

Peripheral Arterial Disease – Diagnosis and Treatment

A Systematic Review

SBU Board of Directors and Scientific Advisory Committee

Secreteriat

MÅNS ROSÉN

Executive Director, SBU

Board of Directors

NINA REHNQVIST

Karolinska Institute, Solna
(Chair)

HÅKAN BILLIG

Swedish Research Council

HÅKAN CEDER

The Nation Board
of Health and Welfare

ANNA-KARIN EKLUND

Swedish Association
of Health Professionals

ANNA ENGSTRÖM-LAURENT

Swedish Society of Medicine

ANN HEDBERG BALKÅ

The Swedish Association
of local Authorities and
Region

SVEN-OLOF KARLSSON

The Swedish Association
of local Authorities and
Region

BJÖRN KLINGE

Karolinska Institute, Solna

EVA NILSSON BÅGENHOLM

Swedish Society of Medicine

HÅKAN SÖRMAN

The Swedish Association
of local Authorities and
Region

GUNNAR ÅGREN

The Swedish National
Institute of Public Health

Scientific Advisory Committee

DAVID BERGQVIST

Uppsala University
Hospital (Chair)

ANDERS ANELL

School of Economics
and Management,
Lund University

BJÖRN BEERMANN

Medical Products Agency,
Uppsala

CECILIA BJÖRKELUND

Göteborgs University

LISA EKSELIUS

Uppsala University

MATS ELIASSON

Sunderby Hospital, Luleå

SÖLVE ELMSTÅHL

University Hospital,
Malmö

MIKAEL HELLSTRÖM

Sahlgrenska Hospital,
Göteborg

ANDERS LINDGREN

The Swedish Ministry of
Health and Social Affairs

KERSTIN NILSSON

University Hospital,
Örebro

OLOF NYRÉN

Karolinska Institute,
Solna

JAN PALMBLAD

Karolinska Institute,
Huddinge

BJÖRN SJÖSTRÖM

University of Skövde

GUNNEVI SUNDELIN

Umeå University

GUNNEL SVENSÅTER

Malmö University

Summary and Conclusions of the SBU Report:

Peripheral Arterial Disease – Diagnosis and Treatment

A Systematic Review

November 2008

Project Group:

David Bergqvist (Chair)

Martin Delle

Ingemar Eckerlund

Jan Holst

Tomas Jogestrand

Gun Jörneskog

Rosemarie Klevsgård

Lars-Åke Marké

Ingrid Mattiasson

Olov Rolandsson

Anneth Syversson

(Project Assistant)

Juliette Säwe

(Project Director)

Thomas Troëng

Eric Wahlberg

Other Authors:

Håkan Ahlström (Chapter 3.2)

Anders Gottsäter (Chapter 1.3)

Scientific Reviewers:

Bengt Fagrell

Jerzy Leppert

Christina Lindholm

Lars Norgren

Ulf Nyman

Stefan Rosfors

Niklas Zethraeus

Report: Peripheral Arterial Disease – Diagnosis and Treatment

Type: Systematic Review • ISBN: 978-91-85413-20-1 • ISSN: 1400-1403

Report no: 187E • Publishing year: 2007

SBU's Conclusions

This report summarises the results of SBU's systematic review of the literature concerning methods of diagnosing and treating symptomatic peripheral arterial disease caused by atherosclerosis or arterial thrombosis in the lower extremities. The project did not include studies of methods to prevent or affect the development or progress of peripheral arterial disease. Many of those methods have been assessed by previous SBU reports: Smoking Cessation Methods (1998), Obesity – Problems and Interventions (2002), Moderately Elevated Blood Pressure (2004), Interventions to Prevent Obesity (2005) and Methods of Promoting Physical Activity (2007).

Conclusions

- *Peripheral arterial disease is common, particularly in the elderly, and poses a high risk of long-term suffering, amputation and premature death*

Peripheral arterial disease is the result of ischaemia (insufficient blood flow) in the lower extremities. In the great majority of cases, the cause is atherosclerosis – which is among the most common diseases and one that rarely affects the blood vessels of the lower extremities alone, but rather the entire cardiovascular system. Thus, all patients who have symptoms of peripheral arterial disease should be assessed for risk of atherosclerosis.

Peripheral arterial disease in its mild form may be limited to intermittent claudication, pain in the lower extremities that is triggered by exertion but that ceases during rest. When ischaemia is chronic, critical or acute – characterised by stenosed or occluded blood vessels – peripheral arterial disease increases the risk of tissue death (gangrene), amputation and premature death.

Because atherosclerosis – the primary cause of peripheral arterial disease – can progress for a long time without producing any direct symptoms, the number of people who have the disease is unknown. The risk increases with age, and peripheral arterial disease occurs among an estimated 10% of people over 60 years. Half (more than 5 000) of the invasive procedures that are performed every year at Swedish hospitals for vascular diseases seek to restore blood flow in patients with various forms of peripheral arterial disease.

- *The most urgent priority for all vascular diseases, including those in the lower extremities, is to persuade and help patients to stop smoking*

The correlation between smoking and peripheral arterial disease is very strong and has been documented by a large number of studies. The risk that a smoker will develop intermittent claudication is almost double that of developing angina pectoris. Smoking cessation reduces the risk of serious ongoing symptoms, amputation and death due to vascular complications.

All treatment of peripheral arterial disease includes aggressively affecting the general risk factors for atherosclerosis, such as smoking, physical inactivity, overweight, hypertension, high lipids and high blood sugar.

- *The scientific evidence for diagnosis and treatment of peripheral arterial disease is limited*

Although a review of the literature identified several thousand articles, close examination revealed that only a small percentage of the studies met the criteria for quality and internal validity that have been established by health technology assessment and SBU particular. As a result, the scientific evidence for the report's conclusions is limited – or moderately strong at best. The benefits and risks of a number of the treatment methods reviewed by the project could not be assessed due

to a lack of studies characterised by sufficient quality and internal validity. Such methods include anticoagulant therapy for intermittent claudication, oestrogen and testosterone therapy, hyperbaric oxygen therapy, spinal cord stimulation, electromagnetic therapy, ultraviolet light therapy and intermittent pneumatic compression. Scientific evidence is also lacking to assess the efficacy of vitamin E, vitamin B/folic acid, Omega-3, garlic and the Padma 28 herbal preparation.

- *While the patient's experience of symptoms should always form the basis of diagnosing and treating peripheral arterial disease, clinically relevant studies are generally lacking that compare how various interventions impact quality of life*

Peripheral arterial disease has a decisive – often disabling – impact on quality of life, the experience of which varies from person to person. Quality of life, which is among the key goals of all medical treatment, may be defined as an aggregate measure of physical and mental functioning, along with a sense of wellbeing and satisfaction. But clinical practice still takes only limited advantage of opportunities to assess quality of life, ie, how the patient deals with daily activities and responds to treatment.

- *Diagnostic methods*

The basic method for diagnosis and assessment of patients with symptomatic peripheral arterial disease includes assessing medical history with walking distance palpation, and a simple physical examination with a stethoscope, sphygmo-manometer cuff and Doppler probe to compare blood pressure in the arms and legs. Such examinations, which may be performed at any health centre or hospital, can identify most patients with peripheral arterial disease.

To more precisely locate stenoses and any thrombi requires additional assessment. While conventional angiography is

still the most common approach, technical progress in recent years has generated a number of new methods for reliably diagnosing peripheral arterial disease. These methods are just as dependable as conventional angiography for designing a treatment strategy, but are gentler, easier, faster and less risky.

- Duplex ultrasonography has the same high reliability as conventional angiography when it comes to confirming or ruling out vascular disease in the lower abdominal aorta, as well as the arteries of the pelvis, thigh and knee. The scientific evidence is, however, weaker with respect to the certainty of the method for diagnosing changes in the lower leg and foot.
- Magnetic resonance angiography (MRA) using an injected contrast agent has the same high reliability as conventional angiography when it comes to confirming or ruling out vascular disease in the abdominal aorta below the kidneys, as well as the arteries of the pelvis and thigh. The scientific evidence is not as strong in terms of identifying stenoses in the arteries of the lower leg.
- MRA that does not use an injected contrast agent has the same high reliability as conventional angiography when it comes to confirming or ruling out vascular disease in the arteries of the thigh and lower leg. MRA is not as reliable for identifying changes in the abdominal aorta below the kidneys and in the pelvic arteries.
- Computed tomographic angiography (CTA) has the same high reliability as conventional angiography when it comes to confirming or ruling out vascular disease in all blood vessels, from the abdominal aorta to the arteries of the foot.

□ *Treating intermittent claudication*

No drug has been approved in Sweden for specifically treating peripheral arterial disease, and there is no therapy that can be said to cure the condition.

Nevertheless, the following has been established:

- Physical training, walking or Nordic walking – particularly when organised or supervised – improves walking distance.
- Revascularisation, which is an intervention intended to restore or improve blood flow, should generally be avoided. But there is limited scientific evidence that open revascularisation in claudication patients with disabling symptoms may be somewhat more effective than walking training.
- Percutaneous transluminal angioplasty (PTA) with selective placement of a stent is cost-effective in comparison with other revascularisation methods that were reviewed.
- There is limited scientific evidence that Ginkgo biloba, a natural remedy, and levocarnitine can improve walking distance.
- There is limited scientific evidence that intravenous prostaglandin E1 increases walking distance.

□ *Treating chronic critical limb ischaemia*

Patients who have symptoms of critical limb ischaemia must receive prompt treatment to relieve the pain and minimise or eliminate the risk of deterioration leading to ulcers and tissue death (gangrene).

- Open or endovascular revascularisation using thrombolysis therapy or PTA should be offered when critical limb ischaemia may lead to amputation.
 - Adjunctive therapy using a platelet inhibitor or vitamin K antagonist whose (warfarin) improves results after revascularisation therapy.
 - Adjunctive therapy using a vitamin K antagonist causes more bleeding complications than platelet inhibit.
- *Treating acute limb ischaemia*
- Acute limb ischaemia is caused by abrupt occlusion of a major artery. The patient often experiences severe pain. Treatment must start immediately. The leg may have to be amputated.
- Immediate invasive treatment normally permits amputation-free survival for many years.
 - There is no decisive difference between open surgical intervention and endovascular revascularisation through the blood vessels (thrombolysis therapy) in terms of amputation-free survival.
 - Acute limb ischaemia often occurs at the end of life. In such cases, lower limb ischaemia results from a gradual slowdown in the functioning of the organs. Surgery is not indicated, and pain relief may be the proper treatment from a medical and compassionate point of view.

□ *Ethical aspects*

Following are some of the ethical issues that must be taken into consideration when diagnosing and treating peripheral arterial disease:

- Reconstructive procedures for critical and acute limb ischaemia are often associated with the risk of serious complications, as well as death in some cases. Such risks must be weighed against the opportunity to improve health and quality of life.
- One problem in particular is that caregivers may have difficulty refraining from the use of new methods even when the documentation is substandard or incomplete.
- A patient's lifestyle, such as continued smoking, must not lead to discriminatory treatment.
- While attempts to avoid amputation are a worthy goal, they must be weighed against risks and suffering in patients for whom it may turn out to be necessary after all. Resource utilisation is also an ethical issue in such cases.

□ *Survey of clinical practice*

Diagnosis, medical treatment and referral procedures for peripheral arterial disease patients in primary care can be improved. The disease is an uncommon diagnosis in Swedish primary care. Many patients are referred for diagnosis and assessment prior to possible intervention, but only a few undergo invasive treatment. SBU's survey of clinical practice

also reveals major regional differences in the number of patients who are referred for such diagnosis and assessment.

Educational efforts, as well as guidelines for diagnosis and treatment of peripheral arterial disease in primary care, would raise awareness about patients with vascular disease who are at high risk of cardiovascular disease and death.

❑ *Assessment and reporting*

Major inadequacies remain when it comes to assessing new technologies. Systematic efforts in that area should be given high priority.

The results of treatment should be reported to, and compiled in, a central registry. For the past 20 years, most vascular surgery – including radiological interventions such as thrombolysis therapy and PTA – has been reported to the Swedish Vascular Registry (Swedvasc). Amputation due to peripheral arterial disease is however not systematically reported to the registry.

❑ *Research needs*

Multicentre randomised trials could be arranged in Sweden to address two key questions:

- Which therapy is better for intermittent claudication – intervention or walking training and best medical treatment?
- Which therapy is better for critical limb ischaemia – surgical/endovascular intervention or best medical treatment?



SBU's Summary

Introduction

The initial signs of peripheral arterial disease are often so indistinct that a number of explanations may be more likely than disease: flabby muscles, temporary overexertion, etc. Not until a lot of pain is present, particularly in the calf muscles when walking, do most people suspect that something is wrong. The pain is often experienced as a cramp that goes away after the person stops and rests for a while. That is why the most common form of peripheral arterial disease is referred to as intermittent claudication, which comes from the Latin verb *claudicare*, “to limp”. The cause is insufficient blood flow in the muscles of the lower extremities when walking.

In more severe cases, peripheral arterial disease can deteriorate to chronic critical limb ischaemia (substantially impaired blood flow) characterised by pain during rest as well, cold feet, ulcers that fail to heal and/or tissue death (gangrene) that require prompt treatment.

Acute limb ischaemia, often due to a thrombus that totally occludes a blood vessel, may be a life-threatening condition unless the occlusion is immediately removed. In severe cases, the leg may have to be amputated.

With rare exceptions, peripheral arterial disease is due to atherosclerosis. The arteries that carry blood from the heart acquire deposits of fat and other substances, an inner “shell” that eventually causes the arterial walls to harden. The become

narrow constrict and less elastic. The blood, which must supply every cell of the body with vital oxygen and nutrients, as well as transport toxic waste products to the eliminatory organs, cannot flow as easily. The heart must work harder to maintain blood flow, even in the extremities.

Most people eventually develop atherosclerosis in one form or another. The disease is closely related to contemporary lifestyles. Cardiovascular diseases stemming from atherosclerosis is now responsible for more than half of all deaths in the industrialised countries. According to WHO estimates, cardiovascular disease will be the predominant cause of death around the world within two decades.

Atherosclerosis begins early in life and can progress for decades without producing any symptoms. While there is no way of knowing exactly how many people have peripheral arterial disease, an estimated 10–20% of all Swedish retirees have some form of the condition. Approximately 5 000 interventions are performed at Swedish hospitals every year to restore blood flow in patients with various forms of peripheral arterial disease. That corresponds to 550–600 per million inhabitants.

Risk Factors

Although the mechanisms that cause atherosclerosis are not known in detail, a series of risk factors have been shown to affect and accelerate its progress:

- The overwhelming risk factor for peripheral arterial disease is smoking. Non-smokers have peripheral arterial disease only in exceptional cases.
- Diabetes mellitus.
- Hypertension.

- High lipids.
- Age – the risk increases starting at age 50, especially in diabetics or former smokers.
- Gender – more men than women have intermittent claudication.
- Inactivity, impaired mobility.
- Overweight.

Because many people have an asymptomatic peripheral arterial disease, known risk factors should be treated.

Symptoms

By the time the initial symptoms of peripheral arterial disease become manifest, atherosclerosis has often narrowed the arteries to less than half their normal diameter.

Following are the predominant early symptoms of peripheral arterial disease:

- Pain when walking, which often goes away when the person stops and rests. Some people cannot walk more than 10 meters on a flat surface, whereas others can go several hundred meters before the pain starts.
- Muscular weakness – “my legs refuse to go any further”.

As the disease progress, symptoms arise such as:

- Cold legs and feet, particularly certain specific areas.
- Discolouration of the skin.
- Foot ulcers that fail to heal normally.
- Gangrene.

Pain and Reduced Quality of Life

Common to all types of peripheral arterial disease is pain – from the manageable transient type in mild intermittent claudication to the inescapable, difficult-to-treat type in chronic critical limb ischaemia. The pain of acute limb ischaemia is described by patients as unbearable and cannot be alleviated by drug therapy.

Combined with what is often limited walking ability, the stubborn pain reduces quality of life. Although the process affects people in different ways, the impact is always far-reaching and often disabling.

A Warning Sign

Peripheral arterial disease is rarely limited to the lower extremities, even when it first manifests there. In the great majority of cases, pathological changes can be found in other parts of the cardiovascular system as well. That is why even intermittent claudication is associated with increased incidence of, and death from, both myocardial infarction and stroke.

Thus, peripheral arterial disease should always be regarded as a serious warning sign.



Structure of the Project

The purpose of the project was to systematically and critically review the scientific evidence for methods available in Sweden to diagnose and treat symptomatic peripheral arterial disease. Assessment of overall treatment for atherosclerosis was not part of the project. Health economic and ethical aspects were also taken into consideration.

A 14-person group compiled the report. Seven external experts, as well as the SBU Board of Directors and Scientific Advisory Committee, examined the final version. The review of the literature covered all studies published until summer 2005, with a supplementary update in summer 2006. The Medline database alone contains approximately 7 000 studies involving peripheral arterial disease. The Cochrane Library also published several reviews during the course of the project, and the report includes the relevant ones.

The selection of studies was limited to randomised, blinded, controlled trials, ie, those that randomly allocates patients to different groups in order to compare the efficacy of various treatments. The assessment of methods for open or endovascular revascularisation included open, prospective studies with a control group. For the assessment of diagnostic methods, the study must have performed an independent comparison with the efficacy of a recognised reference method that has been adopted by clinical practice. Beyond study design requirements, topic-specific quality criteria – such as length of the observation period, concurrent therapy or the number of subjects who should participate – deemed necessary in order to reliably address the question were established.

Surveys of Clinical Practice

Patients with complaints in the lower extremities generally go to a primary care facility. To gain an overview of the frequency of peripheral arterial disease in the primary care population, as well

as how the disease is assessed and treated, a survey was conducted of clinical practice in three Swedish primary care areas.

The survey confirmed that there is a strong correlation between peripheral arterial disease and cardiovascular disease. Diagnosis, medical treatment and referral procedures for peripheral arterial disease patients showed significant regional differences. Fewer than half of the patients were treated for high lipids. Given the high risk of cardiovascular disease among that group of patients, a reasonable conclusion is that lipid-lowering drugs are underprescribed to them. The survey also revealed that a high percentage of patients with peripheral arterial disease were referred for diagnosis and assessment prior to possible intervention, but that only a small percentage actually underwent surgery.

These results were confirmed by the second survey, which examined the flow of referrals of patients with peripheral arterial disease at six hospitals associated with SBU's project. Almost two thirds of the referrals contained information that permitted an assessment of the urgency of the case. Half of the patients were rereferred after having seen a doctor. Thirty percent of the patients were scheduled for hospitalisation and invasive treatment after having seen a doctor. A survey including all the departments of clinical physiology in Sweden showed that most of them performed ankle and toe blood pressure measurements, as well as duplex ultrasonography.

Costs

Total direct costs for the diagnosis and treatment of peripheral arterial disease in 2005 are estimated at more than SEK 1 billion. That does not include costs for primary care, municipal health care and social services. More than SEK 600 million of the direct costs was for inpatient hospital care.

Limits and Main Questions

The project addressed the following main questions:

- What diagnostic methods should be used to survey, identify and assess the severity of peripheral arterial disease?
- What medical, adjunctive and alternative methods are effective in symptomatic peripheral arterial disease?
- Does open or endovascular revascularisation, two methods of improving local blood flow, increase walking distance and quality of life in intermittent claudication patients?
- Can all patients with peripheral arterial disease receive equal treatment with open or endovascular revascularisation?
- Does open or endovascular revascularisation reduce the risk of amputation in acute and chronic peripheral arterial disease?
- How cost-effective are the various methods?

Synthesising and Grading Conclusions

For each question, the results of the studies that met the baseline quality criteria were compiled. After that, the total quality and internal validity of the scientific evidence was assessed as a basis for determining evidence grade. The conclusions for each chapter were based only on the studies deemed to have high or medium study quality and relevance. Thus, evidence grade represents the total scientific evidence for a conclusion, ie, how many high-quality studies support it. The evidence grade appears in parentheses following each conclusion. Fact Box 1 defines study quality and relevance, as well as evidence grade.

Fact Box 1 Study Quality and Relevance, Evidence Grade.

Study Quality and Relevance refers to the scientific quality of a particular study and its ability to reliably address a specific question.

Evidence Grade refers to the total scientific evidence for a conclusion.

Evidence Grade 1 – Strong Scientific Evidence

A conclusion assigned Evidence Grade 1 is supported by at least two studies with high quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the evidence grade may be lower.

Evidence Grade 2 – Moderately Strong Scientific Evidence

A conclusion assigned Evidence Grade 2 is supported by at least one study with high quality and relevance and two studies with medium quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the evidence grade may be lower.

Evidence Grade 3 – Limited Scientific Evidence

A conclusion assigned Evidence Grade 3 is supported by at least two studies with medium quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the scientific evidence may be regarded as insufficient or contradictory.

Insufficient Scientific Evidence

If no studies meet the quality and relevance criteria, the scientific evidence is rated as insufficient to draw any conclusions.

Contradictory Scientific Evidence

If different studies are characterised by equal quality and relevance but generate conflicting results, the scientific evidence is rated as contradictory and no conclusions are drawn.

Although evidence grading of the conclusions should not be viewed as irrefutable, those that are assigned Evidence Grade 1 (and to a certain extent Evidence Grade 2) should be taken more seriously in clinical practice than those that are assigned Evidence Grade 3. Important to keep in mind is that insufficient scientific evidence for a method is not equivalent to saying that it is ineffective. On the other hand, a conclusion that a method is ineffective may be assigned Evidence Grade 1, 2 or 3.

Results of the Systematic Review of the Literature

Diagnostic Methods

Diagnosis of peripheral arterial disease is based primarily on the patient's description of her/his symptoms, medical history and status (results of a physical examination). The examination may be performed during the first appointment, given that all health centres and hospitals have the requisite equipment.

The patient's medical history should include a thorough analysis of walking pain, walking distance, resting pain, the appearance and location of ulcers and gangrene (tissue death due to occluded arteries), and other diseases and medications.

Status includes palpating the pulse in the groin, knee and "on" the feet, listening with a stethoscope for murmurs from stenoses in the major blood vessels (particularly in the groin) and measuring blood pressure, both with the ordinary method in the arm and with a Doppler monitor just above the ankle joint. Significantly lower blood pressure in the ankle than the arm is a sign of peripheral arterial disease even if none of the other typical symptoms are present. A simple walking test in the hallway can supplement the clinical assessment.

For diabetes and advanced atherosclerosis, measuring blood pressure in individual toes may be necessary. But that requires more sophisticated equipment, usually at the department of clin-

ical physiology. Additional examinations are also performed there in order to obtain the best possible impression of changes in the blood vessels.

This report does not examine measurements of ankle and toe blood pressure, which are well-established and evaluated diagnostic methods. Nor does the report look at methods that are still in the research stage. Such methods include those that are used to assess microcirculation: transcutaneous PO₂ measurement, laser Doppler technique and capillary microscopy.

Evaluation of a diagnostic method requires a standard or reference method to which it can be compared. The reference method must have the best scientific evidence of actually detecting the disease and have been used traditionally for diagnostic purposes.

Angiography, an x-ray examination of an artery after having injected a contrast agent, is the most accurate way of imaging the arterial system and is used as a reference method. The arterial puncture entails a certain risk of serious complications. Another disadvantage is that a contrast agent containing iodine may affect the kidneys – particularly in patients with renal impairment, often the elderly and diabetics. As a result, many patients are hospitalised before angiography is performed. In the absence of risk factors, the procedure can be successfully performed on an outpatient basis. Despite the disadvantages, conventional angiography is still the most widely used method for anatomic evaluation. Furthermore, it often serves as a basis for further assessment and treatment strategy.

The technological progress of the past few decades has produced alternatives to conventional angiography that are gentler and less risky. In addition, the new methods can often be performed quickly, less expensively and in an ambulatory setting.

The review of the literature in this report covers three of those diagnostic methods: duplex ultrasonography, magnetic resonance angiography (MRA) and computed tomographic angiography (CTA). The systematic review aims to determine the diagnostic

certainty and usefulness of the methods in routine assessment of patients with peripheral arterial disease. The criterion when comparing the accuracy of the various methods to conventional angiography was that sensitivity (the percentage of people with the disease who were correctly identified) and specificity (the percentage of healthy people who were correctly identified) be at least 80%. Following is a summary of the most important conclusions of the assessment.

Duplex Ultrasonography

State-of-the-art duplex ultrasonography images the blood vessels while measuring and calculating blood flow velocity. In order to address a specific question, the examination is often performed within a limited arterial segment. But the entire arterial system can be studied, from the abdominal aorta to the small vessels of the foot. However, that takes a long time (60–90 minutes), particularly when arterial disease is extensive.

The examination, which is entirely safe, requires neither punctures of the blood vessels nor a contrast agent. Generally speaking, it can be performed (and repeated when necessary) without causing any discomfort.

While the method is gentle on the patient, it is that much more strenuous for the technician. The ergonomic problems – including what is often an uncomfortable working position and static, arduous muscular effort – can be minimised by means of aids that ease the burden, as well as the avoidance of long shifts. The method demands an experienced technician with 6–12 months of training in order to reliably identify hemodynamically significant stenoses or occlusions.

A comparison of the results of studies with duplex ultrasonography and those with conventional angiography yielded the following:

- In the lower abdominal aorta – as well as the arteries of the pelvis, thigh and knee – the diagnostic accuracy of duplex ultrasonography (sensitivity and specificity $\geq 80\%$) is comparable to conventional angiography for confirming or ruling out hemodynamically significant stenoses (≥ 50 diameter reduction) or occlusions (Evidence Grade 2).
- In the arteries of the lower leg and foot, there is limited scientific evidence that the diagnostic accuracy of duplex ultrasonography (sensitivity and specificity $\geq 80\%$) is comparable to conventional angiography for confirming or ruling out hemodynamically significant stenoses (≥ 50 diameter reduction) or occlusions (Evidence Grade 3).
- When examining patients with peripheral arterial disease, duplex ultrasonography is as reliable in terms of treatment strategy as conventional angiography ($\geq 80\%$ agreement or kappa value > 0.6) (Evidence Grade 2). When looking at a limited arterial segment, agreement between duplex ultrasonography and conventional angiography or actual intervention is however better above the groin and poorer below the groin.

Magnetic Resonance Angiography (MRA)

An MR scanner produces the same type of image as conventional angiography, but without the risk of radiation injury. MRA is based on the way that the body's hydrogen atoms react to radio waves in a very strong magnetic field. The examination with an MR scanner is painless, and it is performed either with or without intravenous injection of a contrast agent in the arm. The contrast agent is different from the iodine-based kind used in conventional angiography. It is administered in lower doses and thereby less harmful to the kidneys, but it should be avoided in patients with substantial renal impairment.

Patients with electronic medical implants or magnetic metal in their bodies must not be examined with an MR scanner.

MRA now has the potential to replace conventional angiography in a majority of patients. The entire arterial system from the abdominal aorta to the lower leg and foot can be quickly examined while maintaining high image quality. Poor availability, often in combination with long waiting times, poses the main obstacle to greater use of MRA.

A number of studies have compared the diagnostic value of MRA with conventional angiography.

The results show the following for MRA *with* an intravenous contrast agent:



- In the lower abdominal aorta – as well as the arteries of the pelvis, thigh and knee – the diagnostic accuracy of MRA with an intravenous contrast agent (sensitivity and specificity $\geq 80\%$) is equivalent to conventional angiography for confirming or ruling out hemodynamically significant stenoses (≥ 50 diameter reduction) or occlusions (Evidence Grade 2).

Figure 1 MR angiographic image with intravenous gadolinium-based contrast agent of the abdominal aorta, as well as the arteries of the pelvis, thigh and lower leg. The image is generated from 3-dimensional sequences using the maximum intensity projection (MIP) technique (see Chapter 3.2, Info Box 3.2.1 of the main report). Studies of the diagnostic certainty of MRA divide the arterial system into short anatomical segments that are compared with conventional angiography (independent comparison).

- In the arteries of the lower leg and foot, there is limited scientific evidence that the diagnostic accuracy of MRA with an intravenous contrast agent (sensitivity and specificity $\geq 80\%$) is equivalent to conventional angiography for confirming or ruling out hemodynamically significant stenoses (≥ 50 diameter reduction) or occlusions (Evidence Grade 3).

The results show the following for MRA *without* an intravenous contrast agent:

- In the lower abdominal aorta and the pelvic arteries, the diagnostic accuracy of MRA without an intravenous contrast agent (sensitivity and specificity $< 80\%$) is poorer than conventional angiography for confirming or ruling out hemodynamically significant stenoses (≥ 50 diameter reduction) or occlusions (Evidence Grade 2).
- In the arteries of the thigh, knee, lower leg and foot, the diagnostic accuracy of MRA without an intravenous contrast agent (sensitivity and specificity $\geq 80\%$) is equivalent to conventional angiography for confirming or ruling out hemodynamically significant stenoses (≥ 50 diameter reduction) or occlusions (Evidence Grade 2).
- Comparisons of the results of MRA and conventional angiography yield moderately strong scientific evidence that MRA (with or without a contrast agent) is essentially as reliable as conventional angiography ($\geq 80\%$ agreement or kappa value > 0.6) as a basis for designing a treatment strategy in peripheral arterial disease (Evidence Grade 2).

Computed Tomographic Angiography (CTA)

Spiral computed tomography is a radiological method of imaging thin layers or cross-sections of the body. It is easy to read,

gentle on the patient and one of the ordinary outpatient services at all emergency hospitals. The method is very fast, and dynamic changes such as contrast density of the arteries can be captured at high resolution. CTA can be used to quickly image long vascular systems, such as from the abdominal aorta to the leg arteries, while retaining high resolution longitudinally in the body when the contrast agent passes through for a short time.

The quantity of contrast agent is the same, or somewhat higher, than in conventional angiography. Because the contrast agent contains iodine, the patient's renal function – as well as the possible presence of diabetes or dehydration – must be taken into consideration.

Studies that compare the diagnostic certainty of CTA with conventional angiography show that:

- CTA has diagnostic accuracy (sensitivity and specificity $\geq 80\%$) equivalent to conventional angiography for confirming or ruling out hemodynamically significant stenoses (≥ 50 diameter reduction) or occlusions at all levels from the abdominal aorta to the arteries of the lower leg and foot (Evidence Grade 2).
- CTA as a basis for choosing a treatment strategy in peripheral arterial disease is basically as certain as conventional angiography ($\geq 80\%$ agreement or kappa value > 0.6) (Evidence Grade 2).

Treating Symptomatic Peripheral Arterial Disease

Comprehensive treatment of risk factors for cardiovascular disease in patients with atherosclerosis was not part of the systematic review in this report, but is discussed only in a general way with reference to overviews and national guidelines.

That smoking cessation is the most important measure for treating all types of vascular disease cannot be overemphasised.

Regular physical exercise and walking training alleviates the symptoms of existing peripheral arterial disease. Weight loss and physical activity also improve risk factors such as hypertension, high lipids and high blood sugar.

All lifestyle changes should be regarded as a long-term investment, not as temporary restrictions or attitudes.

The specific treatments for symptomatic peripheral arterial disease reviewed by this report are certain drug therapies, physical methods, natural remedies and alternative therapies, as well as invasive treatment or revascularisation in order to improve blood flow. Following is a summary of the report's most important conclusions about treatment.

Drug therapies, Physical Methods, Natural Remedies and Alternative Therapies

Walking Training for Intermittent Claudication

Walking training increases walking distance in patients with intermittent claudication. The scientific evidence is based primarily on supervised training (Evidence Grade 2).

Antihypertensives

Many patients with peripheral arterial disease also have hypertension and are treated with antihypertensives, primarily to minimise the risk of myocardial infarction and stroke. Because lower blood pressure also means reduced blood flow, attempts have been made to ascertain whether there is any scientific evidence for choosing or ruling out certain groups of antihypertensives in patients with peripheral arterial disease. The systematic review of the literature reveals a lack of scientific evidence for assessing the differences among various groups of antihypertensive drugs in that respect.

Anticoagulants

Scientific evidence is lacking to assess the efficacy of anticoagulants (unfractionated or low molecular heparin and vitamin K antagonists) for intermittent claudication and the healing of diabetic foot ulcers.

Prostanoids

Prostanoids have been used to treat peripheral arterial disease, primarily because several substances in the group have a dilatory effect on small blood vessels. There is limited scientific evidence that intravenous prostaglandin E₁ increases walking distance in patients with intermittent claudication (Evidence Grade 3).

Infusions of iloprost, a prostacyclin analogue, for at least two weeks in chronic critical limb ischaemia patients has a positive impact on the risk of amputation, as well as the aggregate effect variable of amputation and death (Evidence Grade 3).

Sex Hormones

Scientific evidence is lacking to assess the benefits of treating peripheral arterial disease with either oestrogen preparations or testosterone.

Pentoxifyllin

Pentoxifyllin has been approved in the United States and several European countries for treatment of intermittent claudication and venous leg ulcers. The preparation may be subscribed in Sweden under licence. The review of the literature showed no significant difference between the efficacy of pentoxifyllin and placebo for improving walking distance in intermittent claudication (Evidence Grade 2).

Chelators

Chelator therapy is based on the hypothesis that the injection of ethylenediamine tetraacetate (EDTA), which binds calcium ions, can reduce atherosclerosis and thereby the symptoms. But there is no scientific evidence to assess the efficacy of the therapy in intermittent claudication.

Hyperbaric Oxygen Therapy

Hyperbaric (decompression chamber) oxygen therapy has been used as an adjunct to established wound treatment and is alleged to promote healing of chronic wounds. The method lacks admissible scientific evidence.

Spinal Cord Stimulation

Spinal cord stimulation was used chiefly in the 1980's in an attempt to alleviate pain and improve blood flow in critical limb ischaemia when surgical reconstruction was not feasible. The method is costly, and scientific evidence is lacking to assess its analgesic effect or its ability to reduce the risk of amputation.

Electromagnetic Therapy

Electromagnetic therapy has been marketed in the Swedish press as a method of improving poor blood flow in the legs. Scientific evidence is lacking.

Natural Remedies and Alternative Therapies

Traditional medicine has used various herbal extracts and preparations for centuries. There is limited scientific evidence that Ginkgo biloba (an extract of dried leaves) improves initial walking distance (Evidence Grade 3). Scientific evidence is lacking to assess the efficacy of Padma 28 (a Tibetan preparation of some 20 herbs), garlic, Omega-3, vitamin E and vitamin B/folic acid.

There is limited scientific evidence that levocarnitine, which is synthesised in the liver and kidney and assists in metabolism of fatty acids, can increase maximum walking distance in intermittent claudication (Evidence Grade 3).

Scientific evidence is lacking to assess the efficacy of ultraviolet light therapy and intermittent pneumatic compression, both of which are alternative therapies.

Invasive Treatment

Revascularisation to improve blood flow can be either open or endovascular.

Open revascularisation is surgical reconstruction of the artery by means of bypass or endarterectomy. Bypass involves rerouting the stenosis or blockage using a vein or synthetic vascular prosthesis, whereas endarterectomy involves peeling the blockage away from the artery.

Endovascular revascularisation is a minimally invasive procedure with small incisions and various techniques to treat the stenosis or blockage through a catheter in the artery: percutaneous transluminal angioplasty (PTA), stenting (implantation of a wire mesh tube) or thrombolysis – a therapy that uses a thrombolytic (thrombus dissolving) agent. Endovascular intervention is often gentler and less risky than open surgery.

Various invasive procedures are frequently combined to achieve successful results.

Without the use of anticoagulants, no revascularisation method – whether open or endovascular – is clinically feasible.

Following is a summary of the report's key conclusions about invasive treatment for symptomatic peripheral arterial disease:

- Open revascularisation improves walking distance better than walking training in claudication patients for whom invasive treatment is indicated (Evidence Grade 3).

- The scientific evidence is insufficient to assess whether open revascularisation reduces the risk of amputation in patients with chronic critical limb ischaemia.
- The scientific evidence is insufficient to assess the efficacy of endovascular revascularisation in patients with intermittent claudication and chronic critical limb ischaemia.
- Active treatment of acute lower limb ischaemia leads to amputation-free survival after one year in 65–80% of cases. There is no decisive difference between open and endovascular revascularisation (thrombolysis therapy) in terms of amputation-free survival (Evidence Grade 2).
- The amputation incidence after active treatment in patients with acute lower limb ischaemia is 3–12% after 30 days and 10–30% after one year. Following treatment for acute lower limb ischaemia, 4–11% of patients die within 30 days and 6–42% within one year (Evidence Grade 2).
- Patients with milder forms of ischaemia – either in terms of duration (1–2 weeks) or clinical degree (without blisters or muscle soreness) – have a higher incidence of amputation-free survival (Evidence Grade 3).
- No decisive differences in treatment results have been found between thrombosis, embolism and graft occlusion – three separate causes of acute limb ischaemia (Evidence Grade 3).
- The scientific evidence is insufficient to assess whether various techniques of catheter-delivered endovascular therapy (thrombolysis) yield similar results.
- Catheter-delivered endovascular therapy (thrombolysis, locally and arterially) gives rise to a higher incidence of local bleeding

than open revascularisation in acute occlusion (lower limb ischaemia) (Evidence Grade 3).

- The scientific evidence is insufficient to determine whether increased vascular surgery can reduce the number of amputations in the general population.
- A platelet inhibitor increases the percentage of open bypass reconstructions below the groin (Evidence Grade 3).
- Therapy with a vitamin K antagonist does not appear to be more effective than platelet inhibitors with respect to open reconstruction (Evidence Grade 3).
- Bleeding complications more frequently accompany therapy with a vitamin K antagonist than with a platelet inhibitor (Evidence Grade 2).
- Open or endovascular revascularisation improves quality of life in patients who have peripheral arterial disease, with intermittent claudication and chronic critical limb ischaemia (Evidence Grade 3). However, complication risks must be considered.

Health Economic Aspects

Through both concrete measurements and modelling, health economic studies explore the relative costs and benefits (cost-effectiveness) of various diagnostic and treatment methods. When it comes to peripheral arterial disease, the number of studies with good quality is limited, only a handful of questions have been addressed, and the results are sometimes contradictory or inapplicable to Swedish conditions.

MRA is a cost-effective diagnostic alternative to conventional angiography when designing a treatment strategy for peripheral arterial disease.

Compared to other methods, PTA with selective stent implantation is a cost-effect treatment strategy for patients who have intermittent claudication.

Ethical Aspects

Most people who develop peripheral arterial disease are elderly with concurrent cardiovascular or cerebrovascular conditions due to general atherosclerosis. Because their biological age is often greater than their chronological age, they have a shorter than average life expectancy for their peer group. Patients with acute limb ischaemia and chronic critical limb ischaemia live with stubborn pain and often face the imminent threat of amputation. They are a weak social group with limited ability to make their voices heard or assert their rightful needs and interests.

Ethical considerations constantly accompany patients with peripheral arterial disease in their experience of the healthcare system, from primary care to invasive treatment. Diagnoses may raise unrealistic expectations, indications may change, reconstructive therapy may be risky, and the patients may be both undertreated and overtreated. While the interests of patients, research and the market may be difficult to separate, it is important to uphold the ethical principle that the lines between them be clearly demarcated.

Knowledge Gaps and Future Research

Looking back at SBU's 1990 review, "Vascular Surgery and Atherosclerosis of the Lower Extremities" (published in Swedish only), which was approved by the SBU Board of Directors, the following remarks may be of interest and relevance in 2007 as well.

The smoking cessation requirement remains. There is scientific evidence for walking training in the treatment of intermittent claudication (Evidence Grade 2).

Revascularisation should usually be avoided for claudication but offered for critical limb ischaemia when there is a threat of amputation, but the scientific evidence is still insufficient to deter-

mine whether increased vascular surgery reduces the number of amputations in the population.

Vascular surgery services should be consolidated, but the arguments for doing so must be based on considerations other than scientific evidence.

Results should be reported to a central registry. Open and endovascular revascularisation are reported to the Swedish Vascular Registry (Swedvasc), while amputations are reported only as a complication following vascular surgery.

The assessment of new technologies still suffers from inadequacies. This report's methodology section addresses the problem in greater detail. As with all new treatment technologies, a systematic effort to deal with the issue should be given high priority.

Like other technologies, new grafts must be subject to well-designed clinical trials.

The scientific literature for a comprehensive assessment remains insufficient. That fact is reflected in the extensive literature identified by our searches, of which few studies met SBU's criteria for high or medium quality and relevance. Health economic assessments were few.

Interventions to prevent early atherosclerosis fall outside the purview of this report.

Concerning physical activities the report found scientific evidence that supervised walking, training, primarily in a group, increases walking distance for patients with claudication (Evidence Grade 2).

Multicentre randomised trials could be arranged in Sweden to address two key questions:

- Which therapy is better for intermittent claudication – intervention or walking training and best medical practice?
- Which therapy is better for critical limb ischaemia – surgical/endovascular intervention or best medical practice?

Reports *published by SBU*

SBU Reports in English

Dementia, three volumes (2008), no 172E

Obstructive Sleep Apnoea Syndrome (2007), no 184E

Interventions to Prevent Obesity (2005), no 173E

Moderately Elevated Blood Pressure (2004), Volume 2, no 172/2

Sickness Absence – Causes, Consequences, and Physicians' Sickness Certification Practice, Scandinavian Journal of Public Health, suppl 63 (2004), 167/suppl

Radiotherapy for Cancer (2003), Volume 2, no 162/2

Treating and Preventing Obesity (2003), no 160E

Treating Alcohol and Drug Abuse (2003), no 156E

Evidence Based Nursing: Caring for Persons with Schizophrenia (1999/2001), no 4E

Chemotherapy for Cancer (2001), Volume 2, no 155/2

CABG/PTCA or Medical Therapy in Anginal Pain (1998), no 141E

Bone Density Measurement, Journal of Internal Medicine, Volume 241 Suppl 739 (1997), no 127/suppl

Critical Issues in Radiotherapy (1996), no 130E

Radiotherapy for Cancer, Volume 1, Acta Oncologica, Suppl 6 (1996), no 129/1/suppl

Radiotherapy for Cancer, Volume 2, Acta Oncologica, Suppl 7 (1996), no 129/2/suppl

Mass Screening for Prostate Cancer, International Journal of Cancer, Suppl 9 (1996), no 126/suppl

Hysterectomy – Ratings of Appropriateness... (1995), no 125E

Moderately Elevated Blood Pressure, Journal of Internal Medicine, Volume 238 Suppl 737 (1995), no 121/suppl

CABG and PTCA. A Literature Review and Ratings... (1994), no 120E

Literature Searching and Evidence Interpretation (1993), no 119E

Stroke (1992), no 116E

The Role of PTCA (1992), no 115E

The Problem of Back Pain – Conference Report (1989), no 107E

Preoperative Routines (1989), no 101E

SBU Summaries in English (1999–2008)

Peripheral Arterial Disease – Diagnosis and Treatment (2008), no 510-42

Tympanostomy Tube Insertation for Otitis Media in Children (2008), no 510-40

Caries – Diagnosis, Risk Assessment and Non-Invasive Treatment (2008), no 510-39

Moderately Elevated Blood Pressure (2007), no 510-41

Methods of Early Prenatal Diagnosis (2007), no 510-38

Light Therapy for Depression and Other Treatment of Seasonal Affective Disorder (2007), no 510-37

Dyspepsia and Gastro-oesophageal Reflux (2007), no 510-36

Obstructive Sleep Apnoea Syndrome (2007), no 510-35
Benefits and Risks of Fortifying Flour with Folic Acid to Reduce the Risk of Neural Tube Defects (2007), no 510-34
Methods of Promoting Physical Activity (2007), no 510-33
Mild Head Injury – In-hospital Observation or Computed Tomography? (2007), no 510-32
Methods of Treating Chronic Pain (2006), no 510-31
Malocclusions and Orthodontic Treatment in a Health Perspective (2005), no 510-30
Psychiatric Risk Assessment Methods – Are Violent Acts Predictable? (2005), no 510-29
Treatment of Anxiety Disorders (2005), no 510-28
Interventions to Prevent Obesity (2005), no 510-27
Chronic Periodontitis – Prevention, Diagnosis and Treatment (2004), no 510-26
Moderately Elevated Blood Pressure (2004), no 510-25
Treatment of Depression (2004), no 510-24
Prescribed Sick Leave – Causes, Consequences, and Practices (2004), no 510-23
Osteoporosis – Prevention, Diagnosis and Treatment (2003), no 510-22
Radiotherapy for Cancer (2003), no 510-21
Hearing Aids for Adults (2003), no 510-20
Prevention of Dental Caries (2002), no 510-19
Prevention, Diagnosis & Treatment of Venous Thromboembolism (2002), no 510-18
Obesity – Problems and Interventions (2002), no 510-17
Hormone Replacement Therapy (2002), no 510-16
Treatment of Alcohol and Drug Abuse (2001), no 510-15
Chemotherapy for Cancer (2001), no 510-14
Treatment of Asthma and COPD (2000), no 510-13
Dyspepsia – Methods of Diagnosis and Treatment (2000), no 510-12
Back Pain, Neck Pain (2000), no 510-11
Urinary Incontinence (2000), no 510-9
The Patient–Doctor Relationship (2000), no 510-8
Prognostic Methods for Acute Coronary Artery Disease (1999), no 510-10

SBU Alert Reports

Early assessment of new health technologies. Find them at www.sbu.se/alert in PDF format.

To Order SBU Reports?

All SBU reports are published in Swedish. The summaries and a few reports are also published in English. Summaries and reports can be ordered at www.sbu.se, by e-mail (info@sbu.se), by phone (+46-8-412 32 00) or by fax (+46-8-411 32 60).

SBU Evaluates Health Care Technology

Below is a brief summary of the mission assigned to SBU by the Swedish Government:

- SBU shall assess healthcare methods by systematically and critically reviewing the underlying scientific evidence.
- SBU shall assess new methods as well as those that are already part of established clinical practice.
- SBU's assessments shall include medical, ethical, social and economic aspects, as well as a description of the potential impact of disseminating the assessed health technologies in clinical practice.
- SBU shall compile, present and disseminate its assessment results such that all parties concerned have the opportunity to take part of them.
- SBU shall conduct informational and educational efforts to promote the application of its assessments to the rational use of available resources in clinical practice, including dental care.
- SBU shall contribute to the development of international co-operation in the field of health technology assessment and serve as a national knowledge centre for the assessment of health technologies.

Peripheral Arterial Disease – Diagnosis and Treatment

The SBU report is based on a systematic and critical review of the scientific literature. It is one of a series of scientific reports published by SBU (The Swedish Council on Technology Assessment in Health Care).

The Summary and Conclusions of the report, presented in this booklet, have been approved by the SBU Board of Directors and the Scientific Advisory Committee.