Short interval or continuous training programs to improve walking distance for intermittent claudication: Pilot study

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Short title: Training with active recovery for intermittent claudication

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Abstract

Objective. Supervised exercise training is part of first-line therapies for intermittent claudication. Short periods of intensive treadmill training have been found efficient; however, the optimal modalities remain to be determined, especially interval training with active recovery (ITAR). In this prospective assessor-blinded single-centre pilot study, we assessed the feasibility of a randomised controlled trial comparing parallel 4-week intensive rehabilitation programs comprising treadmill training performed as ITAR or conventional training with constant slope and speed interspersed with rest periods (CT).

Methods. A total of 38 in- or out-patients were randomised to the ITAR or CT program for 5 days/week for 4 weeks. The primary outcome was change in maximum walking distance measured on a graded treadmill before and after the program.

Results. Adherence was high. All training sessions were completed in the ITAR program and only a few were not completed in the CT program (median 100% [Q1–Q3 96-100]). Tolerance was excellent (no adverse events). VO_{2peak} was low in both groups, corresponding to moderate to severe exercise intolerance. The 2 groups did not differ in the primary outcome (median ITAR vs CT 480 [135-715] vs 315 m [0-710]; p=0.62) or other walking distances (constant speed and gradient treadmill test). For all 38 participants, both programs greatly increased maximum walking distance in the graded treadmill test: median 415 [240-650] to 995 m [410-1490], with a large effect size ($p<10^{-4}$).

Conclusion. A 4-week intensive rehabilitation program with ITAR or CT for intermittent claudication showed high adherence, was well tolerated, and improved walking distance as much as that reported for longer conventional programs. These findings prompt the design of a larger multicenter randomised controlled trial.

Key Words: peripheral arterial disease; intermittent claudication; physical therapy; exercise physiology; treadmill training with active recovery; supervised exercise

ClinicalTrials.gov registration**:** NCT01734603

Introduction

Peripheral artery disease (PAD) with intermittent claudication (IC) affects about 2% of the general population, severely limiting walking ability and physical activity [1-5]. We now have strong evidence that individuals with IC should receive management of cardiovascular risk factors [1, 3, 6-9], therapeutic education [1, 3, 8-10], and medical treatment [1, 3, 8, 9] and should perform supervised exercise therapy [1, 6, 7, 11-15] and home exercises [7, 14, 16, 17].

Since the 1970s [5], treadmill exercise therapy has become an important part of rehabilitation programs for individuals with IC [6, 18, 19], although other training modalities may also be efficient [7, 20]. The benefits are multifactorial, attributed to metabolic and microcirculatory adaptations of the muscles and to improvements in cardiorespiratory fitness [21-23]. However, the duration and frequency of sessions (number of hours per day and days per week) is debated, as is the total length of rehabilitation programs. Programs may last from 6 weeks to 6 months, the frequency of sessions inversely proportional to the total length [24, 25].

The interest in short intensive programs of several days per week is increasing [6, 18, 26]. Such programs induce a rapid gain in walking abilities (within the first 2 months), maintained with further training [27]. Relatively short rehabilitation programs (6-8 weeks) might have better adherence than less intensive programs spread out over 6 months as well as less cost, thereby allowing more individuals to be treated [26-28]. As well, the duration and frequency of rehabilitation sessions might be reduced to reduce the total length of the program to 4 weeks [28]. Hence, individuals living far from the rehabilitation centre might more easily benefit from such programs [28].

Conventional training (CT) on a treadmill is often performed at an intensity close to the maximum tolerated before the onset of claudication pain. When claudication pain occurs, the pain imposes complete rest before continuing the exercise. During interval training with active recovery (ITAR), exercise is at a level well below the pain threshold and is interspersed with periods of low-level exercise but not rest. Such low-intensity active recovery facilitates lactate removal [29] favouring better metabolic recovery of muscles [30]. Hence, ITAR is efficient and safe for cardiac [31-33], respiratory [34], and metabolic [35] rehabilitation, with preliminary evidence suggesting that it might provide benefits for patients with IC [26].

The results of our preliminary pilot study of individuals with PAD, involving 2 weeks of the ITAR modality only, were encouraging, with walking distance clearly increased as compared to baseline [28]. In the present study, we investigated the feasibility of a parallel-group randomised study design, this time comparing two 4-week intensive treadmill exercise programs, ITAR versus CT, at constant speed and slope with rest recovery if necessary.

Methods

Study design and setting

This study was a prospective assessor-blinded single-center randomised controlled trial that compared 2 parallel rehabilitation interventions. It took place at Grenoble Alpes University Hospital (France) from November 2012 to March 2014. The objectives were to assess the feasibility of intensive 4-week treadmill exercise programs for PAD and compare 2 modes of treadmill training: ITAR and CT. All physiotherapists and rehabilitation physicians involved had received specific training and had at least 10 years of experience working with PAD patients in a university hospital setting.

Ethics

The study protocol was approved by the regional medical research ethics committee (French *Comité de Protection des Personnes* CPP Sud-Est V: no. 2011 A00969-32). The study was financed by Grenoble Alpes University Hospital and registered at ClinicalTrials.gov (NCT01734603). Written informed consent was obtained from all participants. The CONSORT guidelines for reporting randomised trials of non-pharmacological treatments were followed.

Inclusion and non-inclusion criteria

Individuals, with or without prior revascularization, were referred by their vascular surgeon, specialist in vascular medicine, or general practitioner. All eligible participants had been examined by their cardiologist and vascular physician less than 3 months before inclusion. This examination included evaluation of potential acute cardiac comorbidities, such as myocardial ischemia, severe heart rhythm disorders or conduction disorders by exercise myocardial perfusion scintigraphy, a graded maximal exercise test on an ergocycle or stress echocardiography (exercise or dobutamine). The inclusion criteria were out-patient or hospitalized patient 18 to 80 years old with claudication (in one or both lower limbs) due to PAD diagnosed by a trained vascular physician based on a duplex scan, ankle–brachial index < 0.90 at rest and a 20% decrease in ankle–brachial index after a constant speed (3 km/hr) and constant gradient (10%) treadmill test (C-test, often called the "Strandness test"). Non-inclusion criteria were exercise tolerance limited by factors other than claudication (poorly controlled blood pressure, acute coronary artery disease, dyspnea, severe osteoarticular or neurological deficiencies) or abdominal aortic aneurysm with diameter > 40 mm.

Common therapeutic program

All participants received therapeutic education on the management of cardiovascular risk factors. Their regular medication remained unchanged during the study. They were advised on the need to walk for at least 1 hr a day, at a pain-free level, if they wanted to maintain the benefits of training. All participants followed a 4-week rehabilitation program (20 working days, 3 hr/day) that combined supervised treadmill training (CT or ITAR) plus additional daily 2-hr supervised physical therapy sessions. During this program, all individuals had a daily medical check-up to detect any adverse events and ensure that the training was well tolerated.

Treadmill training was performed on a TechmedPhysio® treadmill (Auxerre, France) allowing precise speed and slope adjustments (speed accuracy 0.1 km/hr [0.06 mph] and slope accuracy 0.5%). For each participant, training was adjusted according to their baseline maximal walking speed, determined without slope but with a speed increased by 1 km/hr every 3 min to find the speed at which maximum tolerable pain occurred. Then during the training period, the intensity incremental was based on the achievement of the previous session. After each successfully completed session, either the slope or the speed was increased (Fig. 1).

Additional supervised exercises combined 20 min of continuous arm-cycling (starting at 10 watts and increased by 5 watts weekly, depending on upper-limb tolerance), 20 min of stationary ergocycle (starting at 25 watts and increased by 5 watts weekly) and 45 min of soft floor gymnastics. Each workshop was separated by about 5 min of passive recovery.

Specific interventions

The 2 arms differed in the modality of the treadmill training (Fig. 1). In the CT arm, individuals walked at the predetermined constant speed, completely stopping if in pain and resting until the pain ceased. In ITAR, individuals alternated 2 different walking speeds and slope, constituting the exercise and recovery periods. Each session lasted 40 min, including warm-up.

Conventional training (CT)

This program, presented in Figure 1 (left side) was based on that proposed by Hiatt et al. [22]. Each treadmill session lasted 50 min, including a 5-min warm-up, 40 min of exercise at constant speed and slope (including a 10-min run-in period), then 5 min of relaxation. The initial speed was set at 3.2 km/hr (2 mph) with 0% slope, but 11 individuals unable to walk at this speed started at 1.6 km/hr with 0% slope. If claudication pain occurred (≥3 on the 4-point claudication pain rating scale of the American College of Sports Medicine) [22], individuals could stop walking until all pain ceased, before restarting [10]. For this reason, the total duration of CT sessions was set at 10 min longer than the ITAR program. The training intensity was increased the next session if the individual was able to walk for at least 8 min.

Interval training with active recovery (ITAR)

This training program is also presented in Figure 1 (right side). Each session lasted 40 min starting with 5-min warm up, then 5 cycles of 6 min: 3 min of walking at the targeted intensity followed by 3 min of active recovery, and finally 5 min of relaxation.

At the first session, the walking speed was set at 70% and active recovery speed at 40% of baseline walking speed. If no claudication pain occurred during the training session, the intensity was increased at the next session.

Randomisation and blinding

The randomisation procedure was centralised, using a computer random-number generator with random block size. Participants were included after screening for eligibility and randomised after baseline assessments. Participants were aware of the type of training program (ITAR or CT) but were assumed to have no idea as to which one was thought to be superior. Assessments were performed by 2 physiotherapists and physicians who were blinded to treatment allocation.

Assessments

The battery of assessments was performed at baseline during the week before the start of training and in the week after the end of the program, when walking distances and cardiovascular, respiratory and psychological parameters were collected, in addition to general medical data.

Walking distance tests were performed with at least a 20-min rest between each test, in the following order: 6-min walk test (6MWT) [36, 37], maximum distance at constant speed and gradient before onset of claudication (C-test) [38], a graded treadmill test (G-test) derived from the Gardner test [39], and finally a treadmill test of maximal walking speed before onset of maximum tolerable pain with measurement of $VO_{2peak,}$.

For the 6MWT, participants were instructed to walk at their fastest comfortable speed on a flat surface (e.g., along a corridor) for 6 min, with or without stopping for rests. As recommended for patients with PAD [40], the 6MWT was performed after 15 min of rest. The C-test was performed at 3.2 km/hr (2 mph) on a 10% slope (TechmedPhysio® treadmill). The G-test started at 3.2 km/hr and 0% slope. With speed remaining constant, the slope was increased by 0.5% every 2 min until limited by pain (claudication). The slope increment was less than in the original version (2%) for better feasibility for severely affected patients able to achieve only very short walking distances [41]. For participants with the most severe disease and balance disorders, handrail support was allowed during all treadmill tests. Running during treadmill tests was not allowed.

Cardiopulmonary exercise testing was performed at baseline and during certain treadmill tests to assess exercise tolerance and energy expenditure. Aerobic capacity and cardiovascular, metabolic and respiratory parameters were measured during a graded exercise test on a Gymrol Super 2500 treadmill (Tecmachine SA, Andrezieux-Boutheon, France). The initial speed was 2.4 km/hr with no slope. The speed or slope was increased every 2 min by 2% or 0.8-km/hr increments, respectively, until pain limitation or exhaustion. Gas exchange was measured continuously on an automated ergospirometer with a mixing chamber method (Metasys TRM, Brainware, Toulon France), allowing for monitoring oxygen uptake (VO_2).

Outcomes

The primary outcome was the change in maximum walking distance (MWD) on the G-test. Secondary outcomes were feasibility and safety of the program (adverse effects during the sessions or reported at the daily medical check-up), adherence to rehabilitation (total number of sessions attended*100/total number of sessions planned), and changes in other walking distances (6MWT, C-test) and cardiorespiratory and exercise parameters.

Sample size

Taking into account the results of our previous non-randomised pilot study [28] we hypothesized an improvement of 650 m (±350) in the ITAR group and an improvement of 300 m (±350) in the CT group in a graded treadmill test. To show this clinically significant between-group difference in walking distance of 350 m (Mann-Whitney test), with power of 80% and alpha risk of 5%, we estimated that we needed 36 participants (18 in each group). We planned to include 10% more participants (i.e., 40 individuals) in anticipation of potential dropouts.

Statistical analysis

The statistician was blinded to the intervention group. Statistical analysis was according to intention to treat and by using Stata v13.0 (Stata Corp., College Station, TX). $P<0.05$ was considered statistically significant. Categorical variables are expressed with number (percentage) and continuous variables with median (interquartile range [Q1–Q3]). For quantitative variables, we used the Mann-Whitney (non-parametric) test to compare the 2 groups. The effect sizes of significant differences were calculated with the z values of the Mann-Whitney test [$r = \frac{z}{\sqrt{N}}$] and interpreted according to Cohen's guidelines (1988) as medium difference with $r > 0.29$ and large difference with $r > 0.49$.

Results

Participant characteristics

Among the 60 individuals screened, 40 were enrolled between November 2012 and April 2014. The flow chart of the study in Figure 2 respects the extension of the CONSORT statement for randomised pilot and feasibility trials [42]. Characteristics of participants are in Table 1. Because 2 participants in the CT arm were included in error and were excluded soon after randomisation, and given the relatively small sample size of the study, some variables differed between the 2 arms (Table 1). ITAR participants were older, tended to be diabetic, and had higher body mass index and bilateral IC than CT participants. All received antiplatelet agents and statins; none was on pentoxyfylline or cilostazol.

Adherence and safety

No adverse event related to the training programs was reported. Adherence to the ITAR program was excellent throughout the entire study; all 20 individuals successfully completed all daily training sessions. Three participants in the CT program did not complete all training sessions. One participated only sporadically in the study due to alcohol abuse; chronic heart failure was discovered in a second participant, and the steering committee decided to stop this participant’s participation prematurely for safety reasons and delete the data from the database considering that he/she had been wrongly included. A third individual missed a few training sessions but finished the study. Finally in the CT arm, the median number of completed sessions was 100% [Q1–Q3 96–100]. This procedure maintained intention to treat.

Walking distances

Table 2 and Figure 3 show maximum walking distances before and after the training programs. The main outcome criterion (MWD measured with the G-test) improved in both arms ($p=0.007$ for CT and $p <0.001$ for ITAR), but this improvement was not significantly different between the groups ($p=0.62$). Likewise, the secondary outcome MWD was improved in both groups, with no significant difference between the groups whatever the test used: C-test ($p=0.76$) or 6MWT ($p=0.84$). Because of the lack of difference between the 2 groups, we compared the MWD for the whole study population of 38 participants before and after the program. The improvement in treadmill walking distances reached nearly 100% with very large effect sizes: median distance before vs after was 415 [240-650] vs 995 m [410-1490], respectively, with $r=0.71$ and $p<10^{-4}$ for the G-test, and 150 [90-290] vs 290 m [140-530], respectively, with $r=0.84$ and $p<10^{-4}$ for the C-test. The before-after difference was less marked when walking along the floor at comfortable speed (6MWT): median 355 [298-398] vs 378 m [338-428], respectively with $r=0.54$ and $p<10^{-3}$. For several participants, claudication was not reached until after 6 min.

Exercise tolerance

Table 2 shows that VO_{2peak} was low in both arms for participants' age, corresponding to about 65% to 70% of the predicted value. This finding corresponds to a moderate to severe exercise intolerance. We found no significant difference in VO_2 change between the 2 groups after the training.

Discussion

To our knowledge, this is the first randomised trial to assess the efficiency of a short exercise program for PAD, lasting 4 weeks; almost all other reported programs lasted at least 6 weeks.

A short program is feasible, safe and efficient

Both programs, CT and ITAR, were safe, with no adverse events. Hence, individuals with severe IC may follow an intensive rehabilitation program of 3 hr/day for 4 weeks, provided potential cardiovascular complications have been previously identified. In our study, all individuals underwent assessment by 2 specialists, in cardiology and vascular medicine, and eligibility to participate in the program was carefully weighed for each participant. Our study exhibited one of the highest rates of adherence to treatment ever reported in IC rehabilitation, but this is likely due to the duration of the program, the shortest proposed so far. Indeed, a 6-month trial found that adherence to exercise progressively declines [27]. This observation clearly argues in favour of short programs, which seem more suitable for individuals who are still working, and also might be less costly for both patients and the community. Future medico-economic studies need to investigate this issue.

The major finding of this study was that individuals who completed an ITAR or CT program improved their physical capabilities without any significant differences in the primary or secondary criteria. Indeed, the increases in walking distance of 315 and 480 m in CT and ITAR groups, respectively, along with doubling the MWD on the Gardner test with a very large effect size, were greater than the minimally important improvement considered in the field (305 m) [43], and higher than that reported in most studies [7, 12, 15, 18, 26, 34, 44] .

The second finding was that a 4-week exercise training program increased the MWD by a clinically relevant level in individuals with PAD, as shown by the main (G-test) and secondary outcomes (6MWT, C-test), and the results were similar to those from previous trials with exercise programs lasting 6 months [45].

Differences between the 2 programs

Similar improvements in walking distance were observed in both groups despite lower intensity relative to the VO_{2peak} in the ITAR arm. This finding could be explained by both programs being performed at relatively low intensities regarding percentage of VO_{2peak} (about 50%) because the included participants had shown exercise intolerance. Also, we cannot exclude that the other exercise activities that formed part of the rehabilitation along with the treadmill training may have played a role in the improved physical functioning in both groups.

Strengths and limitations

The strengths of the study include the training being intensive (> 3 hr/day) with daily medical check-ups to detect adverse events and assessments by 2 different physiotherapists and physicians.

Although the results of this trial support the efficacy of both 4-week physical therapy programs for individuals with PAD as compared with results obtained by previous published studies, our study had several limitations. In retrospect, the study was underpowered to be able to conclude for the main objective, and the comparison between the two groups featured a risk of randomization in which participants of the control group were significantly younger. Also, the relatively small sample size (calculated for the primary outcome) may explain why some results for the secondary outcomes did not reach significance, although other studies have been able to show improvements in basic cardiorespiratory parameters [12, 31]. Most assessments were performed with blinding to treatment group, but there were some exceptions regarding walking tests for some participants due to the unforeseen unavailability of physiotherapists. Treadmill training made up only one-third of the daily rehabilitation. This situation may explain the lack of significant difference between the 2 types of program. Indeed, the other exercises performed during the common part of the rehabilitation have also been found effective in increasing aerobic capacity and walking abilities in people with PAD [44]. Current smokers were included in the study, which might have influenced response to training with altered muscular or cardiorespiratory adaptations, but the number of current smokers did not differ significantly between the 2 groups. The long-term maintenance of progress achieved during a course of exercise training (long or short) remains a challenge, and a panel of strategies is needed to encourage patients to continue exercising. This will require long-term patient follow-up, but for logistic reasons the present study was not designed to do this. Long-term follow-up with regular simple home-based exercises, possibly using information technology, should be included in future trials of exercise strategies.

Exercise has multiple effects on the physiology of PAD, influencing quality of life, morbidity and mortality. Analysing the neurovegetative and metabolic effects of the exercise programs would have been of interest.

Concerning the tests used, because claudication was not reached in some participants during the 6MWT, this test may not be well adapted to the context of this study. In addition, the question of the most-effective intensity of effort to increase the walking distance remains (should the pain of claudication be induced during walking?): for certain authors, the answer is no [44,46,47], for others it is yes [7, 48].

Conclusion

This study showed the tolerance, high adherence, and efficacy of a 4-week supervised intensive rehabilitation program based on ITAR or conventional treadmill training (3 hr/day except weekends) designed for individuals with intermittent claudication. With both programs, walking ability improved as much as with less-intensive (3 days/week) and longer (6-month) programs described in the literature, with maximal walking distance on treadmill tests multiplied by 2 and very large effect sizes. These results appeal for further studies with larger sample sizes and long-term follow-up.

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Conflict of interest. None declared.

Figure legends

Figure 1. Four-week **t**readmill training programs: left part, conventional training (CT) and right part, interval training with active recovery (ITAR). Wk, week

Figure 2. Flow chart of the study, according the extension of the CONSORT statement for randomised pilot and feasibility trials [44]. ITAR, interval training with active recovery; VO_2, oxygen uptake

Figure 3. Maximum walking distance (m) before and after interval training with active recovery (ITAR) or conventional training (CT) in a graded treadmill test (G-test). Maximum walking distance improved in both arms ($p=0.007$ for CT and $p<0.001$ for ITAR), without significant difference between gains in both arms ($p=0.62$).

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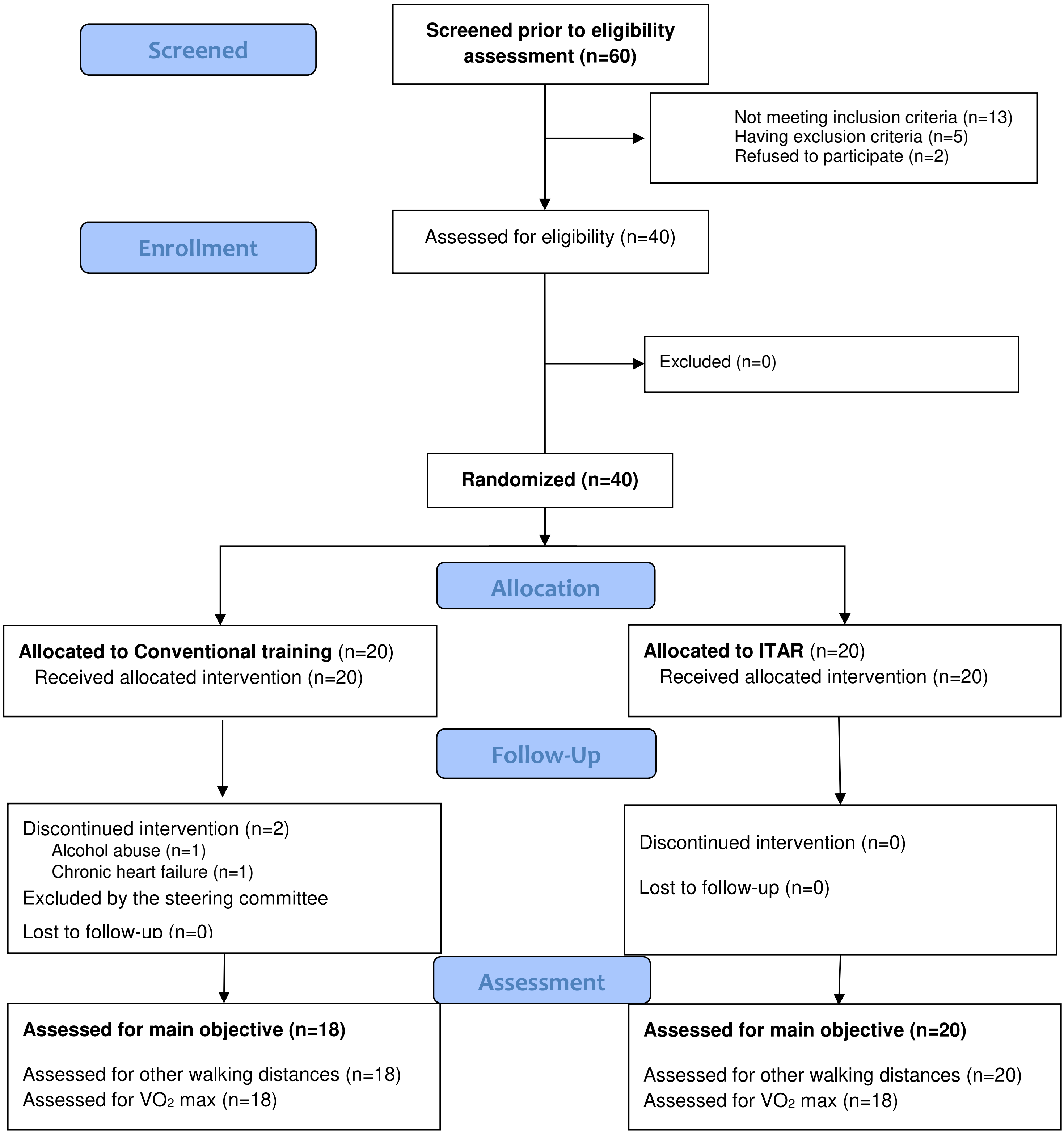
4 week treadmill training program

	Conventional training group	ITAR group
Week 1	**1st day**: 3.2 km/h and 0% slope (1.6 km/h if too difficult) **Slope increased by 0.5 % each day**	**1st day** - Work period: speed = 70% of the maximum, slope = 0% - Active recovery: speed = 40% of the maximum, slope = 0% **Speed increased by 0.1km/h each day**
Week 2	**1st day**: speed at 3.2 km/h and slope at the maximum of Wk1 **Speed increased by 0.32 km/h each day**	**1st day** - Work period: speed = average of Wk1, slope = average of Wk1 - Active recovery: speed = average of Wk1, slope = 0% **Slope increased by 0.5 % each day**
Week 3	**1st day**: speed at maximum of Wk2, Slope +2% of the maximum of Wk2 **Slope increased by 2 % each day**	**1st day** - Work period: speed = maximum of Wk1, slope = average of Wk2 - Active recovery: speed = maximum of Wk1, slope= 0% **Speed increased by 0.1km/h each day**
Week 4	**1stday**: speed + 0.32 km/h of the maximum of Wk3, slope at the maximum of Wk3 **Speed increased by 0.32 km/h each day**	**1stday** - Work period: speed = maximum of Wk1, slope = average of W2 - Active recovery: speed = maximum of Wk1, slope = 0%. **Slope increased by 0.5 % each day**


Screened
Screened prior to eligibility assessment (n=60)
Not meeting inclusion criteria (n=13)
Having exclusion criteria (n=5)
Refused to participate (n=2)
Enrollment
Assessed for eligibility (n=40)
Excluded (n=0)
Randomized (n=40)
Allocation
Allocated to Conventional training (n=20)
Received allocated intervention (n=20)
Allocated to ITAR (n=20)
Received allocated intervention (n=20)
Follow-Up
Discontinued intervention (n=2)
Alcohol abuse (n=1)
Chronic heart failure (n=1)
Excluded by the steering committee
Lost to follow-up (n=0)
Discontinued intervention (n=0)
Lost to follow-up (n=0)
Assessment
Assessed for main objective (n=18)
Assessed for other walking distances (n=18)
Assessed for VO2 max (n=18)
Assessed for main objective (n=20)
Assessed for other walking distances (n=20)
Assessed for VO2 max (n=18)

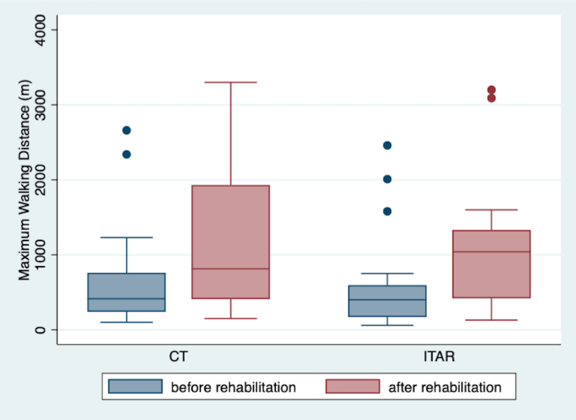

Maximum Walking Distance (m)
4000
3000
2000
1000
0
CT
ITAR
before rehabilitation
after rehabilitation

Table 1. Baseline clinical characteristics of participants undergoing conventional (treadmill) training (CT) and interval training with active recovery (ITAR).

	CT group (n=18)	ITAR group (n=20)	p-value
Age (years), median [Q1–Q3]	62 [51-64]	68 [63-70]	0.03
Male, n (%)	15 (83%)	16 (80%)	1.00
Body mass index, kg/m^{-2}	27.2 [24.4-29.5]	29.8[27.9-32.1]	0.05
High blood pressure, n (%)	14 (78%)	18 (90%)	0.39
Diabetes, n (%)	6 (33%)	12 (60%)	0.10
Dyslipidemia, n (%)	15 (83%)	18 (90%)	0.65
Tobacco consumption (%)			
Never	0%	2 (10%)	
Former	11 (61%)	15 (75%)	0.13
Current	7 (39%)	3 (15%)	
Previous surgery of lower limb arteries, n (%)	6 (33%)	4 (20%)	0.47
Claudication side, n (%)			
Unilateral	9R+4L (72%)	5R+4L (45%)	0.09
Bilateral	5 (28%)	11 (55%)	
Arterial Doppler ultrasound			
Hemodynamically significant arterial stenosis, n (%)	13 (72%)	14 (70%)	0.88
Distal	2 (15%)	0%	
Proximal	10 (77%)	12 (86%)	
Both	1 (8%)	2 (14%)	
Artery occlusion, n (%)	14 (78%)	14 (70%)	0.72
Distal	2 (14%)	3 (21%)	
Proximal	11 (79%)	9 (64%)	
Both	1 (7%)	2 (14%)	

R, right; L, left

Table 2. Walking measurements. 415 [240-650] vs 995m [410-1490]

Variables	Pre-training (baseline)	Post-training	Change in score	P-value (CT vs ITAR)
Graded treadmill test:				
MWD (m)				
CT (n=18)	415 [240-760]	815 [410-1930]	315 [0-710]	0.62
ITAR (n=20)	400 [170-595]	1040 [420-1330]	480 [135-715]	
C-test: MWD (m)				
CT (n=18)	135 [100-270]	205 [140-500]	110 [20-230]	0.76
ITAR (n=20)	170 [85-295]	350 [165-620]	130 [35-325]	
6MWT (m)				
CT (n=18)	357 [245-398]	363 [330-403]	40 [-40-98]	0.84
ITAR (n=20)	356 [306-403]	390 [342-436]	37 [14-49]	
$VO_{2\ peak}$ (mL/kg/min)				
CT (n=18)	18.2 [13.9-21.0]	17.7 [15.0-23.4]	1.1 [-2.2-4.6]	0.72
ITAR (n=20)	17.9 [15.7-21.8]	17.8 [14.7-25.1]*	0.7 [-0.5-3.0]*	

Mann-Whitney tests comparing gain after rehabilitation between ITAR and CT.
Data are median [Q1–Q3].
MWD, maximum walking distance; 6MWT, 6-min walk test.
* 2 missing values