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Supervised exercise for acute coronary patients in primary care: a randomized clinical trial

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The CONSORT guidelines were followed. A flowchart of the study profile is shown in Figure 1 and a checklist is attached.

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Abstract

Background. Functional capacity is a prognostic factor for coronary patients; accordingly, they are recommended to walk.

Objective. To assess whether an exercise program supervised in primary care increases their functional capacity more than unsupervised walking.

Methods. A randomized clinical trial was carried out at eight primary care centres of the Spanish Health Service and involving 97 incident cases of low-risk acute coronary patients, <80 years old, randomly assigned to either an unsupervised walking program (UW group; $n = 51$) or a 6-month cycle ergometer exercise program with gradually increasing frequency and workload intensity supervised by primary care nurses (SE group; $n = 46$). The two groups received the same common components of secondary prevention care. Changes in functional capacity were assessed in terms of peak oxygen consumption (VO_2peak) during exercise testing measured at baseline and at 7 months by cardiologists blinded to group assignment.

Results. Overall, 76% of participants completed the study, 30 in the SE and 44 in the UW. Both groups increased baseline-adjusted VO_2peak: 5.56 ml/kg per minute in the SE (95% confidence interval [CI] 3.38–7.74) and 1.64 ml/kg per minute in the UW (95% CI –0.15 to 3.45). The multivariate-adjusted difference between groups was 4.30 ml/kg per minute (95% CI 1.82–6.79; $P = 0.001$) when analyzing completers and 2.83 ml/kg per minute (95% CI 0.61–5.05; $P = 0.01$) in the intention-to-treat analysis, including all participants with baseline values carried forward for those lost to follow-up.

Conclusions. A cycle ergometer exercise program supervised by primary care nurses increased the functional capacity of coronary patients more than unsupervised walking with a clinically relevant difference.

Key words: Coronary disease, exercise capacity, exercise training, myocardial infarction, primary health care, prognosis

Introduction

Functional capacity has been shown to be inversely associated with all-cause (1) and cardiovascular (2) morbidity and mortality in coronary heart disease (CHD) patients. Increases in this parameter reflect an improvement in heart function, as assessed by resting heart rate (HR) and its response to exercise, which, in turn, have been recognized to be prognostic factors for morbidity and mortality in individuals with and without CHD (3–7).

People who have suffered a CHD event, and are not included in cardiac rehabilitation programs, are usually recommended unsupervised walking (UW) by their family physicians, with more emphasis on amount (frequency/duration) than on intensity. Walking is a form of exercise of sufficient intensity to achieve cardiovascular benefits (8) and to increase functional capacity (9).

We showed in a previous pilot study that while a supervised exercise (SE) program, with progressively increasing workloads, was capable of achieving the target intensity (>40% HR reserve) for 97% of the time during the sessions, UW was not (10). Considering that the increase in functional capacity seems to be more dependent on exercise intensity than on amount (11), we hypothesized that patients would get more benefit from our training program under supervision in their primary care centre (PCC), compared to walking without supervision. Therefore, the aim of this study was to test whether low-risk patients who have suffered an acute CHD event increase their functional capacity more with our SE program at their PCC or with UW.

Methods

Setting and design

This was a parallel, randomized clinical trial carried out from February 2005 to June 2010 at 8 PCCs of the Spanish Health Service with two groups: intervention (SE) and comparison (UW). The Clinical Research Ethics Committee from every participant PCC reviewed and approved the study protocol.

Participants

All low-risk incident cases of myocardial infarction, coronary artery bypass grafting, angioplasty, stable angina, or angiographic CHD were eligible for the study, provided that patients were <80 years old. Low-risk criteria included all of the following: an uncomplicated course, functional capacity ≥7 metabolic equivalents (METs), ejection fraction >50%, no resting or exercise myocardial ischemia or complex arrhythmia (12). As well as age (≥80 years old), the exclusion criteria were that the individual was assessed as moderate or high risk, was already participating in a cardiac rehabilitation program, was unable to attend SE sessions, had medical conditions in which exercise was an absolute or relative contraindication (13),or the time from when the patients were discharged from the hospital was >12 weeks.

A primary care research nurse established an active surveillance system to identify all new cases of CHD that occurred from February 2005 to December 2009 within the health region of each of the eight PCCs collaborating in the study and contacted the cardiology services of the referral hospitals every week. Only eight supervised patients were recruited per PCC at any given time, due to the constraints of equipment and space available. All of the identified and eligible CHD patients, having been classified as low risk by a cardiologist within 12 weeks of their event, were referred to the family physician investigator at each PCC for the preliminary visit. The patients were invited to participate and sign an informed consent form after receiving information about the study objectives and other details.

Once the patients had given informed consent, they were referred to research nurses for baseline measurement visit. After taking all the patient's baseline measures, research nurses telephoned the Primary Care Research Unit of Bizkaia to register the participant and to have the patient randomly assigned to one of the two study groups. For this, a randomization procedure of blocks of four patients stratified by PCC was used.

Interventions

At the initial visit, physician investigators provided both groups with the following standardized common elements of CHD secondary prevention (14): psychopharmacological treatment, teaching of a relaxation technique, advice concerning work and sexual activity, diet/nutritional counselling, weight control management, lipid management, blood pressure monitoring, and smoking cessation.

The UW comparison group was, in addition, provided with written guidelines on following the walking program, which is detailed in Appendix 1.

The SE group was offered a SE program at the PCC lasting 24–28 weeks, which was the maximum time to complete 96 sessions of 38 minutes spent pedalling on a cycle ergometer. HR monitoring was realized using a HR monitor with audible alarms (Polar S625X), which recorded all data into its memory. The research nurse monitored all the patient's exercise sessions throughout the program and measured his/her blood pressure during the initial sessions. The schedule followed was three sessions/week until the end of week 8, four sessions/week from week 9 to 16, and five sessions/week from week 17 to the end. All the details of the SE program are offered in Appendix 2.

To ensure that the patient's HR did not go beyond the prescribed upper conditioning HR, the HR monitor alarm was programmed to beep when it reached that level.

Physician investigators and research nurses were provided training through a 20-hour workshop to enable them to acquire the knowledge and skills needed to standardize the two interventions being compared, as well as to study measurements and procedures. They were assisted in measurements and interventions by computer software.

Measurements

The main outcome variable was the functional capacity as measured by peak oxygen consumption (VO_2peak) in ml/kg per minute. This was measured before and after the intervention, in a blind manner, at the referral centre for cardiology by using the Bruce treadmill exercise stress test (15).

Secondary outcome variables included blood lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), resting blood pressure, HR, and body weight, measured by research nurses before and after the intervention. The following variables were recorded as potential confounders: sex, age, PCC, social class, level of education, current health problems, smoking habit, and use of medication (see Table 1).

Follow-up

Three follow-up appointments were held with research physicians at 4, 10 and 16 weeks. These follow-up appointments included discussion of relevant health education topics, reinforcement of favourable changes made in diet/nutrition and smoking, and emphasizing the need to change the remaining unhealthy behaviours, such as unhealthy diet/poor nutrition and smoking. In these appointments, the physician investigators also evaluated and reviewed the impact of the intervention on weight, lipids and blood pressure control and checked adherence to the exercise program. Finally, the HR of patients in the UW group was recorded using a HR monitor for one walking session on the same day as the clinical follow-up appointment. On that day, the research nurse placed the same HR monitor that was used for SE on the patient's chest (transmitter) and wrist (receptor), and then the patient began a walking session. When he/she finished this session, he/she returned to the research nurse who removed the HR monitor and took the data from the memory to be saved to a computer file.

Sample size

A sample size of 144 patients (72 per group) would have meant that the study had 95% power and a two-sided level of significance of 5% to detect a difference of 2.4 ml/kg per minute in VO_2peak between the SE and UW groups, assuming a 15% loss to follow-up in both groups. That figure is considered the minimum difference clinically relevant because it allows activity performance at 0.7 MET higher intensity, i.e. walking 1 km/hour faster than the reference group. Unfortunately, we were only able to include 97 patients in the study (Figure 1) due to restrictions on funding.

Statistical analysis

Baseline characteristics of the two groups were compared using a two-tailed Student's *t*-test for continuous variables and Fisher's exact test or chi-square test for categorical variables. Logistic regression analysis was performed to identify characteristics associated with loss to follow-up. Change scores were calculated for the outcome variables by subtracting the 7-month follow-up results from the corresponding baseline values. Differences between the SE and UW groups in these changes in outcome variables were analysed on an intention-to-treat basis. First, we focused on only the participants that completed the final assessment, and second, all participants included in the study were analysed, with baseline observations carried forward for those who failed to attend the final assessment. We tested the treatment group effect and assessed the differences between the two treatment groups using analysis of covariance, adjusting each patient's follow-up score for his/her baseline score. In addition, these statistical models were expanded to include other possible confounding variables, those with unbalanced baseline distributions and those associated with withdrawal. Finally, to take into account the multicenter nature of the study, collaborating centres were included as random effects on the intercept and on the treatment effect. Likelihood ratio tests (level of significance; $P = 0.05$) were used to simplify the models using a backward stepwise method. All the analyses were performed using the SAS™ statistical software (version 9.2; SAS Institute, Cary, NC).

Results

A total of 128 patients with acute CHD were identified (Figure 1). Of these, 115 (90%) were eligible and 97 (84%) were randomized: 46 to SE and 51 to UW group. In all cases, the reason that potential participants were considered ineligible was that they were classified as moderate or high risk.

Baseline characteristics of the 97 patients who initiated the study were well balanced between the two comparison groups (Table 1).

Thirty (63.8%) and 44 (86.2%) patients finished the study in SE and UW groups, respectively. Five men and three women in the SE group were withdrawn from the study by their physician due to concurrent illness (respiratory tract infection, depression and ankle fracture) or side effects of the training (trochanteric bursitis, two cases of excessive muscle fatigue, persistent knee

Table 1. Baseline characteristics of the 97 patients included in the study

Variable	Supervised exercise group		Unsupervised walking group	
	n		*n*	
Main outcome variable, mean (SD)				
VO_2peak, ml/kg per minute	46	35.4 (7.5)	51	35.5 (7.6)
Secondary outcome variables, mean (SD)				
Total cholesterol, mg/dl*	42	143.0 (26.3)	51	157.2 (38.5)
HDL cholesterol, mg/dl	42	44.2 (12.8)	51	45.1 (13.3)
LDL cholesterol, mg/dl	42	78.8 (27.0)	50	87.2 (31.6)
Triglycerides, mg/dl	42	119.1 (64.5)	51	131.3 (72.6)
Systolic blood pressure, mmHg	45	119.0 (19.2)	47	112.2 (15.4)
Diastolic blood pressure, mmHg	45	72.7 (10.8)	47	75.6 (9.5)
Body weight, kg	46	80.5 (13.6)	51	78.5 (13.2)
Sociodemographic variables				
Sex, No. (%)	46		51	
Men		40 (87.0)		42 (82.4)
Women		6 (13.0)		9 (17.6)
Age, mean (SD), y	46	55.4 (11.2)	51	56.1 (12.7)
Smoking habit, No. (%)	46		51	
Never smoked		6 (13.0)		13 (25.5)
Past smoker		15 (32.6)		21 (41.2)
Current smoker		25 (54.4)		17 (33.3)
Work situation, No. (%)	46		50	
Work outside of home		29 (63.0)		30 (60.0)
Homemaker		2 (4.4)		1 (2.0)
Retired		14 (30.4)		19 (38.0)
Disabled		1 (2.2)		0 (0.0)
Level of education, No. (%)	45		50	
None		3 (6.7)		2 (4.0)
Elementary school		10 (22.2)		12 (24.0)
Middle/high school		28 (62.2)		31 (62.0)
University qualifications		4 (8.9)		5 (10.0)
Social class, No. (%)	44		49	
Low		26 (59.1)		30 (61.2)
Middle		16 (36.4)		16 (32.7)
High		2 (4.5)		3 (6.1)
Primary care centre, No. (%)	46		51	
Basauri		10 (21.7)		12 (23.5)
Galdakao		9 (19.6)		10 (19.6)
Cuenca		2 (4.3)		2 (3.9)
Salamanca		12 (26.1)		12 (23.5)
Madrid		5 (10.9)		7 (13.7)
Valladolid		5 (10.9)		4 (7.8)
Torrelavega		0 (0.0)		2 (3.9)
Toledo		3 (6.5)		2 (3.9)
Medication, No. (%)				
Antithrombotic agents	46	45 (97.8)	50	48 (96.0)
Lipid-lowering agents	46	44 (95.6)	50	46 (92.0)
Beta-blockers	46	31 (67.4)	50	31 (62.0)
Antihypertensive agents	46	33 (71.7)	50	32 (64.0)
Antidiabetic agents	46	6 (13.0)	50	6 (12.0)
Nitrates	46	20 (43.5)	50	26 (52.0)
Others*	46	27 (58.7)	50	39 (78.0)

Test of equality between groups: *t*-test for continuous variables, Fisher's test for categorical variables.
*$p < 0.05$.

pain and angina). Eight other men in this group, as well as four men and three women in the UW group, did not finish the study for unknown reasons. The number of patients lost to follow-up was different in the two study groups, but the baseline characteristics of dropouts and completers were similar. The probability of being lost to follow-up was 2.5 times higher in the SE group (adjusted odds ratio=3.6; $P = 0.01$).

Workout sessions of those who finished and those who did not finish the study in the SE group are described in Table 2. In both cases, a progression in workloads as well as in the estimated O_2 consumed during the exercise can be observed, with the same or lower peak HR and a similar HR recovery.

With regard to the UW group, the 44 patients who finished the study walked a mean of 55.7 ± 17.3 minutes/session. On the other hand, the six patients who did not complete the program, but who did attend some follow-up appointments, walked a mean of 36.0 ± 16.0 minutes/session.

The mean of HR recorded in follow-up sessions of the 24 patients for whom data were available in the UW group was compared with the mean of HR recorded during main conditioning periods of the similar date sessions in the 16 patients of the SE group with data available. The mean (100 ± 15 bpm) of HR recorded in the 16 patients of the SE group during their 30-minute exercise was significantly higher ($P = 0.02$) than that (91 ± 11 bpm) recorded in the 24 patients of the UW group during their 62.6 minutes of walking, and only in SE group patients was this mean above 50% of the HR reserve.

Table 3 shows changes in outcome variables for both groups from baseline to the end of the study, as well as differences attributed to the SE program, adjusted for sex, age, PCC, social class, level of education, current health problems, smoking habit, and use of medication, without and with observations carried forward for those lost to follow-up. VO_2 peak increased significantly in the SE group without (5.56 ml/kg per minute; 95% CI 3.38–7.74) and with (3.47 ml/kg per minute; 95% CI 1.76–5.18) values carried forward, and also in the UW group, though not in a significant way (1.64 ml/kg per minute; 95% CI –0.15 to 3.45; and 1.54 ml/kg per minute; 95% CI –0.06 to 3.19; respectively), yielding significant differences in favour of the SE group both without (4.30 ml/kg per minute; 95% CI 1.82–6.79) and with (2.83 ml/kg per minute; 95% CI 0.61–5.06) the values carried forward. The effect of the SE program on VO_2 peak was not significantly modified by sex ($p > 0.4$), that is, the effect attributable to the SE program was independent from patient's sex: 3.78 ml/kg per minute for men and 4.02 ml/kg per minute for women. Additionally, in the analysis without and with the 'carrying forward', the SE group lost more weight, with a multivariate-adjusted difference of 4.56 kg (95% CI 0.91–8.21; $p < 0.05$) and 3.60 kg (95% CI 0.78–6.42; $p < 0.05$), respectively, and had increased their diastolic blood pressure by the end of the study, 4.46 mmHg (95% CI 0.17–8.76; $p < 0.05$)

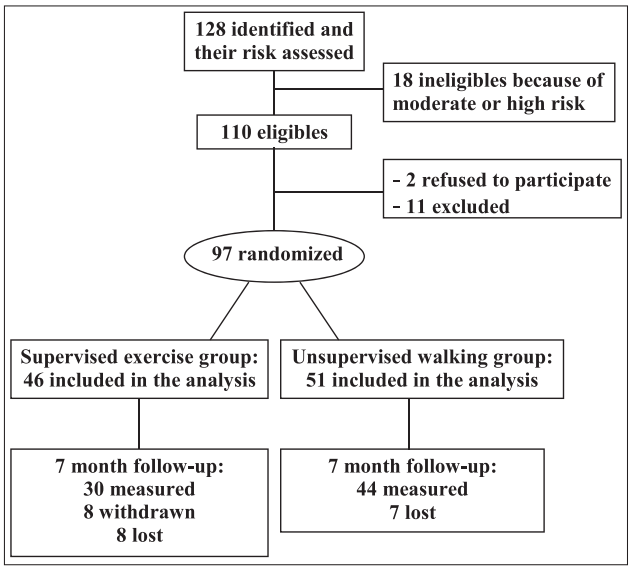

Figure 1. Flowchart of the ESCAP study.

Table 2. Description of workout sessions in the supervised exercise group, mean (SD)

	Finished the study ($n = 30$)			Dropouts[a] ($n = 16$)		
	First measured session	Last measured session	*P*-value	First measured session	Last measured session	*P*-value
No. of sessions	–	88.1 (17.8)	–	–	40.3 (33.1)	–
No. of weeks	–	26.4 (6.4)	–	–	12.7 (9.8)	–
Exercise duration, min	36 (0)	36 (0)	–	36 (0)	36 (0)	–
Workload, W	70.8 (6.8)	90.8 (19.4)	<0.001	65.0 (16.7)	76.6 (22.3)	0.005
Estimated VO_2, ml/kg per min	13.05 (2.4)	15.97 (2.9)	<0.001	12.60 (1.9)	14.37 (3.0)	0.006
Peak HR, bpm	97.6 (15.2)	100.6 (16.0)	0.09	116.2 (19.0)	109.6 (14.0)	0.02
HR recovery at 3 min, bpm	85.9 (14.5)	86.2 (14.4)	0.45	96.7 (18.9)	95.2 (10.5)	0.38
HR recovery at 5 min, bpm	74.4 (14.1)	75.2 (14.7)	0.34	85.6 (20.1)	84.8 (11.8)	0.44

HR, heart rate.

[a]Data from those who were trained >2 weeks ($n = 9$).

Table 3. Changes in primary and secondary outcome measures from baseline to 7-month follow-up without and with carry-forward imputation for dropouts

	Baseline-adjusted change (95% CI)		Multivariate-adjusted attributable difference[b] (95% CI)
	Supervised exercise group	Unsupervised walking group	
Analysis of the 74 patients who finished the study	*n* = 30	*n* = 44	
Main outcome variable			
VO_2peak, ml/kg per min	5.56 (3.38–7.74)	1.64 (–0.15 to 3.45)	4.30 (1.82–6.79)
Secondary outcome variables[a]			
Total cholesterol, mg/dl	1.62 (–9.93 to 13.17)	–3.09 (–12.79 to 6.62)	4.71 (–10.64 to 20.05)
HDL cholesterol, mg/dl	0.96 (–3.33 to 5.25)	2.44 (–1.19 to 6.07)	–0.03 (–3.18 to 3.11)
LDL cholesterol. mg/dl	2.84 (–6.50 to 12.17)	–4.40 (–12.26 to 3.47)	6.12 (–5.75 to 18.00)
Triglycerides, mg/dl	–0.30 (–20.08 to 20.69)	–11.43 (–28.66 to 5.80)	1.93 (–22.11 to 25.97)
Systolic blood pressure, mmHg	5.25 (–1.26 to 11.76)	–1.23 (–6.72 to 4.27)	4.57 (–4.10 to 13.23)
Diastolic blood pressure, mmHg	2.30 (–0.95 to 5.54)	–2.17 (–4.91 to 0.58)	4.46 (0.17–8.76)
Body weight, kg	–2.97 (–5.87 to 0.06)	0.20 (–2.28 to 2.67)	–4.56 (–8.21 to –0.91)
Carry-forward analysis for all included patients	*n* = 46	*n* = 51	
Main outcome variable			
VO_2peak, ml/kg per min	3.47 (1.76–5.18)	1.54 (–0.06 to 3.19)	2.83 (0.61–5.06)
Secondary outcome variables			
Total cholesterol. mg/dl	2.24 (–6.93 to 11.42)	–3.44 (–11.75 to 4.87)	5.70 (–6.83 to 18.21)
HDL cholesterol. mg/dl	1.11 (–2.24 to 4.47)	1.66 (–1.38 to 4.71)	0.40 (–2.28 to 3.08)
LDL cholesterol. mg/dl	2.97 (–4.41 to 10.36)	–4.49 (–11.25 to 2.28)	5.84 (–3.88 to 15.57)
Triglycerides, mg/dl	–0.86 (–16.89 to 15.17)	–8.83 (–23.07 to 6.01)	1.94 (–17.08 to 20.97)
Systolic blood pressure, mmHg	4.75 (–0.16 to 9.66)	–2.12 (–6.82 to 2.58)	4.73 (–2.17 to 11.73)
Diastolic blood pressure, mmHg	1.88 (–0.61 to 4.37)	–2.18 (–4.56 to 0.20)	4.06 (0.59–7.51)
Body weight, kg	–2.07 (–4.22 to 0.08)	0.17 (–1.87 to 2.22)	–3.60 (–6.42 to –0.78)

[a]Total cholesterol, *n* = 72; HDL cholesterol, *n* = 72; LDL cholesterol, *n* = 72; triglycerides, *n* = 72; systolic blood pressure, *n* = 74; diastolic blood pressure, *n* = 74; body weight, *n* = 76.
[b]Adjusted for sex, age, primary care centre, social class, level of education, current health problems, smoking habit and use of medication.

and 4.06 mmHg (95% CI 0.59–7.51; $p < 0.05$), compared to the UW group.

Discussion

The exercise training program on cycle ergometers, supervised at PCCs following a protocol with pre-established initial workloads and rates of progression over 6 months, increased the functional capacity of low-risk CHD patients by 8% and reduced their body weight by 4.5% compared to another program of unsupervised walking. Given that functional capacity is inversely associated with cardiovascular morbidity and mortality (1,2), these findings indicate that these patients may be able to obtain more health benefits from exercise training at the PCC with this program than from walking without supervision.

The supervision of exercise provided the difference between these two exercise programs, because it allows patients to be trained with careful control of the amount and intensity of exercise needed to achieve the optimal effect on their cardiorespiratory fitness, while preventing injuries and any adverse effects of exercise. Therefore, higher and safer exercise intensities can be reached with supervision, despite the training being of shorter duration and fewer muscle groups being involved during pedalling than in walking (16).This is illustrated by the following results in our study: the 9.5% higher mean HR during the SE program workouts, as well as the difference between the mean estimated VO_2 during sessions of the SE and UW groups (14.51 ml/kg per minute versus 11.55 ml/kg per minute), given a mean walking speed of 5 km/hour, which resulted in 3.3 METs/hour.

To our knowledge, no research findings have been published that directly compare these two exercise modalities and their implementation in CHD patients.

Related studies have compared high- versus low-intensity aerobic exercise in patients with myocardial infarction without significant differences in VO_2max (11% versus 14%) (17); high-intensity interval aerobic exercise versus continuous aerobic exercise in stable CHD patients with greater increase in VO_2peak in former group (17.9% versus 7.9%) (18); and high versus low frequency of physical training (10 versus 2 sessions/week for a total of 2 hours) without significant differences in VO_2max (15% versus 12%) (19).These results represent slightly larger differences than those found in our groups.

The main limitation of our study lies in the high drop-out rate (34.7%) in the SE group, owing to the withdrawal

of patients with concurrent illnesses or training side effects, which are complications expected as a result of exercise training with workloads greater than walking (20). Those withdrawals would not have prevented patients from continuing with this exercise program after recovery, but prevented them from meeting the requirements for continuing in the study. If, however, the withdrawals are discounted, the number of losses to follow-up from this group (eight) was similar to that from the UW group (seven). We do not know how this might have influenced the results, because baseline characteristics of those patients who did not finish the study were similar in the two groups, and those who did not finish the study in the SE group, but trained for >2 weeks, had already significantly ($P < 0.01$) increased their workloads (by 17.8%) at a significantly ($P = 0.02$) lower peak HR at the time of discontinuation.

The choice of functional capacity, instead of clinical end points, as the main outcome measure could also be regarded a limitation. However, we believe that, initially, we had to demonstrate that this SE program at PCCs improved oxygen transport system performance more than unsupervised walking, the usual recommendation for the majority of CHD patients. Afterwards, and this remains a pending research task, we need to assess whether such increases in functional capacity will result in lower morbidity and mortality in these patients, though there is already some evidence (2) that, in men with CHD, a VO_2peak increase of 3.5 ml/kg per minute is related to a 13% and 31% reduced risk for nonfatal and fatal cardiac events, respectively.

The main strength of this study is that it sets out a detailed exercise training program that is easy to implement and feasible to carry out at any PCC or other health facility, given that only two inexpensive devices (a cycle ergometer and a HR monitor) are required, and that a health professional, such as a nurse, a physical therapist, or an exercise specialist, can supervise the patient at the same time as he/she performs other tasks in the same room. This program allows patient progression to be monitored using the increase in workloads and HR during the sessions, and its training protocol can be modified according to individual patient characteristics so as to maximize benefits and safety.

However, one must keep in mind that this is an individualized training program, just like the training programs of those athletes who look for excellence, and which cannot be implemented in a large number of patients at the same time. Fortunately, the number of patients with acute CHD per family physicians and per year is very low, and therefore, all the new cases might be trained at their PCC.

In conclusion, our data indicate that this exercise program, supervised at PCCs and which allows training intensity and duration to be adapted at each session, according to the characteristics and clinical status of patients who have suffered a CHD event, seems to increase functional capacity and reduce body weight more than walking without supervision. This greater increase in functional capacity can be expected to result in a better prognosis in these patients.

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Declaration

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Appendix 1: Unsupervised walking program

This unsupervised walking program included: a warm-up, which consisted of walking slowly for 3–5 minutes and then some stretching exercises for all of the major leg muscle groups; a main conditioning period, which consisted of walking briskly ('walk continuously so that you feel you are breathing harder than when at rest'), starting with a duration of 30 minutes and a frequency of twice a week the first week and gradually increasing the duration and frequency in the following weeks until reaching and maintaining a duration of at least 60 minutes everyday from week 16 onwards; and, finally, a cool-down, which consisted of walking slowly for 2–3 minutes and then performing the same exercises as in the warm-up.

Appendix 2: Supervised exercise program

In the initial phase (the first 2 weeks), the 38 minutes of the exercise session were distributed in the following manner: a warm-up lasting for 3 minutes, consisting of pedalling, either with a 50 W load (workload) for the first minute, 60 W for the second minute and 70 W for the third minute, for those patients <70 years of age, or 40, 48 and 56 W, respectively, for those ≥70 years of age; a main conditioning period, consisting of pedalling with either 75 W (<70 years) or 60 W (≥70 years) from minutes 3 to 30 as long as their heart rate (HR) did not exceed

either 85% of HR reserve in patients who were not on beta-blockers (BB) or 40 beats per minute (bpm) over resting HR in patients who were on BB (upper limit of the exercise training intensity); and a cool-down, consisting of pedalling with the same workload as at the beginning of the warm-up (50 or 40W, depending on age) from minute 33 to 36 and staying seated on the cycle ergometer, without pedalling, from minute 36 to 38. When the patients' HR exceeded the aforementioned thresholds, they stopped pedalling and rested until their HR fell below either 50% of HR reserve in patients who were not on BB or 20 bpm over resting HR in patients who were on BB (lower limit of the exercise training intensity), at which point they started a new exercise episode to complete a total of 30 minutes, which included exercise episodes and resting pauses.

In the progression phase (from week 3 to the end), only the warm-up and main conditioning period were modified. For those patients who had completed 30 minutes of continuous pedalling with the prescribed watts, the main conditioning period consisted of increasing every other week from the third week, by either 5W (<70 years) or 4W (≥70 years), if the peak HR during the prior week workouts was either 70% to 80% of HR reserve (without BB) or 32–38 bpm over resting HR (with BB); by either 10W (<70 years) or 8W (≥70 years), if the peak HR during the prior week workouts was either 60% to 70% of HR reserve (without BB) or 26–32 bpm over resting HR (with BB); and by either 15W (<70 years) or 12W (≥70 years), if the peak HR during the prior week workouts was either below 60% of HR reserve (without BB) or <26 bpm over resting HR (with BB). When the peak HR during the workouts of the previous week was either 80–85% of HR reserve (without BB) or 38–40 bpm over resting HR (with BB), the workload was kept at the same level for the following 2 weeks. Those patients who had been alternating exercise with pauses to rest progressed by increasing the time spent exercising and shortening the pauses. During the warm-up, the workload remained the same for the first minute, was increased by a third of the difference between either 50W (<70 years) or 40W (≥70 years) and the workload prescribed for the main conditioning period of that week for the second minute, and was increased further by a third of that difference for the third minute.

CONSORT 2010 checklist of information to include when reporting a randomized trial[a]

Section/topic	Item No.	Checklist item	Reported on page No. (File)
Title and abstract			
	1a	Identification as a randomized trial in the title	1
	1b	Structured summary of trial design, methods, results and conclusions (for specific guidance, see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	1 and 2
	2b	Specific objectives or hypotheses	2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	2
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	2
	4b	Settings and locations where the data were collected	2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	2, 8 and 9
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	2 and 3
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	3
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomization			
Sequence generation	8a	Method used to generate the random allocation sequence	2
	8b	Type of randomization; details of any restriction (such as blocking and block size)	2

Section/topic	Item No.	Checklist item	Reported on page No. (File)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	2
Implementation	10	Who generated the random allocation sequence, who enrolled participants and who assigned participants to interventions	2
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	2
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	3
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	3
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment and were analysed for the primary outcome	3 and Figure 1
	13b	For each group, losses and exclusions after randomization, together with reasons	3
Recruitment	14a	Dates defining the periods of recruitment and follow-up	2 and 3
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	5 and Table 3
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group and the estimated effect size and its precision (such as 95% confidence interval)	5 and Table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	3, 4, 5 and Tables 2 and 3
Harms	19	All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms)	3 and 6
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision and, if relevant, multiplicity of analyses	6 and 7
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	7
Interpretation	22	Interpretation consistent with results, balancing benefits and harms and considering other relevant evidence	5 and 6
Other information			
Registration	23	Registration number and name of trial registry	7
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	7

[a]We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacological treatments, herbal interventions and pragmatic trials. Additional extensions are forthcoming; for these and for uptodate references relevant to this checklist, see www.consort-statement.org.