinical CLI. The natural history of this subgroup of severe PAD is not well-characterized, but outcomes of excess mortality and amputation would be expected. The term 'chronic subclinical ischemia' has been ascribed to this subgroup.

Natural history studies of claudication document that few patients progress to CLI. Many patients who present with CLI are asymptomatic prior to its development.<sup>54</sup> However, research in this area is lacking, understandably, for patients who are asymptomatic and can only be detected by more routine ABI testing.

**D1.2 Prognosis**

It is important to diagnose CLI because it confers a prognosis of high risk for limb loss and for fatal and non-fatal vascular events, myocardial infarction and stroke. In general, the prognosis is much worse than that of patients with intermittent claudication. Observational studies of patients with CLI who are not candidates for revascularization suggest that a year after the onset of CLI, only about half the patients will be alive without a major amputation, although some of these may still have rest pain, gangrene or ulcers (see section A). Approximately 25% will have died and 25% will have required a major amputation. Their prognosis is in many ways similar to that of some malignancies. The diagnosis of CLI thus predicts a poor prognosis for life and limb. Patients should have aggressive modification of their cardiovascular risk factors and should be prescribed antiplatelet drugs. Ultimately, much of the care of CLI patients is palliative in nature, an issue that is very important when considering revascularization or amputation.

**Recommendation 17**

Cardiovascular risk modification in critical limb ischemia (CLI)

- CLI patients should have aggressive modification of their cardiovascular risk factors [A].

**D2 CLINICAL PRESENTATION AND EVALUATION****D2.1 Pain**

CLI is dominated by pedal pain (except in diabetic patients, where superficial pain sensation may be altered and they may experience only deep ischemic pain, such as calf claudication and ischemic rest pain). In most cases, the

pedal pain is intolerably severe; it may respond to foot dependency, but otherwise responds only to opiates. The pain is caused by ischemia, areas of tissue loss, ischemic neuropathy or a combination of these; it occurs or worsens with reduction of perfusion pressure. In most cases, walking capacity is very severely impaired, with walking often becoming almost impossible.

Ischemic rest pain most typically occurs at night (when the limb is no longer in a dependent position) but in severe cases can be continuous. The pain is localized in the distal part of the foot or in the vicinity of an ischemic ulcer or gangrenous toe. The pain often wakes the patients at night and forces them to rub the foot, get up, or take a short walk around the room. Partial relief may be obtained by the dependent position, whereas elevation and cold increase the severity of the pain. Often, patients sleep with their ischemic leg dangling over the side of the bed, or sitting in an armchair; as a consequence ankle and foot edema develop. In severe cases, sleep becomes impossible because pain sets in after only a short period of supine rest, causing in many patients a progressive further decline of their general physical and psychological condition.

Ischemic rest pain is often accompanied by pain caused by peripheral ischemic neuropathy, the mechanism of which is not well established. This results in severe, sharp, shooting pain that does not necessarily follow the anatomic distribution of the nerves but usually is most pronounced at the distal part of the extremity. The pain often occurs at night, with episodes lasting minutes to hours but with constant diffuse pain remaining in between. Ischemic rest pain should not be confused with neuropathic pain (see section D4.1).

**D2.2 Ulcer and gangrene**

Patients with CLI may also present with ischemic ulcers or gangrene. It is important to note that some patients may progress through rest pain into tissue loss. However, in many patients, notably those with diabetic neuropathy, the initial presentation is with a neuroischemic ulcer or gangrene. There are significant differences between patients with and without diabetes at this stage of CLI; these are delineated in section D2.4 which specifically addressed diabetic foot ulcers.

Gangrene usually affects the digits or, in a bedridden patient, the heel (as this is a pressure point). In severe cases, gangrene may involve the distal parts of the forefoot. It is usually initiated by a minor local trauma. Local pressure (ill fitting shoes) or the use of local heat (increasing metabolic demands) can also lead to ulcer and gangrene formation on other locations on the foot or leg. Gangrenous tissue, if not infected, can form an eschar, shrink and eventually mummify and, if the underlying circulation is adequate enough (or has been made adequate enough by treatment) to support the process, spontaneous amputation may follow. In contrast to the focal and proximal atherosclerotic lesions of PAD found typically in other high-risk patients, in patients with CLI and diabetes the occlusive lesions are more likely to be more diffuse and distally located, particularly in

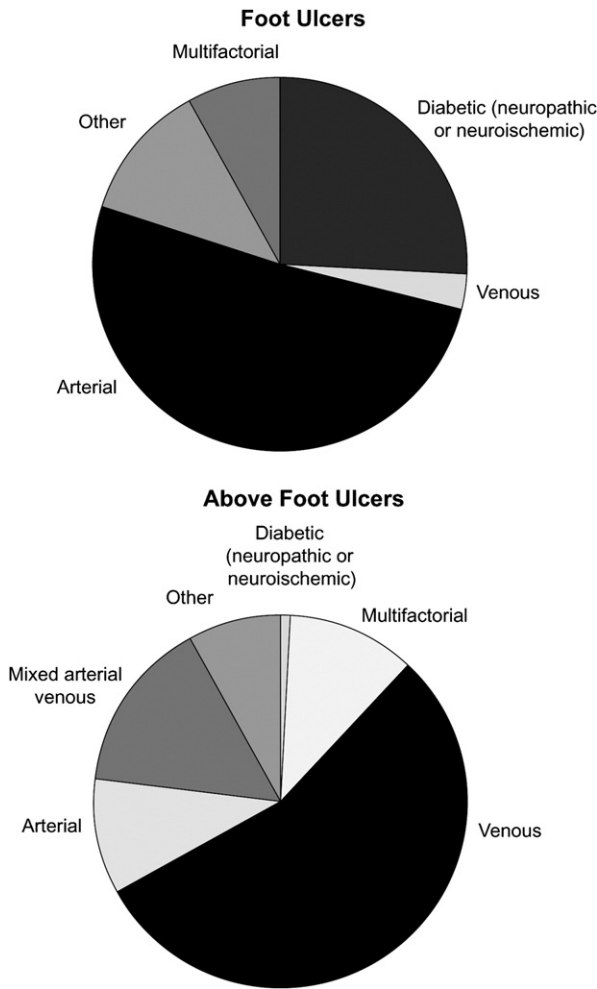


Fig. D1. Approximate frequencies of various ulcer etiologies.

infrageniculate arteries. Importantly, PAD in patients with diabetes is usually accompanied by peripheral neuropathy with impaired sensory feedback, enabling the silent progression of the ischemic process. Thus, a patient with diabetes and severe, asymptomatic PAD could also have a ‘pivotal event’ that leads acutely to an ischemic ulcer and a limb-threatening situation. A common example is the use of new, tight or ill fitting shoes in a patient with neuropathy. Thus, an asymptomatic, usually undiagnosed patient can lapse, apparently abruptly, into CLI. By identifying a patient with sub-clinical disease and instituting preventive measures, it may be possible to avoid CLI or at least prompt early referral if the patient develops CLI.

### D2.3 Differential diagnosis of ulcers

The majority of lower-leg ulcers above the ankle have a venous origin whereas ulcers in the foot are most likely due to arterial insufficiency (see Fig. D1).

Table D2 depicts the common characteristics of foot and leg ulcers.

### D2.4 Diabetic foot ulcers

While CLI is a significant risk factor for non-healing of diabetic foot ulcers, it is not the sole major factor associated with the development of diabetic foot lesions. Diabetic foot ulcers are, therefore, discussed separately in this section. Fig. D2 demonstrates the distribution of diabetic foot ulcers. Diabetic foot complications are the most common cause of non-traumatic lower extremity amputations in the world. It is estimated that 15% of people with diabetes will develop a foot ulcer during their lifetime and approximately 14%–24% of people with a foot ulcer will require an amputation. Up to 85% of amputations may be prevented by early detection and appropriate treatment.<sup>124</sup> Risk factors for ulcer formation include peripheral neuropathy, which leads to an insensate foot and structural foot deformity. It is estimated that approximately 30% of people with diabetes have mild-to-severe forms of diabetic nerve damage. Many diabetic foot ulcers and lower extremity amputations can be prevented through early identification of the patient at risk and preventive foot care, by both the health care provider and the patient, as described in the section D6 on the prevention of CLI.

**D2.4.1 Pathways to ulceration.** The most common pathway associated with the development of diabetic ulcers include: neuropathy (loss of protective sensation), coupled with pressure points (foot deformity) and repetitive activity.<sup>126</sup> Motor nerve defects and limited joint mobility can cause foot deformities, with pressure points further predisposing the patient to foot lesions. Consequences of autonomic neuropathy include loss of sweating, dry fissured skin and increased arteriovenous shunting. Healing requires a greater increase in perfusion than needed to maintain intact skin.

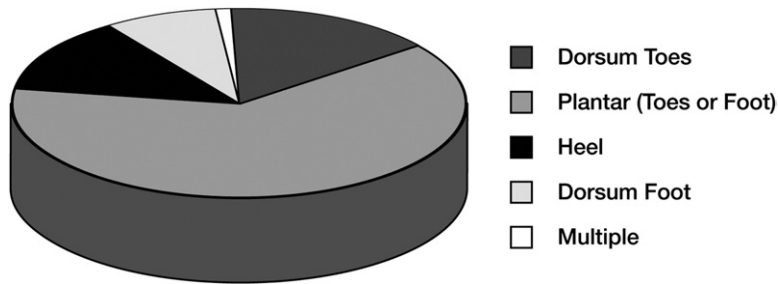
**D2.4.2 Types of ulcers and presentation.** Diabetic foot ulcerations can be divided into three broad categories: ischemic, neuro-ischemic and neuropathic ulcers. The presentation of the classical neuropathic and ischemic ulcers is depicted in Table D3. Although the majority of diabetic ulcers are neuropathic (Fig. D3), ischemia has to be excluded in all ulcers given its major impact on outcome. All patients with a foot ulcer should have an objective assessment of their vascular status at first presentation and on a regular basis; the assessment should include history (claudication), pulses and ABI. Pulse examination alone is an inadequate vascular examination in these patients. Any diabetic patient with a foot ulcer should be further evaluated in the vascular laboratory (see section G).

Increased arteriovenous shunt blood flow, due to autonomic neuropathy, can result in a relatively warm foot, falsely reassuring the clinician. The clinician should be aware of the relative incompressibility of calcified distal arteries in a diabetic, such that the ABI may be within normal limits. Due to the possibility of a falsely elevated ABI, the importance of toe pressures and tcPO<sub>2</sub> measurements cannot be underestimated (see section D5). Some patients have clear signs of critical limb ischemia – for example a toe or tcPO<sub>2</sub> pressure <30 mmHg – while in



**Table D2.** Characteristics of common foot and leg ulcers

<i>Origin</i>	<i>Cause</i>	<i>Location</i>	<i>Pain</i>	<i>Appearance</i>	<i>Role of revascularization</i>
Arterial	Severe PAD, Buerger's disease,	Toes, foot, ankle	Severe	Various shape, pale base, dry	Important
Venous	Venous insufficiency	Malleolar, esp. medial	Mild	Irregular, pink base, moist	None
Mixed venous/arterial	Venous insufficiency+PAD	Usually malleolar	Mild	Irregular, pink base	If non-healing
Skin infarct	Systemic disease, embolism	Lower third of leg, malleolar	Severe	Small, often multiple	None
Neuropathic	Neuropathy from diabetes, vitamin deficiency, etc	Foot/plantar surface (weight-bearing), associated deformity	None	Surrounding callus, often deep, infected	None
Neuroischemic	Diabetic neuropathy+ischemia	Locations common to both ischemic and neuroischemic As arterial	Reduced due to neuropathy	As arterial	As arterial



**Fig. D2.** Distribution of diabetic foot ulcers.<sup>125</sup> Copyright © 1999 American Diabetes Association from *Diabetes Care*, Vol. 22, 1999; 157–162. Modified with permission from The American Diabetes Association.

others the blood flow is impaired to a lesser degree – for example toe pressures between 30–70 mmHg – but they are still unable to heal foot lesions.

Symptoms and signs of neuropathic versus ischemic ulcers appear in Table D3.

**Recommendation 18**  
Evaluation of peripheral arterial disease (PAD) in patients with diabetes

- All diabetic patients with an ulceration should be evaluated for PAD using objective testing [C].

**D3 MACROCIRCULATORY PATHOPHYSIOLOGY IN CRITICAL LIMB ISCHEMIA**

CLI occurs when arterial lesions impair blood flow to such an extent that the nutritive requirements of the tissues cannot be met. This is usually caused by multilevel arterial

**Table D3.** Symptoms and signs of neuropathic versus ischemic ulcers

<i>Neuropathic ulcer</i>	<i>Ischemic ulcer</i>
Painless	Painful
Normal pulses	Absent pulses
Regular margins, typically punched-out appearance	Irregular margins
Often located on plantar surface of foot	Commonly located on toes, glabrous margins
Presence of calluses	Calluses absent or infrequent
Loss of sensation, reflexes and vibration	Variable sensory findings
Increase in blood flow (AV shunting)	Decrease in blood flow
Dilated veins	Collapsed veins
Dry, warm foot	Cold foot
Bony deformities	No bony deformities
Red appearance	Pale, cyanotic



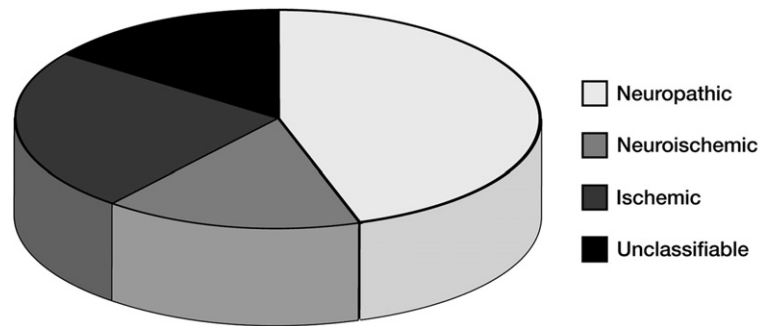


Fig. D3. Relative prevalence of different diabetic ulcer etiologies.<sup>127</sup>

occlusive disease.<sup>128</sup> In some cases, the hemodynamic consequences of arterial lesions may be compounded by a decreased cardiac output.

CLI is considered to be the result of multisegment arterial occlusive disease in most cases. Realizing this is most important in managing patients with presumed rest pain, as the influence of circulation on the pain syndrome can be difficult to determine, particularly in a patient with neuropathy.

- Patients with diffuse multisegment disease, both supra and infrainguinal are significant management problems, as proximal revascularizations may not remain patent due to lack of arterial outflow without additional infrainguinal procedures. Should a major amputation be required, the risk of non-healing is considerable due to proximal occlusive disease
- In patients with diabetes, arteries proximal to the knee joint are often spared or moderately diseased, and the majority of occlusions occur at the tibial peroneal trunk and distally. Often, the peroneal artery and the dorsalis pedis artery are open beyond these occlusions and serve as potential distal targets for a bypass.

### D3.1 Skin microcirculation

The skin microcirculation is unusual in many ways, most notably that nutritional capillary blood flow only represents approximately 15% of the normal total blood flow in the foot, the remainder having a non-nutritive thermoregulatory function only. Patients with CLI develop microcirculatory defects including endothelial dysfunction, altered hemorheology and white blood cell activation and inflammation. The normal function of the skin microcirculation can be considered in regard to two aspects: a complex microvascular flow regulatory system and a series of defense mechanisms. The microvascular flow-regulating system includes extrinsic neurogenic mechanisms, intrinsic local mediators and modulation by circulating humoral and blood-borne factors. The endothelium also participates in the regulation of flow by the release of vasodilatory mediators such as prostacyclin and nitric oxide and several endothelium-derived contractile factors (e.g. endothelin). In addition to the microvascular flow-regulating system, there are several microvascular defense mechanisms. In CLI, there is

a maldistribution of the skin microcirculation in addition to a reduction in total blood flow. The importance of the local microcirculatory response in individual patients with CLI is suggested by the wide overlap in ankle or toe blood pressure, which assess the macrocirculation, in patients with and without CLI.

Capillary microscopy studies have confirmed an heterogeneous distribution of skin microcirculatory flow. This is also accompanied by a reduction in  $tcPO_2$ .<sup>129</sup>

In summary, although PAD is the underlying and principal defect in patients with CLI, the low tissue perfusion pressure sets up a number of complex local microcirculatory responses, which may contribute to rest pain and trophic changes. Many of these processes can be viewed as an inappropriate response of the microcirculatory flow regulatory mechanism and its normal defense mechanisms. Therefore, although the primary aim of treatment must be the correction of the PAD, attempts to manipulate and normalize the microcirculatory changes pharmacologically may enhance the results of revascularization and may be one option in patients in whom revascularization is impossible or has failed.

## D4 DIFFERENTIAL DIAGNOSIS OF ISCHEMIC REST PAIN

The various causes of foot pain that may be mistaken for ischemic rest pain are considered in their approximate order of frequency.

### D4.1 Diabetic neuropathy

Diabetic neuropathy usually results in a decrease in sensation. In some patients neuropathy can result in severe, seriously disabling pain in the foot. This is often described as a burning or shooting sensation that is frequently worse at night, when there is less distraction, making it more difficult to distinguish from atypical ischemic rest pain. (It should be noted that this type of pain is seen in the relatively early 'neuritic' phase of diabetic neuropathy, often before diabetic neuropathy has been clinically recognized.) Diagnostic features that may be helpful in distinguishing diabetic neuropathy from ischemic rest pain are a symmetrical distribution in both legs, association with cutaneous hypersensitivity and failure to relieve it by dependency of

the foot. The patient may have other signs of a diabetic neuropathy, such as decreased vibratory sensation and decreased reflexes.

#### D4.2 Complex regional pain syndrome

Patients with complex regional pain syndrome (formerly named causalgia or reflex sympathetic dystrophy) are often referred to vascular specialists for evaluation of their limb circulation. In general, the circulation is adequate (ABI, toe-brachial index [TBI] normal). One form of complex regional pain syndrome is caused by inadvertent ischemic damage to peripheral nerves that may be associated with delayed revascularization and, therefore, may be classified as a postoperative complication. This is one of the rare conditions in which lumbar sympathectomy may be indicated.

#### D4.3 Nerve root compression

A number of spinal conditions may result in nerve root compression, giving rise to continuous pain. It is typically associated with backache and the pain distribution following one of the lumbosacral dermatomes.

#### D4.4 Peripheral sensory neuropathy other than diabetic neuropathy

Any condition giving rise to isolated sensory neuropathy can produce pain in the foot, which can be confused with ischemic rest pain. Peripheral neuropathy other than that caused by diabetic neuropathy may be caused by vitamin B<sub>12</sub> deficiency, or syringomyelia. Leprosy also may rarely result in a neuropathic ulcer. Alcohol excess, toxins, and some commonly used drugs, such as some cancer chemotherapy agents, may on rare occasion produce a peripheral neuropathy.

#### D4.5 Night cramps

Night cramps, as opposed to restless legs, are very common and occasionally difficult to diagnose. They are usually associated with muscle spasm and usually involve the calf, very rarely the foot alone. They may be associated with chronic venous insufficiency, but their precise cause is unknown.

#### D4.6 Buerger's disease (thrombangitis obliterans)

Buerger's disease also may present with rest pain in the toes or feet, usually in younger smokers, and is no longer exclusively seen in male patients. The pathophysiology is distal limb ischemia, due to an occlusive, inflammatory vascular process involving both arteries and veins.

#### D4.7 Miscellaneous

A number of other miscellaneous conditions can give rise to pain in the foot, including local inflammatory diseases such as gout, rheumatoid arthritis, digital neuroma, tarsal tunnel nerve compression or plantar fasciitis.

## D5 INVESTIGATIONS OF CRITICAL LIMB ISCHEMIA

### D5.1 Physical examination

As a majority of patients with CLI have not suffered earlier symptoms of PAD (intermittent claudication) it is important to have the diagnosis of CLI in mind when examining any patient with leg pain or ulcer development.

A first step is to document the location and quality of the pulses. Other less specific findings may include hair loss, muscle atrophy, atrophy of subcutaneous tissues and skin and appendages, dry fissured skin, discoloration and dependant hyperemia.

In patients with ulcers there may be other etiologies besides arterial disease (see Fig. D1 and Table D2). Swelling is usually only a feature when there is active infection or rest pain that prevents patients from elevating their foot in bed at night.

### D5.2 Investigations

- General investigations of atherosclerotic disease (see section B)
- Physiologic – Confirmation of the diagnosis and quantification of the arterial flow
  - Ankle pressure – In patients with ischemic ulcers the ankle pressure is typically 50–70 mmHg, and in patients with ischemic rest pain it is typically 30–50 mmHg
  - Toe pressures – should include toe pressures in diabetic patients (critical level <50 mmHg)
  - tcPO<sub>2</sub> (critical level <30 mmHg)
  - Investigation of microcirculation (usually used as a research tool) – CLI is associated with reduced total flow as well as maldistribution of flow and activation of an inflammatory process. A combination of tests to assess healing and quantify flow may be indicated due to the rather poor sensitivity and specificity of the single test. Tests include:
    - Capillaroscopy
    - Fluorescence videomicroscopy
    - Laser Doppler fluxometry
- Anatomic (Imaging) – Refer to section G.

#### Recommendation 19

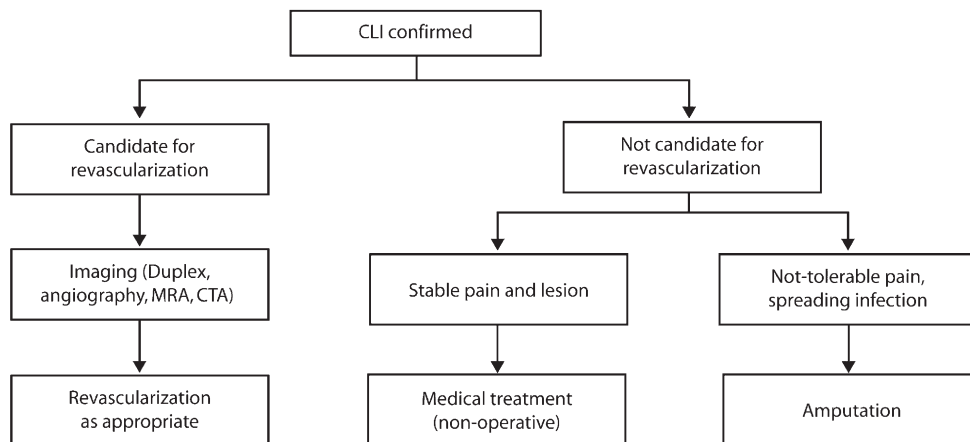
Diagnosis of critical limb ischemia (CLI)

- CLI is a clinical diagnosis but should be supported by objective tests [C].

#### Recommendation 20

Indications for evaluation for critical limb ischemia

- All patients with ischemic rest pain symptoms or pedal ulcers should be evaluated for CLI [B].



**Fig. D4.** Algorithm for treatment of the patient with critical limb ischemia. Contraindications are: patients not fit for revascularization; revascularization not technically possible; benefit cannot be expected (i.e. widespread ulceration-gangrene – see also section D7.5). CLI – critical limb ischemia; MRA – magnetic resonance angiography; CTA – computed tomographic angiography.

## D6 PREVENTION OF CRITICAL LIMB ISCHEMIA

As with all forms of systemic atherosclerosis, early detection of PAD and aggressive management of cardiovascular risk factors should reduce the incidence and severity of CLI. For example, smoking cessation is associated with a decreased risk of progression from earlier stages of PAD to CLI<sup>130</sup> (see section B).

### D6.1 Risk factors associated with the foot

Early identification of the patient who is at risk for CLI is essential in order to recognize potential problems and develop preventive intervention strategies to avoid complications. Patients with atherosclerotic PAD, Buerger’s disease, diabetes and any other condition that can cause a loss of protective sensation to the foot or interferes with wound healing are at risk of developing ulcerations and a future amputation. Persons with diabetes are at a higher risk for developing lower extremity complications. A thorough foot examination will assist in identifying those patients who are at risk. Once an individual is classified as high risk, a visual foot inspection should be performed at every visit and referral to a foot care specialist for further assessment is recommended.

### D6.2 The role of peripheral neuropathy

Loss of protective sensation or peripheral neuropathy places the patient at a higher risk for developing foot related complications. Foot deformities may be the result of motor neuropathy. Therefore, recognition of structural deformities such as hammer toes and bunions, or altered biomechanics such as callus formation due to prominent bony deformity, as well as limited joint mobility identify the patient as high risk. Footwear should be inspected to determine if it provides adequate support and protection for the foot. Properly fitting shoes must accommodate any foot

deformities. Improper or poorly fitting shoes are a major contributor to foot ulcerations, especially for people with diabetes.

Preventive foot care strategies for patients at risk of developing foot complications is essential for limb preservation. These strategies include patient education and appropriate management of high-risk patients. Patients should be educated on the importance of self-care of the feet, including proper foot care and footwear assessment. Early detection of foot problems and early intervention may decrease the frequency and severity of lower extremity complications. Soft, conforming rather than correctional orthotics are valuable. Therefore, patients (or their family if their vision is impaired) should be performing daily foot inspections at home.

#### Recommendation 21

Importance of early identification of peripheral arterial disease (PAD)

- Early identification of patients with PAD at risk of developing foot problems is essential for limb preservation [C]. This can be achieved by daily visual examination by the patient or their family and, at every visit, referral to the foot specialist.

## D7 TREATMENT OF CRITICAL LIMB ISCHEMIA

### D7.1 Overall strategy (Fig. D4)

The primary goals of the treatment of CLI are to relieve ischemic pain, heal (neuro)ischemic ulcers, prevent limb loss, improve patient function and quality of life and prolong survival. A primary outcome would be amputation-free survival. In order to achieve these outcomes, most patients will ultimately need a revascularization procedure

requiring referral to a vascular specialist. Other components of treatment of patients with CLI are medical interventions to control pain and infection in the ischemic leg, prevention of progression of the systemic atherosclerosis, and optimization of cardiac and respiratory function. For some CLI patients with severe co-morbidities or a very limited chance of successful revascularization, a primary amputation may be the most appropriate treatment. Cardiovascular risk factor control is mandatory in CLI patients as well as in all PAD patients (see section B).

### D7.2 Basic treatment: pain control

Pain management is essential in improving function and quality of life. The hallmark of CLI is ischemic rest pain and painful ulceration. Pain is usually located to skin and possibly bone structures. Pain control is a critical aspect of the management of these patients. Ideally, relief of pain is achieved by reperfusion of the extremity. However, while planning the revascularization, adequate pain control must be a goal of management in all patients. Furthermore, in patients for whom revascularization is not an option, narcotic pain relief is commonly needed.

Physicians should assess pain severity and adequacy of pain relief in all patients at regular visits. Initial attempts at pain relief should include the use of acetaminophen/paracetamol or nonsteroidal anti-inflammatory medications, although the latter are rarely effective and narcotic medications are frequently required. Caution should be used in the latter in patients with hypertension, or renal insufficiency. Control of pain is usually more effective if analgesia is given regularly rather than on demand. Placing the affected limb in the dependent position provides partial relief of ischemic pain in some patients. Therefore, tilting the bed downward may be a helpful measure in addition to analgesia. Patients with CLI are often depressed and pain control can be improved by use of antidepressant medications.

#### Recommendation 22

Early referral in critical limb ischemia (CLI)

- Patients with CLI should be referred to a vascular specialist early in the course of their disease to plan for revascularization options [C].

#### Recommendation 23

Multidisciplinary approach to treatment of critical limb ischemia

- A multidisciplinary approach is optimal to control pain, cardiovascular risk factors and other co-morbid disease [C].

### D7.3 Revascularization

The natural history of CLI is such that intervention is indicated to salvage a useful and pain-free extremity. The treatment chosen depends upon the pre-morbid condition

of the patient and the extremity as well as estimating the risk of intervention based on co-morbid conditions and the expected patency and durability of the reconstruction. In CLI, multi-level disease is frequently encountered. Adequate inflow must be established prior to improvement in the outflow.

After revascularization, ulcer healing may require adjunctive treatments that may be best achieved in collaboration between the vascular specialist and specialists in foot care.

(See also section F.)

### D7.4 Management of ulcers

The management of the patient with CLI and foot ulcers illustrates the need for a multidisciplinary approach to the treatment of CLI patients. These patients should be treated according to the following principles.

#### *Restoration of perfusion*

The successful treatment of a foot ulcer rests with the possibility of increasing the perfusion to the foot. The determination of whether or not a revascularization procedure is possible will set the tone for the ensuing treatment. A revascularization procedure should be considered if clear signs of CLI are present or if healing does not occur in a neuro-ischemic ulcer despite optimal off-loading, treatment of infection, if present, and intensive wound care. After revascularization, local wound care and possibly foot salvage procedures must be considered.

#### *Local ulcer care and pressure relief*

Prior to a revascularization procedure the ulcer can be treated with a non-adherent gauze and should be off-loaded if there is an increase in pressure or shear stress. Off-loading can be achieved by several methods including shoe modifications, orthotics and casting techniques,<sup>16,131,132</sup> depending on the localization of the ulcer and the severity of the ischemia. Once perfusion is improved, adequate off-loading becomes more important as the increase in blood flow may not compensate for the repetitive tissue trauma due to poorly fitted shoes. The local treatment of a revascularized foot ulcer can be carried out in many fashions and a multitude of products exist. An in-depth discussion of each ulcer care product is beyond the scope of this work but the basic principles of wound care should be adhered to. These principles include: removing necrotic/fibrotic tissue from the ulcer, keeping a moist wound environment and eliminating infection, as discussed below.

#### *Treatment of infection*

Local infection is a severe complication of a neuro-ischemic ulcer, as it tends to run a more severe course and should be treated urgently. Signs of systemic toxicity, such as fever or elevated C-reactive protein, are uncommon. The infection should be identified as early as possible and its level of involvement assessed and aggressively treated. Severe foot infections in diabetic patients are usually polymicrobial with gram positive cocci, gram negative rods and anaerobic organisms.<sup>133</sup> Once the

**Table D4.** Different levels of local foot amputations

Digit (partial or total)
Ray (digit and metatarsal)
Midfoot (transmetatarsal; tarso-metatarsal; transverse tarsal)
Symes (ankle)

clinical diagnosis of an infection is made and cultures of the wound obtained, empiric antibiotic treatment should be initiated immediately. Broad spectrum antibiotic therapy can be adjusted once the causative micro-organisms are determined and results of the culture sensitivity have been obtained. A growing concern is the rise in the incidence of multidrug-resistant *Staphylococcus aureus*, which is up to 30% in some studies.<sup>134</sup> Management of a deep infection usually also includes drainage and debridement of necrotic tissue. Antibiotic therapy is believed to be important in the prevention of further spreading of infection in patients with CLI. Once the acute infection is under control, a revascularization procedure can be performed in a second stage.

**Recommendation 24**

Optimal treatment for patients with critical limb ischemia (CLI)

- Revascularization is the optimal treatment for patients with CLI [B].

**Recommendation 25**

Treatment for infections in critical limb ischemia (CLI)

- Systemic antibiotic therapy is required in CLI patients who develop cellulitis or spreading infection [B].

*Salvage procedures*

Limb salvage after revascularization is defined as preservation of some or all of the foot. An attempt at a foot salvage procedure should take place after a revascularization procedure has been performed if possible. A waiting period of at least 3 days has been suggested, this allows for sufficient time for the restoration of perfusion and for demarcation to occur.

The level of adequate circulation, extent of infection, if any and remaining function of the foot are factors considered when choosing the level of a foot salvage procedure. Foot salvage procedures can be divided into two categories. The first category involves amputation of some part of the foot. Table D4 shows the different levels of local foot amputations.

The natural history of a minor foot amputation should be considered when choosing the appropriate level of amputation in order to account for the subsequent changes in mechanical force and pressure on the foot. For example, a hallux or partial first ray amputation increases the resultant

vector of force on the second ray (through metatarsal shaft). This increase in force traversing through the second ray can cause a contracture of the second toe, leading to an increased pressure at both the sub metatarsal head area and the distal pulp of the toe. These changes in pressure require appropriate shoe and insole modifications to avoid foot complications. A high percentage of patients with a great toe and/or first ray amputation go on to have a second amputation either on the same foot or the contralateral foot.

Amputation of the lateral toes and rays (fourth and fifth digits) does not cause the same increase in mechanical force and pressure on the adjacent digits as described above. Hence, the considerations of shoe wear and inner sole modifications are different with this scenario.

When multiple medial rays are involved or the ischemia is proximal to the metatarsal heads, but distal to the tarso-metatarsal joint, a mid foot amputation should be considered. A transmetatarsal amputation provides a stump adequate for walking with minimal shoe and innersole modifications.

The second category of foot salvage involves the debridement of the wounds, including excision of bone. These procedures permit the foot to keep its general outward appearance intact, while disturbing the internal architecture that is causing the increased pressure. Foot salvage procedures, short of amputation, that can be used in the revascularized foot include exostectomy, arthroplasty, metatarsal head excision and calcaneotomy.

*Diabetes control and treatment of co-morbidity*

As in all patients with diabetes, those with concomitant CLI should have optimization of glycemic control. Diabetic patients with a neuro-ischemic foot ulcer frequently have a poor health status. Factors that can negatively affect wound healing such as cardiac failure or poor nutritional status should be evaluated and treated appropriately.

**Recommendation 26**

Multidisciplinary care in critical limb ischemia (CLI)

- Patients with CLI who develop foot ulceration require multidisciplinary care to avoid limb loss [C].

**D7.5 Amputation**

Major amputation (above the ankle) in CLI is necessary and indicated when there is overwhelming infection that threatens the patient's life, when rest pain cannot be controlled, or when extensive necrosis has destroyed the foot. Using these criteria, the number of major limb amputations should be limited.

Primary amputation is defined as amputation of the ischemic lower extremity without an antecedent attempt at revascularization. Amputation is considered as primary therapy for lower limb ischemia only in selected cases. Unreconstructable arterial disease is generally due to the progressive nature of the underlying atherosclerotic occlusive disease.



**Table D5.** Ambulatory status 6–12 months following amputation

Author (year)	N	Percentage fitted with a prosthesis	Percentage* Ambulatory	Comments
Ruckley (1991) <sup>139</sup>	191	80%	74%	Randomized trial
Siriwardena (1991) <sup>140</sup>	267	–	63%	US VAMC Data
Hagberg (1992) <sup>141</sup>	24	100%	96%	
Houghton (1992) <sup>142</sup>	193	–	16%	20% LFU
Stirnemann (1992) <sup>143</sup>	126	70%	70%	Primary versus Failed bypass
McWhinnie (1994) <sup>144</sup>	61	66%	52%	
Nehler (2003) <sup>145</sup>	94	–	39%	11% LFU

LFU – lost to follow up; VAMC – Veterans Affairs Medical Center.

\*Time intervals are 6–12 months postoperatively from below-knee amputation (BKA). Modest ambulatory results are due to 1) mortality prior to rehabilitation; 2) failure to heal BKA; 3) failure to complete rehabilitation program.

Revascularization of the lower extremity remains the treatment of choice for most patients with significant arterial occlusive disease.

Unreconstructable vascular disease has become the most common indication for secondary amputation, accounting for nearly 60% of patients. Secondary amputation is indicated when vascular intervention is no longer possible or when the limb continues to deteriorate despite the presence of a patent reconstruction. Persistent infection despite aggressive vascular reconstruction is the second most common diagnosis.

Many amputations can be prevented and limbs preserved through a multi-armed, limb-salvage treatment of ischemic necrosis with antibiotics, revascularization and staged wound closure that may necessitate the use of microvascular muscle flaps to cover major tissue defects. On the other hand, and very importantly, amputation may offer an expedient return to a useful quality of life, especially if a prolonged course of treatment is anticipated with little likelihood of healing. Non-ambulatory elderly patients with CLI represent a particularly challenging group. These patients frequently have flexion contractures that form from the prolonged withdrawal response to the pain. Aggressive vascular reconstruction does not provide these patients with a stable and useful limb, and primary amputation is a reasonable option.<sup>135</sup> Therefore, the important issue is to identify a subgroup of CLI patients better served by an amputation than attempts of revascularization. Technical aspects, foot wound healing issues and co-morbidities of the patients should be considered.

It is the implicit goal of amputation to obtain primary healing of the lower extremity at the most distal level possible. The energy expenditure of ambulation increases as the level of amputation rises from calf to thigh. Preservation of the knee joint and a significant length of the tibia permits the use of lightweight prostheses, minimizes the energy of ambulation, and enables older or more frail patients to walk independently.<sup>136</sup> Therefore, the lowest level of amputation that will heal is the ideal site for limb transection.

Clinical determination of the amputation level results in uninterrupted primary healing of the below-knee stump in around 80% and the above-knee stump in around 90% of

cases.<sup>137</sup> Measurement of tcPO<sub>2</sub> combined with clinical determination may be of value to predict healing at various levels of amputation.<sup>138</sup> Figures from specialized centers are better than the global figures shown in Fig. A6. Amputations have variable outcome and more risk with higher proximal amputations. Ambulatory status of patients after amputation is shown in Table D5.

A major amputation that is above the foot will require a prosthesis. Meticulous technique is essential to ensure a well-formed and well-perfused stump with soft tissue covering the transected end of the bone. Major amputations are usually performed at the below-knee (preferred) or above-knee level depending on the level of arterial occlusion and tissue ischemia. A return to independent ambulation is the ultimate challenge for patients undergoing major amputation of the lower extremity. Patients with a well-healed below-knee amputation stump have a greater likelihood of independent ambulation with a prosthesis than those with an above-knee amputation, who have a less than 50% chance of independent ambulation.

#### Recommendation 27

Amputation decisions in critical limb ischemia (CLI)

- The decision to amputate and the choice of the level should take into consideration the potential for healing, rehabilitation and return of quality of life [C].

#### D7.6 Pharmacotherapy for critical limb ischemia

When open or endovascular intervention is not technically possible or has failed, the question arises as to whether pharmacological treatment is an option. The consequences of the severely reduced perfusion pressure on the distal microcirculation have to be overcome. Pharmacotherapy, or any other treatment that produces modest improvements in circulation, is more likely to be successful in patients who were asymptomatic before developing their foot lesion and in those with shallow foot lesions where the level of ischemia is close to the margin (i.e. those with borderline perfusion pressures).

**D7.6.1 Prostanoids.** Prostanoids prevent platelet and leukocyte activation and protect the vascular endothelium, which could play a role in the management of CLI. These drugs are administered parenterally over several weeks. Side effects include flushing, headache, and hypotension of a transient nature. Nine double-blind randomized trials on prostanoid treatment have been published.<sup>146–154</sup> Three PGE<sub>1</sub> studies showed a benefit on reducing ulcer size, but these studies did not show favorable outcomes on other critical clinical endpoints. Six studies of the stable PGI<sub>2</sub> analog, iloprost, were performed, not all of which were positive. A meta-analysis of the data demonstrated that patients on active treatment had a greater chance (55% vs. 35%) to survive and keep both legs during the follow-up period. In clinical practice, iloprost seems to be of benefit to about 40% of patients in whom revascularization is not possible. In a recent trial of lipo-ecraprost versus placebo, this prostanoid failed to reduce death and amputation during 6 months follow-up.<sup>155</sup> Prediction of response is, however, difficult and prostanoids are rarely used due to these facts.

**D7.6.2 Vasodilators.** Direct-acting vasodilators are of no value, as they will primarily increase blood flow to non-ischemic areas.

**D7.6.3 Antiplatelet drugs.** Although long-term treatment with aspirin/ASA and ticlopidine may reduce progression of femoral atherosclerosis and exert a beneficial effect on the patency of peripheral by-passes (Cochrane review<sup>156</sup>) there is no evidence that these drugs would improve outcomes in CLI. However, as in all patients with PAD, antiplatelet drugs do reduce the risk of systemic vascular events.

**D7.6.4 Anticoagulants.** Unfractionated heparin is frequently used as prophylaxis and as adjuvant treatment to vascular surgical procedures, but has not been tried for symptoms of CLI. Two studies have looked at low molecular weight heparin (LMWH) in CLI patients with ulcers. These were negative trials. Vitamin K antagonists have not been tried for the treatment of symptoms of CLI.

Defibrinating agents have not been shown to improve healing of ischemic ulcers or to reduce the number of amputations.

**D7.6.5 Vasoactive drugs.** A Cochrane review<sup>157</sup> evaluated eight trials on intravenous naftidrofuryl for CLI. The drug was not effective in reducing the symptoms of CLI. Pentoxifylline was evaluated in two placebo controlled studies in patients with CLI, with inconclusive results.<sup>158,159</sup>

#### Recommendation 28

Use of prostanoids in critical limb ischemia (CLI)

- Previous studies with prostanoids in CLI suggested improved healing of ischemic ulcers and reduction in amputations [A].
- However, recent trials do not support the benefit of prostanoids in promoting amputation-free survival [A].
- There are no other pharmacotherapies that can be recommended for the treatment of CLI [B].

#### D7.7 Other treatments

**D7.7.1 Hyperbaric oxygen.** A Cochrane review<sup>160</sup> concluded that hyperbaric therapy significantly reduced the risk of major amputation in patients with diabetic ulcers. However, the results should be interpreted with caution because of methodological shortcomings. Other pathologies related to PAD and diabetes were not evaluated using this kind of treatment. Therefore, given the absence of proven benefit and high cost, this therapy is not generally recommended. Nonetheless, hyperbaric oxygen may be considered in selected patients with ischemic ulcers who have not responded to, or are not candidates for, revascularization.

**D7.7.2 Spinal cord stimulation.** A Cochrane review<sup>161</sup> of six studies including patients with CLI concluded that spinal cord stimulation was significantly better than conservative treatment in improving limb salvage in patients without any option to vascular reconstruction.

#### D8 HEALTH ECONOMICS

Studies published on the cost of treating CLI present data on surgical revascularization, percutaneous transluminal angioplasty and stenting and primary amputation.<sup>162–166</sup>

Whatever the treatment considered, the costs are multiplied by a factor 2 to 4 when the procedure initially planned has failed, for example angioplasty requiring immediate or delayed crossover grafting, bypass requiring revision after thrombosis or secondary amputation, and when renal and pulmonary co-morbidities or complications are present. Results are consistent across countries, although individual costs of procedures vary. The order of magnitude for the cost of PTA is \$10,000 (\$20,000 if the procedure fails initially or later), the cost for bypass grafting is \$20,000 (\$40,000 if revision is required), the cost for amputation is \$40,000. Adding rehabilitation will usually double the costs.

#### D9 FUTURE ASPECTS OF TREATMENT OF CRITICAL LIMB ISCHEMIA

The most striking feature of CLI is the dismal prognosis for both life and limb outcomes no matter what treatment is employed. This is because most patients have generalized atherosclerosis. One may, therefore, consider what magnitude of treatment options is realistic for the single patient. A successful revascularization may reduce pain and improve quality of life for a limited period of time, but frequently this goal is not achieved. Amputation may be a good alternative to reduce pain, though amputees may have an even more reduced life expectancy. Medical treatment that favorably modifies cardiovascular risk is recommended for all patients, while symptomatic treatment of the limb has to be individualized.

Preliminary trials of intramuscular gene transfer utilizing naked plasmid DNA encoding phVEGF165 have given promising results on symptoms of CLI<sup>167</sup> while others have

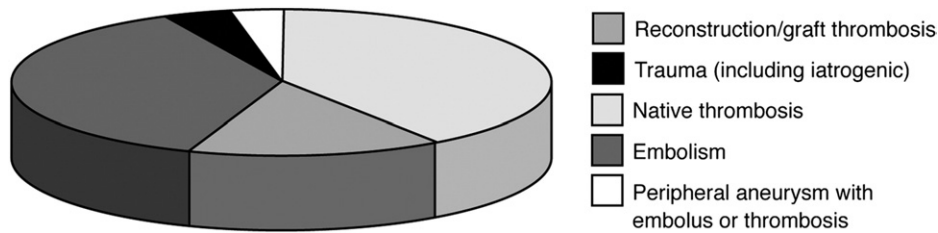


Fig. E1. Etiology of acute limb ischemia. (Summarizes Berridge *et al.* 2002 and Campbell *et al.* 1998<sup>172,173</sup>).

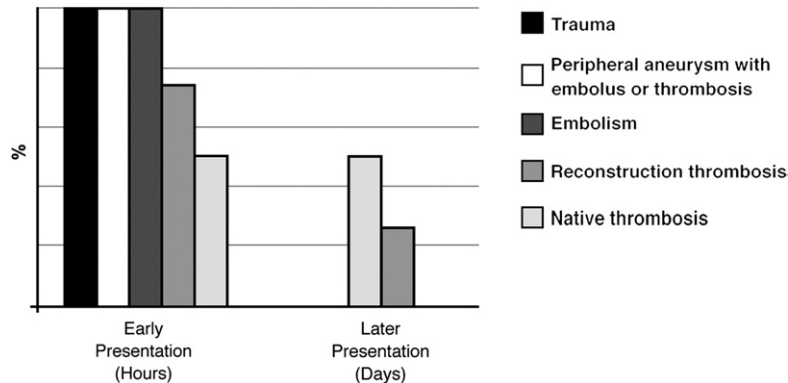


Fig. E2. Time to presentation in relation to etiology.

been negative. Several trials are using viral vectors to increase gene transfer efficiency. Besides vascular endothelial growth factor (VEGF), fibroblast growth factor, angiopoietin and other growth factors are under investigation.<sup>168</sup> Preliminary trials of intramuscular injection of autologous bone-marrow mononuclear cells to stimulate vascular growth<sup>169</sup> have been promising. Most trials are in Phase I or II and the appropriate use of gene therapy in vascular practice remains to be proven.

In conclusion, there is low-level evidence for spinal cord stimulation to improve outcome of patients with CLI, should revascularization not be possible. Prostanoid treatment may also be of value; however, only a limited proportion of patients will respond to this treatment, as mentioned. Results of other pharmacotherapies are far from good.<sup>170,171</sup> Gene therapy has shown promising early efficacy but further trials are warranted.

## SECTION E – ACUTE LIMB ISCHEMIA

### E1 DEFINITION AND NOMENCLATURE FOR ACUTE LIMB ISCHEMIA

#### E1.1 Definition/etiology of acute limb ischemia

Acute limb ischemia (ALI) is any sudden decrease in limb perfusion causing a potential threat to limb viability. Presentation is normally up to 2 weeks following the acute event. Fig. E1 shows the frequency of different etiologies for ALI.

Timing of presentation is related to severity of ischemia and access to healthcare. Patients with embolism, trauma, peripheral aneurysms with emboli and reconstruction occlusions tend to present early (hours) due to lack of collaterals, extension of thrombus to arterial outflow, or a combination of both. On the other hand, later presentations – within days – tend to be restricted to those with a native thrombosis or reconstruction occlusions (Fig. E2).

## E2 EVALUATION

### E2.1 Clinical evaluation of acute limb ischemia

**E2.1.1 History.** The history should have two primary aims: querying leg symptoms relative to the presence and severity of limb ischemia (present illness) and obtaining background information (e.g. history of claudication, recent intervention on the proximal arteries or diagnostic cardiac catheterization), pertaining to etiology, differential diagnosis and the presence of significant concurrent disease.

#### *Present illness*

Leg symptoms in ALI relate primarily to pain or function. The abruptness and time of onset of the pain, its location and intensity, as well as change in severity over time, should all be explored. The duration and intensity of the pain and presence of motor or sensory changes are very important in clinical decision-making and urgency of revascularization. For example, thrombolysis may be less effective for thrombosis of >2 weeks duration compared with

**Table E1.** Separation of threatened from viable extremities<sup>175</sup>

Category	Description/prognosis	Findings		Doppler signals <sup>†</sup>	
		Sensory loss	Muscle weakness	Arterial	Venous
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginal	Salvageable if promptly treated	Minimal (toes) or none	None	(Often) inaudible	Audible
b. Immediate	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	(Usually) inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

<sup>†</sup>Obtaining an ankle pressure is very important. However, in severe ALI, blood flow velocity in the affected arteries may be so low that Doppler signals are absent (see section C for technical description of method). Differentiating between arterial and venous flow signals is vital: arterial flow signals will have a rhythmic sound (synchronous with cardiac rhythm) whereas venous signals are more constant and may be affected by respiratory movements or be augmented by distal compression (caution needs to be taken not to compress the vessels with the transducer). Reproduced with permission from Rutherford RB et al. *J Vasc Surg* 1997;26(3):517-538.

more acute thrombosis (post hoc analysis of the STILE data<sup>174</sup>).

*Past history*

It is important to ask whether the patient has had leg pain before (e.g. a history of claudication), whether there have been interventions for ‘poor circulation’ in the past, and whether the patient has been diagnosed as having heart disease (e.g. atrial fibrillation) or aneurysms (i.e. possible embolic sources). The patient should also be asked about serious concurrent disease or atherosclerotic risk factors (hypertension, diabetes, tobacco abuse, hyperlipidemia, family history of cardiovascular disease, strokes, blood clots or amputations). A more complete discussion of risk factors can be found in section A.

**E2.1.2 Physical examination.** The findings of ALI may include “5 P’s”:

- **Pain:** time of onset, location and intensity, change over time
- **Pulselessness:** the accuracy of pedal pulse palpation is highly variable and, therefore, absent pulse findings are suggestive but not diagnostic of ALI and palpable pulses alone do not rule it out. Bedside measurement of ankle blood pressure should be performed immediately (technique see section C). Usually, very low pressure is obtained or the Doppler signal may be absent. If performed correctly, the finding of absent flow signals in the foot arteries is highly consistent with a diagnosis of ALI
- **Pallor:** change in color and temperature is a common finding in ALI (although temperature may be subject to environmental conditions); the finding is most important when different from the contralateral limb. Venous filling may be slow or absent
- **Paresthesia:** numbness occurs in more than half of patients
- **Paralysis:** is a poor prognostic sign.

**Recommendation 29**

Assessment of acute limb ischemia (ALI)

- Due to inaccuracy of pulse palpation and the physical examination, all patients with suspected ALI should have Doppler assessment of peripheral pulses immediately at presentation to determine if a flow signal is present [C].

**E2.1.3 Clinical classification of acute limb ischemia.** The main question to be answered by the history and physical examination is the severity of the ALI, which is the major consideration in early management decisions. Is the limb viable (if there is no further progression in the severity of ischemia), is its viability immediately threatened (if perfusion is not restored quickly), or are there already irreversible changes that preclude foot salvage?

The three findings that help separate ‘threatened’ from ‘viable’ extremities (Table E1) are:

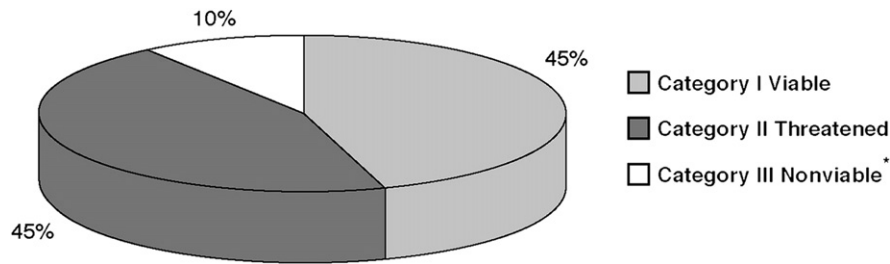
- Presence of rest pain,
- Sensory loss, or
- Muscle weakness

Muscle rigor, tenderness, or findings of pain with passive movement are late signs of advanced ischemia and probable tissue loss.

**Recommendation 30**

Cases of suspected acute limb ischemia (ALI)

- All patients with suspected ALI should be evaluated immediately by a vascular specialist who should direct immediate decision making and perform revascularization because irreversible nerve and muscle damage may occur within hours [C].



**Fig. E3.** Categories of acute limb ischemia on presentation. \*Some of these patients are moribund. In some series this group is up to 15%.

Data presented summarize both registry and clinical trial data and show the frequency of different categories of acute limb ischemia on presentation (Fig. E3).

- Category III: all patients from registries who undergo primary amputation
- Category II: all patients from randomized trials who present with sensory loss
- Category I: all patients from randomized trials who present without sensory loss

**E2.1.4 Differential diagnosis of acute limb ischemia.** There are three levels of differential diagnosis in ALI:

1. Is there a condition mimicking arterial occlusion?
2. Are there other non-atherosclerotic causes of arterial occlusion present and, if not,
3. Is the ischemia caused by an arterial thrombosis or embolus?

The conditions that can cause or mimic acute arterial occlusion are listed in Table E2.

#### *Arterial trauma or dissection*

Overt arterial trauma is not difficult to diagnose, but iatrogenic trauma, especially as a result of recent arterial catheterization, is often overlooked. It should be considered in all hospitalized patients undergoing invasive diagnosis and treatment who present with femoral artery occlusion.

Thoracic aortic dissections may progress distally to involve the abdominal aorta and also an iliac artery. Tearing interscapular or back pain associated with hypertension would obviously point to such a thoracic aortic dissection, but these may be obscured by other events and the patient's inability to give a good history. It should be considered when faced with acute unilateral or bilateral iliac occlusion.

#### *Ergotism*

Ergotism is rare. It may affect almost any artery and may progress to thrombosis but rarely presents as an immediately threatened limb.

#### *HIV arteriopathy*

HIV patients with severe immune compromise and CD4 counts less than 250/cm<sup>3</sup> can develop acute ischemia of upper or lower extremities. This entity involves the distal arteries with an acute and chronic cellular infiltrate in the

**Table E2.** Differential diagnosis of acute limb ischemia

- \*Conditions mimicking acute limb ischemia
- Systemic shock (especially if associated with chronic occlusive disease)
  - Phlegmasia cerulea dolens
  - Acute compressive neuropathy

Differential diagnosis for acute limb ischemia (other than acute PAD)

- Arterial trauma
- Aortic/arterial dissection
- Arteritis with thrombosis (e.g. giant cell arteritis, thromboangiitis obliterans)
- HIV arteriopathy
- Spontaneous thrombosis associated with a hypercoagulable state
- Popliteal adventitial cyst with thrombosis
- Popliteal entrapment with thrombosis
- Vasospasm with thrombosis (e.g. ergotism)
- Compartment syndrome

#### Acute PAD

- Thrombosis of an atherosclerotic stenosed artery
- Thrombosis of an arterial bypass graft
- Embolism from heart, aneurysm, plaque or critical stenosis upstream (including cholesterol or atherothrombotic emboli secondary to endovascular procedures)
- Thrombosed aneurysm with or without embolization

\*Two of the three conditions (deep vein thrombosis, neuropathy) that may mimic arterial occlusion should be expected to have arterial pulses, except if occult chronic peripheral arterial disease existed prior to the acute event. Low cardiac output makes the chronic arterial ischemia more manifest in terms of symptoms and physical findings.

vasa vasorum and viral protein in the lymphocytes. Occasionally, a hypercoagulable focus is found, but primarily the occlusion appears due to the underlying vasculopathy. Standard therapies including thrombectomy, bypass and thrombolysis have been used, with relatively high reocclusion and amputation rates.

#### *Popliteal adventitial cysts and popliteal entrapment*

Popliteal adventitial cysts and popliteal entrapment may be discovered before they induce thrombosis if they cause claudication, but they sometimes first present with thrombosis. Like a thrombosed popliteal aneurysm, the degree of ischemia is often severe. Popliteal entrapment



affects younger patients, but popliteal adventitial cysts can present at an older age and may be indistinguishable from peripheral arterial disease (PAD). The absence of atherosclerotic risk factors and the location of the obstruction, best ascertained by duplex scan, should suggest the etiology.

#### *Thrombosed popliteal artery aneurysm*

Thrombosed popliteal artery aneurysms are commonly mistaken for acute arterial embolism. The popliteal artery is the sole axial artery traversing the knee. Severe ischemia results either because thrombosis occurs in the absence of previous arterial narrowing and the lack of collateral vessels or because prior asymptomatic or symptomatic embolization has occluded the majority of the tibial outflow. As popliteal aneurysms are bilateral in approximately 50% of cases, detecting a prominent popliteal pulse in the opposite leg may help to identify the cause. These patients also tend to have dilated femoral arteries and may have abdominal aortic aneurysms. Once suspected, duplex ultrasound is the quickest way to confirm the diagnosis.

#### *Thromboembolism*

Arterial embolism is suspected in patients with atrial arrhythmia (flutter/fibrillation), congestive heart failure, or valvular heart disease. A rare cause can be paradoxical embolization in a patient with venous thromboembolism and a cardiac septal defect. The contralateral limb is often normal. Patients usually do not have any antecedent claudication symptoms. Arteriographic findings include multiple areas with arterial filling defects (particularly at bifurcations), morphology (meniscus sign) consistent with embolus, lack of collaterals and absence of atherosclerotic disease in unaffected segments. Echocardiography (often transesophageal) is useful to locate the source of thromboemboli.

#### *Atheroembolism*

Embolism of cholesterol crystals and other debris from friable atherosclerotic plaques in proximal arteries may lodge in the distal circulation and infarct tissue. Although also called “blue toe syndrome” for the appearance of painful cyanotic lesions on the toes of affected patients, more proximal organs such as the kidneys, bowel and pancreas may also be affected by atheroemboli.

#### *Thrombosed arterial segment*

Patients with thrombosed arterial segments often have atherosclerotic disease at the site of thrombosis. They may have an antecedent history of claudication and the contralateral limb often has abnormal circulation. Some hypercoagulable states, such as antiphospholipid antibody syndrome or heparin-induced thrombocytopenia can also cause thrombosis in situ, and these should be considered in patients without other overt risk factors for arterial disease.

#### *Thrombosed arterial bypass graft*

Patients with thrombosed arterial bypass grafts have a prior history of vascular disease, limb incisions from previous surgery and a thrombosed graft that can be visualized on duplex imaging.

#### *Compartment syndrome*

See section E3.7.1.

## E2.2 Investigations for acute limb ischemia

Patients with ALI should be evaluated in the same fashion as those with chronic symptoms (see section G) but the severity and duration of ischemia at the time of presentation rarely allow this to be done at the outset. Ideally, all patients with acute ischemia should be investigated with imaging, however, the clinical condition and access to appropriate medical resources may preclude such investigations.

**E2.2.1 Other routine laboratory studies.** The following laboratory studies should be obtained in patients with ALI: electrocardiogram, standard chemistry, complete blood count, prothrombin time, partial thromboplastin time and creatinine phosphokinase level. Patients with a suspected hypercoagulable state will need additional studies seeking anticardiolipin antibodies, elevated homocysteine concentration and antibody to platelet factor IV.

**E2.2.2 Imaging – arteriography.** Arteriography is of major value in localizing an obstruction and visualizing the distal arterial tree. It also assists in distinguishing patients who will benefit more from percutaneous treatment than from embolectomy or open revascularization procedures.

In limb-threatening ischemia, an important consideration is whether the delay in performing formal angiography in an angiographic suite can be tolerated. Angiography makes the most sense when catheter-based treatment is an option.

**E2.2.3 Other imaging techniques.** *Computed tomographic angiography/Magnetic resonance angiography*

Computed tomographic angiography (CTA) and magnetic resonance (MR) angiography may also be used in the setting of ALI to diagnose and delineate the extent of disease. MR imaging of the vasculature can be cumbersome and time-consuming which may delay treatment. The advantages of CTA include its speed, convenience and ability for cross-sectional imaging of the vessel. The main disadvantage of CTA is its dependence on iodinated contrast media. In patients with ALI who may also require catheter angiography and intervention, this added load of contrast might increase the risk of renal injury to the patient.

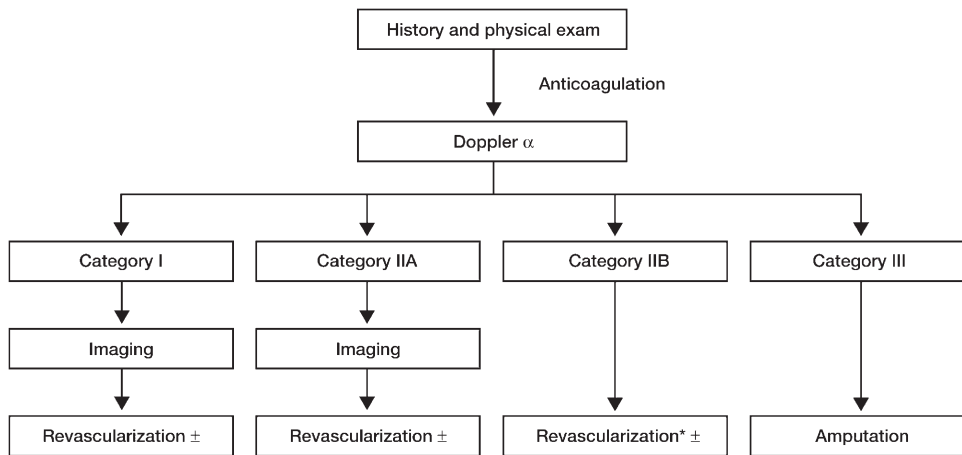
### **Recommendation 31**

Anticoagulant therapy in acute limb ischemia (ALI)

- Immediate parenteral anticoagulant therapy is indicated in all patients with ALI. In patients expected to undergo imminent imaging/therapy on arrival, heparin should be given [C].

## E3 TREATMENT OF ACUTE LIMB ISCHEMIA

The initial goal of treatment for ALI is to prevent thrombus propagation and worsening ischemia. Therefore, immediate anticoagulation with heparin is indicated. The standard therapy (except in cases of heparin antibodies) is unfractionated heparin intravenously (Fig. E4). Based on the results of randomized trials,<sup>172</sup> there is no clear superiority for thrombolysis versus surgery on 30 day limb salvage or mortality. Access to each is a major issue, as time is often



**Fig. E4.** Algorithm for management of acute limb ischemia. Category I – Viable Category IIA – Marginally Threatened Category IIB – Immediately Threatened;  $\alpha$  Confirming either absent or severely diminished ankle pressure/signals; \*In some centers imaging would be performed.

critical. National registry data from Europe<sup>176</sup> and the United States<sup>177</sup> indicate that surgery is used three- to five-fold more frequently than thrombolysis.

### E3.1 Endovascular procedures for acute limb ischemia

**E3.1.1 Pharmacologic thrombolysis.** Three randomized studies have confirmed the important role of catheter-directed thrombolytic therapy in the treatment of ALI.<sup>174,178,179</sup> The less invasive nature of a catheter-based approach to this patient population can result in reduced mortality and morbidity compared with open surgery. Thrombolytic therapy is, therefore, the initial treatment of choice in patients in whom the degree of severity allows time (i.e. severity levels I and IIA). More recent advances in endovascular devices and techniques, however, allow for more rapid clot removal and may permit treatment of patients with more advanced degree of ischemia. Advantages of thrombolytic therapy over balloon embolectomy include the reduced risk of endothelial trauma and clot lysis in branch vessels too small for embolectomy balloons. Gradual low-pressure reperfusion, may be advantageous to the sudden, high-pressure reperfusion associated with balloon embolectomy. Systemic thrombolysis has no role in the treatment of patients with ALI.

The choice of lytic therapy depends on many factors such as location and anatomy of lesions, duration of the occlusion, patient risk factors (co-morbidities) and risks of procedure. Because emboli newly arrived in the leg may have previously resided for some time at their site of origin, these 'old' emboli may be more resistant to pharmacologic thrombolysis than 'recent' in-situ thrombus. Contraindications to pharmacologic thrombolysis must be taken into consideration.

#### E3.1.2 Contraindications to thrombolysis.

See Table E3

**E3.1.3 Other endovascular techniques.** When thrombolysis reveals underlying localized arterial disease,

**Table E3.** Contraindications to thrombolysis

#### Absolute contraindications

1. Established cerebrovascular event (excluding TIA within previous 2 months)
2. Active bleeding diathesis
3. Recent gastrointestinal bleeding (within previous 10 days)
4. Neurosurgery (intracranial, spinal) within previous 3 months
5. Intracranial trauma within previous 3 months

#### Relative contraindications

1. Cardiopulmonary resuscitation within previous 10 days
2. Major nonvascular surgery or trauma within previous 10 days
3. Uncontrolled hypertension (systolic >180 mmHg or diastolic >110 mmHg)
4. Puncture of noncompressible vessel
5. Intracranial tumor
6. Recent eye surgery

#### Minor contraindications

1. Hepatic failure, particularly those with coagulopathy
2. Bacterial endocarditis
3. Pregnancy
4. Active diabetic proliferative retinopathy

These contraindications were established for systemic thrombolysis. The markedly improved safety profile of regional thrombolysis is well recognized, and the risk benefit of regional thrombolysis in various above conditions is highly dependent on individual physician practice/experience. The only contraindication in the TOPAS trial was pregnancy.

catheter-based revascularization becomes an attractive option. Stenoses and occlusions are rarely the sole cause of ALI or even severe chronic symptoms but these commonly lead to superimposed thrombosis and, therefore, should be treated to avoid recurrent thrombosis.

Percutaneous aspiration thrombectomy (PAT) and percutaneous mechanical thrombectomy (PMT) provide alternative non-surgical modalities for the treatment of ALI without the use of pharmacologic thrombolytic agents. Combination of these techniques with pharmacologic thrombolysis may substantially speed up clot lysis, which is important in more

advanced ALI where time to revascularization is critical. In practice, the combination is almost always used.

#### *Percutaneous aspiration thrombectomy (PAT)*

PAT is a technique that uses thin-wall, large-lumen catheters and suction with a 50-mL syringe to remove embolus or thrombus from native arteries, bypass grafts and run-off vessels. It has been used together with fibrinolysis to reduce time and dose of the fibrinolytic agent or as a stand-alone procedure.

#### *Percutaneous mechanical thrombectomy (PMT)*

Most PMT devices operate on the basis of hydrodynamic recirculation. According to this concept, dissolution of the thrombus occurs within an area of continuous mixing referred to as the “hydrodynamic vortex.” This selectively traps, dissolves, and evacuates the thrombus. Non-recirculation devices, which function primarily by direct mechanical thrombus fragmentation, have been used less frequently for peripheral arterial disease because of the higher risk of peripheral embolization and higher potential for vascular injury. The efficiency of PMT depends mainly on the age of the thrombus; fresh thrombus responds better than older organized clot. Small clinical series have demonstrated short-term (30 day) limb salvage of 80%–90%.

### **E3.2 Surgery**

**E3.2.1 Indications.** Immediate revascularization is indicated for the profoundly ischemic limb (class IIB) (Table E1). It may also be considered in those with profound sensory and motor deficits of very short duration, as revascularization completed within a few hours of onset of severe symptoms may produce remarkable recovery. Beyond this short window, major neuromuscular damage is inevitable. The method of revascularization (open surgical or endovascular) may differ depending on anatomic location of occlusion, etiology of ALI, contraindications to open or endovascular treatment and local practice patterns. Previously, urgency of treatment made surgery the treatment of choice in many cases. However, recent methodological advances within endovascular management, and recognition that improved circulation significantly precedes patency with this approach, have made the time factor less important if endovascular service is readily available.

In considering operative versus percutaneous revascularization, it must be recognized that the time from the decision to operate until reperfusion may be substantially longer than anticipated because of factors outside of the surgeons’ control (e.g. operating theater availability, anesthesia preparation, technical details of the operation).

#### *Anatomic location of the acute occlusion*

In cases of suprainguinal occlusion (no femoral pulse) open surgery may be the preferred choice of treatment. For instance, a large embolus in the common proximal iliac artery or distal aorta may most effectively be treated with catheter embolectomy. Also, suprainguinal graft occlusion may best be treated with surgery in most cases. Endovascular management with femoral access of a proximal lesion (often involving thrombosis) may not be possible/appropriate or available (see below).

Infrainguinal causes of ALI, such as embolism or thrombosis, are often treated with endovascular methods. Initial therapy with catheter-based thrombolysis should be considered in cases of acute thrombosis due to vulnerable atherosclerotic lesions or late bypass graft failures. In this manner, the underlying occlusive disease is revealed and appropriate adjunctive management may be chosen.

In cases of trauma, for many reasons, surgery will be the treatment of choice in the majority of cases. Infrainguinal grafts often occlude due to obstructive lesions proximal to, within and distal to the graft, thus, simple thrombectomy will not solve the underlying lesion. Catheter-based thrombolysis, on the other hand, will dissolve clot and identify the responsible underlying lesion. Endovascular treatment of these lesions may then be employed. If the lesion is discrete this may suffice, and even if the underlying disease is diffuse and extensive, it may serve as a temporizing measure, a bridge to a later bypass.

**E3.2.2 Surgical technique.** Emboli are preferentially removed surgically if they are lodged proximally in the limb or above the inguinal ligament. Surgery may also be considered if the involved limb has no underlying atherosclerosis. When no further clot can be retrieved, some form of intraoperative assessment of the adequacy of clot removal is required. The most common of these is ‘completion’ angiography; alternatively, ultrasound-based methods may be used.

Distal clot may be treated by intraoperative thrombolysis with instillation of high doses of thrombolytic agents for a brief period followed by irrigation or additional passages of the balloon catheter. Repeat angiography followed by clinical and Doppler examination of the patient should be performed on the operating table. However, as described in section E3.2.1, catheter-directed thrombolysis may have advantages if conditions allow its use.

In patients with arterial thrombosis, an underlying local lesion and residual thrombus must be sought after clot extraction. Often this may be suspected from the tactile sensations and need for deflation at points during the withdrawal of the inflated balloon catheter. Here completion angiography will help decide between proceeding with a bypass or PTA. Fortunately, arterial thrombosis superimposed on an already narrowed artery will ordinarily cause a less severe degree of ischemia because of predeveloped collaterals. Under these circumstances, patients may not be operated on initially but rather undergo catheter-directed lytic therapy.

In patients with suprainguinal occlusion extra-anatomic bypass surgery may be required.

#### **Recommendation 32**

##### Completion arteriography

- Unless there is good evidence that adequate circulation has been restored, intraoperative angiography should be performed to identify any residual occlusion or critical arterial lesions requiring further treatment [C].

**Table E4.** Comparison of catheter-directed thrombolysis and surgical revascularization in treatment of limb ischemia

	Results at	Catheter-Directed Thrombolysis (CDT)			Surgical Revascularization		
		Patients	Limb salvage	Mortality	Patients	Limb salvage	Mortality
Rochester <sup>178</sup>	12months	57	82%	16%	57	82%	42%
STILE <sup>174</sup>	6months	246	88.2%	6.5%	141	89.4%	8.5%
TOPAS <sup>179</sup>	12months	144	82.7%	13.3%	54	81.1%	15.7%

### E3.3 Results of surgical and endovascular procedures for acute limb ischemia

Catheter-directed thrombolysis (CDT) has become a commonly employed technique in the treatment of ALI. Between 1994 and 1996, three large, prospective, randomized trials<sup>174,178,179</sup> were reported that focused on the comparison of CDT and surgical revascularization for treatment of ALI. Limb salvage and mortality rates are recognized as the most important outcome, and the 1-year data are summarized in Table E4.<sup>172</sup> Comparison of these studies is limited by certain differences in protocol and case mix (e.g. acute vs. subacute or chronic limb ischemia; thrombotic vs. embolic occlusion; native vs. bypass graft occlusion; proximal vs. distal occlusions). End points in each of the studies also vary: the Rochester study used “event free survival”; the STILE trial used “composite clinical outcome”; and the TOPAS study used “arterial recanalization and extent of lysis.” Only the Rochester trial showed any advantage for CDT by primary end points. However, the late end point of limb salvage, required in these trials, may have favored surgery, as CDT was naturally linked with endovascular treatment of the underlying lesions (the patient being in a radiology suite at the time). Except for discrete lesions, PTA is not as durable as bypass, the inevitable result of being randomized to surgery. Such linkage may be inevitable in randomized trials, but in practice the underlying lesion(s) should be treated by the method giving the most durable results.

The data from the randomized, prospective studies in ALI, suggest that CDT may offer advantages when compared with surgical revascularization. These advantages include reduced mortality rates and a less complex surgical procedure in exchange for a higher rate of failure to avoid persistent or recurrent ischemia, major complications and ultimate risk of amputation. In addition, it appears that reperfusion with CDT is achieved at a lower pressure and may reduce the risk of reperfusion injury compared to open surgery. Thus, if the limb is not immediately or irreversibly threatened, CDT offers a lower-risk opportunity for arterial revascularization. Using this approach, the underlying lesions can be further defined by angiography, and the appropriate percutaneous or surgical revascularization procedure can be performed. Therefore, it seems reasonable to recommend CDT as initial therapy in these particular settings, to be potentially followed by surgical revascularization as needed.

### E3.4 Management of graft thrombosis

In general, at least one attempt to salvage a graft should be done, although individual considerations may apply. When treating late graft thrombosis, the main goals are to remove the clot and correct the underlying lesion that caused the thrombosis. Alteration in the inflow and outflow arteries is usually caused by the progression of atherosclerosis and should be treated with either PTA/stent or bypass grafting, as detailed elsewhere. Lesions intrinsic to the graft are dependent on the type of conduit. Venous bypass grafts may develop stenoses, typically at the site of a valve. After thrombolysis and identification of the lesion, it may be treated with either PTA/stent or surgical revision, the latter usually being favored for its superior long-term results. Prosthetic grafts develop intimal hyperplasia, typically at the distal anastomosis. These rubbery lesions respond differently to PTA than do the typical eccentric atherosclerotic plaque and do not yield as durable results. Many surgeons have suggested that treatment should be exposure of the involved anastomosis, with graft thrombectomy and patch angioplasty of the narrowed graft/artery anastomosis or replacement of the graft. However, in case of the latter, the expected patency using another type of graft should be considered (i.e. replacing a failing vein graft).

### E3.5 Management of a thrombosed popliteal aneurysm

Patients with thrombosed popliteal artery aneurysms initially undergo arteriography. If a distal tibial target is present, then they are treated as a critical limb ischemia case with tibial bypass. If no tibial targets are identified on arteriography, regional thrombolysis is the treatment of choice providing the limb is viable. Small series demonstrate successful identification of tibial targets in over 90% and successful surgical revascularization.

### E3.6 Amputation

Amputation in ALI may be complicated by bleeding due to an increased prevalence of concomitant anticoagulation. In addition, the site of amputation is more often proximal, as the calf muscle is usually compromised. The ratio of above-knee to below-knee amputation is 4:1 compared to the usual 1:1 for critical limb ischemia. The incidence of major amputation is up to 25%. When further evaluated, 10%–15% of patients thought to be salvageable undergo therapy and ultimately require major amputation, and 10% of patients with ALI present unsalvageable.



### E3.7 Immediate post-procedural issues

#### E3.7.1 Reperfusion injury. *Compartment syndrome*

Fasciotomy following successful revascularization for ALI was required in 5.3% of cases in the United States from 1992–2000. Fasciotomy for presumably more severe cases in tertiary referral hospitals is 25%.<sup>177</sup> With extremity reperfusion, there is increased capillary permeability, resulting in local edema and compartment hypertension. This leads to regional venule obstruction, nerve dysfunction and, eventually, capillary and arteriolar obstruction and muscle and nerve infarction. Clinical presentation includes pain out of proportion to physical signs, paresthesia and edema. Compartment pressures can be measured, and pressures of  $\geq 20$  mmHg are a clear indication for fasciotomy. The anterior compartment is most commonly involved, but the deep posterior compartment (in which the tibial nerve is located) is the most functionally devastating if affected.

#### Recommendation 33

Treatment of choice for compartment syndrome

- In case of clinical suspicion of compartment syndrome, the treatment of choice is a four-compartment fasciotomy [C].

#### *Rhabdomyolysis*

Laboratory evidence for myoglobinuria is observed in up to 20%. Half of patients with creatine kinase levels  $>5000$  units/L will develop acute renal failure. Urine myoglobin  $>1142$  nmol/L ( $>20$  mg/dL) is also predictive of acute renal failure. The pathophysiology involves tubular necrosis by myoglobin precipitates (favored in a acidic urine), tubular necrosis due to lipid peroxidation and renal vasoconstriction (exacerbated by fluid shifts into the damage muscle compartment). Clinical features include tea colored urine, elevated serum creatine kinase and positive urine myoglobin assay. Therapy is primarily hydration, alkalinizing the urine and eliminating the source of myoglobin. Mannitol and plasmapheresis have not been found to be beneficial.

### E4 CLINICAL OUTCOMES

#### E4.1 Systemic/limb

Mortality rates for ALI range from 15%–20%. The cause of death is not provided in most series and randomized trials. Major morbidities include major bleeding requiring transfusion/and or operative intervention in 10%–15%, major amputation in up to 25%, fasciotomy in 5%–25% and renal insufficiency in up to 20%. Functional outcomes have at present not been studied.

Improvement in arterial circulation is relatively simple to assess in that the vast majority of patients with ALI have no pedal Doppler signals at presentation or they have an ankle-brachial index (ABI)  $\leq 0.20$ . Therefore, any improvement in these parameters postoperatively is considered successful.

#### E4.2 Follow-up care

All patients should be treated with heparin in the immediate postoperative period. This should be followed by warfarin often for 3–6 months or longer. Patients with thromboembolism will need long-term anticoagulation, from years or life long. However, there are no clear guidelines regarding duration of therapy. The risk of recurrent limb ischemia in the randomized trials was high during the follow-up interval.<sup>174,178,179</sup> Therefore, prolonged warfarin therapy is an appropriate strategy, despite the cumulative bleeding risk. It is important to seek the source of embolism after revascularization, whether cardiac or arterial; however, in many cases no source is identified.

Certainly, if long-term anticoagulation is contraindicated, due to bleeding risk factors, platelet inhibition therapy should be considered. Appropriate systemic therapies as outlined above (see section B) should be provided.

### E5 ECONOMIC ASPECTS OF ACUTE LIMB ISCHEMIA

The recent literature has added very little to the findings presented in the first TASC document. When thrombolysis is used in association with angioplasty, the costs are identical to those of surgical revascularization at roughly \$20,000. The relative benefits of surgery have been discussed above. The choice of strategy is based on availability and outcome rather than on cost considerations.<sup>180</sup>

### E6 FUTURE MANAGEMENT

The increased use of percutaneous therapies with or without surgical revascularization is the trend for future therapy in ALI. The use of protection devices to prevent embolization, as in the carotid circulation, will also become part of therapy. Alternative oral therapies for anticoagulation may hold promise.

## SECTION F – REVASCULARIZATION

### F1 LOCALIZATION OF DISEASE

The determination of the best method of revascularization for treatment of symptomatic peripheral arterial disease (PAD) is based upon the balance between risk of a specific intervention and the degree and durability of the improvement that can be expected from this intervention. Adequate inflow and appropriate outflow are required to keep the revascularized segment functioning. The location and morphology of the disease must be characterized prior to carrying out any revascularization to determine the most appropriate intervention. A variety of methods yielding both anatomic and physiologic information are available to assess the arterial circulation. (Refer to section G for preferred imaging techniques.)

In a situation where a proximal stenosis is of questionable hemodynamic significance, pressure measurements across it to determine its significance (criteria: threshold peak systolic difference 5–10 mmHg pre-vasodilatation and 10–15 mmHg post-vasodilatation) may



be made. A recent development, that is yet to be validated, is direct flow measurements using a thermodilution catheter rather than pressure gradients. Hyperemic duplex scanning has also been suggested.

#### Recommendation 34

Intra-arterial pressure measurements for assessment of stenosis

- If there is doubt about the hemodynamic significance of partially occlusive aortoiliac disease, it should be assessed by intra-arterial pressure measurements across the stenosis at rest and with induced hyperemia [C].

In general, the outcomes of revascularization depend upon the extent of the disease in the subjacent arterial tree (inflow, outflow and the size and length of the diseased segment), the degree of systemic disease (co-morbid conditions that may affect life expectancy and influence graft patency) and the type of procedure performed. Results of large-scale clinical trials must be considered within the context of the individual patient's situation, considering all co-morbidities when deciding upon a recommended treatment course for that individual.

The endovascular techniques for the treatment of patients with lower extremity ischemia include balloon angioplasty, stents, stent-grafts and plaque debulking procedures. Thrombolysis and percutaneous thrombectomy have been described in the section on acute limb ischemia. Surgical options include autogenous or synthetic bypass, endarterectomy or an intra-operative hybrid procedure.

Outcomes of revascularization procedures depend on anatomic as well as clinical factors. Patency following percutaneous transluminal angioplasty (PTA) is highest for lesions in the common iliac artery and progressively decreases for lesions in more distal vessels. Anatomic factors that affect the patency include severity of disease in run off arteries, length of the stenosis/occlusion and the number of lesions treated. Clinical variables impacting the outcome also include diabetes, renal failure, smoking and the severity of ischemia.

#### Recommendation 35

Choosing between techniques with equivalent short- and long-term clinical outcomes

- In a situation where endovascular revascularization and open repair/bypass of a specific lesion causing symptoms of peripheral arterial disease give equivalent short-term and long-term symptomatic improvement, endovascular techniques should be used first [B].

#### F1.1 Classification of lesions

While the specific lesions stratified in the following TASC classification schemes have been modified from

the original TASC guidelines to reflect inevitable technological advances, the principles behind the classification remain unchanged. Thus 'A' lesions represent those which yield excellent results from, and should be treated by, endovascular means; 'B' lesions offer sufficiently good results with endovascular methods that this approach is still preferred first, unless an open revascularization is required for other associated lesions in the same anatomic area; 'C' lesions produce superior enough long-term results with open revascularization that endovascular methods should be used only in patients at high risk for open repair; and 'D' lesions do not yield good enough results with endovascular methods to justify them as primary treatment. Finally it must be understood that most PAD requiring intervention is characterized by more than one lesion, at more than one level, so these schemes are limited by the necessity to focus on individual lesions.

#### F1.2 Classification of inflow (aorto-iliac) disease (Fig. F1, Table F1)

##### Recommendation 36

Treatment of aortoiliac lesions

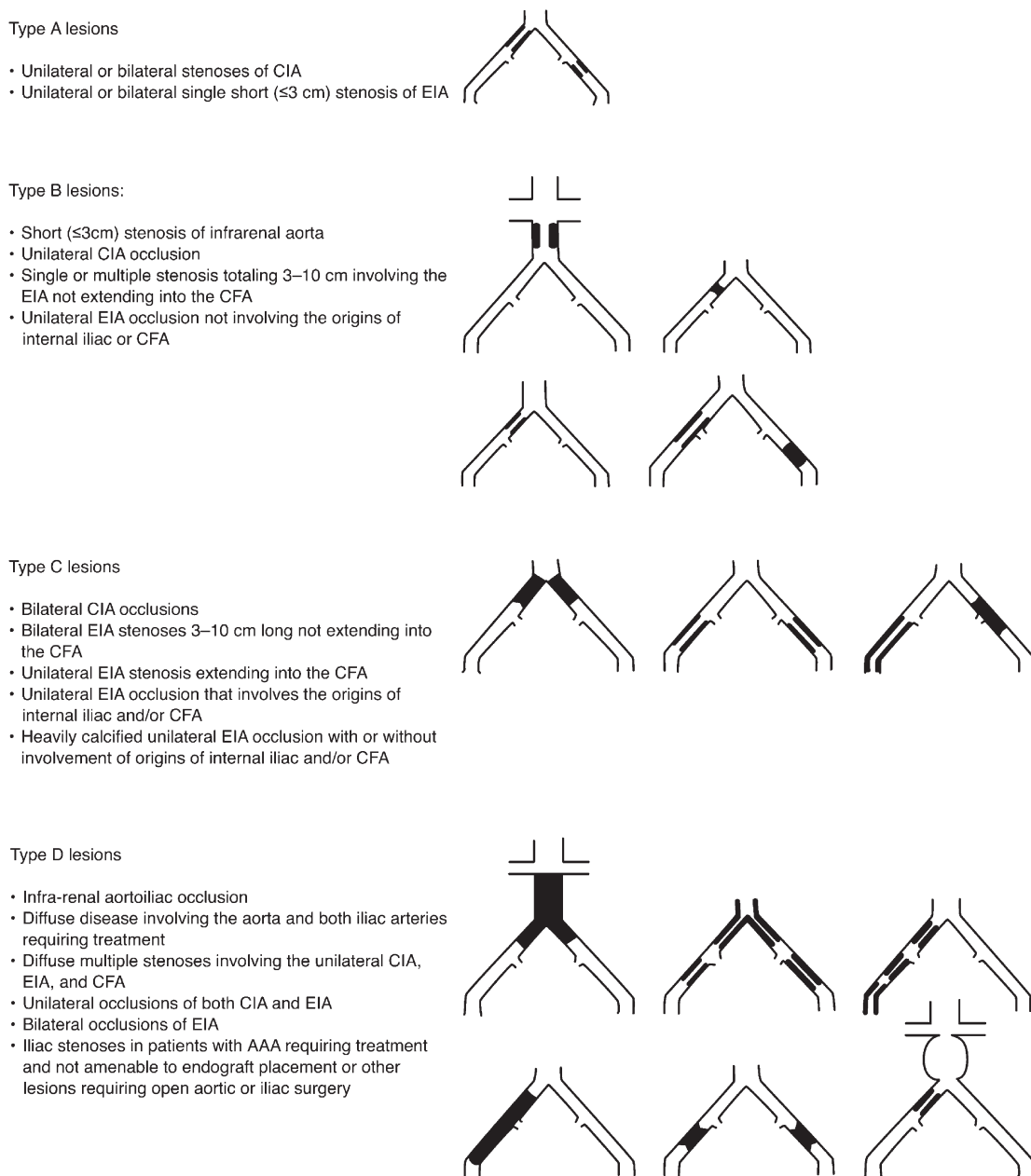
- TASC A and D lesions: Endovascular therapy is the treatment of choice for type A lesions and surgery is the treatment of choice for type D lesions [C].
- TASC B and C lesions: Endovascular treatment is the preferred treatment for type B lesions and surgery is the preferred treatment for good-risk patients with type C lesions. The patient's co-morbidities, fully informed patient preference and the local operator's long-term success rates must be considered when making treatment recommendations for type B and type C lesions [C].

#### F1.3 Classification of femoral popliteal disease (Fig. F2, Table F2)

##### Recommendation 37

Treatment of femoral popliteal lesions

- TASC A and D lesions: Endovascular therapy is the treatment of choice for type A lesions and surgery is the treatment of choice for type D lesions [C].
- TASC B and C lesions: Endovascular treatment is the preferred treatment for type B lesions and surgery is the preferred treatment for good-risk patients with type C lesions. The patient's co-morbidities, fully informed patient preference and the local operator's long-term success rates must be considered when making treatment recommendations for type B and type C lesions [C].



**Fig. F1.** TASC classification of aorto-iliac lesions. CIA – common iliac artery; EIA – external iliac artery; CFA – common femoral artery; AAA – abdominal aortic aneurysm.

## F2 AORTOILIAC (SUPRA INGUINAL) REVASCULARIZATION

### F2.1 Endovascular treatment of aorto-iliac occlusive disease

Although aortobifemoral bypass appears to have better long-term patency than the currently available endovascular strategies for diffuse aortoiliac occlusive disease, the risks of surgery are significantly greater than the risks of an endovascular approach, in terms of not only mortality but also major morbidity and delay in return to

normal activities. Therefore, the assessment of the patient's general condition and anatomy of the diseased segment(s) become central in deciding which approach is warranted.

The technical and initial clinical success of PTA of iliac stenoses exceeds 90% in all reports in the literature. This figure approaches 100% for focal iliac lesions. The technical success rate of recanalization of long segment iliac occlusions is 80%–85% with or without additional fibrinolysis. Recent device developments geared

**Table F1.** TASC classification of aorto-iliac lesions

Type A lesions	<ul style="list-style-type: none"> <li>■ Unilateral or bilateral stenoses of CIA</li> <li>■ Unilateral or bilateral single short (<math>\leq 3</math> cm) stenosis of EIA</li> </ul>
Type B lesions	<ul style="list-style-type: none"> <li>■ Short (<math>\leq 3</math> cm) stenosis of infrarenal aorta</li> <li>■ Unilateral CIA occlusion</li> <li>■ Single or multiple stenosis totaling 3–10 cm involving the EIA not extending into the CFA</li> <li>■ Unilateral EIA occlusion not involving the origins of internal iliac or CFA</li> </ul>
Type C lesions	<ul style="list-style-type: none"> <li>■ Bilateral CIA occlusions</li> <li>■ Bilateral EIA stenoses 3–10 cm long not extending into the CFA</li> <li>■ Unilateral EIA stenosis extending into the CFA</li> <li>■ Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA</li> <li>■ Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA</li> </ul>
Type D lesions	<ul style="list-style-type: none"> <li>■ Infra-renal aortoiliac occlusion</li> <li>■ Diffuse disease involving the aorta and both iliac arteries requiring treatment</li> <li>■ Diffuse multiple stenoses involving the unilateral CIA, EIA and CFA</li> <li>■ Unilateral occlusions of both CIA and EIA</li> <li>■ Bilateral occlusions of EIA</li> <li>■ Iliac stenoses in patients with AAA requiring treatment and not amenable to endograft placement or other lesions requiring open aortic or iliac surgery</li> </ul>

CIA – common iliac artery; EIA – external iliac artery; CFA – common femoral artery; AAA – abdominal aortic aneurysm.

towards treatment of total occlusions, however, have substantially improved the technical success rate of recanalization.<sup>181</sup>

Becker *et al.* found 5-year patency rate of 72% in an analysis of 2697 cases from the literature, noting a better patency of 79% in claudicants.<sup>182</sup> Rutherford and Durham found a similar 5-year patency of 70%.<sup>183</sup> A recent study reported a primary patency of 74% (primary assisted patency of 81%) 8 years after stent placement suggesting durability of patency of iliac artery stenting.<sup>184</sup> Factors negatively affecting the patency of such interventions include quality of run off vessels, severity of ischemia and length of diseased segments. Female gender has also been suggested to decrease patency of external iliac artery stents.<sup>185</sup> Table F3 presents the estimated success rate of iliac artery angioplasty from weighted averages (range) from reports of 2222 limbs.

Choice of stent versus PTA with provisional stenting was addressed in a prospective randomized, multicenter study.<sup>186</sup> Results showed that PTA with provisional stenting had a similar outcome to primary stenting with 2-year reintervention rates of 7% and 4%, respectively, for PTA and primary stenting (not significant). The 5-year outcomes of the groups were also similar with 82% and 80% of the treated iliac artery segments remaining free of

revascularization procedures after a mean follow-up of 5.6 years  $\pm 1.3$ .<sup>187</sup> A meta-analysis by Bosch and Hunink compared the results of aortoiliac PTA versus aortoiliac stenting using a Medline search of the post-1989 literature and yielded only six articles (including 2116 patients) with sufficient detail to allow stratification over subgroups with various risk levels for long-term patency.<sup>188</sup> Technical success was higher for stenting, whereas complication rates and 30-day mortality rates did not differ significantly. In patients with intermittent claudication the severity-adjusted 4-year primary patency rates ( $\pm 95\%$  confidence intervals) after excluding technical failures, for PTA and stenting, were: 68% (65%–71%) and 77% (72%–81%), respectively. Including technical failures, the 4-year primary patency rates are 65% (PTA) versus 77% (stent) for stenosis and 54% (PTA) versus 61% (stent) for occlusion. The relative risk of long-term failure was reduced by 39% after stent placement compared with PTA. This robust report uses data from older studies and it is reasonable to expect that the newer techniques and equipment available today would lead to even better results.

The outcome of two different self-expanding stents for the treatment of iliac artery lesions was compared in a multicenter prospective randomized trial.<sup>189</sup> The 1-year primary patencies were 94.7% and 91.1% (not significant), respectively, with similar complication and symptomatic improvement rates regardless of the type of stent.

## F2.2 Surgical treatment of aorto-iliac occlusive disease

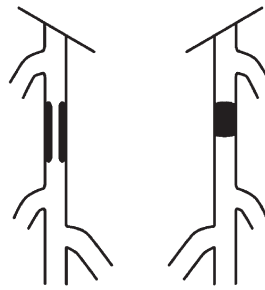
Bilateral surgical bypass from the infra-renal abdominal aorta to both femoral arteries is usually recommended for diffuse disease throughout the aortoiliac segment (Fig. F3). The aorta may be approached via a transperitoneal or retroperitoneal approach. Interest is increasing in laparoscopic approach. The configuration of the proximal anastomosis (end-to-end versus end-to-side) has not been reliably shown to influence patency. The use of PTFE versus Dacron as a conduit in this position is based on the preference of the surgeon. Younger patients (<50 years of age) with lower primary and secondary patency have a greater need for secondary bypass.<sup>190</sup>

Recent interest in endarterectomy has been revived although it is not as widely practiced as bypass grafting and may be more technically challenging. Reported 5-year primary patency rates range from 60% to 94%, reflecting a degree of variability depending upon the operator.

In some situations, when an abdominal approach is to be avoided due to anatomic considerations ('hostile abdomen') or cardiac and/or pulmonary risks, a modified retroperitoneal approach or a unilateral bypass with a femoro-femoral crossover may be used. Consideration should be given to using an axillo (bi) femoral (Fig. F4) or cross-over

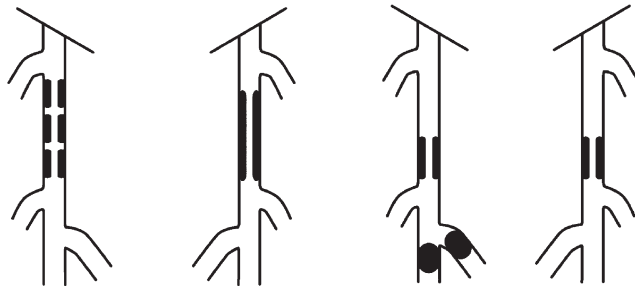
Type A lesions

- Single stenosis  $\leq 10$  cm in length
- Single occlusion  $\leq 5$  cm in length



Type B lesions:

- Multiple lesions (stenoses or occlusions), each  $\leq 5$  cm
- Single stenosis or occlusion  $\leq 15$  cm not involving the infrageniculate popliteal artery
- Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass
- Heavily calcified occlusion  $\leq 5$  cm in length
- Single popliteal stenosis



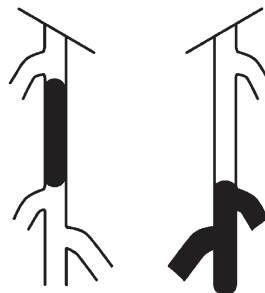
Type C lesions

- Multiple stenoses or occlusions totaling  $>15$  cm with or without heavy calcification
- Recurrent stenoses or occlusions that need treatment after two endovascular interventions



Type D lesions

- Chronic total occlusions of CFA or SFA ( $>20$  cm, involving the popliteal artery)
- Chronic total occlusion of popliteal artery and proximal trifurcation vessels



**Fig. F2.** TASC classification of femoral popliteal lesions. CFA – common femoral artery; SFA – superficial femoral artery.

femoral (Fig. F5) bypass in patients with increased comorbidities, making a transabdominal approach less desirable. Patency rates depend upon the indication for the reconstruction and the justification for the unilateral bypass (normal inflow artery versus high surgical risk). In some cases, patency of unilateral bypass can be supplemented by endovascular means. The thoracic aorta has also been used as an inflow artery.

Extra-anatomic bypass rarely performs as well as aorto-bifemoral bypass in diffuse disease and, therefore, is seldom recommended for claudication. Evidence is lacking in recommending the preferred material for anatomic or extra-anatomic prosthetic bypass procedures. Table F4 summarizes the patency at 5 and 10 years after aortobifemoral bypass and Table F5 the patency rates at 5 years after extra-anatomic bypass.

**Table F2.** TASC classification of femoral popliteal lesions

Type A lesions	<ul style="list-style-type: none"> <li>■ Single stenosis <math>\leq 10</math> cm in length</li> <li>■ Single occlusion <math>\leq 5</math> cm in length</li> </ul>
Type B lesions	<ul style="list-style-type: none"> <li>■ Multiple lesions (stenoses or occlusions), each <math>\leq 5</math> cm</li> <li>■ Single stenosis or occlusion <math>\leq 15</math> cm not involving the infra geniculate popliteal artery</li> <li>■ Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass</li> <li>■ Heavily calcified occlusion <math>\leq 5</math> cm in length</li> <li>■ Single popliteal stenosis</li> </ul>
Type C lesions	<ul style="list-style-type: none"> <li>■ Multiple stenoses or occlusions totaling <math>&gt;15</math> cm with or without heavy calcification</li> <li>■ Recurrent stenoses or occlusions that need treatment after two endovascular interventions</li> </ul>
Type D lesions	<ul style="list-style-type: none"> <li>■ Chronic total occlusions of CFA or SFA (<math>&gt;20</math> cm, involving the popliteal artery)</li> <li>■ Chronic total occlusion of popliteal artery and proximal trifurcation vessels</li> </ul>

CFA – common femoral artery; SFA – superficial femoral artery.

### F3 INFRAINGUINAL REVASCULARIZATION

#### F3.1 Endovascular treatment of infrainguinal arterial occlusive disease

Endovascular treatment of infrainguinal disease in patients with intermittent claudication is an established treatment modality. The low morbidity and mortality of endovascular techniques such as PTA makes it to the preferred choice of treatment in limited disease such as stenoses/occlusions up to 10 cm in length.

The technical and clinical success rate of PTA of femoropopliteal artery stenoses in all series exceeds 95% (range 98%–100%, standard error 1.0%).<sup>192</sup> Device developments such as hydrophilic guide wires and technical developments, such as subintimal recanalization, provide high recanalization rates in total occlusions of more than 85% (range 81%–94%, standard error 2.9%).<sup>193</sup> The technique of subintimal angioplasty is not as dependent on length, but rather on the presence of normal vessel above and below the occlusion to allow access.<sup>194</sup> Table F6 summarizes pooled results of femoral popliteal dilatations.

The mid- and long-term patency rates were summarized in a meta-analysis by Muradin<sup>192</sup> and in three randomized studies assessing the efficacy of stents.<sup>195–197</sup>

Risk factors for recurrence were analyzed by multivariate stepwise backward regression analyses in various studies. Clinical stage of disease (intermittent claudication versus critical limb ischemia), length of lesion and outflow disease were most commonly found as independent risk factors for restenoses. Recently, a study by Schillinger of 172 patients successfully undergoing PTA of the superficial femoral and popliteal arteries observed that 6-month patency rates were related to hs-CRP levels at baseline and at 48 hours after intervention.<sup>198</sup> SSA and fibrinogen level were not significantly predictive.

There is general agreement that for acute failure of PTA of an SFA lesion, stent placement is indicated. A recent randomized trial has demonstrated significantly higher primary patency rates of stenting vs. PTA of femoropopliteal artery lesions TASC A and B at 1-year follow up.<sup>199</sup>

Randomized trials comparing PTA versus bypass surgery (BP) in infrainguinal arterial obstructive disease are almost nonexistent. This can be explained partially by the following facts: BP is more commonly performed in extensive disease with long lesions and CLI. PTA is more commonly performed in limited disease with IC and short obstructions (following the original TASC recommendations 34 and 35). However, Wolf *et al.* published a multicenter, prospective randomized trial comparing PTA with BP in 263 men who had iliac, femoral or popliteal artery obstruction.<sup>200</sup> This study of patients randomly assigned to BP or PTA showed no significant difference in outcomes during a median follow-up of 4 years (survival, patency and limb salvage). In 56 patients, cumulative 1-year primary patency after PTA was 43% and after bypass surgery was 82%, demonstrating that for long superficial femoral artery (SFA) stenoses or occlusions, surgery is better than PTA. This contrasts a recent randomized study of 452 patients which demonstrated no difference in amputation-free survival at 6 months; however, surgery was somewhat more expensive.<sup>201</sup>

Medical treatment after PTA and stent placement is recommended to prevent early failure because of thrombosis at the site of intervention. Standard therapy is heparinization during the intervention to increase activated clotting time to 200–250 seconds. After PTA and stenting of femoropopliteal arteries, a life-long antiplatelet medication is recommended to promote patency (acetylsalicylic acid or clopidogrel). Life-long antiplatelet therapy is also recommended to prevent cardiovascular events as recommended in section B. Much of the supporting evidence for peri-procedural antiplatelet and adjuvant therapy is extrapolated from that related to the coronary circulation.

#### F3.2 Endovascular treatment of infrapopliteal occlusive disease

Endovascular procedures below the popliteal artery are usually indicated for limb salvage and there are no data comparing endovascular procedures to bypass surgery for intermittent claudication in this region.

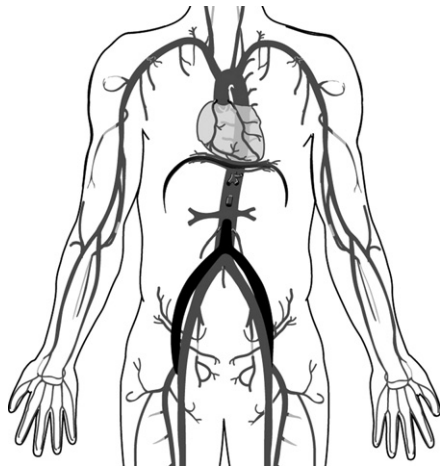
Angioplasty of a short anterior or posterior tibial artery stenosis may be performed in conjunction with popliteal or femoral angioplasty. Use of this technique is usually not indicated in patients with intermittent claudication.

There is increasing evidence to support a recommendation for angioplasty in patients with CLI and infrapopliteal artery occlusion where in-line flow to the foot can be re-established and where there is medical co-morbidity. In the case of infrapopliteal angioplasty, technical success may approach 90% with resultant clinical success of approximately 70% in some series of patients with CLI. Salvage rates are reported as being slightly higher.

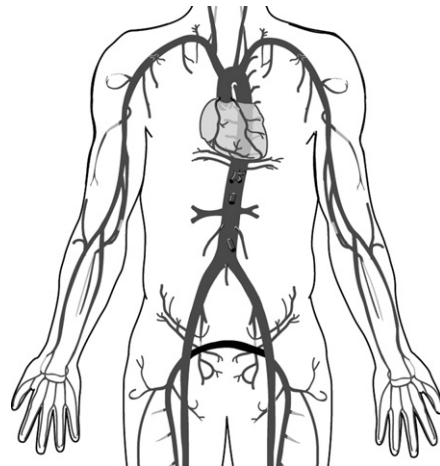


**Table F3.** Estimated success rate of iliac artery angioplasty from weighted averages (range) from reports of 2222 limbs

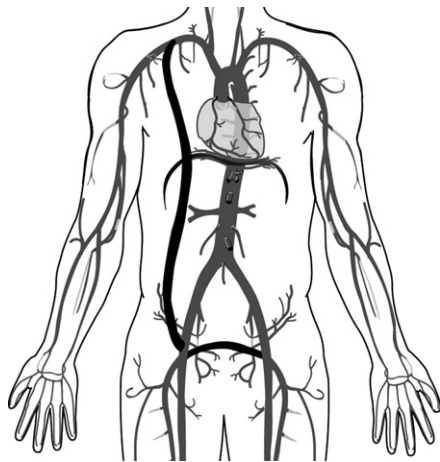
% Claudication	Technical success	Primary patency		
		1 yr	3 yr	5 yr
76% (81–94)	96% (90–99)	86% (81–94)	82% (72–90)	71% (64–75)



**Fig. F3.** Bilateral bypass from infra renal abdominal aorta to both femoral arteries.



**Fig. F5.** Cross-over femoral bypass.



**Fig. F4.** Axillo (bi) femoral bypass.

Predictors of successful outcome include a shorter length of occlusion and a lesser number of vessels treated. The complication rate (2.4%–17% depending upon the definition) can usually be treated by endovascular or surgical techniques and a failed angioplasty does not preclude subsequent bypass.

It remains controversial whether infrapopliteal PTA and stenting should be performed in patients with IC for improvement of outflow and for an increased patency of proximal PTA, stenting and bypass surgery. There is insufficient evidence to recommend infrapopliteal PTA and stenting in patients with intermittent claudication.

### F3.3 Surgical treatment of infrainguinal occlusive disease

In the case of multilevel disease, the adequacy of inflow must be assessed anatomically or with pressure measurements and occlusive disease treated prior to proceeding with an outflow procedure. In some situations, a combined approach with dilatation of proximal lesions and bypassing of distal lesions should be performed.

A recent study has shown a trend towards increasingly complex bypass grafts (composite and spliced vein) to more distal arteries in patients with greater co-morbidities, such as diabetes, renal failure and coronary artery disease; however, mortality rates have remained constant.<sup>202</sup> A recent large study showed that gender did not adversely affect the morbidity or mortality of lower extremity revascularization.

**F3.3.1 Bypass.** Infrainguinal bypass procedures need to arise from a patent and uncompromised inflow artery although the actual level (common femoral artery versus superficial femoral or popliteal artery) does not correlate with patency. If the infrainguinal bypass is constructed following an inflow procedure, patency is improved by making the proximal anastomosis to a native artery rather than the inflow graft (usually limb of aortobifemoral bypass).<sup>203</sup> The quality of the outflow artery is a more important determinant of patency than the actual level where the distal anastomosis is performed. A distal vessel of the best quality should be used for the distal anastomosis. There is no objective evidence to preferentially select either tibial or peroneal artery,

**Table F4.** Patency at 5 and 10 years after aortobifemoral bypass<sup>191</sup>

Indication	5-year % patency (range)		10-year % patency (range)	
	Claudication	CLI	Claudication	CLI
Limb based	91 (90–94)	87 (80–88)	86 (85–92)	81 (78–83)
Patient based	85 (85–89)	80 (72–82)	79 (70–85)	72 (61–76)

CLI – critical limb ischemia.

**Table F5.** Patency rates at 5 years after extra-anatomic bypass

Procedure	5-year % patency (range)
Axillo uni femoral bypass	51 (44–79)
Axillo bi femoral bypass	71 (50–76)
Femoral femoral bypass	75 (55–92)

since they are typically of equal caliber. The results of femoral crural bypass have not been subjected to meta-analysis. Five-year assisted patency rates in grafts constructed with vein approach 60% and those constructed with prosthetic material are usually less than 35%. Reports have documented the suitability of constructing bypass grafts to plantar arteries with reasonable success rates (5-year salvage 63%, 5-year primary patency 41%).

**Recommendation 38**

Inflow artery for femorodistal bypass

- Any artery, regardless of level (i.e. not only the common femoral artery), may serve as an inflow artery for a distal bypass provided flow to that artery and the origin of the graft is not compromised [C].

**Recommendation 39**

Femoral distal bypass outflow vessel

- In a femoral tibial bypass, the least diseased distal artery with the best continuous run-off to the ankle/foot should be used for outflow regardless of location, provided there is adequate length of suitable vein [C].

**F3.3.2 Conduit.** Vein has better long-term patency than prosthetic in the infra inguinal region (Table F7). Over the short term, PTFE has delivered near equivalent results in the above-knee position (Fig. F6). A meta-analysis suggests much less satisfactory results of polytetrafluoroethylene-coated grafts (PTFE) to the infrapopliteal arteries (5-year patency: primary 30.5%, secondary 39.7%).<sup>204</sup> The consequences of a prosthetic graft occlusion may be more severe than a vein graft occlusion.<sup>205</sup> A recent study questioned the wisdom of using a prosthetic graft when accept-

able vein was available in order to ‘save the vein’. Using this strategy, up to 33% of subsequent secondary bypass grafts did not have adequate vein available at that time. The long saphenous vein (also known as the greater saphenous vein), either in a reversed or in situ configuration offers the best match of size and quality. In its absence, other venous tissue including contralateral long saphenous vein, short (lesser) saphenous vein, femoral vein and arm vein have been used (Fig. F7). There is no difference in patency rates between in situ and reversed vein grafts. Differences in outcome will depend upon indications for surgery, the quality of the vessels, and co-morbidities. Venous grafts all have better results than prosthetic materials.

**Recommendation 40**

Femoral below-knee popliteal and distal bypass

- An adequate long (greater) saphenous vein is the optimal conduit in femoral below-knee popliteal and distal bypass [C]. In its absence, another good-quality vein should be used [C].

**F3.3.3 Adjunct procedures.** When a prosthetic bypass graft is placed into the below-knee popliteal or distal artery adjunct procedures, such as arteriovenous fistula at or distal to the bypass and the use of a vein interposition/cuff, have been suggested. However, randomized trials<sup>210</sup> have shown that the addition of a distal arteriovenous fistula adds no benefit with respect to patency and, therefore, cannot be recommended. The use of a venous cuff or patch has been promising in the below-knee popliteal or distal anastomosis in some series, although no comparison trials indicate the best type of patch technique.<sup>211</sup>

**F3.3.4 Profundoplasty.** Stenosis at the origin of the profunda femoris artery may lead to decreased flow through collateral vessels in the presence of a SFA occlusion and may compromise the patency of an aortic/extra anatomic inflow operation. In the presence of SFA occlusion it is recommended that a stenosis of the profunda femoris artery be corrected during inflow procedures. Isolated profundoplasty as an inflow procedure (sparing a femoral distal bypass) may be considered in the presence of: 1) excellent inflow; 2) >50% stenosis of the proximal 1/3 profunda; and 3) excellent collateral flow to the tibial vessels.

**F3.3.5 Secondary revascularization procedures.** Secondary patency results from the salvage of an occluded bypass and assisted patency results from pre-occlusion intervention. The non-tolerance of vein grafts to thrombosis and

**Table F6.** Pooled results of femoral popliteal dilatations

	1-year % patency (range)	3-year % patency (range)	5-year % patency (range)
PTA: stenosis	77 (78–80)	61 (55–68)	55 (52–62)
PTA: occlusion	65 (55–71)	48 (40–55)	42 (33–51)
PTA+stent: stenosis	75 (73–79)	66 (64–70)	
PTA+stent: occlusion	73 (69–75)	64 (59–67)	

PTA – Percutaneous Transluminal Angioplasty.

**Table F7a.** 5-year patency following femoral popliteal bypass<sup>191</sup>

	Claudication	CLI
Vein	80	66
Above-knee PTFE	75	47
Below-knee PTFE	65	65

CLI – critical limb ischemia; PTFE – polytetrafluoroethylene graft.

**Table F7b.** Randomized trials of types of conduits<sup>206–209</sup>

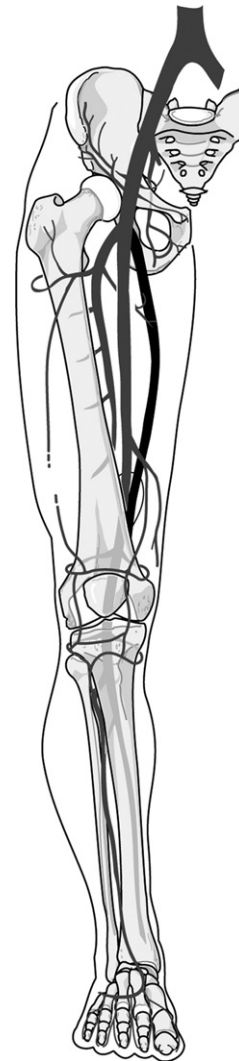
Above-knee femoral popliteal bypass	5-year patency
Vein	74–76%
PTFE	39–52%

PTFE – polytetrafluoroethylene graft.

the success of assisted patency support the previous recommendations that all venous bypass grafts be followed by a regular regime of duplex scanning with set parameters for intervention including angioplasty (open or transluminal) or short segment interposition. This recommendation has recently been questioned by a randomized, controlled trial showing no cost benefit of such an approach.<sup>212</sup> In the presence of an occluded but established graft, thrombolysis may be indicated in the very early stages to remove clot and reveal the cause of the thrombosis. When limb salvage is assessed following failure of an infrainguinal bypass the original indication for surgery is an important factor. The 2-year limb salvage rates for occluded grafts done for claudication is 100%, for rest pain is 55% and when done for tissue loss is 34%. The early occlusion of a graft (<30 days occlusion) led to a very poor 2-year limb salvage rate of 25%.<sup>213</sup>

#### F4 ANTIPLATELET AND ANTICOAGULANT THERAPIES

Adjuvant therapy has been recommended to improve the patency rate following lower extremity bypass grafts. Antiplatelet agents have a beneficial effect that is greater in prosthetic than in autogenous conduits.<sup>156</sup> A meta-analysis published in 1999 demonstrated that the relative risk of infra inguinal graft occlusion in patients on aspirin/ASA was 0.78.<sup>214</sup> The recommendation for aspirin/ASA therapy is similar for patients undergoing lower extremity balloon angioplasty.<sup>59</sup> The addition of dipyridamole or ticlopidine has been supported by some studies but larger



**Fig. F6.** Above-knee femoral popliteal bypass.

randomized trials will be necessary to make a firm recommendation.<sup>215</sup> Autogenous grafts may be treated with warfarin<sup>216</sup> but this is accompanied by a risk of hemorrhage and this decision must be made on an individual patient basis.<sup>59</sup> All patients should receive antiplatelet therapy following a revascularization. For those receiving anticoagulation, and in those few treated with both antiplatelet agents and anticoagulants, extra vigilance is required due to

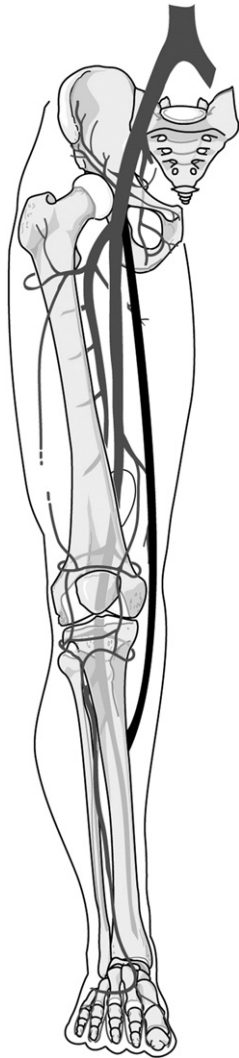


Fig. F7. Femoral tibial bypass.

the increased risk of bleeding. Recent articles have been published expressing concern that patients undergoing intervention for PAD are not receiving the optimal care for their atherosclerotic process. As previously stated, all patients should undergo assessment and treatment for their underlying atherosclerosis regardless of the need for intervention for limb salvage.

#### Recommendation 41

Antiplatelet drugs as adjuvant pharmacotherapy after revascularization

- Antiplatelet therapy should be started preoperatively and continued as adjuvant pharmacotherapy after an endovascular or surgical procedure [A]. Unless subsequently contraindicated, this should be continued indefinitely [A].

#### F5 SURVEILLANCE PROGRAMS FOLLOWING REVASCULARIZATION

Following construction of an infrainguinal autogenous bypass graft, it has been recommended in the past that a program of regular graft review with duplex scanning be undertaken.<sup>217</sup> The purpose of this is to identify lesions that predispose to graft thrombosis and allow their repair prior to graft occlusion. A recent multicentered, randomized, controlled trial has shown that duplex surveillance after venous femoral distal bypass grafts leads to no significant clinical benefit or quality of life improvement at 18 months. The previous recommendation of routine duplex scanning following autogenous lower extremity bypass has proven to be not cost-effective according to this study.<sup>212</sup> In practice, many surgeons continue a program of vein graft surveillance awaiting further confirmation of the findings of this trial.

#### Recommendation 42

Clinical surveillance program for bypass grafts

- Patients undergoing bypass graft placement in the lower extremity for the treatment of claudication or limb-threatening ischemia should be entered into a clinical surveillance program. This program should consist of:
  - Interval history (new symptoms)
  - Vascular examination of the leg with palpation of proximal, graft and outflow vessel pulses
  - Periodic measurement of resting and, if possible, post-exercise ankle-brachial indices
- Clinical surveillance programs should be performed in the immediate postoperative period and at regular intervals (usually every 6 months) for at least 2 years [C].

#### F6 NEW AND ADVANCING THERAPIES

Newer surgical techniques have tended to involve minimally invasive arterial reconstructions including laparoscopic aortic reconstructions. The use of combined therapies (transluminal and operative) may lead to 'minimally' invasive surgery. In infrainguinal reconstruction the use of semi-closed endarterectomy is gaining some interest. Additionally, in the attempt to reduce the morbidity of wound complications and the negative effects of this on patency, the use of endoscopic vein preparation and/or harvest is being investigated.

Recently drug-eluting stents were tested in a randomized study against bare stents in femoropopliteal artery obstructive disease in claudicants.<sup>218</sup> This study evaluated the effectiveness of nitinol self-expanding stents coated with a polymer impregnated with sirolimus (rapamycin) versus uncoated nitinol stents in patients with IC and SFA obstructions. The in-stent mean lumen diameter was significantly larger in the sirolimus-eluting stent group (4.95 mm versus 4.31 mm in the uncoated stent group;  $p=0.047$ ). The results of this trial require further confirma-

**Table F8.** Cumulative observed morbidity outcomes for bypass in critical limb ischemia

Parameter	Short term (first year)	Long term (3–5 years)
Mean time to pedal wound healing	15–20 weeks	–
Incisional wound complications*	15%–25%	–
Persistent severe ipsilateral lymphedema <sup>§</sup>	10%–20%	Unknown
Graft stenosis**	20%	20%–30%
Graft occlusion	10%–20%	20%–40%
Graft surveillance studies	100%	100%
Major amputation	5%–10%	10%–20%
Ischemic neuropathy	Unknown	Unknown
Graft infection <sup>†</sup>	1%–3%	–
Perioperative death (primarily cardiovascular)	1%–2%	–
All death (primarily cardiovascular)	10%	30%–50%

\*Not all requiring reoperation.

<sup>§</sup>Not well-studied.

\*\*Greater in series of composite and alternate vein conduit.

<sup>†</sup>Greatest in prosthetic grafts.

tion and longer-term follow up. Results of a recent small randomized trial suggest early results of primary nitinol stenting of SFA dilatations had a superior result to dilatation alone.<sup>199</sup>

The impact of ePTFE coated stents (stentgrafts) was tested in a randomized trial by Saxon *et al.*<sup>219</sup> At 2 years follow-up, primary patency remained 87% (13 of 15 patients) in the stentgraft group versus only 25% (three of 12 patients) in the PTA group ( $p=0.002$ ).

Endovascular brachytherapy (BT) with  $\gamma$ -emitting sources such as <sup>192</sup>Ir was investigated with respect to the rate of intimal hyperplasia and restenoses.<sup>220</sup> Minar *et al.* tested endovascular BT in femoropopliteal obstructions and IC in a randomized trial. The overall recurrence rate after 6 months was significantly lower (28.3% versus 53.7%) for the PTA+BT group compared with the PTA. Cumulative patency was also significantly higher at 12 months (63.6% versus 35.5%). Advice for general use will require more extensive and longer-term study.

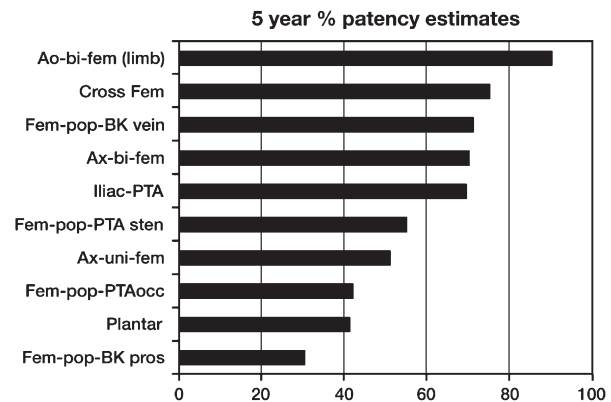
The focus of newer adjuvant therapies is to increase the robustness of percutaneous interventions making them more applicable and durable to a broader range of lesions. These local therapies must be combined with systemic management of the atherosclerotic process.

Table F8 summarizes the cumulative observed morbidity outcomes for bypass in critical limb ischemia, and Fig. F8 summarizes the average results for surgical treatment.

## SECTION G – NON-INVASIVE VASCULAR LABORATORY AND IMAGING

### G1 NON-INVASIVE VASCULAR LABORATORY

The routine evaluation of patients with peripheral arterial disease (PAD) can include a referral to the vascular



**Fig. F8.** Results summary: Average results for surgical treatment. Ao-bi-fem – Aortobifemoral bypass; Fem-pop – femoropopliteal; BK – below knee; Ax-bi-fem – Axillobifemoral; PTA – Percutaneous Transluminal Angioplasty; Ax-uni-fem – Axillounifemoral bypass; pros – prosthetic.

laboratory. Non-invasive hemodynamic measurements can provide an initial assessment of the location and severity of the arterial disease. These tests can be repeated over time to follow disease progression.

#### G1.1 Segmental limb systolic pressure measurement

Segmental limb pressure (SLP) measurements are widely used to detect and segmentally localize hemodynamically significant large-vessel occlusive lesions in the major arteries of the lower extremities. Segmental pressure measurements are obtained in the thigh and calf in the same fashion as the ankle pressure. A sphygmomanometer cuff is placed at a given level with a Doppler probe over one of the pedal arteries, and the systolic pressure in the major arteries under the cuff is measured. The location of occlusive lesions is apparent from the pressure gradients between the different cuffs. Limitations of the method include: (1) missing isolated moderate stenoses (usually iliac) that produce little or no pressure gradient at rest; (2) falsely elevated pressures in patients with diabetes calcified, incompressible arteries; and (3) the inability to differentiate between arterial stenosis or occlusion.

#### G1.2 Segmental plethysmography or pulse volume recordings

A plethysmograph is an instrument that detects and graphically records changes in limb volume. Limb cuffs are placed around the leg at selected locations and connected to a plethysmograph, which produces a pulse volume recording (PVR). Normally, a single large thigh cuff is used along with regular-sized calf and ankle cuffs, plus a brachial cuff that reflects the undampened cardiac contribution to arterial pulsatility. The latter is useful in standardizing the lower-limb PVR and in detecting poor cardiac function as a cause of low-amplitude tracings. To obtain accurate PVR waveforms the cuff is inflated to ~60–65 mmHg, which is sufficient to detect volume changes without resulting in arterial occlusion.



SLP and PVR measurements alone are 85% accurate compared with angiography in detecting and localizing significant occlusive lesions. Furthermore, when used together, the accuracy approached 95%.<sup>221</sup> For this reason, these two diagnostic methods are commonly used together when evaluating PAD. Using SLP and PVR in combination ensures that patients with diabetes who have calcified arteries sufficient to produce falsely elevated SLP will be readily recognized and correctly assessed by PVR.

### G1.3 Toe pressures and the toe-brachial index

Patients with long-standing diabetes, renal failure and other disorders resulting in vascular calcification can develop incompressible tibial arteries, which cause falsely high systolic pressures. Non-compressible measurements are defined as a very elevated ankle pressure (e.g.  $\geq 250$  mmHg) or ankle-brachial index (ABI)  $> 1.40$ . In this situation, measurement of toe pressures provides an accurate measurement of distal limb systolic pressures in vessels that do not typically become non-compressible. A special small occlusion cuff is used proximally on the first or second toe with a flow sensor, such as that used for digital plethysmography. The toe pressure is normally approximately 30 mmHg less than the ankle pressure and an abnormal toe-brachial index (TBI) is  $< 0.70$ . The measurement of toe pressures requires a non-invasive vascular laboratory with standard environmental conditions, expertise and equipment necessary to make the measurement. False positive results with the TBI are unusual. The main limitation in patients with diabetes is that it may be impossible to measure toe pressure in the first and second toes due to inflammatory lesions, ulceration, or loss of tissue.

### G1.4 Doppler Velocity Wave Form analysis

Arterial flow velocity can be assessed using a continuous-wave Doppler at multiple sites in the peripheral circulation. Doppler waveforms evolve from a normal triphasic pattern to a biphasic and, ultimately, monophasic appearance in those patients with significant peripheral arterial disease (PAD). When assessed over the posterior tibial artery, a reduced or absent forward flow velocity was highly accurate for detecting PAD (and also isolated tibial artery occlusive disease that may occur in patients with diabetes).<sup>12</sup> While the test is operator-dependent, it provides another means to detect PAD in patients with calcified tibial arteries.

## G2 IMAGING TECHNIQUES

### G2.1 Indications for and types of imaging in patients with intermittent claudication or critical limb ischemia

Imaging is indicated if some form of revascularization (endovascular or open surgical) would be advised if a suitable lesion is demonstrated. The patient's disability and functional limitations due to impaired walking ability should be the major determinant in deciding on revascularization. This is considered in terms of claudi-

cation distance and the effect of this limitation on the patient's lifestyle, as well as their independence and capacity for self care. In cases of critical limb ischemia (CLI), imaging and revascularization are mandatory, provided contraindications do not prohibit surgical or endovascular intervention.

The expense and morbidity rate for duplex scanning and other non-invasive methods are far less than for invasive angiography. With the introduction of magnetic resonance angiography (MRA) and computed tomographic angiography (CTA), it is now possible to use non-invasive imaging in many situations to assess the suitability of the underlying lesions for the proposed intervention before committing to invasive angiography.

### G2.2 Choice of imaging methods

The main reason for imaging is to identify an arterial lesion that is suitable for revascularization with either an endovascular or open surgical technique. The current options for imaging are angiography, duplex ultrasound, MRA and CTA. Potential side effects and contraindications should be considered in choosing the imaging modality. Intra-arterial angiography requires contrast medium that is potentially nephrotoxic. Multidetector computed tomographic angiography (MDCTA) requires a contrast medium load of  $> 100$  mL. Several methods exist to reduce renal injury, including hydration and protective drugs such as *N*-acetylcysteine. The usage of alternate contrast agents (see G2.2.1) may also be considered. Where the use of iodinated contrast medium is to be restricted or avoided, MRA and also duplex ultrasonography may allow planning for surgery.

**G2.2.1 Angiography.** Angiography, considered the "gold standard" imaging test, carries certain risks: approximately 0.1% risk of severe reaction to contrast medium, 0.7% complications risk severe enough to alter patient management, and 0.16% mortality risk and significant expense. Other complications include arterial dissection, atheroemboli, contrast-induced renal failure and access site complications (i.e. pseudoaneurysm, arteriovenous fistula and hematoma). These problems have been greatly mitigated by technological improvements in the procedure, including the use of nonionic contrast agents, digital subtraction angiography, intra-arterial pressure measurements across a stenosis with and without vasodilator (significance peak systolic difference 5–10 mmHg pre-vasodilatation and 10–15 mmHg post-vasodilatation), and more sophisticated image projection and retention. Alternatively, carbon dioxide and magnetic resonance contrast agents (i.e. gadolinium) can be used instead of conventional contrast media. In high-risk (e.g. renal impairment) patients, restriction to a partial study with selected views rather than visualizing the entire infrarenal arterial tree has decreased the contrast load, length of study and associated risks. Despite this, full angiography, with visualization from the level of the renal arteries to the pedal arteries using digital subtraction angiography (DSA) techniques, remains the choice in most cases.

### G2.2.2 Color-assisted duplex ultrasonography.

Color-assisted duplex imaging has been proposed as an attractive alternative to angiography. In addition to being completely safe and much less expensive, duplex scanning, in expert hands, can provide most of the essential anatomic information plus some functional information (for instance, velocity gradients across stenoses). The lower extremity arterial tree can be visualized, with the extent and degree of lesions accurately assessed and arterial velocities measured. Disadvantages include the length of the examinations and variability of skill of the technologist. In addition, crural arteries are challenging to image in their entirety.

**G2.2.3 Magnetic resonance angiography.** In many centers, MRA has become the preferred imaging technique for the diagnosis and treatment planning of patients with PAD. The advantages of MRA include its safety and ability to provide rapid high-resolution three-dimensional (3D) imaging of the entire abdomen, pelvis and lower extremities in one setting. The 3D nature of magnetic resonance imaging implies that image volumes can be rotated and assessed in an infinite number of planes. MRA is useful for treatment planning prior to intervention and in assessing suitability of lesions for endovascular approaches. Pre-procedure MRA may minimize use of iodinated contrast material and exposure to radiation.

The high magnetic field strength in MRA excludes patients with defibrillators, spinal cord stimulators, intracerebral shunts, cochlear implants etc., and the technique also excludes the <5% patients affected by claustrophobia that is not amenable to sedation. Stents within segments of peripheral vessels may produce a susceptibility artifact that can render evaluation of these segments difficult. However, the signal loss with stents is extremely dependent on the metallic alloy, with nitinol stents producing minimal artifact. In contrast to CTA (see section G2.2.4), the presence of calcium in vessels does not cause artifacts on MRA and this may represent a potential advantage in examining diffusely calcified vessels in patients with diabetes and patients with chronic renal failure.

MRA techniques can be gadolinium contrast-based (contrast-enhanced MRA or CE-MRA) or non-contrast-based (time-of-flight techniques). In general, CE-MRA techniques utilize a moving table (floating table) approach and sequentially following a bolus of contrast through multiple (usually 3–4) stations extending from the abdomen to the feet. CE-MRA has replaced non-contrast MRA for the assessment of peripheral vessels, as this technique provides rapid imaging with substantively better artifact-free images.<sup>222</sup> Time-resolved CE-MRA is usually performed in conjunction with moving table CE-MRA, providing an additional examination of infra-inguinal vessels and dynamic images free of venous contamination.

CE-MRA has a sensitivity and specificity of >93% for the diagnosis of PAD compared with invasive angiography.<sup>222</sup> A number of studies have demonstrated that CE-MRA has better discriminatory power than color-guided duplex ultrasound for the diagnosis of PAD. Recent ad-

vancements in CE-MRA methodologies that include refinements such as usage of a venous occlusion cuff around the thigh to modulate contrast delivery to the foot, and parallel imaging methods have greatly improved the ability to image distal vessels in a high resolution manner (<1×1 mm in plane).<sup>223,224</sup> MRA may consistently pick up more patent vessels than DSA below the knee and could potentially obviate the need for invasive angiography.<sup>225</sup>

**G2.2.4 Multidetector computed tomography angiography.** Multidetector computed tomography angiography (MDCTA) is being widely adopted for the initial diagnostic evaluation and treatment planning of PAD. The rapid evolution of technology and the deployment of fast MDCTA multislice systems in the community and the familiarity with CT technology and ease of use are some factors driving its popularity. Multislice MDCTA enables fast imaging of the entire lower extremity and abdomen in one breath-hold at sub-millimeter isotropic voxel resolution. Although prospectively designed studies with MDCTA are currently lacking, there are emerging data that the sensitivity, specificity and accuracy of this technique may rival invasive angiography.<sup>226,227</sup>

The major limitations of MDCTA include the usage of iodinated contrast (≈120 mL/exam), radiation exposure and the presence of calcium.<sup>226</sup> The latter can cause a ‘blooming artifact’ and can preclude assessment of segments with substantive calcium. Stented segments can also cause significant artifact and may preclude adequate evaluation. However, the ability to evaluate vessel wall lumen in stented and calcified segments is dependent on the technique (window/level, reconstruction kernel, and type of image [maximum intensity projection versus multiplanar reformation etc]).

### Recommendation 43

Indications and methods to localize arterial lesions

- Patients with intermittent claudication who continue to experience limitations to their quality of life after appropriate medical therapy (exercise rehabilitation and/or pharmacotherapy) or patients with critical limb ischemia, may be considered candidates for revascularization if they meet the following additional criteria: (a) a suitable lesion for revascularization is identified; (b) the patient does not have any systemic contraindications for the procedure; and (c) the patient desires additional therapy [B].
- Initial disease localization can be obtained with hemodynamic measures including segmental limb pressures or pulse volume recording [B].
- When anatomic localization of arterial occlusive lesions is necessary for decision making, the following imaging techniques are recommended: duplex ultrasonography, magnetic resonance angiography and computed tomographic angiography (depending on local availability, experience, and cost) [B].

**Table G1.** Comparison of different imaging methods

<i>Modality</i>	<i>Availability</i>	<i>Relative risk and complications</i>	<i>Strengths</i>	<i>Weaknesses</i>	<i>Contraindications</i>
X-Ray contrast angiography	Widespread	High Access site complications Contrast nephropathy Radiation exposure	“Established modality”	2D images Limited planes Imaging pedal vessels and collaterals in the setting of occlusion requires prolonged imaging and substantial radiation	Renal insufficiency Contrast allergy
MDCTA	Moderate	Moderate Contrast nephropathy Radiation exposure	Rapid imaging Sub-millimeter voxel resolution 3D volumetric information from axial slices Plaque morphology	Calcium causes “blooming artifact” Stented segments difficult to visualize	Renal insufficiency Contrast allergy
MRA	Moderate	None	True 3D imaging modality; Infinite planes and orientations can be constructed Plaque morphology from proximal segments with additional sequences Calcium does not cause artifact	Stents cause artifact but alloys such as nitinol produce minimal artifact	Intracranial devices, spinal stimulators, pace-makers, cochlear implants and intracranial clips and shunts are absolute contraindications
Duplex	Widespread	None	Hemodynamic information	Operator dependent and time consuming to image both lower extremities Calcified segments are difficult to assess	None

MDCTA – Multidetector computed tomography angiography; MRA – magnetic resonance angiography.

To summarize, if a patient qualifies for invasive therapy, angiography will, ultimately, be required in almost all elective cases, preoperatively for surgical reconstruction and before or during catheter-based interventions. Duplex scanning is used selectively mainly to characterize specific lesions in regard to their suitability for endovascular treatment. However, it should be kept in mind that arterial reconstructive surgery can be performed on the basis of duplex scanning alone in some cases. The different imaging methods are compared in Table G1.

#### TASC WRITING GROUP – CONFLICT OF INTEREST DISCLOSURES

The following authors have declared no competing interests: Kevin Bell; Joseph Caporusso; John Dormandy; Isabelle Durand-Zaleski; Kenneth A Harris; Kimihiro Komori; Johannes Lammer; Christos Liapis; Salvatore Novo; Mahmood Razavi; John Robbs; Nicholaas Schaper; Hiroshi Shigematsu; Marc Sapoval; Christopher White, John White.

The following authors have declared competing interests:

- Denis Clement has been invited to lecture at congresses and symposia by all major pharmaceutical companies

- Mark Creager serves as a consultant for Bristol Myers Squibb, sanofi-aventis, Genzyme, Sigma Tau, and KOS. He receives research support from sanofi-aventis and is on the speakers bureau for the Bristol-Myers Squibb/sanofi-aventis Partnership
- Gerry Fowkes has received research support and ad hoc consulting fees from sanofi-aventis
- Kenneth Harris has been a speaker for sanofi-aventis on the TASC project
- William Hiatt has received research support and is on the speakers bureau of the Bristol-Myers Squibb/sanofi-aventis Pharmaceuticals Partnership. He has received honoraria from Otsuka Pharmaceuticals and research support from Sigma Tau Pharmaceuticals and Kos Pharmaceuticals
- Michael Jaff has been paid consulting fees for Cordis Endovascular and is on the speakers bureau of the Bristol-Myers Squibb/sanofi-aventis Pharmaceuticals Partnership
- Emile Mohler III is on the speakers bureau of the Bristol-Myers Squibb/sanofi-aventis Pharmaceuticals Partnership, Merck, Pfizer and Astra-Zeneca
- Mark Nehler has received grants from sanofi-aventis and Mitsubishi Pharma, and royalties from Elsevier

- Lars Norgren has been paid consulting fees as a member/chairman of clinical trials and as a speaker for Mitsubishi Pharma, sanofi-aventis, Schering AG and Merck-Sante
- Robert B Rutherford acts as a consultant for Endovasc, Inc.
- Peter Sheehan has received research grants from Genzyme and Nissan, and is on the speakers bureau of the Bristol-Myers Squibb/sanofi-aventis Pharmaceuticals Partnership
- Henrik Sillesen has received consulting fees from Pfizer, sanofi-aventis and Merck. Speakers fees from Pfizer, sanofi-aventis, Merck, Astra-Zeneca, Solvay and Bristol-Myers Squibb. Financial support was provided for a research assistant from Vivolution, Pfizer, Bristol-Myers Squibb and Gore
- Kenneth Rosenfield is on the scientific Advisory board for Abbott, Boston Scientific, CardioMind, Cordis, ev3 and Medtronic; serves as a consultant for Abbot, Bard, Endotex, Genzyme, Pathway Medical and Xtent; and is a shareholder of CardioMind, Medical Simulation and Xtent. In addition, he has received education/research grants from Abbott, Accumetrix, Bard, Boston Scientific, Cordis, The Medicines Co. and Medtronic

## REFERENCES

1. TASC. Management of peripheral arterial disease (PAD). TransAtlantic Inter-Society Consensus (TASC). *Eur J Vasc Endovasc Surg* 2000; 19(Suppl A):S1-xxviii. S1-250.
2. TASC. Management of Peripheral Arterial Disease (PAD) TransAtlantic Intersociety Consensus (TASC). *J Vasc Surg* 2000;31(1 part 2):S1-287.
3. TASC. Management of peripheral arterial disease (PAD). TransAtlantic Inter-Society Consensus (TASC). *Int Angiol* 2000;19(1 Suppl. 1):I-XXIV. 1-304.
4. Clement DL, Boccalon H, Dormandy J, Durand-Zaleski I, Fowkes G, Brown T. A clinical approach to the management of the patient with coronary (Co) and/or carotid (Ca) artery disease who presents with leg ischaemia (Lis). *Int Angiol* 2000;19(2):97-125.
5. Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *J Am Coll Cardiol* 2006;47:1239-312.
6. AHCP. United States Department of Health and Human Services Agency for Health Care Policy and Research. Acute pain management: operative on medical procedures and trauma. [107]. Rockville MD, AHCP, 1993.
7. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. *Circulation* 1985;71(3):510-51.
8. Hiatt WR, Hoag S, Hamman RF. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. *Circulation* 1995;91(5):1472-9.
9. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. *Circulation* 2004; 110(6):738-43.
10. Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1991;20(2):384-92.
11. Hirsch A, Criqui M, Treat-Jacobson D, Regensteiner J, Creager M, Olin J, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 2001;286(11):1317-24.
12. Criqui MH, Vargas V, Denenberg JO, Ho E, Allison M, Langer RD, et al. Ethnicity and peripheral arterial disease: the San Diego Population Study. *Circulation* 2005;112(17):2703-7.
13. Kullo IJ, Bailey KR, Kardia SL, Mosley TH Jr, Boerwinkle E, Turner ST. Ethnic differences in peripheral arterial disease in the NHLBI Genetic Epidemiology Network of Arteriopathy (GENOA) study. *Vasc Med* 2003;8(4):237-42.
14. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004;141(6):421-31.
15. Muntner P, Wildman RP, Reynolds K, Desalvo KB, Chen J, Fonseca V. Relationship between HbA1c level and peripheral arterial disease. *Diabetes Care* 2005;28(8):1981-7.
16. ADA. Peripheral arterial disease in people with diabetes. *Diabetes Care* 2003;26(12):3333-41.
17. Senti M, Nogues X, Pedro-Botet J, Rubies-Prat J, Vidal-Barraquer F. Lipoprotein profile in men with peripheral vascular disease. Role of intermediate density lipoproteins and apolipoprotein E phenotypes. *Circulation* 1992;85(1):30-6.
18. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA* 2001;285(19):2481-5.
19. O'Hare AM, Vittinghoff E, Hsia J, Shlipak MG. Renal insufficiency and the risk of lower extremity peripheral arterial disease: results from the Heart and Estrogen/Progestin Replacement Study (HERS). *J Am Soc Nephrol* 2004;15(4):1046-51.
20. McDermott MM, Criqui MH, Greenland P, Guralnik JM, Liu K, Pearce WH, et al. Leg strength in peripheral arterial disease: associations with disease severity and lower-extremity performance. *J Vasc Surg* 2004;39(3):523-30.
21. Widmer L, Biland L. Risk profile and occlusive peripheral arterial disease. Proceedings of 13th International Congress of Angiology. 1985;28.
22. Kannel WB, Skinner JJ, Jr, Schwartz MJ, Shurtleff D. Intermittent claudication. Incidence in the Framingham Study. *Circulation* 1970; 41(5):875-83.
23. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004;363(9413):915-24.
24. Tunis SR, Bass EB, Steinberg EP. The use of angioplasty, bypass surgery, and amputation in the management of peripheral vascular disease. *N Engl J Med* 1991;325(8):556-62.
25. Dormandy J, Belcher G, Broos P, Eikelboom B, Laszlo G, Konrad P, et al. Prospective study of 713 below-knee amputations for ischaemia and the effect of a prostacyclin analogue on healing. Hawaii Study Group. *Br J Surg* 1994;81(1):33-7.
26. Bhatt D, Steg P, Ohman E, Hirsch A, Ikeda Y, Mas J, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006;295:180-9.
27. Aronow WS, Ahn C. Prevalence of coexistence of coronary artery disease, peripheral arterial disease, and atherothrombotic brain infarction in men and women > or = 62 years of age. *Am J Cardiol* 1994;74(1):64-5.
28. Dormandy JA, Murray GD. The fate of the claudicant—a prospective study of 1969 claudicants. *Eur J Vasc Surg* 1991;5(2):131-3.
29. Mehler PS, Coll JR, Estacio R, Esler A, Schrier RW, Hiatt WR. Intensive blood pressure control reduces the risk of cardiovascular



- events in patients with peripheral arterial disease and type 2 diabetes. *Circulation* 2003;107(5):753-6.
30. Criqui M, Langer R, Fronck A, Feigelson H, Klauber M, McCann T, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992;326:381-6.
  31. Fowkes F, Lee A, Murray G. On behalf of the ABI collaboration. Ankle-brachial index as an independent indicator of mortality in fifteen international population cohort studies. *Circulation* 2005;112:3704.
  32. CAPRIE. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;348(9038):1329-39.
  33. HPS-2. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360(9326):7-22.
  34. Resnick HE, Lindsay RS, McDermott MM, Devereux RB, Jones KL, Fabsitz RR, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. *Circulation* 2004;109(6):733-9.
  35. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. *JAMA* 2003;290(1):86-97.
  36. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005;142(4):233-9.
  37. Tonstad S, Farsang C, Klaene G, Lewis K, Manolis A, Perruchoud AP, et al. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. *Eur Heart J* 2003;24(10):946-55.
  38. Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;340(9):685-91.
  39. Willigendael EM, Teijink JA, Bartelink ML, Peters RJ, Buller HR, Prins MH. Smoking and the patency of lower extremity bypass grafts: a meta-analysis. *J Vasc Surg* 2005;42(1):67-74.
  40. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366(9493):1267-78.
  41. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of eight societies and by invited experts). *Atherosclerosis* 2004;173(2):381-91.
  42. Grundy SM, Cleeman JI, Merz CN, Brewer HB, Jr, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110(2):227-39.
  43. Smith SC Jr, Blair SN, Bonow RO, Brass LM, Cerqueira MD, Dracup K, et al. AHA/ACC Scientific Statement: AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update: A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation* 2001;104(13):1577-9.
  44. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999;341(6):410-8.
  45. Blankenhorn DH, Azen SP, Crawford DW, Nessim SA, Sanmarco ME, Selzer RH, et al. Effects of colestipol-niacin therapy on human femoral atherosclerosis. *Circulation* 1991;83(2):438-47.
  46. Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation* 2004;110(23):3512-7.
  47. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42(6):1206-52.
  48. ESH/ESC. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;21(6):1011-53.
  49. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342(3):145-53.
  50. Radack K, Deck C. Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease. A meta-analysis of randomized controlled trials. *Arch Intern Med* 1991;151(9):1769-76.
  51. UKPDS. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352(9131):837-53.
  52. DCCT. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. *Am J Cardiol* 1995;75(14):894-903.
  53. ADA. Standards of medical care in diabetes—2006. *Diabetes Care* 2006;29(Suppl. 1):S4-42.
  54. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitazone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005;366(9493):1279-89.
  55. Bona K, Njolstad I, Ueland P, Schirmer H, Tverdal A, Steigen T, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006;354:1578-88.
  56. Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006;354(15):1567-77.
  57. ATC. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Br Med J* 2002;324(7329):71-86.
  58. ATC. Collaborative overview of randomised trials of antiplatelet therapy—II: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *Br Med J* 1994;308(6921):81-106.
  59. Clagett P, Sobel M, Jackson M, Lip G, Tangelder M, Verhaeghe R. Antithrombotic therapy in peripheral arterial disease: The Seventh ACCP Conference on antithrombotic and thrombolytic therapy. *Chest* 2004;126:S609-26.
  60. Neri Serneri GG, Coccheri S, Marubini E, Violi F. Picotamide, a combined inhibitor of thromboxane A2 synthase and receptor, reduces 2-year mortality in diabetics with peripheral arterial disease: the DAVID study. *Eur Heart J* 2004;25(20):1845-52.
  61. Janzon L, Bergqvist D, Boberg J, Boberg M, Eriksson I, Lindgarde F, et al. Prevention of myocardial infarction and stroke in patients with intermittent claudication; effects of ticlopidine. Results from STIMS, the Swedish Ticlopidine Multicentre Study. *J Intern Med* 1990;227(5):301-8.
  62. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345(7):494-502.
  63. Bhatt D, Fox K, Hacke W, Berger P, Black H, Boden W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706-17.
  64. Murray CJ, Lauer JA, Hutubessy RC, Niessen L, Tomijima N, Rodgers A, et al. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *Lancet* 2003;361(9359):717-25.
  65. Fischer MA, Avorn J. Economic implications of evidence-based prescribing for hypertension: can better care cost less?. *JAMA* 2004;291(15):1850-6.



66. Gaspoz JM, Coxson PG, Goldman PA, Williams LW, Kuntz KM, Hunink MG, et al. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. *N Engl J Med* 2002;346(23):1800-6.
67. Lancaster T, Silagy C, Fowler G. Training health professionals in smoking cessation. *Cochrane Database Syst Rev* 3):2000;CD000214.
68. Song F, Raftery J, Aveyard P, Hyde C, Barton P, Woolacott N. Cost-effectiveness of pharmacological interventions for smoking cessation: a literature review and a decision analytic analysis. *Med Decis Making* 2002;22(Suppl):S26-37.
69. Hillsdon M, Foster C, Thorogood M. Interventions for promoting physical activity. *Cochrane Database Syst Rev* 1):2005;CD003180.
70. Lowensteyn I, Coupal L, Zowall H, Grover SA. The cost-effectiveness of exercise training for the primary and secondary prevention of cardiovascular disease. *J Cardiopulm Rehabil* 2000;20(3):147-55.
71. Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, et al. Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation. *Health Technol Assess* 2004;8(38):iii-iv. 1-196.
72. Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R. Cost-effectiveness of simvastatin in people at different levels of vascular disease risk: economic analysis of a randomised trial in 20,536 individuals. *Lancet* 2005;365(9473):1779-85.
73. Lamy A, Yusuf S, Pogue J, Gafni A. Cost implications of the use of ramipril in high-risk patients based on the Heart Outcomes Prevention Evaluation (HOPE) study. *Circulation* 2003;107(7):960-5.
74. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004;110(9):e82-292.
75. Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol* 2003;41(1):159-68.
76. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol* 2002;39(3):542-53.
77. McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med* 2004;351(27):2795-804.
78. Poldermans D, Boersma E, Bax JJ, Thomson IR, Paclincx B, van de Ven LL, et al. Bisoprolol reduces cardiac death and myocardial infarction in high-risk patients as long as 2 years after successful major vascular surgery. *Eur Heart J* 2001;22(15):1353-8.
79. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med* 1999;341(24):1789-94.
80. Kertai MD, Boersma E, Bax JJ, Thomson IR, Cramer MJ, van de Ven LL, et al. Optimizing long-term cardiac management after major vascular surgery: Role of beta-blocker therapy, clinical characteristics, and dobutamine stress echocardiography to optimize long-term cardiac management after major vascular surgery. *Arch Intern Med* 2003;163(18):2230-5.
81. Adams RJ, Chimowitz MI, Alpert JS, Awad IA, Cerqueria MD, Fayad P, et al. Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: a scientific statement for healthcare professionals from the Stroke Council and the Council on Clinical Cardiology of the American Heart Association/American Stroke Association. *Circulation* 2003;108(10):1278-90.
82. Chaturvedi S, Bruno A, Feasby T, Holloway R, Benavente O, Cohen SN, et al. Carotid endarterectomy—an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2005;65(6):794-801.
83. Rundback JH, Sacks D, Kent KC, Cooper C, Jones D, Murphy T, et al. Guidelines for the reporting of renal artery revascularization in clinical trials. *J Vasc Interv Radiol* 2003;14(9 Pt 2):S477-92.
84. Plouin PF, Clement DL, Boccalon H, Dormandy J, Durand-Zaleski I, Fowkes G, et al. A clinical approach to the management of a patient with suspected renovascular disease who presents with leg ischemia. *Int Angiol* 2003;22(4):333-9.
85. McDermott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Dolan NC, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA* 2001;286(13):1599-606.
86. Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. *Circulation* 1985;71(3):516-22.
87. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol* 2002;40(8):1531-40.
88. Labs KH, Dormandy JA, Jaeger KA, Stuerzebecher C, Hiatt WR. Trans-atlantic conference on clinical trial guidelines in PAOD (Peripheral arterial occlusive disease) clinical trial methodology. *Eur J Vasc Endovasc Surg* 1999;18(3):253-65.
89. Gardner A, Poehlman E. Exercise rehabilitation programs for the treatment of claudication pain: a meta-analysis. *JAMA* 1995;274:975-80.
90. Stewart K, Hiatt W, Regensteiner J, Hirsch A. Exercise training for claudication. *N Engl J Med* 2002;347(24):1941-51.
91. Hiatt W, Wolfel E, Meier R, Regensteiner J. Superiority of treadmill walking exercise vs. strength training for patients with peripheral arterial disease. Implications for the mechanism of the training response. *Circulation* 1994;90:1866-74.
92. Regensteiner J, Ware JJ, McCarthy W, Zhang P, Forbes W, Heckman J, et al. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. *J Am Geriatr Soc* 2002;50(12):1939-46.
93. Dawson D, Cutler B, Hiatt W, Hobson R, Martin J, Bortey E, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *Am J Med* 2000;109(7):523-30.
94. Pratt C. Analysis of the cilostazol safety database. *Am J Cardiol* 2001;87(12A):28D-33D.
95. Lehert P, Comte S, Gamand S, Brown TM. Naftidrofuryl in intermittent claudication: a retrospective analysis. *J Cardiovasc Pharmacol* 1994;23(Suppl. 3):S48-52.
96. Boccalon H, Lehert P, Mosnier M. Effect of naftidrofuryl on physiological walking distance in patients with intermittent claudication. *Ann Cardiol Angeiol (Paris)* 2001;50(3):175-82.
97. Kieffer E, Bahni A, Mouren X, Gamand S. A new study demonstrates the efficacy of naftidrofuryl in the treatment of intermittent claudication. Findings of the Naftidrofuryl Clinical Ischemia Study (NCIS). *Int Angiol* 2001;20(1):58-65.
98. Spengel F, Clement D, Boccalon H, Liard F, Brown T, Lehert P. Findings of the Naftidrofuryl in Quality of Life (NIQOL) European study program. *Int Angiol* 2002;21(1):20-7.
99. Brevetti G, Diehm C, Lambert D. European multicenter study on Propionyl-L-carnitine in intermittent claudication. *J Am Coll Cardiol* 1999;34:1618-24.

100. Hiatt W, Regensteiner J, Creager M, Hirsch A, Cooke J, Olin J, et al. Propionyl-L-carnitine improves exercise performance and functional status in patients with claudication. *Am J Med* 2001;110(8):616-22.
101. Mohler E III, Hiatt W, Creager M. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation* 2003;108(12):1481-6.
102. Mondillo S, Ballo P, Barbati R, Guerrini F, Ammataro T, Agricola E, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. *Am J Med* 2003;114(5):359-64.
103. Girolami B, Bernardi E, Prins M, ten Cate J, Hettiarachchi R, Prandoni P, et al. Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl: a meta-analysis. *Arch Intern Med* 1999;159(4):337-45.
104. Hood SC, Moher D, Barber GG. Management of intermittent claudication with pentoxifylline: meta-analysis of randomized controlled trials. *CMAJ* 1996;155(8):1053-9.
105. Moher D, Pham B, Aulsebrook M, Saenz A, Hood S, Barber G. Pharmacological management of intermittent claudication: a meta-analysis of randomised trials. *Drugs* 2000;59(5):1057-70.
106. Cosmi B, Conti E, Coccheri S. Anticoagulants (heparin, low molecular weight heparin and oral anticoagulants) for intermittent claudication. *Cochrane Database Syst Rev* 2001;CD001999.
107. Coffman J. Vasodilator drugs in peripheral vascular disease. *N Engl J Med* 1979;300:713-7.
108. Maxwell AJ, Anderson BE, Cooke JP. Nutritional therapy for peripheral arterial disease: a double-blind, placebo-controlled, randomized trial of HeartBar. *Vasc Med* 2000;5(1):11-9.
109. Hiatt WR, Klepack E, Nehler M, Regensteiner JG, Blue J, Imus J, et al. The effect of inhibition of acyl coenzyme A-cholesterol acyltransferase (ACAT) on exercise performance in patients with peripheral arterial disease. *Vasc Med* 2004;9(4):271-7.
110. Thulesius O, Lundvall J, Kroese A, Stranden E, Hallbook T, Brunel L, et al. Ketanserin in intermittent claudication: effect on walking distance, blood pressure, and cardiovascular complications. *J Cardiovasc Pharmacol* 1987;9(6):728-33.
111. Verstraete M. The PACK trial: morbidity and mortality effects of ketanserin. Prevention of atherosclerotic complications. *Vasc Med* 1996;1(2):135-40.
112. Hiatt WR, Hirsch AT, Cooke JP, Olin JW, Brater DC, Creager MA. Randomized trial of AT-1015 for treatment of intermittent claudication. A novel 5-hydroxytryptamine antagonist with no evidence of efficacy. *Vasc Med* 2004;9(1):18-25.
113. Norgren L, Jawien A, Matyas L, Rieger H, Arita K. the European MCI-9042 Study Group. Sarpogrelate, a 5-HT<sub>2A</sub> receptor antagonist in intermittent claudication. A phase II European Study. *Vasc Med* 2006;11:75-83.
114. Belch J, Bell P, Creissen DeaDormandy JA, Kester RC, McCollum RD, et al. Randomised, placebo-controlled, double-blind study evaluating the efficacy and safety of AS-013, a prostaglandin E1 prodrug, in patients with intermittent claudication. *Circulation* 1997;95:2298-302.
115. Lievre M, Morand S, Besse B, Fiessinger J, Boissel J. Oral beraprost sodium, a prostaglandin I<sub>2</sub> analogue, for intermittent claudication: a double-blind, randomized, multicenter controlled trial. Beraprost et Claudication Intermittente (BERCI) Research Group. *Circulation* 2000;102(4):426-31.
116. Mohler E III, Hiatt W, Olin J, Wade M, Jeffs R, Hirsch A. Treatment of intermittent claudication with beraprost sodium, an orally active prostaglandin I<sub>2</sub> analogue: a double-blinded, randomized, controlled trial. *J Am Coll Cardiol* 2003;41(10):1679-86.
117. de Backer T, Vander Stichele R, Bogaert M. Buflomedil for intermittent claudication. *Cochrane Database Syst Rev* 2001;CD000988.
118. de Backer T, Vander Stichele R, Warie H, Bogaert M. Oral vasoactive medication in intermittent claudication: utile or futile?. *Eur J Clin Pharmacol* 2000;56(3):199-206.
119. Laurora G, Ambrosoli L, Cesarone MR, De Sanctis MT, Incandela L, Marelli C, et al. Treatment of intermittent claudication with defibrotide or mesoglycan. A double blind study. *Panminerva Med* 1994;36(2):83-6.
120. Strano A, Fareed J, Sabba C, Albano O, Allegra C, Carlizza A, et al. A double-blind, multicenter, placebo-controlled, dose comparison study of orally administered defibrotide: preliminary results in patients with peripheral arterial disease. *Semin Thromb Hemost* 1991;17(Suppl 2):228-34.
121. Violi F, Marubini E, Coccheri S, Nenci GG. Improvement of walking distance by defibrotide in patients with intermittent claudication—results of a randomized, placebo-controlled study (the DICALIS study). Defibrotide Intermittent CLaudication Italian Study. *Thromb Haemost* 2000;83(5):672-7.
122. Lederman R, Mendelsohn F, Anderson R, Saucedo J, Tenaglia A, JB H, et al. Therapeutic angiogenesis with recombinant fibroblast growth factor-2 for intermittent claudication (the TRAFFIC study): a randomised trial. *Lancet* 2002;359(9323):2053-8.
123. Rajagopalan S, Mohler EI, Lederman R, Mendelsohn F, Saucedo J, Goldman C, et al. Regional angiogenesis with vascular endothelial growth factor in peripheral arterial disease: a phase II randomized, double-blind, controlled study of adenoviral delivery of vascular endothelial growth factor 121 in patients with disabling intermittent claudication. *Circulation* 2003;108(16):1933-8.
124. Armstrong DG, Lavery LA. Diabetic foot ulcers: prevention, diagnosis and classification. *Am Fam Physician* 1998;57(6):1325-32, 1337-8.
125. Reiber GE, Vileikyte L, Boyko EJ, del Aguila M, Smith DG, Lavery LA, et al. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. *Diabetes Care* 1999;22(1):157-62.
126. Armstrong DG, Lavery LA, Kimbriel HR, Nixon BP, Boulton AJ. Activity patterns of patients with diabetic foot ulceration: patients with active ulceration may not adhere to a standard pressure off-loading regimen. *Diabetes Care* 2003;26(9):2595-7.
127. Moulik PK, Mtonga R, Gill GV. Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. *Diabetes Care* 2003;26(2):491-4.
128. Strandness DJ, Sumner D. Hemodynamics for surgeons. New York: Grune & Stratton; 1975. p. 278-81.
129. Franzeck UK, Talke P, Bernstein EF, Golbranson FL, Fronck A. Transcutaneous PO<sub>2</sub> measurements in health and peripheral arterial occlusive disease *Surgery* 1982;91(2):156-63.
130. Smith I, Franks PJ, Greenhalgh RM, Poulter NR, Powell JT. The influence of smoking cessation and hypertriglyceridaemia on the progression of peripheral arterial disease and the onset of critical ischaemia. *Eur J Vasc Endovasc Surg* 1996;11(4):402-8.
131. ADA. Consensus Development Conference on Diabetic Foot Wound Care (American Diabetes Association). *Diabetes Care* 1999;22:1354-60.
132. Nabuurs-Franssen MH, Slegers R, Huijberts MS, Wijnen W, Sanders AP, Walenkamp G, et al. Total contact casting of the diabetic foot in daily practice: a prospective follow-up study. *Diabetes Care* 2005;28(2):243-7.
133. Lipsky B. International consensus group on diagnosing and treating the infected diabetic foot. A report from the international consensus on diagnosing and treating the infected diabetic foot. *Diabetes Metab Res Rev* 2004;20(Suppl 1):S68-77.
134. Frykberg R. An evidence based approach to diabetic foot infections. *Am J Surg* 2003;186:S44-54.
135. Nehler MR, Hiatt WR, Taylor LM Jr. Is revascularization and limb salvage always the best treatment for critical limb ischemia?. *J Vasc Surg* 2003;37(3):704-8.
136. Cutson TM, Bongiorno DR. Rehabilitation of the older lower limb amputee: a brief review. *J Am Geriatr Soc* 1996;44(11):1388-93.
137. Lim RC Jr, Blaisdell FW, Hall AD, Moore WS, Thomas AN. Below-knee amputation for ischemic gangrene. *Surg Gynecol Obstet* 1967;125(3):493-501.
138. Poredos P, Rakovec S, Guzic-Salobir B. Determination of amputation level in ischaemic limbs using tcPO<sub>2</sub> measurement. *Vasa* 2005;34(2):108-12.
139. Ruckley CV, Stonebridge PA, Prescott RJ. Skewflap versus long posterior flap in below-knee amputations: multicenter trial. *J Vasc Surg* 1991;13(3):423-7.

140. Siritwardena GJ, Bertrand PV. Factors influencing rehabilitation of arteriosclerotic lower limb amputees. *J Rehabil Res Dev* 1991;28(3):35-44.
141. Hagberg E, Berlin OK, Renstrom P. Function after through-knee compared with below-knee and above-knee amputation. *Prosthet Orthot Int* 1992;16(3):168-73.
142. Houghton AD, Taylor PR, Thurlow S, Rootes E, McColl I. Success rates for rehabilitation of vascular amputees: implications for preoperative assessment and amputation level. *Br J Surg* 1992;79(8):753-5.
143. Stirnemann P, Walpoh B, Wursten HU, Graber P, Parli R, Althaus U. Influence of failed arterial reconstruction on the outcome of major limb amputation. *Surgery* 1992;111(4):363-8.
144. McWhinnie DL, Gordon AC, Collin J, Gray DW, Morrison JD. Rehabilitation outcome 5 years after 100 lower-limb amputations. *Br J Surg* 1994;81(11):1596-9.
145. Nehler MR, Coll JR, Hiatt WR, Regensteiner JG, Schnickel GT, Klenke WA, et al. Functional outcome in a contemporary series of major lower extremity amputations. *J Vasc Surg* 2003;38(1):7-14.
146. Balzer K, Bechara G, Bisler H, Clevert H, Diehm C, Heisig G, et al. Placebo-kontrollierte, doppel-blinde Multicenterstudie zur Wirksamkeit von Iloprost bei der Behandlung ischämischer Ruheschmerzen von Patienten mit peripheren arteriellen Durchblutungsstörungen. *Vasa* 1987;20(Suppl):379-81.
147. Brock FE, Abri O, Baitsch G, Bechara G, Beck K, Corovic D, et al. Iloprost in the treatment of ischemic tissue lesions in diabetics. Results of a placebo-controlled multicenter study with a stable prostacyclin derivative. *Schweiz Med Wochenschr* 1990;120(40):1477-82.
148. Diehm C, Abri O, Baitsch G, Bechara G, Beck K, Breddin HK, et al. Iloprost, a stable prostacyclin derivative, in stage 4 arterial occlusive disease. A placebo-controlled multicenter study. *Dtsch Med Wochenschr* 1989;114(20):783-8.
149. Diehm C, Hibsich-Müller C, Stammler F. Intravenöse prostaglandin E1-therapie bei patienten mit peripherer arterieller verschlusskrankheit (AVK) im Stadium III: Eine doppelblinde, placebo-kontrollierte studie. In: Heinrich H, Bohme H, Rogatti W, editors. Prostaglandin E1-Wirkungen und therapeutische Wirksamkeit. Heidelberg: Springer-Verlag; 1988. p. 133-43.
150. Ciprostone Study Group. The effect of ciprostone in patients with peripheral vascular disease (PVD) characterized by ischemic ulcers. *J Clin Pharmacol* 1991;31:81-7.
151. UK Severe Limb Ischemia Study Group. Treatment of limb threatening ischemia with intravenous Iloprost: A randomised double-blind placebo controlled study. *Eur J Vasc Surg* 1991;5:511-6.
152. Guilmet J, Diot E. for the French Iloprost Study Group. Treatment of lower limb ischaemia due to atherosclerosis in diabetic and nondiabetic patients with iloprost, a stable analogue of prostacyclin: results of a French Multicentre trial. *Drug Invest* 1991;3:351-9.
153. Norgren L, Alwmark A, Angqvist KA, Hedberg B, Bergqvist D, Takolander R, et al. A stable prostacyclin analogue (iloprost) in the treatment of ischaemic ulcers of the lower limb. A Scandinavian-Polish placebo controlled, randomised multicenter study. *Eur J Vasc Surg* 1990;4(5):463-7.
154. Sakaguchi S. Prostaglandin E1 intra-arterial infusion therapy in patients with ischemic ulcer of the extremities. *Int Angiol* 1984;3:39-42.
155. Brass EP, Anthony R, Dormandy J, Hiatt WR, Jiao J, Nakanishi A, et al. Parenteral therapy with lipo-ecraprost, a lipid-based formulation of a PGE1 analog, does not alter six-month outcomes in patients with critical leg ischemia. *J Vasc Surg* 2006;43(4):752-9.
156. Dorffler-Melly J, Koopman MM, Adam DJ, Buller HR, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database Syst Rev* 3:2003;CD000535.
157. Smith FB, Bradbury AW, Fowkes FG. Intravenous naftidrofuryl for critical limb ischaemia. *Cochrane Database Syst Rev* 2:2000;CD002070.
158. European Study Group. Intravenous pentoxifyllin. *Eur J Vasc Endovasc Surg* 1995;9:426-36.
159. Norwegian Pentoxifyllin Multicenter Trial Group. Efficacy and clinical tolerance of parenteral pentoxifyllin. *Int Angiol* 1996;15:75-80.
160. Kranke Pea. *Cochrane Database Syst Rev*. 2004;CD004123.
161. Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. *Cochrane Database Syst Rev* 3:2003;CD004001.
162. Cardenas DD, Haselkorn JK, McElligott JM, Gnatz SM. A bibliography of cost-effectiveness practices in physical medicine and rehabilitation: AAPM&R white paper. *Arch Phys Med Rehabil* 2001;82(5):711-9.
163. Oostenbrink JB, Tangelder MJ, Busschbach JJ, van Hout BA, Buskens E, Algra A, et al. Cost-effectiveness of oral anticoagulants versus aspirin in patients after infrainguinal bypass grafting surgery. *J Vasc Surg* 2001;34(2):254-62.
164. Sarac TP, Hilleman D, Arko FR, Zarins CK, Ouriel K. Clinical and economic evaluation of the trellis thrombectomy device for arterial occlusions: preliminary analysis. *J Vasc Surg* 2004;39(3):556-9.
165. Whatling PJ, Gibson M, Torrie EP, Magee TR, Galland RB. Iliac occlusions: stenting or crossover grafting? An examination of patency and cost. *Eur J Vasc Endovasc Surg* 2000;20(1):36-40.
166. Wixon CL, Mills JL, Westerband A, Hughes JD, Ichnat DM. An economic appraisal of lower extremity bypass graft maintenance. *J Vasc Surg* 2000;32(1):1-12.
167. Baumgartner I, Pieczek A, Manor O, Blair R, Kearney M, Walsh K, et al. Constitutive expression of phVEGF165 after intramuscular gene transfer promotes collateral vessel development in patients with critical limb ischemia. *Circulation* 1998;97(12):1114-23.
168. Yla-Herttuala S, Alitalo K. Gene transfer as a tool to induce therapeutic vascular growth. *Nat Med* 2003;9(6):694-701.
169. Tateishi-Yuyama E, Matsubara H, Murohara T, Ikeda U, Shintani S, Masaki H, et al. Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. *Lancet* 2002;360(9331):427-35.
170. Norgren L. Pharmacotherapy for critical limb ischaemia. *Diabetes Metab Res Rev* 2000;16(Suppl 1):S37-41.
171. Collinson DJ, Donnelly R. Therapeutic angiogenesis in peripheral arterial disease: can biotechnology produce an effective collateral circulation?. *Eur J Vasc Endovasc Surg* 2004;28(1):9-23.
172. Berridge D, Kessel D, Robertson I. Surgery versus thrombolysis for initial management of acute limb ischaemia. *Cochrane Database Syst Rev* 2002; CD002784(1).
173. Campbell W, Ridler B, Szymanska T. Current management of acute leg ischaemia: results of an audit by the Vascular Surgical Society of Great Britain and Ireland. *Br J Surg* 1998;85:1498-503.
174. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE trial. *Ann Surg* 1994;220:251-66.
175. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997;26(3):517-38.
176. Kuukasjarvi P, Salenius J. Perioperative outcome of acute lower limb ischaemia on the basis of the national vascular registry. The Finnvasc Study Group. *Eur J Vasc Surg* 1994;8:578-83.
177. Eliason JL, Wainess RM, Proctor MC, Dimick JB, Cowan JA Jr, Upchurch GR Jr, et al. A national and single institutional experience in the contemporary treatment of acute lower extremity ischemia. *Ann Surg* 2003;238(3):382-9. discussion 389-390.
178. Ouriel K, Shortell C, DeWeese J, Green R, Francis C, Azodo M, et al. A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischemia. *J Vasc Surg* 1994;19:1021-30.
179. Ouriel K, Veith F, Sasahara A. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. *N Engl J Med* 1998;338:1105-11.
180. Korn P, Khilnani NM, Fellers JC, Lee TY, Winchester PA, Bush HL, et al. Thrombolysis for native arterial occlusions of the lower extremities: clinical outcome and cost. *J Vasc Surg* 2001;33(6):1148-57.
181. Saket RR, Razavi MK, Padidar A, Kee ST, Sze DY, Dake MD. Novel intravascular ultrasound-guided method to create transintimal arterial communications: initial experience in peripheral occlusive disease and aortic dissection. *J Endovasc Ther* 2004;11(3):274-80.



182. Becker GJ, Katzen BT, Dake MD. Noncoronary angioplasty. *Radiology* 1989;170(3 Pt 2):921-40.
183. Rutherford R, Durham J. Percutaneous balloon angioplasty for arteriosclerosis obliterans: long term results. Yao J, Pearce W. *Techniques in Vascular Surgery* 1992;Saunders;Philadelphia329-45.
184. Murphy TP, Ariaratnam NS, Carney WI, Jr, Marcaccio EJ, Slaiby JM, Soares GM, et al. Aortoiliac insufficiency: long-term experience with stent placement for treatment. *Radiology* 2004;231(1):243-9.
185. Timaran CH, Stevens SL, Freeman MB, Goldman MH. External iliac and common iliac artery angioplasty and stenting in men and women. *J Vasc Surg* 2001;34(3):440-6.
186. Tetteroo E, van der Graaf Y, Bosch JL, van Engelen AD, Hunink MG, Eikelboom BC, et al. Randomised comparison of primary stent placement versus primary angioplasty followed by selective stent placement in patients with iliac-artery occlusive disease. Dutch Iliac Stent Trial Study Group. *Lancet* 1998;351(9110):1153-9.
187. Klein WM, van der Graaf Y, Seegers J, Moll FL, Mali WP. Long-term cardiovascular morbidity, mortality, and reintervention after endovascular treatment in patients with iliac artery disease: The Dutch Iliac Stent Trial Study. *Radiology* 2004;232(2):491-8.
188. Bosch JL, Hunink MG. Meta-analysis of the results of percutaneous transluminal angioplasty and stent placement for aortoiliac occlusive disease. *Radiology* 1997;204(1):87-96.
189. Ponc D, Jaff MR, Swischuk J, Feiring A, Laird J, Mehra M. The Nitinol SMART stent vs Wallstent for suboptimal iliac artery angioplasty: CRISP-US Trial results. *J Vasc Interv Radiol* 2004;15(9):911-8.
190. Reed A, Conte M, Donaldson M, Mannick J, Whittemore A, Belkin M. The impact of patient age and aortic size on the results of aortobifemoral bypass grafting. *J Vasc Surg* 2003;37:1219-25.
191. de Vries S, Hunink M. Results of aortic bifurcation grafts for aortoiliac occlusive disease: a meta-analysis. *J Vasc Surg* 1997;26(4):558-69.
192. Muradin G, Bosch J, Stijnen T, Hunink M. Balloon dilation and stent implantation for treatment of femoropopliteal arterial disease: meta-analysis. *Radiology* 2001;221(1):137-45.
193. London N, Srinivasan R, Naylor A, Hartshorne T, Ratliff D, Bell P, et al. Subintimal angioplasty of femoropopliteal artery occlusions: the long-term results. *Eur J Vasc Surg* 1994;8(2):148-55.
194. Desgranges P, Boufi M, Lapeyre M, Tarquini G, van Laere O, Losy F, et al. Subintimal angioplasty: feasible and durable. *Eur J Vasc Endovasc Surg* 2004;28(2):138-41.
195. Cejna M, Thurnher S, Illiasch H, Horvath W, Waldenberger P, Hornik K, et al. PTA versus Palmaz stent placement in femoropopliteal artery obstructions: a multicenter prospective randomized study. *J Vasc Interv Radiol* 2001;12(1):23-31.
196. Grimm J, Muller-Hulsbeck S, Jahnke T, Hilbert C, Brossmann J, Heller M. Randomized study to compare PTA alone versus PTA with Palmaz stent placement for femoropopliteal lesions. *J Vasc Interv Radiol* 2001;12(8):935-42.
197. Vroegindewij D, Vos L, Tielbeek A, Buth J, van der Bosch H. Balloon angioplasty combined with primary stenting versus balloon angioplasty alone in femoropopliteal obstructions: A comparative randomized study. *Cardiovasc Intervent Radiol* 1997;20(6):420-5.
198. Schillinger M, Exner M, Mlekusch W, Rumpold H, Ahmadi R, Sabeti S, et al. Vascular inflammation and percutaneous transluminal angioplasty of the femoropopliteal artery: association with restenosis. *Radiology* 2002;225(1):21-6.
199. Schillinger M, Sabeti S, Loewe C, Dick P, Amighi J, Mlekusch W, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. *N Engl J Med* 2006;354(18):1879-88.
200. Wolf G, Wilson S, Cross A, Deupree R, Stason W. Surgery or balloon angioplasty for peripheral vascular disease: a randomized clinical trial. Principal investigators and their Associates of Veterans Administration Cooperative Study Number 199. *J Vasc Interv Radiol* 1993;4(5):639-48.
201. Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet* 2005;366(9501):1925-34.
202. Conte M, Belkin M, Upchurch G, Mannick J, Whittemore A, Donaldson M. Impact of increasing comorbidity on infrainguinal reconstruction: a 20 year perspective. *Ann Surg* 2001;233:445-52.
203. Lam E, Landry G, Edwards J, Yeager R, Taylor L, Moneta G. Risk factors for autogenous infrainguinal bypass occlusion in patients with prosthetic inflow grafts. *J Vasc Surg* 2004;39:336-42.
204. Albers M, Battistella V, Romiti M, Rodrigues A, Pereira C. Meta-analysis of polytetrafluoroethylene bypass grafts to infrapopliteal arteries. *J Vasc Surg* 2003;37:1263-9.
205. Jackson MR, Belott TP, Dickason T, Kaiser WJ, Modrall JG, Valentine RJ, et al. The consequences of a failed femoropopliteal bypass grafting: comparison of saphenous vein and PTFE grafts. *J Vasc Surg* 2000;32(3):498-504. 504-5.
206. Green R, Abbott W, Matsumoto T, Wheeler JR, Miller N, Veith FJ, et al. Prosthetic above-knee femoropopliteal bypass grafting: five-year results of a randomized trial. *J Vasc Surg* 2000;31:417-25.
207. AbuRahma AF, Robinson PA, Holt SM. Prospective controlled study of polytetrafluoroethylene versus saphenous vein in claudicant patients with bilateral above knee femoropopliteal bypasses. *Surgery* 1999;126(4):594-601. [discussion 601-602].
208. Johnson WC, Lee KK. A comparative evaluation of polytetrafluoroethylene, umbilical vein, and saphenous vein bypass grafts for femoral-popliteal above-knee revascularization: a prospective randomized Department of Veterans Affairs cooperative study. *J Vasc Surg* 2000;32(2):268-77.
209. Klinkert P, van Dijk PJ, Breslau PJ. Polytetrafluoroethylene femorotibial bypass grafting: 5-year patency and limb salvage. *Ann Vasc Surg* 2003;17(5):486-91.
210. Hamsho A, Nott D, Harris PL. Prospective randomised trial of distal arteriovenous fistula as an adjunct to femoro-infrapopliteal PTFE bypass. *Eur J Vasc Endovasc Surg* 1999;17(3):197-201.
211. Griffith C, Nagy J, Black D, Stonebridge P. Randomized clinical trial of distal anastomotic interposition vein cuff in infrainguinal polytetrafluoroethylene bypass grafting. *Br J Surg* 2004;91:560.
212. Davies AH, Hawdon AJ, Sydes MR, Thompson SG. Is duplex surveillance of value after leg vein bypass grafting? Principal results of the Vein Graft Surveillance Randomised Trial (VGST). *Circulation* 2005;112(13):1985-91.
213. Baldwin Z, Pearce B, Curi M, Desai T, McKinsey J, Bassiouny H, et al. Limb salvage following infrainguinal bypass graft failure. *J Vasc Surg* 2004;39:951-7.
214. Tangelder M, Lawson J, Algra A, Eikelboom B. Systematic review of randomized controlled trials of aspirin and oral anticoagulants in prevention of graft occlusion and ischemic events after infrainguinal bypass surgery. *J Vasc Surg* 1999;30:701-9.
215. Girolami B, Bernardi E, Prins M, ten Cate J, Prandoni P, Simioni P, et al. Antiplatelet therapy and other interventions after revascularization procedures in patients with peripheral arterial disease: a meta-analysis. *Eur J Vasc Endovasc Surg* 2000;19:370-80.
216. Dorffler-Melly J, Buller H, Koopman M, Adam D, Prins M, et al. Antithrombotic agents for preventing thrombosis after peripheral bypass surgery. *Cochrane Database Syst Rev* 2003;CD000536.
217. Visser K, Idu MM, Buth J, Engel GL, Hunink MG. Duplex scan surveillance during the first year after infrainguinal autologous vein bypass grafting surgery: costs and clinical outcomes compared with other surveillance programs. *J Vasc Surg* 2001;33(1):123-30.
218. Duda S, Pusch B, Richter G, Landwehr P, Oliva V, Tielbeek A, et al. Sirolimus-eluting stents for the treatment of obstructive superficial femoral artery disease: six-month results. *Circulation* 2002;106(12):1505-9.
219. Saxon R, Coffman J, Gooding J, Natuzzi E, Ponc D. Long-term results of ePTFE stent-graft versus angioplasty in the femoropopliteal artery: single center experience from a prospective, randomized trial. *J Vasc Interv Radiol* 2003;14(3):303-11.

220. Minar E, Pokrajac B, Maca T, Ahmadi R, Fellner C, Mittlbock M, et al. Endovascular brachytherapy for prophylaxis of restenosis after femoropopliteal angioplasty: results of a prospective randomized study. *Circulation* 2000;102(22):2694-9.
221. Rutherford RB, Lowenstein DH, Klein MF. Combining segmental systolic pressures and plethysmography to diagnose arterial occlusive disease of the legs. *Am J Surg* 1979;138(2):211-8.
222. Koelemay MJ, Legemate DA, Reekers JA, Koedam NA, Balm R, Jacobs MJ. Interobserver variation in interpretation of arteriography and management of severe lower leg arterial disease. *Eur J Vasc Endovasc Surg* 2001;21(5):417-22.
223. de Vries M, Nijenhuis RJ, Hoogeveen RM, de Haan MW, van Engelshoven JM, Leiner T. Contrast-enhanced peripheral MR angiography using SENSE in multiple stations: feasibility study. *J Magn Reson Imaging* 2005;21(1):37-45.
224. Vogt FM, Ajaj W, Hunold P, Herborn CU, Quick HH, Debatin JF, et al. Venous compression at high-spatial-resolution three-dimensional MR angiography of peripheral arteries. *Radiology* 2004; 233(3):913-20.
225. Dorweiler B, Neufang A, Schmiedt W, Oelert H. Pedal arterial bypass for limb salvage in patients with diabetes mellitus. *Eur J Vasc Endovasc Surg* 2002;24(4):309-13.
226. Jakobs TF, Wintersperger BJ, Becker CR. MDCT-imaging of peripheral arterial disease. *Semin Ultrasound CT MR* 2004;25(2): 145-55.
227. Ota H, Takase K, Igarashi K, Chiba Y, Haga K, Saito H, et al. MDCT compared with digital subtraction angiography for assessment of lower extremity arterial occlusive disease: importance of reviewing cross-sectional images. *AJR Am J Roentgenol* 2004; 182(1):201-9.