Original Article

Survival and clinical outcomes of diabetic peripheral artery disease patients following a pain-free home-based walking program

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Abstract

Aim: We retrospectively examined the impact on the rate of survival of pain-free home-based exercise in diabetic peripheral artery disease patients compared to patients receiving usual care.

Methods: A total of 202 patients at Fontaine's stage II with diabetes were studied. Half were enrolled in a structured home-based exercise program (E), whereas the other received walking advice as active control group (C). Long-term clinical outcomes at five-year were gathered from the Emilia-Romagna Health Service Registry, with survival probability selected as primary outcome.

Results: At baseline, the two groups did not differ for any demographic or clinical characteristics. High adherence to the program was recorded in the E group (88% of home-walking sessions executed, average distance walked during the program: 174 km). After five years, a survival rate of 90% for the E group and 60% for the C group was observed, with a significantly ($P < 0.001$) higher mortality risk for C group (Hazard ratio, HR: 3.92) Additionally, among secondary outcomes, the E group showed a significantly ($P = 0.048$) lower rate of peripheral revascularizations than C group (15% *vs.* 24% respectively; HR:1.91), all-cause hospitalizations ($P = 0.007$; 61% *vs.* 80%, HR:1.58) and of amputations ($P = 0.049$; 6% *vs.* 13%, HR:2.47). In a Cox multivariate-proportional regression model of entire population, the predictors of survival probability were age (HR: 1.05), Charlson index (HR: 1.24), lower ankle-brachial index (HR: 6.66) and Control group (HR: 4.99).

Conclusion: A simple sustainable program aimed at improving mobility of diabetic patients with claudication at high cardiovascular risk was associated with better survival and long-term clinical outcomes.

Keywords: Exercise therapy, peripheral arterial disease, diabetes, rehabilitation, mortality

INTRODUCTION

Atherosclerotic peripheral artery disease (PAD) is a highly prevalent and undertreated global disease, with a negative association with premature cardiovascular events and death [1]. Atherosclerotic lesions in the arteries of the lower limbs result in impaired blood flow to the legs of patients who experience cramping pain during walking and a limitation of their daily activities [2,3]. In patients with diabetes, PAD is highly prevalent [4], and it represents the most common manifestation of cardiovascular diseases. Indeed, PAD in diabetic subjects reflects a systemic atherosclerotic disease with peculiar characteristics, such as a high incidence of vascular calcifications [5], rapid progression toward more severe PAD stages and prevalent involvement of distal and bilateral arteries [5]. All these factors are ultimately associated with worst long-term clinical outcomes [4,6-7] including a high risk of amputations [8], unfavorable cardiovascular outcomes and higher mortality in diabetic PAD patients as compared to those in non-diabetic PAD patients [9-10].

The first line of treatment in these individuals is lifestyle modification and exercise therapy [11], with supervised treadmill exercise performed at an intensity such as to evoke moderate to severe pain as a first-line recommendation for patients with PAD and intermittent claudication [12].

However, the presence of pain during walking might reduce adherence to programs [12], as well with other barriers as costs, travel and access. The presence of diabetes may also attenuate improvements in walking performance in patients with PAD following exercise [11]. Moreover, repeated cycles of exercise-induced ischemia followed by reperfusion may be associated with signs of muscular damage, an increase in inflammatory markers and reactive oxygen species production, and structural and metabolic changes in the muscle with reduced strength and function [13-16].

In addition, patients with type 2 diabetes need to be carefully checked and monitored before engaging in an exercise program [7]. In particular, patients severely detrained should start exercise at low intensity with close supervision by healthcare professional, aiming at integration of regular physical activity into daily routine [7]. However, regardless of exercise length and modality, regular intensive walking exercise in more effective than usual care [17].

More than a decade ago, a structured low-intensity, pain-free program prescribed at hospital and executed at home was developed and introduced into clinical practice [18-20]. The Test in-Train out program (TiTo) proved itself to be effective on functional capacity and quality of life in patients with PAD and claudication, even in the presence of comorbidities [21,22], when compared to surgical revascularization [23], with favorable long-term clinical outcomes [24-25]. The program was also successfully translated to stroke survivors, patients with end-stage kidney disease and people with multiple sclerosis [26-30].

Therefore, given the high risk of mortality reported in diabetic PAD patients and the protective effect of exercise programs, we hypothesize that a different risk of mortality rates at 5 years would be observable in diabetic PAD patients enrolled or not into an exercise program.

The aim of this retrospective study was to examine the rate of survival, hospitalizations and lower extremity amputations in a cohort of diabetic PAD patients in the TiTo home-based exercise program compared to another matched cohort of diabetic PAD patients acting as a control group.

METHODS

Study design and setting

This single-center cohort study was conducted at University Hospital of Ferrara, Italy, between 2013 and 2014. The study was approved by The Local Ethics Committee (CE-AVEC) (approval number 277/2019) but written informed consent was not attainable from all participants.

This study retrospectively analyzed a prospectively collected database of patients with PAD who were recruited at Unit of Vascular Surgery and referred for the training program at the Unit of Rehabilitation Medicine. A follow-up period of 5 years was considered. Long-term outcomes were gathered from the Emilia-Romagna Regional Health Service Registry.

Subjects

A cohort of diabetic PAD patients were enrolled in the rehabilitation program. Patients included presented with PAD at Leriche-Fontaine stage II, diagnosis of type 2 diabetes with habitual use of oral hypoglycemic agents, insulin or both; and no contraindications to low-intensity exercise training (e.g., heart failure, amputations, severe cognitive impairments, etc.).

During the same temporal frame, a parallel control group patients with PAD with the same inclusion criteria were also studied from those screened at the outpatients clinics of Department of Vascular Surgery.

Patients were then classified into two groups according to the study objectives: exercise (E) and control (C).

Data regarding clinical status (including medication, risk factors and comorbidities), PAD severity (including type of lesions) and ankle-brachial index were collected from the medical records of each patient. An independent researcher blinded to the group allocations of the patients created the dataset with the clinical information.

Exercise group: training program

All patients received the “test in–train out” home-based pain-free exercise program [19,20].

This low-intensity structured exercise program was prescribed during circa-monthly visits at the hospital, and it was executed at home. The program is scheduled with two daily 10 minutes sessions of intermittent walking (with a 1:1 walk:rest ratio) at a prescribed speed. This training speed, which is converted into a walking cadence (steps/minute) and maintained at home by the use of a metronome, was slower than the individual's walking speed at the beginning and progressively increased weekly. A daily log to monitor the program execution was provided to the patients, and a feedback was requested at each hospital visit. The program lasted within 6 and 12months. Patients were discharged when they perceived a satisfactory upgrade of mobility, and a stable improvement in the pain-free walking distance was attained (e.g., when they reached a measured symptom-free walking speed normal for sex and age, which was confirmed in two subsequent tests). Discharge was also possible when no changes in walking ability were observed after repeated measurements (e.g., for intercurrent osteoarticular pathologies) or for the impossibility or willingness to exercise or to complete the program. More details on the exercise program are reported elsewhere [19,20].

Control group

Patients in the control group who underwent duplex examination without functional assessment were instructed to maintain a healthy and active lifestyle, according to the TASC II guidelines [31]. In detail, patients were advised to perform track walking of sufficient intensity to bring on claudication, followed by rest, over the course of a 30–60 minute session, three times per week [31]. A 12-month follow up visit was also scheduled with instrumental and clinical examinations, without intermediate visits.

After discharge, patients of both groups received recommendations to perform physical activity and to maintain an active and healthy lifestyle, according to the guidelines [31].

Study outcomes

Five-year survival probability was the primary outcome. Secondary outcomes included PAD-related lower limb revascularization (including both endovascular and surgical procedures), all-cause hospitalizations and lower limb amputations (minor or major). Outcomes were considered after the date of the entrance of participants into the program for E group and after the vascular surgeon's visit for C group. A five-year follow up period was obtained for all participants; in case of death in absence of a precise outcome (e.g. amputation), data were censored at the date of death.

Statistical analysis

Data distribution was verified with a Kolmogorov-Smirnov test. Differences in baseline characteristics for the two groups were evaluated with a Chi-squared tests, Student's t test or Mann-Whitney test, as appropriate.

Kaplan-Meier estimates of the distribution of time from enrollment to date of death and a log-rank test for trend were used to compare the curves of the patient group.

Multivariate Cox proportional hazards regression analyses were employed to analyze the effect of several predictor variables on the primary outcome for each group. Because of the limited number of events, multivariate hazard ratios (HRs) were calculated using a forward approach, with an entry limit of $p < 0.05$. A p value < 0.05 was considered statistically significant.

All statistical analyses were performed using MedCalc Statistical Software version 19.8 (MedCalc Software bvba, Ostend, Belgium).

RESULTS

The clinical records of 416 claudication patients who visited the Department of Vascular Surgery between 2013 and 2014 were analyzed. A total of 196 patients underwent the rehabilitation program, and the remaining patients underwent vascular screening. A total of 214 patients were excluded, since they were not diagnosed with diabetes (n=187) or did not comply with the other inclusion criteria (n=27). The final sample included 202 diabetic patients with claudication, 101 belonging to the E group, and 101 to the C group (Figure 1).

At baseline, the two groups did not differ for any demographic or clinical characteristics or in PAD severity (Table 1).

In addition, the two groups were also balanced for duration of diabetes (E: 5±4 years vs. C: 5±5 years; p=0.79) and for the proportion of patients with insulin-dependent diabetes (E: 39% vs C: 41%; p=0.58).

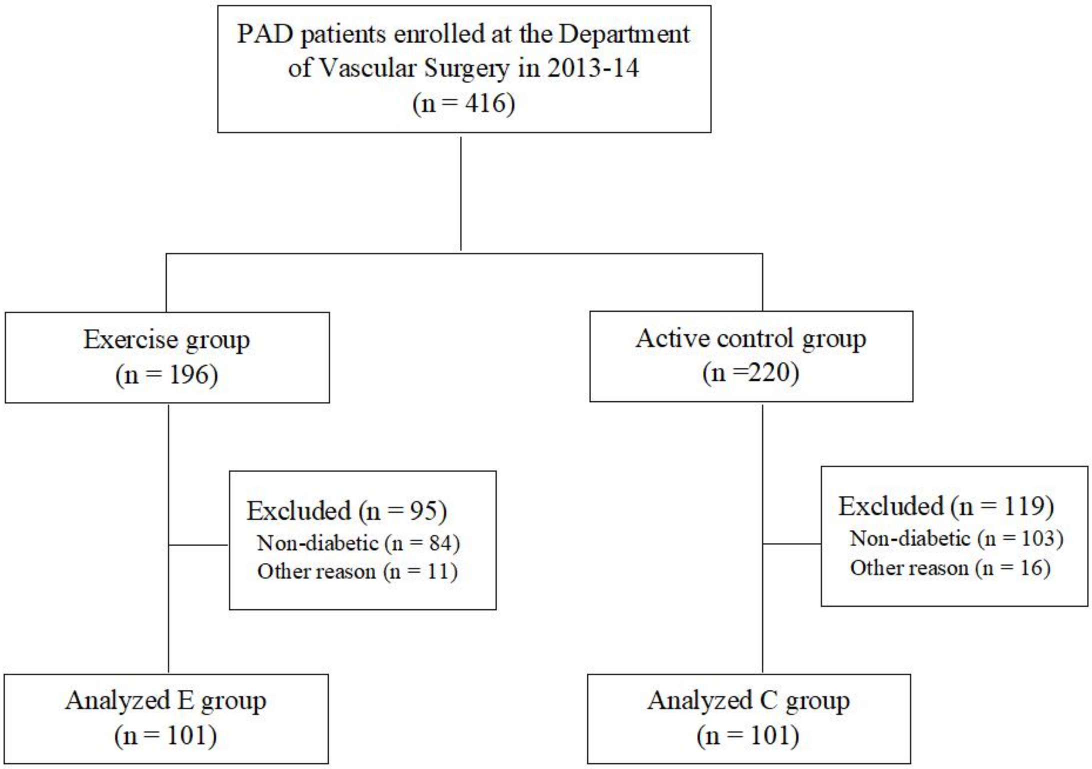

Figure 1. Flow diagram of participants.

Table 1. Baseline comparison between the two study groups

	Exercise (n=101)	**Control (n=101)**	**p**
Age, years	69 ± 10	69 ± 11	n.s.
Males, n(%)	65 (66)	70 (71)	n.s.
Risk factors; n (%)			
Smoking	86 (85)	86 (85)	n.s.
Hypertension	80 (79)	78 (77)	n.s.
Hyperlipidemia	71 (70)	63 (62)	n.s.
Diabetes mellitus	101 (100)	101 (100)	n.s.
Chronic Kidney Disease	34 (34)	33 (33)	n.s.
Comorbidities; n (%)			
Ischemic heart disease	30 (30)	26 (26)	n.s.

Stroke	10 (10)	15 (15)	n.s.
Pulmonary disease	11 (11)	18 (18)	n.s.
Neoplastic disease	10 (10)	18 (18)	n.s.
Age-adjusted Charlson Index	7 ± 2	8 ± 2	n.s.
Laboratory values			
Hemoglobin, g/dl	13.5 ± 1.4	12.6 ± 1.8	n.s.
Total Cholesterol, mg/dl	202 ± 69	174 ± 50	n.s.
Triglycerides, mg/dl	178 ± 98	152 ± 81	n.s.
Serum creatinine, mg/dl	1.45 ± 0.89	1.54 ± 1.07	n.s.
Peripheral artery disease			
Lower limbs revascularization	15 (10)	19 (19)	n.s.
Bilateral disease	82 (81)	79 (78)	n.s.
ABI more impaired limb	0.63 ± 0.16	0.61 ± 0.19	n.s.
ABI less impaired limb	0.85 ± 0.20	0.78 ± 0.19	n.s.

Abbreviations: ABI, ankle-brachial index; n.s., not significant.

Exercise group

A total of 98 patients in the E group safely completed the training program without any adverse events related to the training; the remaining three patients dropped out for health reasons. The program lasted for a mean of 9±1 months, with a high adherence (mean value of 88% of home-walking sessions executed with respect to the prescribed sessions) and a mean distance walked at home of 174±29 km. Seventy-five patients completed 100% of the training sessions prescribed, whereas the remaining 23 patients performed at least 60% of the program.

Primary outcome: survival probability

In the following five years after the baseline data collection, 49 (24%) deaths occurred, 9 in the E group and 40 in the C group, corresponding to a survival rate of 90% for the E group and 60% for the C group.

Kaplan-Meier analysis (Figure 2) confirmed a significantly ($p<0.001$) higher mortality risk for the C group as compared to that for the E group, with a HR of 3.92 (95% confidence interval [CI] 2.24 to 6.87).

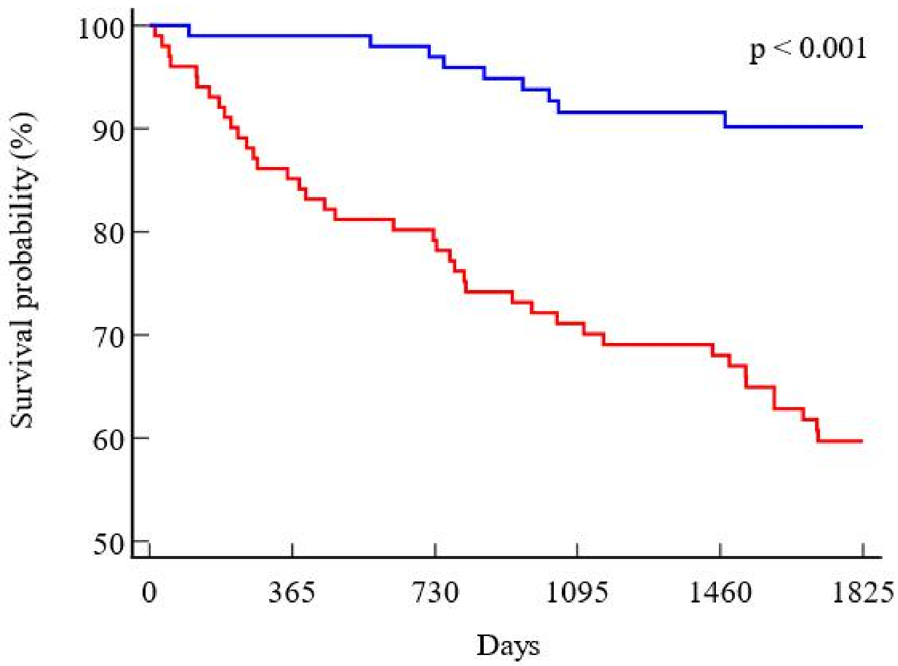

Figure 2. Kaplan–Meier survival curves in the two groups: exercise (blue), control (red).

Secondary outcomes

A between-group significant difference (log-rank p=0.048) was also observed for PAD-related revascularizations, with 15 positive cases in the E group and 24 positive cases in the C group, with a HR of 1.91 (95% CI 1.01 to 3.62) (Figure 3A).

Additionally, for all-cause hospitalizations, a significant difference was found (log-rank p=0.007), with 61 hospitalizations in the E group vs. 79 in the C group, with a HR of 1.58 (95% CI: 1.13 to 2.21) (Figure 3B).

Finally, amputations showed a significant difference (log-rank p=0.049), despite the few positive cases (6 in the E group and 13 in the C group) with a corresponding HR of 2.47 (95% CI 1.00 to 6.10) (figure 3C).

A sub-analysis focusing on only hospitalizations for cardiovascular diseases confirmed the previously observed difference for all-cause hospitalizations; in particular, 43 events were found in the E group vs. 64 events in the C group (log-rank p = 0.031; HR 1.47 [95% CI: 1.07 to 2.12]).

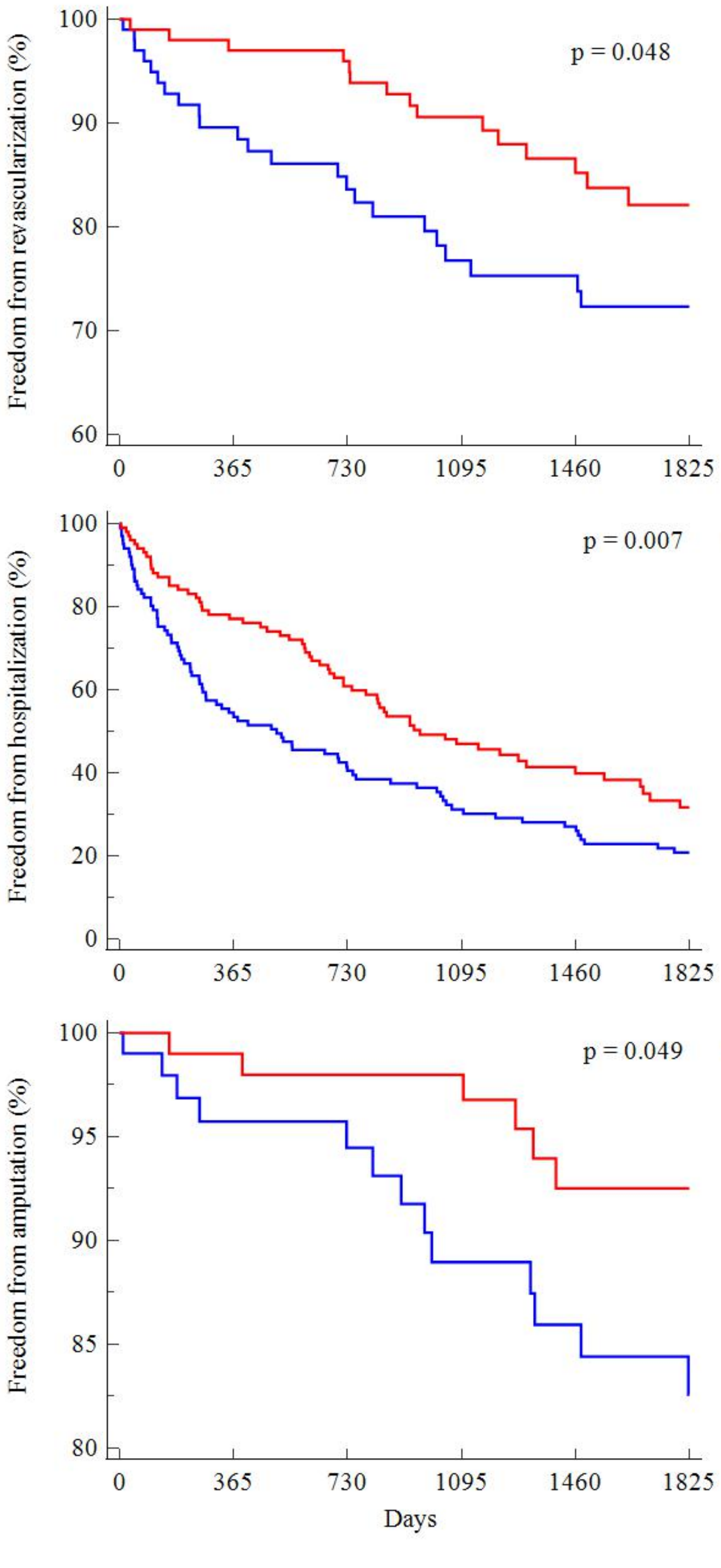

Figure 3. Kaplan-Meier curves for revascularization (A), all-cause hospitalizations (B) and amputation (C) in the two groups. Legend: exercise (blue), control (red).

Predictors of survival probability

Multivariate Cox proportional hazard regression models highlighted that age (HR: 1.05 [95% CI: 1.01 to 1.09]), Charlson index (HR: 1.24 [95% CI: 1.02 to 1.50]) indicating the presence of comorbidities, ABI of the more impaired limb representing PAD severity (HR: 6.66 [95% CI: 1.37 to 32.05]) and Control group (HR: 4.99 [95% CI: 2.40 to 10.40]) were the only predictors of mortality in the entire population.

The multivariate analyses conducted in the two groups confirmed the results observed in the whole population, with age and comorbidities (chronic kidney disease and lung disease) as the more important risk factors for the two groups (Table 2).

Table 2. Multivariate hazard ratios (95% confidence interval) of the study variables for the prediction of 5-year survival probability in the four patients' subgroups

	Exercise (n=101)	**Control (n=101)**
Age		1.06 (1.03–1.10)
Male sex		
Smoking		
Hypertension		
Hyperlipidemia		
Insulin-Dependent Diabetes		
Chronic Kidney Disease	7.69 (1.58–37.35)	
Ischemic heart disease		
Stroke		
Pulmonary disease	6.00 (1.49–24.21)	
Neoplastic disease		
Age-adjusted Charlson Index		
Lower limbs revascularization		
Bilateral disease		
ABI more impaired limb		
ABI less impaired limb		

DISCUSSION

The study has shown a reduction in the risk of long-term mortality and adverse vascular outcomes at 5 years in diabetic PAD patients who were included in the TiTo home exercise program compared to diabetic PAD patients who were simply advised to perform physical activity.

Patients with symptomatic PAD are exposed to a higher risk of the worst clinical outcomes, including major cardiovascular events and amputations, with a 5-year cumulative incidences of 63% and 27% respectively [1]. In the presence of diabetes, the relative risk for mortality has been found to be two- to four-fold greater than that in patients with PAD only [10]. This topic is of importance since the impact on long-term outcomes of the different treatments, including participation in exercise programs, is considered a scientific priority [12]. Peripheral revascularizations have been found to be effective in reducing those relative risks by improving walking ability [6] alone or in combination with exercise programs, which need to be pursued to improve functional capacity, clinical outcomes and quality of life [5,7]. While several high-intensity programs have been found to be effective [7], based not only on walking but also on cycling or arm-cranking [2], comorbidities such as musculoskeletal complaints, hypertension, peripheral neuropathy and especially PAD may reduce the response and adherence to exercise training [7]. In addition, programs' availability, costs, travel and access to supervised exercise program are barriers that need to be considered. In the presence of these factors and considering the reduced pain perception of diabetic PAD patients who report claudication at a three-fold higher degree of muscle deoxygenation [32], low-intensity pain-free walking, such as the TiTo program [19-20], should be encompassed to optimize adherence and to reduce possible adverse reaction to training previously described [7].

The TiTo structured home-based program has already proved its effectiveness in large populations of patients with PAD [19,20], with a lower relative risk for mortality, revascularizations and all-cause hospitalizations considering both those patients who recorded a favorable outcome after the training program [24] and when comparing participants to non-participants to the program [25].

This study confirmed the previous findings in a sample of a population with PAD, including only patients with diabetes. After 5 years, the mortality rate in the control group was 40%, which is very similar to the percentage recently described [10], but this value dropped to 10% when patients were engaged in the TiTo program, leading to an almost four-fold lower risk. Favorable data were also observed for the secondary outcomes, including PAD-related revascularizations, all-cause hospitalizations and amputations, with hazard ratios varying from 1.5 to 2 times higher for the control group.

In a nationwide retrospective analysis after SET programs [33], the five-year freedom from revascularizations was 83%, which is similar to our study (85%) but including a population of claudication patients with and without diabetes. Another study reported similar values (a survival rate of 81% in the SET group) but included only 25% diabetic patients [34]. It is interesting to observe that short bouts of in-home slow interval walking may have an impact on long-term clinical outcomes. However, the increased mobility observed in a poorly active population may represent the explanation. At the end of each week, each patient performed a total of 140 minutes of walking, corresponding to the amount of physical activity recommended by the guidelines [2,7]. Several factors might also be considered. Low-moderate intensity exercise might improve nitric oxide bioavailability, decrease systemic and local oxidative stress and inflammation [15] and induce vascular adaptations (including angiogenetic factors and lower sympathetic activation of the arteriolar tone) that are not observable following intense exercise [14-15].

A crucial key factor in switching such changes is the high adherence reported, which was favored by the characteristic of the TiTo program, such as its indoor execution (facilitating safety and avoiding any weather interference). In addition, low-intensity of exercise, which does not evoke claudication symptoms, may be another factor favoring adherence, particularly in women [22,35].Other pain-free protocols have been proposed and found to be effective performed on a treadmill or using alternative forms of exercise training, such as arm-cranking or leg-cycling ergometers [15,36]. However, these protocols were supervised, with related barriers and limitations in terms of organizational issues (necessity of equipment, presence of a team at the hospital and patients' transportation) and patient enrollment (requested ability to walk on a treadmill for least two minutes at 3.2 km/h). Moreover, these programs, unlike TiTo, may not be able to accustom the patient to ground walking and to favor long-term autonomous adherence to exercise.

Several limitations affect the study, including the sample size being sufficiently limited and the lack of accurate clinical data typical of a retrospective study (e.g. data on glycemic control in the observed period are missing). In addition, the amount of maintenance training suggested to patients at discharge from the exercise program was not collected. To this end, the study reflect a real-world condition (as most of this kind of studies), therefore changes in habits may have occurred randomly in both groups, since a part of E group patients' may have continued exercising, whereas a part of the patients of the C group may have started a rehabilitation program. This fact reduces the potential implication in the results.

In conclusion, a low-intensity structured home-based program was associated with a lower long-term risk of mortality, invasive vascular treatments or amputations in patients with PAD and diabetes, even if a direct association could not be claimed. However, mobility recovery, daily exercise appointments and pain-free maintenance programs may represent favorable factors.
Properly designed exercise programs in patients affected by PAD and diabetes, as in the study presented, may have a clinical impact; however, their effectiveness needs to be confirmed in randomized trials [37].

DECLARATIONS

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Authors' contributions

Wrote and review the manuscript: Lamberti N, Tsolaki E, Guerzoni F, Napoli N, Traina L, Piva G, Gasbarro V, Zamboni P, Straudi S, Manfredini R, Manfredini F

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki and approved by the CE-AVEC Ethics Committee (number 277/2019).

Consent for publication

Not applicable.

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