

Gender Differences in Outcomes Following a Pain-Free, Home-Based Exercise Program for Claudication

Roberto Manfredini, MD,¹⁻³ Nicola Lamberti, MSc, PhD,⁴ Fabio Manfredini, MD,³⁻⁵
Sofia Straudi, MD, PhD,⁵ Fabio Fabbian, MD,¹⁻³ Maria Aurora Rodriguez Borrego, RN, PhD,³
Nino Basaglia, MD,^{4,5} Juan Manuel Carmona Torres, RN, PhD,³ and Pablo Jesus Lopez Soto, RN, PhD³

Abstract

Background: Peripheral artery disease (PAD) is a common cardiovascular pathology that affects mobility. In previous research, supervised exercise, a recommended treatment for claudication, was less effective in women. This study retrospectively investigated whether functional outcomes exhibit sex differences following a pain-free, home-based exercise program for PAD patients.

Materials and Methods: Patients with PAD and claudication enrolled to a structured home-based program from 2003 to 2016 were studied. The program was prescribed at the hospital and based on two daily 10-minute pain-free walking sessions at progressively increasing speed. Outcome measures, which were assessed at baseline and discharge, were pain threshold speed (PTS) and maximal (S_{max}) during a treadmill test and pain-free walking distance (PFWD) and total distance walked in 6 minutes (6MWD). The ankle-brachial index (ABI), program duration, and patient adherence were determined.

Results: A total of 1007 patients (women; $n=264$; 26%) were enrolled. At baseline, compared to men, women exhibited similar ABI values but lower PTS and PFWD values ($p<0.001$). At discharge, with similar adherence (score $3/4 \pm 1$ each) in both groups, superimposable improvements were observed for PTS (0.8 ± 0.8 km/h each), S_{max} (0.4 ± 0.5 km/h each), PFWD (women 95 ± 100 ; men 86 ± 104), 6MWD (women 32 ± 65 ; men 35 ± 58), and ABI (women 0.07 ± 0.12 ; men 0.06 ± 0.11) without between-group differences (confirmed after propensity analysis).

Conclusion: A personalized, structured pain-free exercise program for PAD patients performed inside the home for a few minutes a day was equally effective in both sexes. Programs favoring adherence and functional outcomes in women should be tested in prospective studies.

Keywords: gender, women, peripheral artery disease, exercise therapy, rehabilitation

Introduction

CARDIOVASCULAR DISEASE (CVD) remains the primary cause of death in women, with an estimated 44 million women either living with or at risk of heart disease in the United States.¹ Resistant hypertension,² poor lipid control due to either lack of social support³ or higher discontinuation of lipid-lowering treatment,⁴ and even mild-to-moderate reduced

kidney function⁵ are all novel pieces of the complex puzzle of the gender gap in CVD. Among the wide spectrum of CVDs, peripheral artery disease (PAD) is a highly prevalent pathology in the elderly; it is responsible for disability and reduced quality of life (QoL) at the intermediate stages.⁶ However, the burden of PAD is increasingly striking in young adults⁷ and women. Due to the increased disability and mortality associated with PAD in the past 20 years,⁷ the prevalence in women

¹Department of Medical Sciences, University of Ferrara, Ferrara, Italy.

²Clinica Medica Unit, Azienda Ospedaliera-Universitaria, Ferrara, Italy.

³Instituto Maimonides de Investigacion Biomedica de Cordoba, University of Cordoba, Cordoba, Spain.

⁴Department of Biomedical and Surgical Specialties Sciences, University of Ferrara, Ferrara, Italy.

⁵Rehabilitation Medicine Unit, Azienda Ospedaliera-Universitaria, Ferrara, Italy.

is equal to that in men.⁷⁻⁹ Although women with PAD may be more frequently asymptomatic or report atypical symptoms⁹ in the presence of claudication, compared to men, they show lower functioning even with similar hemodynamic severity,¹⁰ a higher prevalence of mood disturbance, and bodily pain.¹¹

In terms of treatment, the female sex also represents a risk factor that negatively affects vascular intervention outcomes, with a differential impact according to race and intervention type.¹²⁻¹⁷ For the abovementioned reasons, exercise therapy and primary treatment of claudication symptoms⁶ might be crucial for the management of walking disabilities among women. Unfortunately, a lower response or adherence to rehabilitation has been reported in women with various chronic diseases¹⁸⁻²⁰ as well as with PAD, possibly due to interest, comorbidities, or rehabilitation strategies.²¹⁻²³

An alternative model of unsupervised rehabilitation based on a structured, home-based, personalized, symptom-free prescription of exercise with only monthly check-ups at the hospital (test in–train out, Ti-To) has been developed for PAD.^{24,25} The model, which aimed to overcome many barriers to exercise, has also been successfully tested in several selected populations, for example, dialysis patients²⁶⁻²⁸ and stroke survivors,^{29,30} and obtained significant functional and clinical improvements.

Since this model has sustainable and feasible features such as setting, intensity, and low impact that could be suitable for women, we hypothesized that equal improvements in functional outcomes are attainable after rehabilitation in both women and men. The aim of this study was to evaluate whether sex-based differences in PAD patients with claudication are observable at discharge from the program.

Materials and Methods

Study design and setting

This single-center, retrospective cohort study was carried out at the Department of Rehabilitation Medicine of the Azienda Ospedaliero-Universitaria of Ferrara between 2003 and 2016. The study was developed during usual care practice for PAD patients at this hospital. The local ethics committee of the University of Ferrara approved the study; no written informed consent was obtained from the patients because they no longer attended the program. This article was written according to the Strengthening the Reporting of Observation Studies in Epidemiology (STROBE) checklist for cohort studies.³¹

Participants

A total of 1164 PAD patients who had attended the vascular rehabilitation program were analyzed for possible inclusion in the study. PAD was previously diagnosed at the vascular surgery unit of the Hospital of Ferrara by clinical and echo-color-Doppler examination.³²

Patients of all ages and sexes were included in the study based on the presence of PAD at stage II of the Leriche–Fontaine classification, with stable claudication for at least 3 months. Patients with conditions contraindicating safe training execution at home (*e.g.*, unstable angina, severe heart failure, major amputation, or clinical conditions limiting treadmill testing) were excluded from the analysis. Finally, patients who did not complete the exercise program for any reason were not included in this analysis.

Variables and comorbidities at entry

During the first session of the program, information regarding clinical status and functional impairment was collected by consulting patients' medical documents by means of physician examination or by specific tests. Particularly, scholar qualification, cardiovascular risk factors, comorbidities adjunct to PAD (with the Charlson comorbidity index calculation³³), and location of endovascular lesions were identified. Patients' reported claudication distance was also noted.

Outcome measures

Hemodynamic and functional measurements were performed at entry and discharge from the rehabilitation program. All outcome measures were carried out in a temperature-controlled environment in the morning between 8:00 AM and 12:00 PM.

Hemodynamic assessment. After 5 minutes of rest, patients underwent ankle-brachial index (ABI) measurements according to a standard procedure³² using Doppler ultrasound (Stereodop 448.S; Ultrasoned, Milan, Italy) with a 9.3 MHz transducer and a standard blood pressure cuff. The leg with the lowest ABI value was considered the worse leg. The vessels were considered “not compressible” for ABI measurements >1.31 or for a procedure that had been interrupted due to painful symptoms at a cuff pressure of 300 mmHg with a Doppler signal still present.

Functional measurements. An incremental treadmill test based on level walking³⁴ was performed by each patient. Participants were familiarized with the motorized treadmill (Technogym RunRace, Cesena, Italy) by walking on it at a low speed for 1 minute. Use of the handrail to maintain balance was permitted. The testing procedure was explained to the patients who were asked to immediately report the onset, intensity, and location of symptoms. After the warm-up, the test started at a speed of 1.5 km/h, which was progressively increased by 0.1 km/h every 10 m. The pain threshold speed (PTS), as reported by the patient, was noted. The test finished when the patient was unable to maintain the walking speed imposed for any reason (fatigue, dyspnea, and claudication); this walking speed was recorded as the maximal walking speed (Smax).

After a 10-minute resting period, the 6-minute walking test was performed according to the published standard.³⁵ Patients were instructed to walk back and forth along a 22 m corridor alone at their own pace with the aim of covering as much distance as possible in 6 minutes. The total distance walked (6-minute walking distance, 6MWD) and pain-free walking distance (PFWD) were recorded.

Exercise program

The Ti-To structured, home-based exercise program²⁴ was prescribed to all patients. The Ti-To program encompasses a center-based phase and home-based phase with walking exercises. The first phase included circa-monthly visits at the hospital for clinical assessment, ABI and PTS/PFWD measurements, an updated prescription of the home-based walking program, and evaluation of patient adherence to the program. The home-based phase included the execution of

exercise at home, preferably indoors (*e.g.*, hallway or heated room). The program was based on two 10-minute walking sessions per day (6 days/week) of intermittent walking (1-minute work and 1-minute seated rest) at a prescribed speed. The training speed was converted into walking cadence (steps/minute) to be maintained at home by a metronome by patients who were specifically educated to walk in rhythm with it. The exercise program was increased weekly from 60 to 84–100 steps per minute according to the severity of claudication at baseline. Progressively, the length of each bout was amplified with a work:rest ratio from 1:1 to 2:1 and 3:1, while the entire duration of each session remained constant. Patients were also asked to fill out a daily training log, indicating completion of the exercise, which was certified by a caregiver when possible. The exercise program ended when the patients reached a PFWD normal for their sex and age or when no more improvements in functional parameters were registered in two consecutive tests. Additional details on the exercise program are reported elsewhere.^{24,25}

Evaluation of patient adherence

At discharge, rehabilitation team members evaluated the training diaries of each patient to determine the adherence score.²⁵ The arbitrary score ranged from 1 (lowest adherence) to 4 (highest) and was calculated by summing the percentages of certified exercise sessions completed ($\geq 75\% = 3$ points; $\geq 50\%$ and $< 75\% = 2$ points; $\geq 25\%$ and $< 50\% = 1$ point; and

$< 25\% = 0$ point) and with respect to the prescribed training speed (yes = 1 point; no = 0 point).

At discharge, the total duration of the program and number of hospital visits were also recorded.

Study group definition and bias management

The whole population at baseline was divided by sex into WomenPAD (W_{PAD}) and MenPAD (M_{PAD}).

Several potential biases in the interpretation of the study results were foreseeable and mainly related to significant changes in patient clinical status. Nonetheless, considering the hemodynamic and functional outcome measures examined, the main confounding issue was endovascular or surgical lower limb revascularization procedures that have a potential impact on study outcomes. Therefore, all patients who underwent a revascularization procedure during the exercise program were excluded from this analysis.

Sample size calculation

Based on the starting hypothesis, we calculated the power for an equivalence trial. Sample size calculations indicated that 264 participants were required to be 95% certain that the 90% confidence interval (CI) excluded a difference in the change in PFWD greater than the equivalence limit of 20 m, corresponding to the minimal clinically important difference established in this population.³⁶

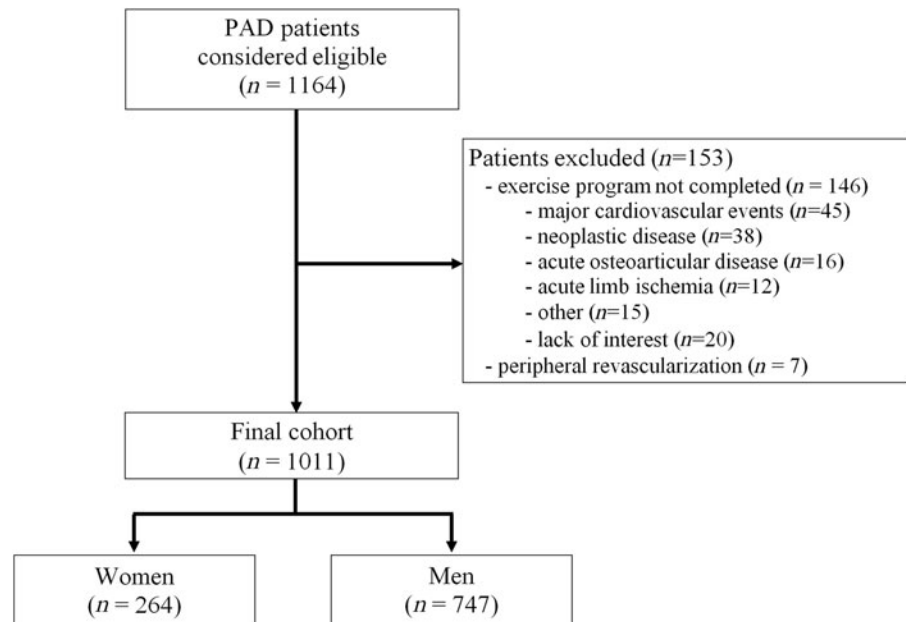
TABLE 1. BASELINE CHARACTERISTICS OF THE PATIENTS INCLUDED IN THE STUDY

	Women (n=264)	Men (n=747)	p
Age (years)	71 ± 10	70 ± 9	0.12
Education, n (%)			
Elementary school	195 (74)	538 (72)	0.56
Middle or secondary school	48 (18)	168 (22)	0.09
Degree	21 (8)	41 (6)	0.13
Risk factors, n (%)			
Smoking	178 (67)	692 (93)	<0.001
Hypertension	196 (74)	572 (77)	0.41
Hyperlipidemia	179 (68)	457 (61)	0.06
Diabetes	79 (30)	273 (37)	0.049
Family history for CVD	49 (18)	128 (17)	0.61
Comorbidities, n (%)			
Coronary heart disease	73 (28)	335 (45)	<0.001
Cerebrovascular disease	18 (7)	96 (13)	0.007
Osteoarticular disease	102 (39)	206 (28)	<0.001
Rheumatic diseases	30 (11)	26 (4)	<0.001
Charlson comorbidity index	6 ± 2	6 ± 2	0.21
Peripheral arterial disease			
Disease duration (years)	5 ± 5	6 ± 7	0.14
Lower limb revascularization	72 (27)	207 (28)	0.87
Self-reported claudication distance (m)	178 ± 144	205 ± 162	0.23
ABI, more affected limb	0.62 ± 0.19	0.62 ± 0.18	0.74
ABI, less affected limb	0.83 ± 0.22	0.85 ± 0.20	1.00
PTS (km/h)	2.3 ± 0.9	3.0 ± 1.1	<0.001
Smax (km/h)	2.8 ± 1.1	3.5 ± 1.1	<0.001
PFWD (m)	132 ± 95	215 ± 115	<0.001
6-minute walking distance (m)	279 ± 73	340 ± 88	<0.001

Statistically significant values have been indicated in bold.

ABI, ankle-brachial index; CVD, cardiovascular disease; PFWD, pain-free walking distance; PTS, pain threshold speed; Smax, maximal speed.

FIG. 1. Study flow diagram.



Statistical analysis

Data are expressed as mean \pm standard deviation, or median and 95% CIs (according to the data distribution), or as the percentage frequency (categorical data). Comparisons between W_{PAD} and M_{PAD} patients were made by independent *t*-test (normally distributed data), the Mann–Whitney test (nonnormally distributed data), or the chi-squared test (categorical data), as appropriate.

Within-group comparisons were performed by paired *t*-test (normally distributed data) or Wilcoxon rank test (nonnormally distributed data), as appropriate. The between-group comparison was performed with one-way analysis of variance. Within- and between-group differences are expressed as mean changes and 95% CIs.

A propensity score model was estimated using the 23 variables described in Table 1. To estimate the propensity score, we used a logistic regression model in which gender (M_{PAD} vs. W_{PAD}) was regressed on the baseline characteristics listed in Table 1. Patients were then pooled and sorted in ascending order according to their propensity score. The selection process began from the cases with the lowest score. If patients were M_{PAD} and W_{PAD} , both were selected as a matched pair according to 1:1, 2:2, 3:3, or 4:4 blocks. A patient who did not have a suitable match within the acceptable rank range was excluded.

Statistical analyses were performed with MedCalc Statistical Software version 18.5 (MedCalc Software bvba, Ostend, Belgium).

Results

A total of 1164 PAD patients were considered eligible; 153 were not included in the final analysis because they did not complete the rehabilitation program or because of biases potentially affecting data interpretation. The reasons for exclusion are reported in Figure 1. Within the excluded sample of patients, the same proportions of W_{PAD} and M_{PAD} were maintained (W_{PAD} $n=40$). Thus, the final study population comprised 1011 PAD patients divided into 264 W_{PAD} and 747 M_{PAD} .

Baseline group comparison

At baseline, the two groups did not differ in age or educational level. Considering cardiovascular risk factors, a smoking habit (93% vs. 67%; $p < 0.001$) and diabetes (37% vs. 30%; $p = 0.049$) were more prevalent among M_{PAD} , whereas W_{PAD} were more affected by hyperlipidemia (68% vs. 61%; $p = 0.059$) but not significantly. No differences were observed for hypertension and family history for CVDs.

In terms of comorbidities, M_{PAD} presented a higher incidence of coronary heart diseases (45% vs. 28%; $p < 0.001$) and cerebrovascular diseases (12% vs. 7%; $p = 0.007$). In contrast, W_{PAD} showed more osteoarticular (39% vs. 28%; $p < 0.001$) and rheumatic diseases (11% vs. 4%; $p < 0.001$). Despite these differences, the Charlson comorbidity index was equal in both groups (6 ± 2 ; $p = n.s.$).

TABLE 2. FEATURES OF THE PROGRAM IN TERMS OF DURATION AND ADHERENCE IN THE TWO GROUPS

	Women (n = 264)	Men (n = 747)	p
Program duration (days) ^a	376 (343–404)	330 (318–350)	0.011
Hospital visits (n) ^b	7.7 (7.3–8.1)	7.4 (7.2–7.7)	0.25
Walking speed (steps/min) ^a	84 (60–94)	90 (62–104)	0.19
Exercise sessions completed (%) ^a	84 (66–100)	86 (69–100)	0.64
Adherence (arbitrary score) ^b	3.0 (2.9–3.1)	3.1 (3.1–3.2)	0.64

Statistically significant values have been indicated in bold.

^aMedian (95% confidence interval); ^bmean (95% confidence interval).

Finally, both groups reported a similar duration of claudication symptoms ($W_{PAD} 5 \pm 5$; $M_{PAD} 6 \pm 7$; $p = n.s.$), as well as similar self-reported claudication distances ($W_{PAD} 178 \pm 144$ m; $M_{PAD} 205 \pm 162$ m; $p = n.s.$; Table 1).

Outcome measures at baseline

At entry, the two groups did not differ in PAD severity for the more affected limb (ABI: $W_{PAD} 0.62 \pm 0.19$; $M_{PAD} 0.62 \pm 0.18$; $p = n.s.$) and the less affected one (ABI: $W_{PAD} 0.83 \pm 0.22$; $M_{PAD} 0.85 \pm 0.20$; $p = n.s.$).

The W_{PAD} group presented a significantly lower functional capacity in the incremental treadmill test and the 6-minute walking test. Furthermore, W_{PAD} exhibited a lower PTS (2.3 ± 0.9 vs. 3.0 ± 1.1 km/h; $p < 0.001$) and S_{max} (2.8 ± 1.1 vs. 3.5 ± 1.1 km/h; $p < 0.001$), as well as a lower PFWD (132 ± 95 vs. 215 ± 115 m; $p < 0.001$) and 6MWD (279 ± 73 vs. 340 ± 88 m; $p < 0.001$; Table 1).

Rehabilitation outcomes

Data concerning the duration, participation, and adherence to the exercise program were similar between the groups except for total rehabilitation days. These data are reported in Table 2.

Both groups showed significant improvements in hemodynamic measurements and functional capacity from baseline to the end of the program.

The W_{PAD} group exhibited a significant improvement in the ABI in both limbs (more diseased; $p < 0.001$; less diseased; $p = 0.001$). Additionally, all exercise capacity parameters showed a significant enhancement, particularly for PTS (+40%; $p < 0.001$) and PFWD (+108%; $p < 0.001$).

Similar outcomes were observed for the M_{PAD} group, with significant ABI variations in both limbs ($p < 0.001$) as well as improvements in all four functional parameters (particularly evident for PTS +35%, $p < 0.001$; PFWD +71%, $p < 0.001$). Similarly, the mean claudication onset time improved in both groups (W_{PAD} from 166 to 253 seconds; M_{PAD} from 207 to 298 seconds). Data are reported in Table 3.

The subsequent between-group comparison showed superimposable variations, without any statistically significant difference for PTS ($W_{PAD} 0.8 \pm 0.9$ km/h; $M_{PAD} 0.8 \pm 0.9$ km/h; $p = n.s.$), S_{max} ($W_{PAD} 0.4 \pm 0.8$ km/h; $M_{PAD} 0.4 \pm 0.7$ km/h; $p = n.s.$), PFWD ($W_{PAD} 95 \pm 100$ m; $M_{PAD} 86 \pm 103$ m; $p = n.s.$), and 6MWD ($W_{PAD} 33 \pm 58$ m; $M_{PAD} 32 \pm 65$ m; $p = n.s.$). Similarly, no differences were observed for ABI variations in both limbs (Table 3).

Propensity score analysis

After propensity score matching, two independent groups comprising 188 patients each without baseline covariate differences were identified (Table 4). In addition, the program duration ($W_{PAD} 402 \pm 245$ vs. $M_{PAD} 356 \pm 202$ days; $p = 0.07$), number of visits ($W_{PAD} 7.4 \pm 3.3$ vs. $M_{PAD} 7.3 \pm 3.3$; $p = 0.57$), and adherence ($W_{PAD} 3.1 \pm 0.8$ vs. $M_{PAD} 3.2 \pm 0.8$; $p = 0.24$) were measured at the end of the program and were balanced between the groups.

The within-group analysis in the reduced samples confirmed the significant improvements for all hemodynamic and functional parameters for both groups. The between-group comparison also showed similar variations, without

TABLE 3. WITHIN- AND BETWEEN-GROUP DIFFERENCES IN REHABILITATION OUTCOMES

	Women (n = 264)				Men (n = 747)				p between-group	
	Baseline	End	Δ	p within-group	Baseline	End	Δ	p within-group		
ABI worst limb	0.62 (0.59–0.64)	0.69 (0.66–0.71)	0.07 (0.06–0.09)	<0.001	0.62 (0.61–0.63)	0.68 (0.66–0.69)	0.06 (0.05–0.07)	<0.001	0.00 (–0.01 to 0.02)	0.68
ABI best limb	0.83 (0.80–0.86)	0.88 (0.85–0.90)	0.05 (0.03–0.07)	0.001	0.85 (0.83–0.86)	0.89 (0.88–0.90)	0.04 (0.02–0.05)	<0.001	0.01 (–0.02 to 0.02)	0.54
PTS (km/h)	2.3 (2.2–2.4)	3.1 (2.9–3.2)	0.8 (0.7–0.9)	<0.001	2.9 (2.8–3.0)	3.7 (3.6–3.8)	0.8 (0.7–0.9)	<0.001	0.0 (–0.1 to 0.1)	0.70
S_{max} (km/h)	2.8 (2.7–2.9)	3.2 (3.1–3.3)	0.4 (0.4–0.5)	<0.001	3.5 (3.5–3.6)	3.9 (3.9–4.0)	0.4 (0.4–0.5)	<0.001	0.0 (–0.1 to 0.1)	0.61
PFWD (m)	132 (120–143)	223 (209–237)	95 (83–108)	<0.001	215 (206–223)	300 (291–309)	86 (77–94)	<0.001	9 (–5 to 24)	0.24
6MWD (m)	279 (270–287)	312 (303–322)	33 (28–39)	<0.001	339 (333–346)	371 (364–377)	32 (27–36)	<0.001	1 (–6 to 10)	0.44

Statistically significant values have been indicated in bold. Data are expressed as mean and 95% confidence interval. ABI, ankle-brachial index; 6MWD, 6-minute walking distance; PTS, pain threshold speed; S_{max} , maximal speed.

TABLE 4. BASELINE CHARACTERISTICS OF THE PATIENTS INCLUDED IN THE STUDY AFTER THE PROPENSITY ANALYSIS

	Women (n = 188)	Men (n = 188)	p
Age (years)	71 ± 10	70 ± 10	0.40
Education, n (%)			
Elementary school	139 (74)	135 (72)	0.64
Middle or secondary school	35 (19)	44 (23)	0.25
Degree	14 (7)	9 (5)	0.28
Risk factors, n (%)			
Smoking	155 (82)	150 (80)	0.51
Hypertension	142 (76)	144 (77)	0.81
Hyperlipidemia	125 (67)	122 (65)	0.74
Diabetes	53 (28)	67 (36)	0.13
Family history for CVD	34 (18)	36 (19)	0.79
Comorbidities, n (%)			
Coronary heart disease	56 (30)	53 (28)	0.73
Cerebrovascular disease	16 (8)	12 (6)	0.43
Osteoarticular disease	71 (37)	56 (30)	0.11
Rheumatic diseases	12 (6)	12 (6)	1.00
Charlson comorbidity index	5.7 ± 1.7	5.7 ± 1.6	0.90
Peripheral arterial disease			
Disease duration (years)	6 ± 6	6 ± 7	0.85
Lower limb revascularization	52 (28)	63 (33)	0.22
Self-reported claudication distance (m)	198 ± 132	201 ± 151	0.48
ABI, more affected limb	0.63 ± 0.19	0.63 ± 0.18	0.78
ABI, less affected limb	0.84 ± 0.20	0.84 ± 0.21	0.99
PTS (km/h)	2.4 ± 0.9	2.5 ± 1.0	0.29
Smax (km/h)	3.0 ± 1.0	3.1 ± 1.1	0.25
PFWD (m)	151 ± 101	162 ± 95	0.25
6MWD (m)	294 ± 71	304 ± 89	0.20

6MWD, 6-minute walking distance; ABI, ankle-brachial index; CVD, cardiovascular disease; PFWD, pain-free walking distance; Smax, maximal speed.

any significant difference for any hemodynamic and functional parameters (Table 5).

Discussion

In this study, compared to men, women with PAD and claudication following a structured low-intensity program obtained the same benefits in terms of reduction in walking disability as well as a similar degree of adherence. This observation was also confirmed after propensity analysis, which balanced the two groups in baseline characteristics and proved that no differences in rehabilitation outcomes existed between sexes.

To the best of our knowledge, the available literature on the response of women to rehabilitation in PAD is poor, and the present results represent a novel report. The only confirmation of previous data^{10,37} is the low walking performance of women compared to that of men in absolute terms. The functional capacity at entrance to the program measured with both treadmill and ground-walking tests was lower in the female population with the same hemodynamic condition. This aspect may refer to the lower aerobic efficiency typical of the female sex or the lower biomechanical efficiency aggravated by deconditioning, possibly related to the presence of comorbidities.^{37,38} In daily activities, women move at a slower rate than men and present a different ambulatory pattern.³⁹ However, after rehabilitation, the same degree of functional improvement, which was the main focus of our study, was observed in the two subpopulations, with an av-

erage variation in exercise capacity between 20% and 110% for patients of both sexes.

Different outcomes following rehabilitation programs in chronic pathologies were reported in women compared to men,^{21–23} with problematic issues related to interest/motivation, adherence to physical activity, or effects achieved.^{18,21,22}

Various reasons were hypothesized to explain these results, such as the presence of comorbidities^{22,37} or the type of intervention. According to the authors, programs for the rehabilitation of cardiovascular patients should not be based on exercise alone^{19,22}; these programs may also benefit from the presence of staff members providing support.⁴⁰ In general, the necessity of sex-based claudication treatment strategies should be considered.²³

Therefore, we hypothesize that the novel results observed in the present study were derived from the rehabilitation program proposed and successfully tested in frail subjects^{24–30} where the type of exercise and organizational model could have favored equal adherence and outcomes in both sexes.

Normally, the exercise recommended for the rehabilitation of patients with chronic PAD is under supervision in specialized facilities. This exercise is based on repeated walking sessions at a level of pain that increases patient tolerance and thus improves tolerance to exercise, thereby obtaining progressively longer gradual sessions.⁴¹ Considering the lower attitude of women toward exercise¹⁸ and the sex difference in the perception of pain,¹¹ a different approach might be favorable in this subgroup, based on a progressively higher pain-free walking cadence supported by the aerobic adaptations

TABLE 5. WITHIN- AND BETWEEN-GROUP DIFFERENCES IN REHABILITATION OUTCOMES IN THE PROPENSITY SCORE-MATCHED GROUPS

	Women (n = 188)				Men (n = 188)				p between-group	
	Baseline	End	Δ	p within-group	Baseline	End	Δ	p within-group		
	Between-group Δ in changes				Between-group Δ in changes					
ABI worst limb	0.63 (0.60–0.65)	0.70 (0.67–0.73)	0.07 (0.05–0.09)	<0.001	0.63 (0.60–0.66)	0.70 (0.67–0.73)	0.07 (0.05–0.08)	<0.001	0.00 (–0.02 to 0.01)	0.46
ABI best limb	0.84 (0.81–0.87)	0.89 (0.86–0.92)	0.05 (0.03–0.07)	<0.001	0.84 (0.81–0.87)	0.89 (0.88–0.90)	0.05 (0.03–0.06)	<0.001	0.00 (–0.02 to 0.02)	0.67
PTS (km/h)	2.4 (2.3–2.6)	3.3 (3.1–3.5)	0.9 (0.8–1.0)	<0.001	2.5 (2.4–2.7)	3.5 (3.3–3.7)	0.9 (0.8–1.1)	<0.001	0.1 (–0.1 to 0.2)	0.35
Smax (km/h)	3.0 (2.8–3.1)	3.5 (3.2–3.7)	0.5 (0.4–0.6)	<0.001	3.1 (2.9–3.3)	3.7 (3.6–3.9)	0.6 (0.5–0.7)	<0.001	0.1 (–0.1 to 0.2)	0.24
PFWD (m)	151 (136–165)	247 (221–264)	96 (83–108)	<0.001	162 (148–176)	278 (261–295)	115 (89–128)	<0.001	19 (–5 to 43)	0.34
6MWD (m)	294 (283–304)	334 (322–345)	40 (29–51)	<0.001	304 (291–317)	352 (339–365)	48 (34–59)	<0.001	8 (–4 to 20)	0.28

Statistically significant values have been indicated in bold. Data are expressed as mean and 95% confidence interval.

6MWD, 6-minute walking distance; ABI, ankle-brachial index; PFWD, pain-free walking distance; PTS, speed at onset of claudication; Smax, maximal speed.

obtained during the program at controlled speed.^{42,43} In a previous study faster ambulatory cadence during a step-monitored, home-based exercise program was associated to greater walking improvements in women.⁴⁴

Walking without pain with interval breaks within each exercise session was well tolerated and often performed with pleasure. A significant improvement in physical functioning⁴² and QoL was observed at discharge from the pain-free program in a sample of 90 subjects with a 50% increase in the bodily pain domain.²⁵

Notably, other authors reported that a low-intensity treadmill program without pain was as effective for subjects with PAD,⁴⁵ with similar benefits in women compared to men.⁴⁶

Moreover, the proposed program based on individualized, low-dose exercise with interval breaks allows the enrollment of patients with severe PAD, important comorbidities, and gait problems who are often excluded from traditional rehabilitation programs due to the exercise intensity used^{41,47}; interestingly, these patients obtain more benefits from the Ti-To program. Among barriers to physical activity, low energy levels related to the presence of diabetes, a low ABI, and a low walking capacity for leg pain have been reported.⁴⁸ Additionally, comorbidities did not influence the outcomes of the study. In the female study population, every rehabilitation outcome parameter is favorably increased with or without diabetes or osteoarticular diseases.³⁸

However, the program in this study aimed to overcome other barriers to exercise through its organizational model.

In recent years, home-based programs have been considered feasible and effective for improving walking ability in PAD patients,^{41,49,50} and recent trials have provided support for this therapeutic option.^{51,52} In the present program, the modality of exercise allows the possibility to comfortably carry out all the exercises at home without giving up the surveillance of the family or the management of the house, which are typical duties of most elderly women in our region (personal observation).

The daily low dose of exercise required for an acceptable and fixed working time, which was inserted into daily life, gives women the possibility to manage housework and grandchildren.

Moreover, compared to a supervised program that requires the need to travel daily or three times a week to facilities for exercise execution,⁵⁰ the present model calls for few visits to the hospital, with low costs and a negligible or sustainable commitment on the part of the family. Finally, the program is offered to patients without cost, which is possible because of the low organizational costs of the procedures.^{25,53}

As a further result, in the study we observed significant changes in the ABI value. This result, which is not usually reported following the traditional programs but confirms to previous observations,^{24,25,43,53,54} was similar in the two groups.

We are aware that our study has several limitations, such as its single-center retrospective design and the lack of a control group. However, being a single-center study performed by the same operators over the entire study period represents an evident strength due to the operator-dependent limitations in the evaluation of the outcome measures.

The percentage of women was ~26%, which is far from the values reported by some authors but is consistent with other articles and representative of the whole population sent to rehabilitation. However, an analysis that considers a

different percentage has also been carried out. Finally, data analysis was not performed in a blinded fashion.

Conclusions

A moderate-intensity, pain-free rehabilitation program in PAD patients was equally effective in men and women in terms of functional and hemodynamic improvements and adherence. Of course, further confirmation by a prospective study is needed. However, the implementation of effective organizational models tailored to the female population for the setting, exercise intensity, time of execution requested, tolerability, and costs warrants further research efforts.

Acknowledgments

We would like to acknowledge the professional editing services of American Journal Experts. This article is supported in part by an institutional research grant from the University of Ferrara, Fondo di Ateneo per la Ricerca (Prof. Roberto Manfredini).

Author Disclosure Statement

No competing financial interests exist.

References

- Raeisi-Giglou P, Volgman AS, Patel H, Campbell S, Villablanca A, Hsich E. Advances in cardiovascular health in women over the past decade: Guideline recommendations for practice. *J Womens Health (Larchmt)* 2018;27:128–139.
- Smith SM, Huo T, Gong Y, et al. Mortality risk associated with resistant hypertension among women: Analysis from three prospective cohorts encompassing the spectrum of women's heart disease. *J Womens Health (Larchmt)* 2016;25:996–1003.
- Goldstein KM, Stechuchak KM, Zullig LL, et al. Impact of gender on satisfaction and confidence in cholesterol control among veterans at risk for cardiovascular disease. *J Womens Health (Larchmt)* 2017;26:806–814.
- Rodriguez F, Olufade TO, Ramey DR, et al. Gender disparities in lipid-lowering therapy in cardiovascular disease: Insights from a managed care population. *J Womens Health (Larchmt)* 2016;25:697–706.
- Pary F, Beceanu A, Avram R, Timar RZ, Timar B, Gadalean F. Association of mild-to-moderate reduction in glomerular filtration rate with subclinical atherosclerosis in postmenopausal women. *J Womens Health (Larchmt)* 2017;26:1201–1213.
- Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007;45 Suppl S:S5–S67.
- Sampson UK, Fowkes FG, McDermott MM, et al. Global and regional burden of death and disability from peripheral artery disease: 21 world regions, 1990 to 2010. *Glob Heart* 2014;9:145–158.
- Hirsch AT, Allison MA, Gomes AS, et al. A call to action: Women and peripheral artery disease: A scientific statement from the American Heart Association. *Circulation* 2012;125:1449–1472.
- Barochiner J, Aparicio LS, Waisman GD. Challenges associated with peripheral arterial disease in women. *Vasc Health Risk Manag* 2014;10:115–128.
- Roumia M, Aronow HD, Soukas P, et al. Sex differences in disease-specific health status measures in patients with symptomatic peripheral artery disease: Data from the PORTRAIT study. *Vasc Med* 2017;22:103–109.
- Oka RK, Szuba A, Giacomini JC, Cooke JP. Gender differences in perception of PAD: A pilot study. *Vasc Med* 2003;8:89–94.
- Vouyouka AG, Egorova NN, Salloum A, et al. Lessons learned from the analysis of gender effect on risk factors and procedural outcomes of lower extremity arterial disease. *J Vasc Surg* 2010;52:1196–1202.
- Arnaoutakis DJ, Scully RE, Sharma G, et al. Impact of body mass index and gender on wound complications after lower extremity arterial surgery. *J Vasc Surg* 2017;65:1713–1718.
- Jain AK, Kalbaugh CA, Farber MA, Marston WA, Vallabhaneni R. Race and gender affect outcomes of lower extremity bypass. *J Vasc Surg* 2014;60:1275–1280.
- Jackson EA, Munir K, Schreiber T, et al. Impact of sex on morbidity and mortality rates after lower extremity interventions for peripheral arterial disease: Observations from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. *J Am Coll Cardiol* 2014;63:2525–2530.
- Bechter-Hugl B, Falkensammer J, Gorny O, Greiner A, Chemelli A, Fraedrich G. The influence of gender on patency rates after iliac artery stenting. *J Vasc Surg* 2014;59:1588–1596.
- Wang J, He Y, Shu C, Zhao J, Dubois L. The effect of gender on outcomes after lower extremity revascularization. *J Vasc Surg* 2017;65:889–906.
- Arthur HM, Blanchard C, Gunn E, Kodis J, Walker S, Toner B. Exercise trajectories of women from entry to a 6-month cardiac rehabilitation program to one year after discharge. *Biomed Res Int* 2013;2013:121030.
- Foy CG, Rejeski WJ, Berry MJ, Zaccaro D, Woodard CM. Gender moderates the effects of exercise therapy on health-related quality of life among COPD patients. *Chest* 2001;119:70–76.
- Anjo D, Santos M, Rodrigues P, et al. The benefits of cardiac rehabilitation in coronary heart disease: A gender issue? *Rev Port Cardiol* 2014;33:79–87.
- Dörenkamp S, Mesters I, de Bie R, Tejjink J, van Breukelen G. Patient characteristics and comorbidities influence walking distances in symptomatic peripheral arterial disease: A large one-year physiotherapy cohort study. *PLoS One* 2016;11:e0146828.
- Gardner AW, Parker DE, Montgomery PS, Blevins SM. Diabetic women are poor responders to exercise rehabilitation in the treatment of claudication. *J Vasc Surg* 2014;59:1036–1043.
- Gommans LN, Scheltinga MR, van Sambeek MR, Maas AH, Bendermacher BL, Tejjink JA. Gender differences following supervised exercise therapy in patients with intermittent claudication. *J Vasc Surg* 2015;62:681–688.
- Manfredini F, Malagoni AM, Mascoli F, et al. Training rather than walking: The test in -train out program for home-based rehabilitation in peripheral arteriopathy. *Circ J* 2008;72:946–952.
- Malagoni AM, Vagnoni E, Felisatti M, et al. Evaluation of patient compliance, quality of life impact and cost-effectiveness of a “test in-train out” exercise-based rehabilitation program for patients with intermittent claudication. *Circ J* 2011;75:2128–2134.
- Manfredini F, Mallamaci F, D'Arrigo G, et al. Exercise in patients on dialysis: A multicenter, randomized clinical trial. *J Am Soc Nephrol* 2017;28:1259–1268.

27. Malagoni AM, Catizone L, Mandini S, et al. Acute and long-term effects of an exercise program for dialysis patients prescribed in hospital and performed at home. *J Nephrol* 2008;21:871–878.
28. Torino C, Manfredini F, Bolignano D, et al. Physical performance and clinical outcomes in dialysis patients: A secondary analysis of the EXCITE trial. *Kidney Blood Press Res* 2014;39:205–211.
29. Malagoni AM, Cavazza S, Ferraresi G, et al. Effects of a “test in-train out” walking program versus supervised standard rehabilitation in chronic stroke patients: A feasibility and pilot randomized study. *Eur J Phys Rehabil Med* 2016;52:279–287.
30. Lamberti N, Straudi S, Malagoni AM, et al. Effects of low-intensity endurance and resistance training on mobility in chronic stroke survivors: A pilot randomized controlled study. *Eur J Phys Rehabil Med* 2017;53:228–239.
31. Vandembroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. *PLoS Med* 2007;4:e297.
32. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries Endorsed by: The European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J* 2018;39:763–816.
33. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994; 47:1245–1251.
34. Manfredini F, Conconi F, Malagoni AM, et al. Speed rather than distance: A novel graded treadmill test to assess claudication. *Eur J Vasc Endovasc Surg* 2004;28:303–309.
35. Montgomery PS, Gardner AW. The clinical utility of a six-minute walk test in peripheral arterial occlusive disease patients. *J Am Geriatr Soc* 1998;46:706–711.
36. Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: A systematic review. *J Eval Clin Pract* 2017;23:377–381.
37. Lozano FS, González-Porras JR, March JR, Carrasco E, Lobos JM; VITAL Investigators. Differences between women and men with intermittent claudication: A cross-sectional study. *J Womens Health (Larchmt)* 2014;23:834–841.
38. Lamberti N, Straudi S, Lissia E, et al. Home-based exercise for elderly patients with intermittent claudication limited by osteoarticular disorders—Feasibility and effectiveness of a low-intensity programme. *Vasa* 2018;1–8. DOI: 10.1024/0301-1526/a000692. [Epub ahead of print].
39. Gardner AW, Parker DE, Montgomery PS, Khurana A, Ritti-Dias RM, Blevins SM. Gender differences in daily ambulatory activity patterns in patients with intermittent claudication. *J Vasc Surg* 2010;52:1204–1210.
40. Moore SM. Women’s views of cardiac rehabilitation programs. *J Cardiopulm Rehabil* 1996;16:123–129.
41. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017;69:1465–1508.
42. Manfredini F, Conconi F, Malagoni AM, et al. Training guided by pain threshold speed. Effects of a home-based program on claudication. *Int Angiol* 2004;23:379–387.
43. Manfredini F, Malagoni AM, Mandini S, et al. Near-infrared spectroscopy assessment following exercise training in patients with intermittent claudication and in untrained healthy participants. *Vasc Endovascular Surg* 2012;46:315–324.
44. Gardner AW, Parker DE, Montgomery PS. Sex-specific predictors of improved walking with step-monitored, home-based exercise in peripheral artery disease. *Vasc Med* 2015;20:424–431.
45. Barak S, Stopka CB, Archer Martinez C, Carmeli E. Benefits of low-intensity pain-free treadmill exercise on functional capacity of individuals presenting with intermittent claudication due to peripheral arterial disease. *Angiology* 2009;60:477–486.
46. Dipnarine K, Barak S, Martinez CA, Carmeli E, Stopka CB. Pain-free treadmill exercise for patients with intermittent claudication: Are there gender differences? *Vascular* 2016;24:304–314.
47. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. *N Engl J Med* 2002;347: 1941–1951.
48. Cavalcante BR, Farah BQ, dos A Barbosa JP, et al. Are the barriers for physical activity practice equal for all peripheral artery disease patients? *Arch Phys Med Rehabil* 2015; 96:248–252.
49. McDermott MM. Exercise rehabilitation for peripheral artery disease: A REVIEW. *J Cardiopulm Rehabil Prev* 2018; 38:63–69.
50. McDermott MM, Polonsky TS. Home-based exercise: A therapeutic option for peripheral artery disease. *Circulation* 2016;134:1127–1129.
51. McDermott MM, Liu K, Guralnik JM, et al. Home-based walking exercise intervention in peripheral artery disease: A randomized clinical trial. *JAMA* 2013;310:57–65.
52. McDermott MM, Spring B, Berger JS, et al. Effect of a home-based exercise intervention of wearable technology and telephone coaching on walking performance in peripheral artery disease: The HONOR randomized clinical trial. *JAMA* 2018;319:1665–1676.
53. Lamberti N, Malagoni AM, Ficarra V, et al. Structured home-based exercise versus invasive treatment: A mission impossible? A pilot randomized study in elderly patients with intermittent claudication. *Angiology* 2016;67:772–780.
54. Manfredini F, Rigolin GM, Malagoni AM, et al. Exercise training and Endothelial Progenitor Cells in haemodialysis patients. *J Int Med Res* 2009;37:534–540.

Address correspondence to:
 Roberto Manfredini, MD
 Department of Medical Sciences
 University of Ferrara
 Via Fossato di Mortara 46
 Ferrara 44121
 Italy

E-mail: roberto.manfredini@unife.it