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1. Introduction

Peripheral arterial occlusive disease (PAOD) commonly results from progressive narrowing or occlusion of arteries in the lower extremities mostly due to atherosclerosis. The atherosclerotic process of progressive narrowing and hardening of arteries can occur in each artery in the human body, however it mainly affects coronary, cerebral and peripheral arteries especially those in the lower extremities(1). The preferential sites of involvement of PAOD are the femoral and popliteal arteries in 80-90%, the tibial and peroneal arteries in 40-50% and in 30% the aorta and iliac arteries(2). The manifestation of PAOD ranges from no symptoms to tissue loss that may eventually requires amputation of an affected limb. The majority of patients with PAOD have asymptomatic or atypical disease (figure 1).

Total disease prevalence based on objective testing has been evaluated in several epidemiologic studies and ranges from 3% to 10% in adults, increasing to 15 to 20% in persons over 70 years. PAOD increases progressively with age, beginning after the age of 40(3). The relationship between PAOD prevalence and age was illustrated on data from the 1999–2000 National Health and Nutrition Examination Survey (NHANES), an ongoing cross-sectional survey of the civilian, non-institutionalized population of the United States. The prevalence of PAOD, defined as an ankle-brachial index (ABI) <0.90 in either leg, was 0.9% between the ages of 40-49, 2.5% between the ages of 50-59, 4.7% between the ages of 60-69, and 14.5% in ages 70 and older(3). These numbers indicate that PAOD affects more than 5 million adults in the United States, while international guidelines reveal some 27 million affected individuals in North America and Europe(1). The PARTNERS study (PAOD Awareness, Risk, and Treatment: New Resources for Survival) screened 6979 subjects for PAOD using the ABI (with PAOD defined as an ABI of ≤0.90 or a prior history of lower extremity revascularization)(4). Subjects were evaluated in primary care practices in the
United States if they were above 70 years of age or between 50–69 years when presenting with a risk factor for vascular disease (smoking, diabetes). PAOD was detected in 1865 patients (29% of the cohort). Classic claudication or symptomatic PAOD was present in only 5.5% of the newly diagnosed patients with PAOD. Some 12.6% of the patients with a prior diagnosis of PAOD had claudication. Other studies have evaluated symptomatic and asymptomatic PAOD 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(1). It may be concluded that PAOD is still growing as a clinical problem due to the increasingly aged population in developed countries.

Legend to figure: PAD – peripheral arterial disease; CLI – critical limb ischemia; CV – cardiovascular; MI – myocardial infarction.

**Figure 1.** 5 years disease prognosis in claudicants (adapted from TASC II guidelines (1)).

### 2. Etiology of symptomatic PAOD (Intermittent Claudication)

50 – 80% of PAOD patients are symptomatic and because of their complaints most of them will present themselves at a patient outdoor clinic. Symptomatic PAOD patients will have in 20-50% of the cases symptoms of typical intermittent claudication (IC, which means ‘to limp’) (figure 1). IC is defined as muscle discomfort in the lower limb reproducibly elicited by exercise and relieved by rest within 10 minutes(1).

Patients with IC have sufficient blood flow at rest and, therefore do not experience limb symptoms at rest. With exercise, occlusive or narrowing lesions in the arterial supply of the leg muscles limit the increase in blood flow resulting in a mismatch of oxygen supply and
muscle metabolic demand that is associated with the symptom of claudication. This mismatch causes cramping or aching pain in the buttock, hip, thigh, calf or in rare occasions the foot, forcing the patient to pause. In rest, the oxygen debt can be redeemed and symptoms are relieved. In women, the incidence rates of IC are approximately 50% lower than in men(5). IC has an approximately 3% prevalence in the general population in patients aged 40 up to 6% in patients aged 60 years and increasing in older age(1).

### Vascular origin - Major causes
- Atherosclerosis
- Thrombosed aneurysm
- Arterial injury
- Arterial dissection
- Atheroembolism
- Thromboembolism
- Thromboangitis obliterans (Buerger’s disease)

### Vascular origin - Other causes
- Aorto-iliac
  - Retroperitoneal fibrosis
  - Radiation fibrosis
  - Tumor
  - Takayas’ disease
- Iliac
  - Fibromuscular dysplasia
  - Iliac endofibrosis (athletic injury)
- Iliofemoral
  - Pseudoxanthoma elasticum
- Popliteal
  - Popliteal entrapment
  - Adventitial cystic disease

### Table 1. Etiology of lower extremity ischemia
- Nerve root compression
- Spinal stenosis
- Hip / foot arthritis
- Arthritic, inflammatory processes
- Compartment syndrome
- Venous claudication
- Symptomatic Bakers cyst

### Table 2. Common differential diagnoses of non – vascular origin.
Eventually any process that results in arterial stenosis or occlusion can cause symptoms of claudication, ischemic pain, or tissue loss but the vast majority of patients with claudication suffer from atherosclerosis. Aetiologies of lower extremity ischemia due to arterial stenosis or occlusion other than atherosclerosis are shown in table 1.

Arterial aneurysms can be the source of embolic debris leading to arterial obstruction resulting in symptoms of lower extremity ischemia. Popliteal entrapment syndrome can also present with IC and should be suspected in the young patient who presents with claudication but lacks atherosclerotic risk factors. In endurance athletes, especially cyclists, an even more unusual cause of claudication is due to repeated trauma (stretching or kinking) of the external iliac artery which can result in endofibrosis of the vessel(6).

Other diseases of non-vascular origin should also be considered in the differential diagnosis of leg pain (table 2). These include neurological, musculoskeletal and venous disorders. Neurological pain (“spinal claudication”) is predominantly due to neurospinal (eg, disc disease, spinal stenosis, tumor) or neuropathic causes (eg, diabetes, alcohol abuse). Musculoskeletal pain derives from the bones, joints, ligaments, tendons, and fascial elements of the lower extremity. Clinical history taking and physical examination can help distinguish between some of the less common causes of these disorders, which is important to instate an effective treatment for a patient with IC complaints.

3. Prognostics and mortality

PAOD and IC are strong predictors for coinciding atherosclerotic disease and related mortality. The prevalence of cerebrovascular disease in patients with PAOD is about 25-50%(7). The 10-year mortality rate due to cardiovascular disease is 62% for men with PAOD compared to 17% in the population of men without PAOD. For women with PAOD the 10-year mortality rate is 33% compared to 12% without PAOD(8). In a subgroup of patients with severe and symptomatic PAOD a 15-fold increase in mortality rate was found(8).

For IC, a 5-year mortality rate of 19.2 % is described, of which 70% is due to cardiovascular causes. Non-fatal cardiovascular events (e.g. myocardial infarction, stroke) in patients with IC are found in 29% at 5 years of follow-up(5). Compared to patients with IC, subjects with asymptomatic PAOD appear to have the same increased risk of cardiovascular events and death(5). Nonetheless, for those afflicted, IC impacts negatively on walking ability and health-related quality of life (QoL)(9, 10).

4. General management of PAOD

PAOD comes with serious health risks. An overall strategy and basic treatment is well described in several international guidelines like the American College of Cardiology/ American Heart Association (ACC/AHA) and Trans-Atlantic Inter-Society Consensus on Management of Peripheral Arterial Disease (TASC II)(1, 11). Treatment of PAOD should consist of a multicomponent therapy of cardiovascular risk reduction (1) including lifestyle coaching (2) and symptomatic treatment (3). The first two components aim to
prevent cardiovascular events (myocardial infarction, stroke) and related morbidity and mortality. The most important modifiable risk factors for atherosclerosis are smoking, hypertension, diabetes mellitus, hyperlipidemia and obesity(12). The third component is to improve QoL and realized with daily exercise supplemented with supervised exercise therapy (SET).

5. Smoking cessation

Smoking is a potent risk factor for symptomatic PAOD, with an important and consistent dose-response relationship(13). The prevalence of symptomatic PAOD was increased 2.3-fold in current smokers. Even in former smokers the prevalence was substantially increased by a factor of 2.6. Smoking cessation is associated with a decline in the incidence of IC. Results from the Edinburgh Artery Study 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)(1). In a meta-analysis of 12,603 smokers who had prior MI, CABG, angioplasty, or known coronary heart disease, the relative risk of mortality for quitters compared with those who continued to smoke was 0.64 (95% CI 0.58-0.71)(14). Observational studies have found that the risk of death, myocardial infarction and amputation is substantially greater, and lower extremity angioplasty and open surgical revascularization patency rates are lower in individuals with PAOD who continue to smoke than in those who stop smoking(15). Efforts to achieve smoking cessation are recommended for patients with lower extremity PAOD(13). A physician advice coupled with frequent follow-up achieves 1-year smoking cessation rates of approximately 5% compared with only 0.1% in individuals who try to quit smoking without a physician’s intervention(16). In patients with PAOD, comprehensive smoking cessation programs that included individualized counseling and pharmacological support significantly increased the rate of smoking cessation at 6 months compared with verbal advice to quit smoking (21.3% versus 6.8%, p<0.02)(17). Therefore the focused update of the guideline for the management of smoking patients recommended that current smokers or former smokers should be asked about their status of tobacco use at every visit (Level of Evidence: A). Furthermore patients should be assisted with counseling and developing a plan for quitting that may include pharmacotherapy and/or referral to a smoking cessation program(15).

6. Hypertension

Hypertension is a major risk factor for PAOD. However, data evaluating whether antihypertensive therapy alters the progression of claudication are lacking. Nevertheless, international guidelines support the treatment of hypertension in patients with PAOD to reduce morbidity from cardiovascular and cerebrovascular disease. In this high-risk group the current recommendation is a goal of 140/90 mmHg, or even 130/80 mmHg if the patient also has diabetes or renal insufficiency. In PAOD, thiazides and ACE inhibitors should be considered as initial blood-pressure lowering drugs to reduce the risk of cardiovascular events. Beta-adrenergic blocking drugs have been discouraged in PAOD because of the possibility of worsening claudication symptoms. In a Cochrane review there was no
supporting evidence that beta blockers adversely affect walking distance in people with IC(18). However, due to the lack of large published trials beta blockers should be used with caution but are not contraindicated in PAOD.

7. Diabetes mellitus

Diabetes increases the risk of PAOD approximately three- to four-fold, and the risk of claudication two-fold. Diabetes is also associated with peripheral neuropathy which may lead to an increased risk of foot ulcers and foot infections. In recent years, there has been much discussion about the optimal treatment strategy of type 2 diabetes mellitus, aggressive or standard glucose lowering therapy. In a meta-analysis, an intensive glucose lowering regime (glycated haemoglobin level below 6.0%) was compared to standard therapy (targeted a level of 7.0-7.9%) in type 2 diabetes mellitus. Overall, intensive therapy significantly reduced coronary events without a significant effect on events of stroke or all-cause mortality(19). However, aggressive control of blood glucose levels (glycated haemoglobin level below 6.0%) is not recommended. The long term results of intensive therapy described a significantly reduced nonfatal myocardial infarction risk but an increased all-cause mortality rate (hazard ratio 1.21; 95% C.I. 1.02-1.44) after 5-year related with aggressive glucose lowering(20). TASC II recommends moderate aggressive control of blood glucose levels with an A1C goal of <7.0% and as close to 6.0% as possible (but not below 6%)(1).

8. Hyperlipidemia

In case of hyperlipidemia, dietary modification should be the initial intervention to control abnormal lipid levels. A 2007 Cochrane meta-analysis of mostly older trials that specifically evaluated patients with lower limb atherosclerosis concluded that lipid-lowering therapy reduced disease progression (improvement in total walking distance (Mean Difference (MD) 152 m; 95% CI 32.11 to 271.88) and pain-free walking distance (WMD 89.76 m; 95% CI 30.05 to 149.47) but no significant impact on ankle brachial index (WMD 0.04; 95% CI -0.01 to 0.09)(21). It was concluded that lipid-lowering therapy is effective in reducing cardiovascular mortality and morbidity in people with PAOD. It may also improve local symptoms. Until further evidence on the relative effectiveness of different lipid-lowering agents is available, use of a statin in people with PAOD and a blood total cholesterol level ≥ 3.5 mmol/litre is indicated. One of the largest included studies in this Cochrane review, the Heart Protection Study demonstrated the benefits of cholesterol-lowering statin therapy in 6.748 patients with PAOD and 13.788 other high-risk participants, allocation to 40 mg simvastatin daily reduced the rate of the first major vascular events by about one-quarter, and that of peripheral vascular events by about one-sixth, with large absolute benefits seen in participants with PAOD because of their high vascular risk. Consequently, according to this study statin therapy should be considered for all patients with PAOD (all patients with total cholesterol level ≥ 3.5 mmol/L). This is in contrast to the older ACC/AHA guidelines as they recommended achieving an LDL cholesterol level <2.59 mmol/L (<100 mg/dL) in all patients with PAOD. In patients with PAOD and a history of other vascular disease (i.e.,
coronary heart disease and cerebrovascular disease) it is reasonable to lower LDL cholesterol levels to 1.81 mmol/L (70 mg/dL)(11). Statins should be the primary lipid-lowering agents to lower LDL cholesterol levels.

9. Blood homocysteine

Elevated homocysteine blood levels are associated with cardiovascular disease but it is uncertain whether this association is causal. Studies investigating the effects of folic acid supplementation on major vascular events in patients with peripheral arterial disease are lacking. However, long-term reductions in blood homocysteine levels with folic acid and vitamin B12 supplementation did not lead to a reduction of cardiovascular events and seems therefore not indicated according to a RCT including 12,064 survivors of myocardial infarction (22).

10. Antiplatelet therapy

Antiplatelet therapy reduces major vascular events (vascular death, nonfatal MI and nonfatal stroke) in patients with PAOD by 23%(23). Therefore, all symptomatic patients with or without a history of other cardiovascular disease should be prescribed antiplatelet therapy on the long term. Antiplatelet therapy is indicated to reduce the risk of MI, stroke and vascular death in individuals with symptomatic atherosclerotic lower extremity PAOD, including those with claudication. Aspirin is the antiplatelet agent of choice; clopidogrel may be used if aspirin cannot be tolerated or in the subgroup of patients with symptomatic PAOD(1). Unfortunately, adherence to cardiovascular medication is fairly low(24). Self-reported consistent use (reported on ≥2 consecutive follow-up surveys and then through death, withdrawal, or study end) of cardiovascular medication was analysed using the Duke Databank for Cardiovascular Disease in patients with coronary artery disease with or without heart failure. In 2002, consistent use was reported: for aspirin, 71%; beta-blockers, 46%; lipid-lowering therapy, 44%; aspirin and beta-blockers, 36%; and all three, 21%. For these reasons the assessment of medication compliance should be incorporated in the standard care for patients with PAOD, which is not the case in contemporary guidelines.

11. Pharmacological therapy for Intermittent Claudication

Pharmacologic treatment for relief of claudication symptoms typically involves other drugs than those used for risk reduction. Cilostazol is currently the most effective drug for IC(25). Approved by the FDA in 1999, the primary action of cilostazol is to inhibit phosphodiesterase type 3, which results in vasodilatation and inhibition of platelet aggregation, arterial thromboses and vascular smooth muscle proliferation. A three to six-month course of cilostazol is a possible first line pharmacotherapy for the relief of claudication symptoms. One study with 2702 patients having stable moderate to severe claudication were randomly assigned to cilostazol or placebo. Patients treated with 100 mg cilostazol twice daily for 12 to 24 weeks experienced significantly greater increases in
maximal and pain-free walking distances (50% and 67%, versus 22% and 40%, respectively) compared to the placebo group(25). Naftidrofuryl can also be considered. In a meta-analysis, naftidrofuryl showed an clinically meaningful improvement in pain-free and maximum walking distance in patients with IC(26). It is a 5-hydroxytryptamine type 2 antagonist and may improve muscle metabolism and reduce erythrocyte and platelet aggregation. Approval of cilostazol or naftidrofuryl for IC is however limited to certain countries.

Other treatments are described such as the use of pentoxifylline (Trental). Pentoxifylline is a rheologic modifier approved by the FDA for the symptomatic relief of claudication. Its mechanism of action includes an increase in red blood cell deformity whereas it decreases fibrinogen concentration, platelet adhesiveness, and whole-blood viscosity. The available data indicate that the benefit of pentoxifylline is marginal and not well established(11).

Ginkgo biloba has been studied in patients with claudication with modest success. The mechanism by which ginkgo may work in this disorder is unclear, but may involve a number of activities including an antioxidant effect, inhibition of vascular injury, and antithrombotic effects. In a meta-analysis of 11 trials, patients who received ginkgo biloba extract had no significant differences in initial claudication distance. However, a trend toward improvement in the absolute claudication distance was observed. With the treadmill distances standardized between the protocols, a mean difference of 3.57 (95% CI -0.10-4.19) was found that corresponded to about 200 feet (64 meters), but the difference was not significant(27). The TASC guidelines concluded that no effect was proven(1).

Several studies have evaluated the role of Vitamin E, chelation therapy, omega-3 fatty acids and estrogen therapies in the treatment of claudication. However, none of these therapies appeared effective(1).

12. Exercise therapy

Exercise therapy is the first suggested therapy for patients with IC. In 1898 the German neurologist Wilhelm Erb described successful results of exercise therapy for a patient with IC(28). The first randomised clinical trial (RCT) was performed by Larsen et Lassen in 1966(29). In this study, 7 patients treated with exercise therapy were compared with a control group of 7 patients who were given ‘medical treatment’ in the form of lactose tablets. For the group treated with exercise, a significant increase in maximum walking time was observed whereas the patients in the control group did not improve.

Nowadays, exercise therapy for patients with IC is extensively studied. In a Cochrane review by Watson et al. exercise therapy was compared with usual care or placebo regarding data of functional capacity outcome measurements(30). A total of twenty-two trials met the inclusion criteria involving a total of 1200 participants. Compared to placebo and usual care, exercise therapy significantly improved maximal walking time with a mean difference of 5.12 minutes (95% confidence interval 4.51 – 5.72) and an improved maximum walking distance of 113.2 metres (range 95.0 to 131.4). Exercise therapy also showed a positive effect on the reduction of cardiovascular risk factors including hypercholesterolemia, hypertension, and diabetes mellitus.
The most common exercise therapy prescription consists of a single oral advice, usually without supervision or follow-up. The adherence of patients given an oral exercise advice appears to be low. Comorbidity, lack of (specific) advice, fear, and lack of discipline and supervision are barriers to actually perform regular walking exercise(31). For these reasons the importance of supervision was recognised.

13. Supervised exercise therapy vs usual care (exercise therapy)
Supervised exercise therapy (SET) entails adequate coaching by a physical therapist (PT) or an other exercise specialist (e.g. exercise physiologist, exercise therapist, specialised cardiovascular nurse) and aims to increase maximal walking distance, physical activity and health-related QoL. The most effective programs employ treadmill walking of sufficient intensity to cause claudication symptoms. Exercise is continued till near maximum pain, followed by rest, and then a next cycle of exercise is started over the course of a 30–60 minute session. During the exercise session, treadmill exercise is performed at a speed and grade that will induce claudication symptoms. 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). Exercise sessions are typically conducted three times a week for 3 months. A Cochrane review by Bendermacher et al. compared SET with non-supervised exercise programmes for patients with IC(32). SET showed statistically significant and clinically relevant differences in improvement of maximal walking distance compared with non-supervised exercise therapy regimens, with an overall effect size of 0.58 (95% confidence interval 0.31 to 0.85) at three months. This translates into an improvement of approximately 150 meters of maximum walking distance in favour of the supervised group. However, additional studies on QoL are needed to definitely demonstrate clinical effectiveness.

Another systematic meta-analysis comparing supervised to unsupervised exercise therapy showed a weighted mean difference in Pain Free Walking Distance (PWD) of 143.8 meters (95% CI; 5.8e281.8) and 250.4 meters (95% CI; 192.4-308.5), respectively. The authors concluded that SET increased the PWD and AWD more than standard care(33). In a recent randomized controlled trial, three groups were compared: usual care (walk advice), home-based exercise and supervised exercise(34). Claudication Onset Time (COT) and Peak Walking Time (PWT) were compared after 3 months. A significant improvement in COT and PWT were obtained in the exercise groups, but not in the usual care group (change after 3 months (sec): usual care; COT -16s, PWT -10s; home-based; COT 134s, PWT 124s; supervised; COT 165s, PWT 215s).

14. Supervised exercise therapy vs endovascular revascularisation
A recent systematic review compared (S)ET with percutaneous transluminal angioplasty (PTA) in patients with intermittent claudication (IC) to obtain the best estimates of their relative effectiveness(35). Eleven studies (reporting data on eight randomized clinical trials) met the inclusion criteria. One trial included patients with isolated aortoiliac artery
obstruction(36). In this MIMIC trial, patients were randomised to receive either PTA or no PTA against a background of SET and best medical therapy. The maximum walking distance was 75% greater in the PTA group (95%; CI 2-202) at 6 months and 78% greater in the PTA group (95%; CI 0-216) (p=0.05) at 24 months. No benefits were found for health-related QoL. Unfortunately this trial did not evaluate results of SET alone versus PTA alone, so there is no evidence that angioplasty alone would produce similar results.

In the review of Frans et al. three trials were included, which studied SET and PTA in femoropopliteal artery obstructions. In summary, SET with additional PTA gave the best improvement in Maximal Walking Distance (MWD), Initial Claudication Distance (ICD) and Ankle Brachial Index (ABI)(35). Changes in MWD, ICD and ABI between PTA alone and SET alone were equivocal, either comparable or in favour of PTA. QoL improved significantly during follow-up compared with baseline of all treatments, without differences between both groups.

The systematic review additionally included five trials that studied combined lesions(35). In summary, PTA plus SET compared with PTA alone demonstrated an improvement in MWD. The two trials evaluating SET versus PTA had inconsistent results: one showed a benefit in terms of MWD and ICD after SET. The other trial demonstrated equal benefit in both groups. QoL data was assessed by seven different instruments with equivalent results. In conclusion there is not yet a well defined consensus for tailoring the optimal treatment for lesions at different anatomical locations. International guidelines (TASC II) still suggests to perform revascularisation when proximal lesions are suspected instead of prescribing SET and medical therapy. Unfortunately these guidelines may seem outdated. Results described above one could conclude that, in general, the effectiveness of PTA and SET was equivalent, although PTA plus SET improved walking distance and some domains of QoL scales compared with SET or PTA alone(35). Evidence to use a combination of PTA and SET for patients with IC complaints is still inconclusive. Moreover, cost-effectiveness data is still missing.

In the United States, another large multicenter RCT was conducted(37). In this so called CLEVER trial, the researchers aimed to find the optimal treatment strategy for IC with endpoints being maximal walking duration and health-related QoL. They randomly assigned 111 patients with aortoiliac peripheral artery disease to receive 1 of 3 treatments: optimal medical care (OMC), OMC plus supervised exercise (SE), or OMC plus stent revascularization (ST). At the 6-month follow-up, the change in peak walking time (the primary end point) was greatest for SE, intermediate for ST, and least with OMC (mean change versus baseline, 5.8±4.6, 3.7±4.9, and 1.2±2.6 minutes, respectively; P<0.001 for the comparison of SE versus OMC, P<0.02 for ST versus OMC, and P<0.04 for SE versus ST). QoL improved with both SE and ST compared with OMC, for most scales, the extent of improvement was greater with ST than SE. The authors concluded that SE results in superior treadmill walking performance than ST, even for those with aortoiliac peripheral artery disease(37). The contrast between better walking performance for SE and better patient-reported quality of life for ST warrants further follow up.
In conclusion, combining results of both studies, one could suggest that all patients with symptomatic PAOD should receive SET first as part of the initial treatment regimen, even patients with proximal lesions. In case of failing (patient dissatisfaction, disappointing results) an additional PTA could be suggested. However this treatment advice is based on moderate-level evidence, therefore results of two new trials have to be awaited (see section “future perspectives”).

15. Supervised exercise therapy versus surgical reconstruction

Only one RCT compared SET to surgical reconstruction(38). This study reported the initial evaluation of treatment efficiency in 75 patients with IC who were randomized to three treatment groups: 1) reconstructive surgery, 2) reconstructive surgery with subsequent physical training, and 3) physical training alone. The walking performance was improved in all three groups at follow-up, 13±0.5 months after randomization. Surgery was most effective, but the addition of training to surgery improved the symptom-free walking distance even further. However, no significant difference was found. Moreover, a higher complication rate and 3 deaths were observed in the surgical groups while no complications occurred in the trained group. Furthermore, the methodological quality of this trial could be questioned.

16. Long term effects of supervised exercise therapy

Few studies consider the long-term (>12 months) effects of SET. Gardner et al. tried to determine whether improvements in physical function after 6 months of SET could be sustained over a subsequent 12-months in older patients with IC(39). They concluded that improvements in maximum walking distance and physical activity level, after 6 months of exercise training, were prolonged for an additional 12 months period using a less intense exercise maintenance program. Ratliff et al. reported a 3-year follow-up of 212 patients with IC who initially were treated with SET with an exercise programme of two sessions a week for 10 weeks(40). Their results show that the maximum walking distance observed at 12 weeks was still present at three years. Based on this limited experience, it appears that SET may have long term benefits for patients with IC.

17. Supervised exercise therapy in hospital or community based setting

An outpatient hospital setting was offered in the majority of all reviewed studies on SET. This approach may seem appropriate in trials but is associated with several limitations in daily clinical practise. First, the capacity of an exercise therapy program in an outpatient clinic is limited and not sufficient to provide SET for all patients with IC. Second, attending a hospital 3 times a week leads to a considerable transportation fee and is time-consuming for an individual patient. For this reason, implementation of a community-based SET program was instigated(41). The first results of a cohort study of patients treated with community-based SET resulted in a highly statistically significant improvement in
maximal walking distance (on a treadmill) after 3 and 6 months (42). The authors concluded that comparison of these results with historical studies on hospital-based SET should be done with caution due to the variability in the prescribed exercise regimens and used treadmill walking tests. However, SET in a community-based setting seemed to be at least as efficacious as programs that are provided in a clinical setting but with a higher capacity.

18. Cost effectiveness of SET

In a multicenter RCT ‘ExitPAD’ trial, Nicolaï et al. compared exercise therapy in the form of a ‘go home and walk’ advice (WA) with community-based SET for patients with IC (43). The data from this ExitPAD trial were also used to assess the cost-effectiveness of SET versus WA. For community-based SET, the incremental cost-effectiveness ratio for cost per QALY was €28,693. The Health Council of the Netherlands has determined that a QALY € 40,000 may cost if the burden of disease for symptomatic PAOD is stated at a value of 0.5. At a willingness-to-pay threshold of this €40,000 SET seemed a cost-effective therapeutic option for patients with PAOD. In another randomized cost-effectiveness analysis SET was compared with endovascular revascularization (angioplasty with or without stenting) (44). This study was unfortunately underpowered so no significant difference was obtained. Endovascular revascularization led to a non-significant increase of 0.01 in QALYs (CI - 0.05 to 0.07). However a significant difference was demonstrated with respect to treatment costs. The costs for endovascular revascularization were significantly higher with a mean difference of € 2,318 per patient. In conclusion, endovascular revascularization was found cost effective if society would be willing to pay € 231,800 per QALY. This amount is far above the threshold of € 40,000. Therefore endovascular revascularization seems not cost effective compared with SET.

Over the last decades, no international randomized cost-effectiveness analyses or health economic models were carried out to configure satisfying treatment strategies or guidelines. This while scientific evidence on the effectiveness of SET compared to endovascular revascularization has grown. Furthermore, the costs of endovascular revascularization will increase significantly as a result of technological innovations. SET seems the most cost-effective treatment for symptomatic PAOD certainly if potential positive effects due to lifestyle changes on other vascular diseases (such as heart failure, myocardial infarction, stroke) and reduction of risk factors (such as hypertension, diabetes mellitus, and hyperlipidaemia) are taken into count. Further research into the extent of cost effectiveness is an urgent need for policy choices in modern health care (see section future perspectives) (45).

19. Future perspectives

Although SET is considered the best evidence-based therapy for all patients with IC, general practitioners, vascular surgeons or vascular specialists do not always have the disposal of (community-based) physical or exercise therapists (PTs) with specific knowledge of IC or
exercise training. Also, not all PT’s have sufficient experience with this specific patient category. Patients suffer from a variety of comorbidities and modifiable lifestyle factors, potentially generating suboptimal results. Unfortunately, too many examples of PT’s treating patients with IC with massage and other alternative, non evidence based treatments exist.

In an ideal situation, all patients with symptomatic PAOD should receive an evidence based standardised form of SET by an exercise specialist. Due to lack of capacity, hospital-based exercise therapy should be reserved for cases with severe (cardiac) comorbidity. For this reason the ClaudicatioNet concept was launched in the Netherlands in January 2011. ClaudicatioNet is a concept representing an integrated care network between PTs, vascular surgeons and general practitioners. ClaudicatioNet aims to implement nationwide coverage of regional networks providing transparent, synergistic and multidisciplinary care according the guidelines of cardiovascular risk management and SET.

Two Dutch multicenter RCT’s are including patients to evaluate the effectiveness and cost-effectiveness of SET. The ERASE-trial compares SET with a PTA complementary to SET. The optimal treatment strategy for IC due to an iliac artery obstruction will be determined in the SUPER-trial. The SUPER-trial compares the (cost-) effectiveness of initial PTA versus initial SET in patients with disabling IC due to an iliac artery obstruction. Results have to be awaited.

Although there is little evidence yet, SET could also be effective for patients with critical limb ischemia as an adjuvant to a revascularisation procedure. Badger et al. evaluated the efficacy of an exercise program following arterial bypass surgery for short distance IC or critical ischemia(46). SET resulted for this group in an increased maximum walking distance of 175% compared to 4% for the group with usual care. These studies indicate that SET is a useful adjunct after a PTA or lower limb bypass surgery. In the Netherlands the PEARL study is designed to confirm the clinical effectiveness of SET after a vascular intervention for the subgroup of patients with critical limb ischemia.

Author details

H.J.P. Fokkenrood1,2, G.J. Lauret1,2, M.R.M. Scheltinga3, H.J.M. Hendriks2, R.A. de Bie2 and J.A.W. Teijink1,2

1Department of Vascular Surgery, Catharina Hospital, Eindhoven, The Netherlands
2CAPHRI Research School, Department of Epidemiology, Maastricht University, The Netherlands
3Department of Vascular Surgery, Maxima Medical Centre, Veldhoven, The Netherlands

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