Objectives: Despite limited scientific evidence for the effectiveness of invasive treatment for intermittent claudication (IC), revascularisation procedures for IC are increasingly often performed in Sweden. This randomised controlled trial compares the outcome after 2 years of primary invasive (INV) versus primary non-invasive (NON) treatment strategies in unselected IC patients.

Materials/Methods: Based on arterial duplex and clinical examination, IC patients were randomised to INV (endovascular and/or surgical, n = 100) or NON (n = 101). NON patients could request invasive treatment if they deteriorated during follow-up. Primary outcome was maximal walking performance (MWP) on graded treadmill test at 2 years and secondary outcomes included health-related quality of life (HRQL), assessed with Short Form (36) Health Survey (SF-36).

Results: MWP was not significantly (p = 0.104) improved in the INV versus the NON group. Two SF-36 physical subscales, Bodily Pain (p < 0.01) and Role Physical (p < 0.05) improved significantly more in the INV versus the NON group. There were 7% crossovers against the study protocol in the INV group.

Conclusions: Although invasive treatment did not show any significant advantage regarding MWP, the HRQL improvements associated with invasive treatment tentatively suggest secondary benefits of this regimen. On the other hand, a primary non-invasive treatment strategy seems to be accepted by most IC patients.

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Intermittent claudication (IC), occurring in 7% of individuals over the age of 60 years in Sweden, is the most frequent symptom of peripheral arterial disease (PAD). IC may cause considerable functional impairment affecting important aspects of health-related quality of life (HRQL). The prognosis for the extremity is benign, and treatment therefore aims at improved walking performance and HRQL. Most IC patients seeking medical attention are offered risk-factor management and exercise training. Regarding walking performance, there is limited evidence for the benefit of adding invasive treatment. In addition, IC patients have a high prevalence of coronary artery disease, leading to a significant risk of ischaemic cardiac events, if invasive procedures are undertaken. In spite of uncertain merits and potential risks, 37% of all open surgical and/or endovascular procedures for PAD in Sweden are performed for IC. Most controlled studies of invasive treatment for IC are performed on selected patients, with lesions in certain arterial segments, suitable for angioplasty.

The generally accepted first-line treatment strategy is medical treatment and exercise training. In our clinical routine, patients referred for IC undergo arterial duplex and a clinical examination and, thereafter, usually a primary non-invasive, or, in some cases, an invasive, treatment strategy is chosen. The aim of this randomised controlled study was to test the hypothesis that a primary invasive surgical/endovascular treatment strategy versus a primary non-invasive strategy improves maximal walking performance (MWP) in unselected patients receiving best medical treatment (BMT) and non-supervised exercise training.

Materials and Methods

Study population, general design and inclusion/exclusion criteria

This prospective, randomised, controlled trial during an initial phase started as a regional multicentre study coordinated at the Vascular Surgical Department at Sahlgrenska University Hospital, Gothenburg, Sweden. During the initial period, 20 of the patients were included and treated in two other hospitals. For logistic reasons, the study subsequently became a single-centre study at the Sahlgrenska University Hospital.

Patients with IC symptoms >6 months were first interviewed and examined by a senior vascular surgeon, who established the diagnosis and assessed risk at the outpatient clinic. All referred IC patients were screened for inclusion in the present study. Patients >85 years, or with incorrect diagnosis and/or other disorders limiting walking performance were excluded as were patients with two or more previously occluded vascular reconstructions. Employees unable to work because of IC and patients with subcritical ischaemia and/or with aortic thrombosis were offered invasive treatment. Patients only seeking advice were offered non-invasive treatment.

The remaining IC patients were eligible for inclusion. These patients underwent duplex ultrasound of the aorto-iliac and femoro-popliteal arterial segments and a treadmill test.

Eligible patients giving informed consent, and who on duplex ultrasound from the infrarenal aorta to the tibioperoneal trunk had treatable lesions in or proximal to the tibioperoneal trunk, were randomised to invasive (INV) or non-invasive treatment (NON). The NON group patients were informed that they could request invasive therapy, if their symptoms deteriorated during follow-up. The INV group patients underwent risk assessment by an anaesthesiologist and, when needed, a cardiologist. If significant operative risk, which was not obvious during basic risk assessment, was detected, randomised INV patients did not receive invasive treatment. If symptoms of IC improved before invasive treatment, the INV patients could decline invasive treatment. Following an arterial digital subtraction angiography (DSA) in INV patients, invasive procedures were applied as soon as possible.

Prospective log lists were not used. In an attempt to estimate referral patterns for IC, the medical records of 88 consecutive IC patients referred during a 12-month period were retrospectively reviewed at the time of final analysis, and in a prospective cohort of 130 patients referred for IC, rates of non-eligibility and exclusions were estimated.

Allocation

For randomisation, we used a computerised minimisation procedure as proposed by Pocock and Simon, taking 15 variables with presumed prognostic influence into account. These variables are presented in Table 1 and were entered into the computer as continuous or dichotomised variables as described in the table. For each new included patient, the computerised procedure minimised differences between groups for all variables. Randomisation was performed independently by a research nurse and reported to the responsible vascular surgeon.

Interventions

Immediately after randomisation, patients in both groups were assigned to risk-factor management and medical intervention for secondary prevention. Every patient received aspirin 75 mg daily (or ticlopidine if there was contraindication to aspirin). Smokers were offered participation in a smoking cessation support programme and received verbal and written information with smoking cessation advice. Hypertension, diabetes and hyperlipidaemia were managed either by a general practitioner or a specialist in internal medicine, according to contemporary national guidelines.

All patients received verbal training advice and a written training programme for IC. The patients were instructed to walk at least 1 h/day and to walk up to their maximal claudication distance as often as possible and to perform an additional exercise programme at home several times a day.

In INV patients, invasive procedures were chosen by the responsible vascular surgeon, based on DSA. In general, aorto-iliac TASC A and B lesions were treated...
endovascularly and TASC C and D lesions with surgery. Femoropopliteal TASC A lesions were offered angioplasty, whereas TASC B–D lesions usually were treated surgically. For lesions in the common femoral artery, endarterectomy with or without patch angioplasty was used.

**Follow-up and outcomes**

Patients were followed at 1 (invasive group only), 6, 12 and 24 months by a vascular surgeon. Two specially trained Vascular Laboratory research nurses monitored the study and registered patient data at 6, 12 and 24 months. Primary outcome was MWP on a graded treadmill with an increasing workload due to progressively increasing slope (0–12°) and speed (1.5–4.5 km h⁻¹). Treadmill tests were performed at baseline, 6, 12 and 24 months and expressed in watts (W), based on speed, slope and body weight. Maximal walking distance (m) on the graded treadmill was registered; and the patients subjectively reported maximal walking distance on a flat surface. Reasons for stopping the treadmill test during follow-up were registered and categorised as maximal bearable claudication pain, general fatigue or other causes.

Secondary outcomes included patient reported HRQL as measured with the Medical Outcomes Study Short Form 36 (SF-36) instrument and Ankle-Brachial Index (ABI) changes. SF-36 quantifies different aspects of HRQL in eight different domains (MH = Mental Health; RE = Role Emotional; SF = Social Functioning; VT = Vitality; GH = General Health; BP = Bodily Pain; RP = Role Physical; and PF = Physical Functioning).

**Ethics committee approval**

Ethical approval was obtained from the Regional Ethical Review Board at the University of Gothenburg.

### Table 1  Demographics and risk factors used in the computerized minimization procedure, presented according to treatment group. Values are given as mean ± SD when applicable.

<table>
<thead>
<tr>
<th></th>
<th>Invasive group</th>
<th>Non-invasive group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (range)</td>
<td>68 (41–84)</td>
<td>68 (44–84)</td>
</tr>
<tr>
<td>Gender male/female, %</td>
<td>62/38</td>
<td>64/36</td>
</tr>
<tr>
<td>Smoking habits, %, yes/ex-smoker/no</td>
<td>41/32/27</td>
<td>42/33/25</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>26 ± 3.8</td>
<td>26 ± 3.4</td>
</tr>
<tr>
<td>Duration of symptoms, &lt;1 y/1–2 y/2 y, patients</td>
<td>1/48/51</td>
<td>0/47/54</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>162 ± 23</td>
<td>158 ± 27</td>
</tr>
<tr>
<td>Ankle pressure, most symptomatic side, mmHg</td>
<td>94 ± 27</td>
<td>94 ± 31</td>
</tr>
<tr>
<td>Ankle–brachial index</td>
<td>0.59 ± 0.17</td>
<td>0.60 ± 0.19</td>
</tr>
<tr>
<td>Pulse in groin (symptomatic side) normal/reduced/absent, %</td>
<td>56/29/15</td>
<td>63/24/14</td>
</tr>
<tr>
<td>Maximal treadmill performance (W, watts)</td>
<td>66 ± 24</td>
<td>67 ± 24</td>
</tr>
<tr>
<td>S-haemoglobin (g/l)</td>
<td>144 ± 14</td>
<td>144 ± 13</td>
</tr>
<tr>
<td>S-cholesterol (mmol/l)</td>
<td>6.0 ± 1.3</td>
<td>6.2 ± 1.3</td>
</tr>
<tr>
<td>S-triglycerides (mmol/l)</td>
<td>2.1 ± 1.2</td>
<td>2.3 ± 2.7</td>
</tr>
<tr>
<td>S-Creatinine (µmol/l)</td>
<td>104 ± 27</td>
<td>107 ± 27</td>
</tr>
</tbody>
</table>

**Additional measurements**

ABI was measured using standard techniques. The highest value at ankle level was used. An ABI improvement of >0.1 in combination with positive clinical findings was defined as a patent vascular reconstruction.

Cotinine, a nicotine metabolite was measured in a urine sample at 12 and 24 months using an immunochemical method. Nicotine use was defined as ≥2.0 µmol l⁻¹ nicotine metabolites per litre.

**Statistical methods**

A sample size of 200 evaluable IC patients with MWP < 70 W in women and <90 W in men was chosen, based on preliminary analysis of an earlier study,¹⁴ power 80% and beta 0.05.

Main analysis was according to intention to treat, and included all randomised patients. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA). Concerning MWP and ABI, significance between baseline and at 2 years was tested using the t-test for paired samples. Between-group comparisons were performed using the t-test for independent samples. For analysis of HRQL parameters, non-parametric tests were used (Wilcoxon signed rank test and Mann–Whitney U test). The magnitude of the change in HRQL variables was estimated using effect size calculations (ES = difference in mean values between baseline and 2 years per SD at baseline). Cohen’s criteria⁰ for interpreting ES were applied (small = 0.2–0.5, moderate = 0.5–0.8 and large >0.8). Correlation analysis (Pearson) was performed between SF-36 subscales and MWP at baseline. Logistic regression was used for comparison of minimisation variables versus MWP.

A per-protocol analysis was also performed, excluding patients in both groups not receiving allocated randomised treatment.
Results are presented as means ± SD (most variables) or median values (subjectively reported walking distance). Statistical significance was determined at \( p < 0.05 \).

Results

Inclusion and baseline data

After inclusion of nearly 200 patients overall in the present study, long delays in invasive treatment for IC patients had become increasingly common due to economic constraints. A study from our group at that time demonstrated >15% improvement in MWP by invasive versus control treatment. With a 15% difference (10 W) in MWP between the INV and NON groups at 2 years, a sample size of 200 patients with 75–80% evaluable at 2 years would allow a power of 77% with beta 0.05. Patient inclusion was stopped at this point.

Fig. 1 shows the flow of randomised patients. Approximately 600 patients were estimated to have been referred for IC during a 7-year inclusion period ending in January 2002. The studied sample of 130 patients suggested that 25% had either incorrect diagnosis, other medical condition limiting MWP or did not seek treatment for IC; 18% were ≥85 years; 11% had subcritical ischaemia, aortic thrombosis or were unable to work due to IC and 3% had multiple previous reconstructions. The remaining 250–260 patients were eligible for inclusion. In the sample of 130 patients, 14% did not consent and 5%, based on duplex ultrasound, needed reconstruction below the tibioperoneal trunk. As many as 201 patients, constituting approximately 60% of all referred patients ≤85 years of age with verified IC limiting MWP, were finally randomised in the study. As expected, baseline demographic and clinical data were nearly identical in the two groups (Table 1).

Logistic regression showed that age, female gender, current smoking and low ABI were related to MWP. Nearly a third (30%) had elevated S-cholesterol (>4.5 mmol l\(^{-1}\)) and approximately two-thirds of these patients had lipid-lowering therapy. HRQL was impaired for all SF-36 domains as compared to age- and gender-matched population data (Fig. 2). The most pronounced differences were noted regarding parameters quantifying physical performance (PF and RP) and BP. At baseline, several SF-36 subscales were related to MWP (correlation coefficients; PF: 0.241, MH: 0.311, RE: 0.307 and VT: 0.225, all significant at the 0.01 level, two-tailed test).

**Figure 1** Diagram showing flow of randomised patients through trial.

**Figure 2** Health related quality of life (HRQL), assessed with SF-36, in patient group at baseline as compared to age and gender-matched population data (reference group).
Outcome

During the 2 years, seven patients (4%) died, including six NON- and one INV-group patients (n.s., (Fig. 3). No amputations were performed. Overall attendance at 6, 12 and 24 months was 85%, 82% and 79%, respectively. Main reasons for not attending at 24 months were deaths (3.5%) or dropouts (8%) due to intercurrent disease making treadmill test and/or HRQL questionnaires impossible or irrelevant (cancer, stroke or severe cardiovascular condition). Nearly a tenth (9%) of all patients for unknown reasons failed to return for outpatient visits. The attendance rate at 24 months was 86% in the INV versus 71% in the NON group.

In the INV group, 80% received invasive treatment after a median time of 14 (3–72; interquartile range (IQR) = 17) weeks. The reasons for not receiving invasive treatment are given in Fig. 1. In the INV group, 13 of the crossovers were according to the study protocol and seven were against. In the NON group, 91% of the patients were treated according to randomisation, all nine crossovers were according to protocol as they were treated invasively because of deterioration (worsening claudication, n = 8 and subcritical limb ischaemia, n = 1).

Thirty-nine procedures (49%) were supra- and 41 (51%) infrainguinal (Table 2) and overall, 53% of all procedures were surgical. ABI improved (p = 0.001) in the INV (+0.19 ± 0.2) versus the NON group. Twenty-one reinterventions were performed on nine patients during follow-up. At 24 months, 70% of the INV patients had a patent vascular reconstruction (Fig. 4). The change in MWP at 2 years in the INV versus the NON group failed to reach significance, (p = 0.104, Fig. 5). Results regarding MWP at 6 and 12 months were similar to the 24 months’ findings. The NON group patients receiving invasive treatment all had an MWP <60 W at baseline. Two-year results in these nine patients were similar to those obtained in the INV group (MWP change +11 ± 28 W).

The change from baseline to 24 months in the per-protocol analysis of MWP was significant (10 W vs. 0.6 W improvement in the INV vs. NON group, p = 0.041).

Changes in HRQOL

The INV group improved significantly compared with the NON group regarding RP (p < 0.05) and BP (p < 0.01) with moderate to large effects regarding RP and BP, respectively, in the INV group. Fig. 6 shows effect sizes for each domain by treatment group.

Smoking habits and additional analyses

On inclusion and 24 months, respectively, 41% and 23% in the invasive group and 43% and 25% in the non-invasive group stated current smoking. Measuring u-cotinine, 55% and 51% were nicotine users at 24 months, respectively. MWP results were not related to u-cotinine levels.

On inclusion, walking performance on the treadmill was limited by claudication pain in all patients. At 24 months, we found a difference in reasons for stopping the treadmill test between the two treatment groups. The NON group most often (56%) stopped because of intolerable claudication, whereas the most common cause (59%) in the INV group was general fatigue (p = 0.042), (Fig. 7).

Discussion

In this ‘real life’ type of study, we randomised patients based on clinical examination and arterial duplex, which reflects our clinical routines regarding the initial choice of treatment strategy for claudicants. Although our calculations of referrals and exclusion rates have some degree of uncertainty, as they are based on analysis of smaller samples and an assumption of constant referral patterns over the years, we opine it is safe to say that we included a large proportion of all IC patients referred to us. In this unselected patient group, the primary invasive treatment strategy did not significantly improve MWP, the primary outcome variable, but resulted in moderate to large effects on SF-36 domains BP and RP (i.e., the ability to perform daily activities). The observed improvement of MWP in the INV group was lower than expected, leading to only 42% power to demonstrate significantly improved MWP. Lacking a clear definition of the clinical significance of the size of a change in SF-36 domain scores, effect sizes (ES) were calculated to assist in interpreting such changes. Effect size estimates have been shown to correspond to patient- and clinician-based assessments of clinical significance. We observed a 91% compliance rate with the primary non-invasive strategy. Invasive treatment in the 9% NON group patients who deteriorated was successful. The primary invasive treatment strategy was completed in 80% of the INV-group patients. Six patients in the INV group were treated non-invasively due to the development of increased risk (myocardial infarction, n = 1; severe angina pectoris, n = 3; heart failure, n = 1; and renal failure, n = 1) after randomisation, reflecting the atherosclerotic burden in these patients. This could be a potential study bias. Moreover, as patency was determined based on indirect measurements, according to our clinical routine, these values may have some degree of uncertainty.

Two previous randomised controlled studies evaluated invasive treatment including open surgery for IC. Lundgren...
et al.,13 in a study from Gothenburg, 1989, demonstrated improved walking capacity with open vascular reconstruction versus physical training. In 2001, we published a study of invasive treatment versus supervised exercise training versus controls receiving only general training advice,14,15 showing benefit for invasive treatment regarding walking performance and HRQL. The effects of invasive treatment were moderate.

In selected IC patients suitable for angioplasty, there are recent randomised studies comparing results of BMT with and without endovascular intervention, respectively. In the Oslo balloon angioplasty versus conservative treatment strategy (OBACT) trial,16 a benefit of angioplasty regarding physiological parameters was demonstrated. Out of 434 IC patients, 56 (13%) were finally randomised. The improvement by angioplasty in this selected group of patients was moderate.

In the multicentre mild-to-moderate intermittent claudication (MIMIC) trial,17 the adjuvant benefit of angioplasty in addition to BMT and supervised exercise training were studied in selected patients suitable for angioplasty, in two separate trials (aorto-iliac and femoropopliteal disease). Only one-tenth of 1401 screened IC patients were finally eligible, mainly because of patient refusal and selective inclusion criteria. Of these, 127 patients were enrolled in the studies. The investigators showed moderate improvement by invasive treatment in physiological parameters in both trials. HRQL improvement was shown in the aorto-iliac but not in the femoropopliteal trial.

In 2008, Spronk et al.18 compared endovascular intervention with a hospital-based supervised exercise training programme and found no difference regarding walking performance or HRQL at 12 months.

In comparison, our study differs in some aspects. Due to our design, allowing lesions anywhere in arterial segments from the aorta to the tibioperoneal trunk and surgical and/or endovascular invasive treatment, we studied the effects of revascularisation, irrespective of the technique used and randomised a significant proportion of all IC patients referred to us. Controlled studies of revascularisation for IC are often hampered by poor recruitment rates,19 making performance of studies as well as generalisation of the

<table>
<thead>
<tr>
<th>Type of procedure</th>
<th>No of procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of interventions</td>
<td>80</td>
</tr>
<tr>
<td>Angioplasty iliac artery</td>
<td>25</td>
</tr>
<tr>
<td>Aorto/iliacofemoral bypass</td>
<td>6</td>
</tr>
<tr>
<td>Axillo–femoral bypass</td>
<td>1</td>
</tr>
<tr>
<td>Femoro–femoral bypass</td>
<td>6</td>
</tr>
<tr>
<td>Surgical exploration only</td>
<td>1</td>
</tr>
<tr>
<td>Procedures above inguinal ligament, total</td>
<td>39</td>
</tr>
<tr>
<td>Angioplasty superficial femoral artery</td>
<td>12</td>
</tr>
<tr>
<td>Angioplasty popliteal artery</td>
<td>1</td>
</tr>
<tr>
<td>Endarterectomy ± patch femoral artery/profundaplasty</td>
<td>3</td>
</tr>
<tr>
<td>Femoropopliteal bypass above knee</td>
<td>14</td>
</tr>
<tr>
<td>Femoropopliteal bypass below knee</td>
<td>8</td>
</tr>
<tr>
<td>Vein bypass distal to the popliteal artery</td>
<td>3</td>
</tr>
<tr>
<td>Procedures below inguinal ligament, total</td>
<td>41</td>
</tr>
</tbody>
</table>

**Table 2** Invasive treatment group: surgical procedures and compliance.

**Figure 4** Cumulative patency (Kaplan–Meier) in the INV group during follow-up. Values represent indirect measures of patency (ABI improvement >0.1).

**Figure 5** Results regarding maximal walking performance (MWP) in the INV versus NON group from baseline to 24 months.
results difficult. Our aim was to compare the outcome of two different primary treatment strategies in unselected patients.

Maximum walking performance assessed in any treadmill protocol is subject to biases and may not entirely reflect daily walking performance. There could be a difference between the ability to perform daily physical activities and the measured performance on a treadmill test. A patient with poor blood flow to the lower limb(s) could have poor performance on the treadmill but might, in theory, be able to walk long distances on flat surfaces slowly. We used a graded treadmill test as primary outcome parameter. This test correlates significantly to HRQL, and graded tests are highly reproducible and reported to be superior to constant treadmill tests. On inclusion, all patients were limited by claudication pain at treadmill test. During follow-up, invasively treated patients often stopped the treadmill test due to general fatigue. Hence, their claudication pain may have been abolished by invasive treatment but other conditions, for example cardiac or respiratory failure, may have been unmasked, limiting MWP.

It can be argued that supervised exercise training is more efficient than non-supervised training. In this study, we chose non-supervised training, as we previously observed poor compliance to our supervised programme with no significant effect versus exercise training advice. Exercise training is known to improve walking performance but improvement may disappear, if the patient stops training. Moreover, strong evidence for extra benefit, regarding HRQL, for supervised versus non-supervised training is lacking.

HRQL was assessed using a generic instrument. Several studies highlight the importance of using both a generic and a disease-specific instrument, as generic instruments may be less sensitive for detecting small but clinically important differences. Nevertheless, we were able to show significant HRQL improvement indicating important effects over time by invasive treatment. Attendance rate at follow-up was less in the NON group and although we have no data to suggest this, we cannot entirely exclude that the unattending subjects performed worse, influencing the results.

In summary, this study in unselected IC patients failed to show significantly improved MWP with a primary invasive versus a primary non-invasive treatment strategy. Invasive treatment resulted in moderate to large positive HRQL effects regarding physical role function and pain. At the same time, the primary non-invasive treatment strategy had a low (9%) crossover rate occurring only in patients with baseline MWP < 60 W. Although our data shows HRQL advantages with invasive treatment, this has to be evaluated further, as HRQL was a secondary end point in this study.

In conclusion, the present results give some further support for improved HRQL by invasive treatment but, overall, there is still only a limited evidence base for invasive treatment of IC patients.

Figure 6  Effect sizes (ES) calculated between baseline and 24-months for INV and NON patients for the 8 SF-36 subscales. Cohen’s criteria for ES: 0.0–0.2 = trivial; 0.2–0.5 = small; 0.5–0.8 = moderate; >0.8 = large * Significant between-group difference between baseline and 24-months (Mann-Whitney U). # Significant improvement between baseline and 24-months (Wilcoxon Signed Rank Test).

Figure 7  Reasons for stopping on treadmill test at 24 months follow-up, according to treatment group. Significant difference was noted between groups regarding the distribution of reasons for ending treadmill test (p = 0.042).
Conflict of Interest

None.

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Bengt Lindberg, MD, PhD, Kungälv Hospital, Vascular Surgery Unit.

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