RANDOMISED CLINICAL TRIAL

Cardiovascular Rehabilitation Increases Walking Distance in Patients With Intermittent Claudication. Results of the CIPIC Rehab Study: A Randomised Controlled Trial

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WHAT THIS PAPER ADDS

This study adds to knowledge that cardiac rehabilitation programmes for patients with intermittent claudication increase walking distance, health related quality of life, physical activity, and healthy diet. Based on this study, recommendations for a specialised rehabilitation programme for patients with intermittent claudication include supervised exercise training as an interdisciplinary intervention in a local community setting with physiotherapists, a specialist vascular nurse, and dietician; a pedometer as a strong motivational tool for patients to increase daily walking; follow up training after 12 weeks and cross sector coordination by vascular nurse; and patient access to a telephone number.

Objective: To examine whether a cardiac rehabilitation programme in a community based setting for patients with intermittent claudication (IC) affects walking ability, quality of life, and changes in health behaviour. The trial investigated a cross sector cardiovascular rehabilitation programme compared with usual care for patients having non-operative management.

Methods: The trial allocated 118 patients, with 1:1 individual randomisation to either an intervention or control group. Data were collected at a department of vascular surgery and at a healthcare centre in Denmark. The rehabilitation intervention consisted of usual care plus 12 weeks of exercise training, pedometer, health education, and text messages. The primary outcome was maximum walking distance at six months measured by treadmill walking test. The secondary outcomes were maximum walking distance at 12 months and pain free walking distance measured by treadmill walking test, healthy diet, level of physical activity, and quality of life (QoL) at six and 12 months.

Results: In the intervention group, 46 participants were analysed, with 47 in the control group. Following three months of rehabilitation, a 37% difference (95% CI 1.10 − 1.70; $p = .005$) was found between groups in maximum walking distance at six and 12 months, in favour of the intervention group. The same positive effect was found in physical activity, QoL, and healthy diet, but was not statistically significant in pain free walking distance and smoking.

Conclusion: A specialised community based cardiac rehabilitation programme for patients with IC showed statistically and clinically significant effects on maximum walking distance, physical activity, quality of life, and healthy diet, but not on pain free walking distance and smoking, compared with usual care without rehabilitation.

Keywords: Cardiovascular rehabilitation, Intermittent claudication, Pedometer, Quality of life, Randomised controlled trial, Walking distance
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INTRODUCTION

Peripheral artery disease (PAD) is a chronic occlusive disease in the lower limb arteries caused by progressive atherosclerosis.[1] The prevalence of PAD is increasing and

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affects more than 200 million people globally and > 10% of the population aged > 70 years.[2] The most common symptom is intermittent claudication (IC), which is defined as a cramping leg pain that occurs during walking and is relieved by a short period of rest. Patients with IC have diminished walking capacity, restricted activity levels and mobility, and reduced health related quality of life.[3] This can lead to social isolation and worsening of the disease with increasing risk of atherosclerotic complications and death.[4] Because of the risk of complications and limited patency of revascularisation, conservative management should be attempted as first line treatment in patients without critical limb ischaemia.[5]

According to the most recent *Cochrane Review*, supervised exercise training (SET) can be effective in alleviating symptoms, increasing walking distance, reducing cardiovascular events, and improving quality of life. Such programmes are also relatively inexpensive and cost effective, compared with other more invasive IC therapies.[6,7] Although evidence for the health benefits of SET is strong, rehabilitation is still poorly implemented and studies exploring how to set up effective community based IC rehabilitation interventions are lacking.[8] Current practice for managing IC in Danish hospital settings involves brief advice to "stop smoking and keep walking", combined with preventive medications including cholesterol lowering treatment with statins and antiplatelet therapy, and this quality does not live up to the recommended SET evidence.[5]

The aim of this trial was to investigate the effects of a cross sector (community/hospital) exercise and lifestyle intervention based on an already established community based rehabilitation programme for patients with ischaemic heart disease compared with the effects of usual care without rehabilitation in patients with IC.

Cardiac rehabilitation programmes have been offered for more than a decade with a mix of exercise and education sessions twice a week for 12 weeks, and are established in Denmark, Sweden, and the UK.[9,10] Different kinds of exercise type and intensity for older people with cardiovascular diseases are recommended by the European Society of Cardiology.[11]

The primary hypothesis was that compared with the control group, a specialised rehabilitation programme in a community based setting for patients with IC (intervention group) improves maximum walking distance in a treadmill walking test after the completed intervention.

METHODS

The design and methods of the CIPIC Rehab Study have been described in a previous design paper[12] and are summarised here. The trial also incorporates a qualitative component, details of which will be published elsewhere. The trial has been registered at clinicaltrials.gov (NCT03730623). The trial complies with the Declaration of Helsinki and was approved by the local ethics committee (J. No.:H-17004183) and the Danish Data Protection Agency (J.No.:2012—58—0004).

Setting and recruitment

Consecutive patients at the Department of Vascular Surgery in Copenhagen, Denmark (Rigshospitalet) were screened for inclusion and approached for study participation. The setting was one hospital and one municipal healthcare centre in the Capital Region of Denmark. None of the patients had any interventions before recruitment.

Inclusion criteria were conservatively treated patients with newly diagnosed IC using clinical assessment and ankle brachial index; age > 18 years; speaks and understands Danish; able to provide informed written content; citizens of one of eight municipalities of Greater Copenhagen belonging to the local healthcare centre; and expected to be able to manage transportation and perform exercise. Exclusion criteria were failure to understand and cooperate according to the trial instructions; comorbidity complicating physical activity and exercise training; and lack of informed consent.

Rehabilitation

The rehabilitation began in the outpatient clinic and continued in the healthcare centre, with an experienced cardiac physiotherapist with specialised knowledge of patients with IC. All patients were followed by the investigator and a direct telephone number to counselling was provided to both groups to secure access to counselling if needed.

Control group: usual care

Patients in the control group followed standard procedure for patients treated for IC[5] and received the department of vascular surgery's usual, brief advice about walking exercise and smoking cessation, and were given preventive medical treatment with antiplatelet therapy and statins. The patients received written information about medication, walking exercise, and a logbook for self reporting walking behaviour.

Intervention group

The intervention group initially received the usual care. Additionally, patients' home municipalities offered courses in smoking cessation. Patients received a pedometer and were asked to self report walking behaviour and steps in a logbook. The patients brought their logbooks to the consultations with the physiotherapist. These consultations included a dialogue about motivational factors and initiation of the training, and informed patients about the goal of the physical activity.

Group course and individual consultation

The group course was a two hour session about the pathophysiology of IC, medications, health behaviour and disease management. Group sessions and the individual consultation were performed by an experienced nurse with

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specific knowledge of IC, based on guidelines.[13] Spouses were invited to participate in group sessions as well as in the individual consultations. A clinical dietician ran a two hour group session about healthy diet and atherosclerosis and offered individual consultations.

Supervised exercise training

Two physiotherapists with specific insight into IC developed and conducted the supervised exercise training. The programme was based on the established cardiac rehabilitation programme according to guidelines,[9] with a primary focus on the leg muscles.

The programme was initiated continuously and offered two weekly exercise sessions for 12 weeks. Patients were required to actively engage in groups of up to 10 patients from the programme. The exercises included varied forms of physical exercise combined to accommodate the patients' own goals regarding walking distance. To increase or sustain daily physical exercise at a level of at least 30 min/day, pedometer and self reported walking behaviour were included in the discussions with patients at their individual consultations.

Outcome evaluation

Both groups underwent outcome assessments at six and 12 months post randomisation.

Primary outcome: maximum walking distance

Maximum walking distance (MWD) was measured by the standardised treadmill walking test based on a graded protocol: 3.2 km/hour with 2% increase every two minutes.[13]

Secondary outcome: pain free walking distance, daily physical activity and diet

Pain free walking distance (PWD) was measured by the standardised treadmill walking test as described above and with a numeric rating scale for pain. Daily physical activity was measured by self reported number of times per week of walking or physical exercise activity of at least 30 minutes.[14] Diet was measured by a diet questionnaire with a fat score and a fish-fruit-green score. To achieve the term "healthy", each score had to be at least 75%.[15]

Exploratory outcomes

Before the treadmill tests at six and 12 months, self reported general condition in the legs compared with baseline was measured. Smoking and alcohol consumption were measured by self reported behaviour.[16,17] The Hospital Anxiety and Depression Scale (HADS)[18] was used to detect symptoms of anxiety and depression (scores $\geq$ 8). The Vascular Quality of Life Questionnaire (VQ6) was used as a disease specific instrument to evaluate QoL, where a higher value indicates better health status.[19]

Randomisation and blinding

The trial allocated 118 patients, with 1:1 individual randomisation to either the intervention group or control group.

When the informed consent was signed, baseline data were collected, and randomisation conducted. Computer generated block randomisation in four blocks was generated by an independent statistician and delivered in envelopes blinded from the investigator. Randomisation was conducted by ongoing inclusion numbers marked on the envelopes. In trials with rehabilitation intervention it is not possible to blind patients and healthcare professionals. However, primary outcome measures and statistical analyses were blinded, and follow up treadmill walking tests were performed by a research assistant blinded to the patients' group.

Statistical analysis

The analyses were performed as intention to treat analysis with use of general linear regression models and logistic regression models. Primary and secondary outcomes were analysed with adjustment for baseline values, sex, and age with a significance level of .050. For all continuous outcomes, violation of the assumption of normally distributed residuals were solved by log transformation of the outcome. Sensitivity analyses were conducted by removal of outliers (Cook's d above 0.1). The exploratory outcomes measured at 0, 6, and 12 months were analysed with linear and logistic mixed models with each participant included as a random effect. In these analyses the interaction between intervention group and time was the significance test of interest. These models were adjusted for sex and age. Exploratory outcomes were assessed as multiple testing with significant effects interpreted in the context of increased risk of type I error. Clinical effect size reported by Cohen's d.[12] Analyses were performed using SAS 9.4.

The expected average baseline value of maximum walking distance was estimated to 120 metres (m) with a detected 50% improvement (60 m), and the standard deviation (SD) was set at 100 m, based on an expected improvement in walking ability of approximately 50% to 200%.[20] Expected dropout rate was set to 25%. With a 5% significance level and 80% power, a total of 88 patients (44 in each group) was needed to detect an improvement of 60 m in MWD in the intervention group.

RESULTS

Between April 2017 and May 2019, 333 patients diagnosed with IC and having non-operative management were screened. A total of 215 patients were excluded, and 118 patients gave consent and were randomised with 59 in each

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group. During the trial, 12 patients from the intervention group and 13 patients from the control group withdrew their consent. The three month intervention was completed by 43 participants. Six patients withdrew before the SET intervention, and 10 patients dropped out after beginning the SET, corresponding to a dropout rate of 17% (see Fig. 1).

Baseline

There were small differences between the intervention and usual care groups at baseline (Table 1). Mean age was 70 years and slightly more than one third were female. Groups were comparable with small baseline differences in smoking, alcohol intake, physical activity, comorbidity, psychological measurements, and medication (Table 1). Participants and non-participants in the trial were comparable with respect to age and sex: mean age ± SD non-participants 68.6 ± 9.0, mean age participants 70.2 ± 7.1 ($p = .13$). Sex distribution was the same in both groups: non-participants 36.9% female and 63.1% male, participants 41.5% female and 58.5% male ($p = .48$).

Primary outcome

MWD increased in both groups at six months, but statistically significantly more in the intervention group compared with the control group as measured by the standardised treadmill walking test. The intervention group had higher median MWD scores at baseline (248 m *vs.* 188 m in the control group), but also had greater improvement at the six month follow up (350.5 m *vs.* 253 m in the control group) (37%; 95% CI 1.10 — 1.70; $p = .005$) and group difference corresponded to a Cohen's d of 0.38 with a small to medium effect size (Table 2).

In the per protocol analyses of the primary and secondary outcomes, 39 patients were included who completed at least 70% of the exercise sessions and also participated in the treadmill follow up test at six months. These findings make estimates and differences stronger in favour of the intervention group with a further 50 m greater walking distance that increased 45% more in the intervention group compared with the control group (95% CI 1.17 — 1.80; $p = .001$). Improvement at the six month follow up was 400 m in the intervention group *vs.* 253 m in the control group, but this does not change the conclusions (Table 3).

Secondary outcomes

PWD distance increased further in the rehabilitation group compared with the usual care group at six months (28%; 95% CI 0.99 — 1.65), but the difference was not statistically significant ($p = .060$) (Table 2).

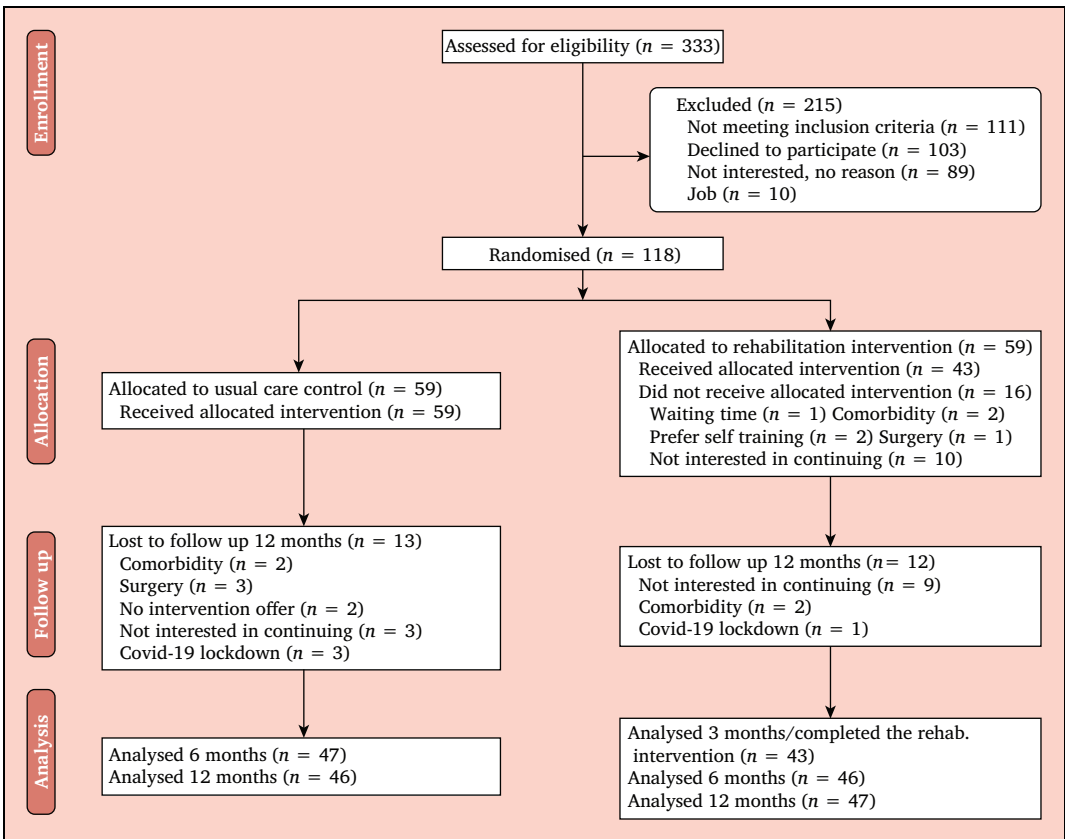

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) study flow diagram of the CIPIC Rehab Study of patients with intermittent claudication receiving usual care (Control) or additional cardiovascular rehabilitation programme (Intervention), 5 December 2017 — 18 May 2020.

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Table 1. Baseline demographic and clinical characteristics of 118 patients with intermittent claudication included in the CIPIC Rehab Study for usual care (Control group) or additional cardiovascular rehabilitation programme (Intervention group)

Variable	Control group (n = 59)	Intervention group (n = 59)
Female sex	26 (44)	23 (39)
Age − y	70.1 ± 7.3	70.5 ± 7.0
BMI − kg/m^2	26.2 ± 6.0	26.8 ± 4.3
Smoking		
Current smoker	25 (42)	28 (47)
Former smoker	29 (49)	27 (46)
Never smoker	5 (8)	4 (7)
Pack years	50.2 ± 31.5	42.9 ± 27.6
Physical activity		
Exercise of 30 min/w		
0 times	32 (54)	42 (71)
1−2 times	15 (25)	9 (15)
3−6 times	8 (14)	7 (12)
≥ 7 times	3 (5)	1 (2)
Walking of 30 min/w		
0 times	24 (41)	26 (44)
1−2 times	6 (10)	7 (12)
3−6 times	10 (17)	9 (15)
≥ 7 times	19 (32)	17 (29)
Physical activity ≥ 30 min/d	21 (36)	18 (31)
Alcohol intake − drinks/w	10.3 ± 12.6	10.4 ± 13.4
Medications		
Aspirin	36 (61)	42 (71)
Clopidogrel	17 (29)	10 (17)
DOAC	1 (2)	2 (3)
Vitamin K-antagonists	0 (0)	2 (3)
Statins	54 (92)	51 (86)
Charlson comorbidity score		
0, no comorbidity	31 (53)	42 (71)
1, mild	15 (25)	7 (12)
2, moderate	9 (15)	5 (8)
≥ 3, severe	4 (7)	5 (8)
Diabetes	7 (12)	11 (19)
Myocardial infarction	8 (14)	9 (15)
Congestive heart failure	6 (10)	6 (10)
Cerebrovascular disease	8 (14)	7 (12)
Chronic pulmonary disease	14 (24)	8 (14)
Renal disease	0 (0)	0 (0)
Psoriasis	5 (8)	2 (3)
Prolapsed disc	7 (12)	7 (12)
Atrial flutter/fibrillation	5 (8)	5 (8)
Spinal stenosis	4 (7)	3 (5)
Osteoporosis	4 (7)	3 (5)
Back pain, undiagnosed	1 (2)	2 (3)
Osteoarthritis	9 (15)	6 (10)
Medically treated hypertension	42 (71)	44 (75)
Treadmill test PWD − m		
Mean	157.9 ± 168.8	151.5 ± 145.7
Median	96.5 (52−175)	115 (54−175)
Treadmill test MWD − m		
Mean	300.7 ± 273.7	309.9 ± 255.1
Median	188 (107−393)	248 (130−384)
VascuQol-6 score	14.7 ± 3.0	14.6 ± 4.0
HADS-A ≥ 8	7 (12)	11 (19)
HADS-D ≥ 8	5 (8)	8 (14)
Haemoglobin − mmol/L	8.7 ± 1.0	8.8 ± 0.9
HbA1c − %	39.4 ± 5.6	42.4 ± 8.1
Creatinine − µmol/L	82.1 ± 20.9	87.0 ± 25.7
Total cholesterol − mmol/L	4.2 ± 0.9	4.4 ± 0.9
Cholesterol LDL − mmol/L	2.0 ± 0.8	2.3 ± 0.8
Cholesterol HDL − mmol/L	1.5 ± 0.6	1.4 ± 0.5
Triglyceride − mmol/L	1.6 ± 0.8	1.9 ± 1.7
CRP − mg/L	2.9 ± 4.3	5.3 ± 11.7

Data are presented as n (%), mean ± standard deviation or median (interquartile range). DOAC = direct oral anticoagulant; PWD = pain free walking distance; MWD = maximum walking distance; VascuQol = Vascular Quality of Life Questionnaire; HADS = Hospital Anxiety and Depression Scale; HbA1c = glycated haemoglobin; LDL = low density lipoprotein; HDL = high density lipoprotein; CRP = C reactive protein.

Physical activity estimated as the odds ratio (OR) for a minimum of 30 daily minutes of physical activity at six months was significantly higher in the rehabilitation group compared with the usual care group (OR 5.59; 95% CI 1.66 − 18.82; p = .002) (Table 2).

None of the participants in the control group and only five participants in the intervention group achieved the term "healthy" with a score of at least 75% after six months (Table 2). Separate analyses of the healthy diet questionnaire showed significantly higher scores for fat and the fish-fruit-green scores (p < .001) in the intervention group at six and 12 months (Table 4).

Exploratory outcomes

The results of the linear and logistic mixed models with exploratory outcomes measured at zero, six, and 12 months are presented in Table 3.

After 12 months there was a statistically significant lasting effect on MWD in the intervention group (p = .020), but no statistically significant difference in PWD (p = .24). Physical activity was statistically significantly higher in the intervention group after 12 months (p = .010) (Table 3). At six months, the general self reported condition in the legs compared with baseline was that 9% of those in the control group and 28% in the intervention group felt that this was much improved. By 12 months, this had risen to 22% of those in the control group and 36% in the intervention group.

The VQ6 scores were statistically significantly better in the rehabilitation group compared with the usual care group at six and 12 months (p = .020). There were no statistically significant differences between the groups in anxiety and depression scale (HADS), alcohol consumption, and smoking (Table 3).

DISCUSSION

To the present authors' knowledge, the present study is the first to show that a specialised cardiac rehabilitation

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Table 2. Results log linear model with continuous primary and secondary outcomes and logistic regression for binary secondary outcomes measured at six months in 118 patients with intermittent claudication receiving usual care (Control group) or additional cardiovascular rehabilitation programme (Intervention group). Available case analysis of the CIPIC Rehab Study

	Baseline		Six months		Exp(estimate) (95% CI)*	p	Cohen's d†
	Control group (n = 59)	Intervention group (n = 59)	Control group (n = 47)	Intervention group (n = 46)			
Primary outcome							
Maximum walking distance‡	188 [300.7]	248 [309.9]	253 [325.4]	350.5 [447.6]	1.37 (1.10–1.70)	.005	0.38
Secondary outcomes							
Pain free walking distance§	96.5 [157.9]	115 [151.5]	96 [165.8]	133.5 [207.9]	1.28 (0.99–1.65)	.060	0.29
Healthy diet	0 (0)	1 (2)	0 (0)	5 (11)	NA‖	NA	
Physical activity	21 (36)	18 (31)	15 (32)	24 (52)	5.59 (1.66–18.82)	.002	

Data are presented as median [mean] or *n* (%) unless stated otherwise. CI = confidence interval; NA = not available.
* Main effect of intervention adjusted for sex, age (continuous), and baseline value (time 0). For maximum walking distance and pain free walking distance, the estimate is the exponential log transformed mean difference meaning the relative extra metres in intervention group compared with control group. For physical activity, the estimate is the odds ratio.
† Cohen's d is the estimate from the log transformed model divided by the standard deviation of the log transformed baseline value.
‡ Sensitivity analyses with removal of outliers (Cook's d > 0.1, $n = 1$) also showed statistically significant differences ($p = .004$).
§ No outliers were identified after log transforming this outcome (Cook's d < 0.1 for all observations).
‖ NA, not estimable as no outcomes in control group.

programme in a community setting improves walking distance in patients with IC. The programme comprised cross sector cooperation between an outpatient clinic and a healthcare centre in the community. Additionally, physical activity, healthy diet, and QoL improved compared with usual care after six and 12 months.

The effects on walking distance, physical activity, and QoL are in line with that resulting from SET programmes, which have proven effective for alleviating symptoms, increasing walking distance, reducing cardiovascular risk factors, and improving QoL,[7] but there is a lack of evidence on how to set up such programmes.[8] Most studies on SET are performed in hospital outpatient clinics and have limitations for implementation, capacity, and adherence.[8] A typical programme includes 45–60 minutes treadmill based exercise, three times a week, for 12 weeks, and is time consuming and expensive, with high dropout rates of 40%.[21] The treadmill based exercise on such a typical programme is relatively painful and can be perceived as boring, which could explain some of the high dropout rates. Cardiac

Table 3. Log linear model with continuous primary and secondary outcomes and logistic regression for binary secondary outcomes measured at six months in 118 patients with intermittent claudication receiving usual care (Control group) or additional cardiovascular rehabilitation programme (Intervention group). Per protocol and available case analysis of the CIPIC Rehab Study

	Baseline		Six months		Exp(estimate) (95% CI)*	p	Cohen's d†
	Control group (n = 59)	Intervention group (n = 41)	Control group (n = 47)	Intervention group (n = 39)			
Primary outcome							
Maximum walking distance	188 [300.7]	281 [350.6]	253 [325.4]	400 [479.7]	1.45 (1.17–1.80)	.001	0.45
Secondary outcomes							
Pain free walking distance	96.5 [157.9]	138 [161.5]	96 [165.8]	147 [223.8]	1.32 (1.02–1.73)	.040	0.33
Healthy diet	1 (2)	0 (0)	0 (0)	5 (13)	NA‖	NA	
Physical activity	21 (36)	12 (29)	15 (32)	20 (51)	6.50 (1.69–25.03)	.002	

Data are presented as median [mean] or *n* (%) unless stated otherwise. CI = confidence interval; NA = not available.
* Main effect of intervention adjusted for sex, age (continuous), and baseline value (time 0). For maximum walking distance and pain free walking distance, the estimate is the exponential log transformed mean difference meaning the relative extra metres in the intervention group compared with the control group. For physical activity, the estimate is the odds ratio.
† Cohen's d is the estimate from the log transformed model divided by the standard deviation of the log transformed baseline value.
‖ NA, not estimable as no outcomes in control group.

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Table 4. Results of linear and logistic mixed models with exploratory outcomes measured at 0, 6 and 12 months in 118 patients with intermittent claudication receiving usual care (Control) or additional cardiovascular rehabilitation programme (Intervention). The estimates are the crude proportions, medians or means and proportions with outcome in intervention and control groups. Available case analysis of the CIPIC Rehab Study

	n*	0 months		6 months		12 months		p value†
		Control	Intervention	Control	Intervention	Control	Intervention	
Exploratory outcomes								
Median maximum walking distance	303	188	248	253	350.5	263.5	370	.020‡
Median pain free walking distance	303	96.5	115	96	133.5	140	170	.25§
Physical activity − %	301	36	31	32	52	25	52	.010
Mean Vascular Quality of Life Questionnaire	303	14.7	14.6	15.6	17.3	16.0	17.1	.002
HADS-A $\geq$ 8 − %	303	12	19	11	17	15	21	.96
HADS-D $\geq$ 8 − %	303	9	14	6	4	2	4	.76
Smoking status − %	299	42	47	38	43	42	40	.58
High alcohol consumption‖ − %	304	24	17	28	13	20	11	.58
Mean fat score	303	0.55	0.56	0.55	0.66	0.57	0.71	<.001
Mean fish-fruit-green score	303	0.43	0.43	0.40	0.53	0.41	0.55	<.001

HADS = Hospital Anxiety and Depression Scale.
* n is the number of observation where each person can have up to three observations.
† p value from interaction term between intervention group and time (0, 6 and 12 months). Adjusted for sex and age (continuous).
‡ p value based on analyses on log transformed maximum walking distance.
§ p value based on analyses on log transformed pain free walking distance.
‖ > 21 weekly units for men; > 14 weekly units for women.

IC rehabilitation exercise can adapt a larger group of patients compared with treadmill exercise because of limited numbers of treadmills per SET. Therefore, the cost of cardiac rehabilitation including dietician and nurse sessions is not more expensive.

The different kind of exercise is adapted and less time consuming and is beneficial in combination with risk factor reduction sessions with a nurse and dietician. The cost of SET alone, and a typical cardiac rehabilitation programme as in this study is 600 € per patient, while a simple iliac cardiovascular procedure costs approximately 9 000 €.[22,23]

The 12 week cardiac rehabilitation programme tested in the present study has been offered to patients with ischaemic heart disease for more than a decade. Rehabilitation has never been offered to PAD patients, as unfortunately they are not considered to be at the same high risk as patients with coronary artery disease, despite the fact that mortality from PAD is similar to that of coronary heart disease and that the mortality is caused by the same underlying condition.[1]

The significant findings on MWD and better QoL are in accordance with findings in a *Cochrane Review* by Lauret *et al.*, who compared SET with alternative modes of exercise therapy including cycling, strength training, and upper arm ergometry, and found improvement in MWD and QoL.[24] The effect on walking distance is also in accordance with findings in a *Cochrane Review* by Lane *et al.*, who found that exercise for IC improved MWD by 108.99 m (95% CI 38.20 − 179.78).[25] Based on these findings, Kruidenier *et al.* suggest that a more pain free mode of training would be more attractive to patients and result in better compliance and lower dropout rates.[21]

The HADS score showed no statistically significant differences, but high anxiety scores ($\geq$ 8) were found in both groups. High prevalence of anxiety and depressive disorders among patients with PAD has been found previously,[26] and such disorders are underdiagnosed in clinical practice and, hence, not properly treated.[27] Both anxiety and depression are risk factors for cardiovascular diseases. There is a need to address anxiety and depression in patients with PAD, and a more focused intervention addressing these issues may have more impact on outcomes.[28]

Improvement in the diet score was found in the intervention group; however, a low percentage of "healthy" was detected in both groups. Very few participants ate vegetables and fruit every day. A recent study of 100 191 adults found that cardiovascular, non-cardiovascular, and all cause mortality increased gradually with increasing non-adherence to dietary guidelines. Cardiovascular mortality was 30% higher, non-cardiovascular mortality 54% higher, and all cause mortality 43% higher compared with those with very high adherence.[29] Despite evidence to support the benefits of dietary modification in risk reduction, adults with IC continue to consume poor diets.[30] There could be several reasons for the lack of differences between groups at the six month stage of the programme. Health behaviour is, by nature, difficult to change. A smoking cessation course was not a specific part of the design in the programme. The participants were informed about local smoking cessation courses and given cards with contact information. A systematic review and meta-analysis by Papadakis *et al.* concludes that the method "Very brief advice" where the initiative and direct registration to a smoking cession course is taken by the healthcare provider without giving any advice is effective,[31] and this method may have improved the outcome.

Limitations

External validity is high as this population was included following Clinical Practice Guidelines on Diagnosis and Treatment of

Peripheral Arterial Diseases from 2017. However, about one third of potential eligible patients were randomised and this may represent bias. Even though there were no statistically significant differences between participants and non-participants in age and sex, some of the reasons for not participating included being in a job or doing self training. Self training is an important part of the treatment, and some of the patients can do it on their own, which might also explain improvements in MWD in both groups of the trial. A larger percentage of younger participants might welcome a rehabilitation programme with a flexible timespan.

The primary outcome MWD was obtained using a standardised treadmill walking test with random temporal variation from day to day and for the time of day the test was performed. However, these conditions were the same for both groups and group affiliation was blinded in the follow up treadmill test. Furthermore, to minimise detection bias, a manual was developed to guide the research assistant during the test. MWD measured by treadmill test was chosen as the primary outcome as a reliable measuring tool.[13]

Some studies use measurement of ankle brachial index before and after exercise interventions but were deselected in accordance with a *Cochrane Review* by Lane *et al.*, who concluded that exercise does not improve the ABI.[25] The secondary and exploratory outcomes were measured by self reported questionnaires. This kind of patient reported outcome is, by nature, subjective and relies on patient memory, which carries the risk of recall bias. Data management and analysis were conducted by two blinded statisticians independently of the researchers who interpreted data.

In conclusion, the present study showed that a specialised community based three month cardiovascular rehabilitation programme improved maximum walking distance, physical activity, quality of life, and healthy diet, but not pain free walking distance and smoking, compared with usual care without rehabilitation.

Guidelines on cardiac rehabilitation, for example from the European Society of Cardiology, Danish Health Authority, and British Heart Foundation, can be used as inspiration for how to set up a rehabilitation programme for patients with IC.

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CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2021.04.004.

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