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Patients With Peripheral Artery Disease Who Complete 12-Week Supervised Exercise Training Program Show Reduced Cardiovascular Mortality and Morbidity

Shingo Sakamoto, MD; Naoyuki Yokoyama, MD; Yuiichi Tamori, MD;
Koichi Akutsu, MD; Hideki Hashimoto, MD*; Satoshi Takeshita, MD**

Background Exercise training improves walking ability in patients with peripheral arterial disease (PAD), but whether exercise training improves the long-term outcome of these patients remains unknown.

Methods and Results Participants were 118 PAD patients who were enrolled in a 12-week supervised exercise program. The long-term outcomes of 64 patients who completed the training were compared with the outcomes of 54 patients who did not. The primary endpoint was cardiovascular mortality, and the secondary endpoint was cardiovascular morbidity. Mean follow-up was 5.7±3.9 years. The cardiovascular death-free rate was higher in patients who completed the training program than in those who did not (P=0.022). Multivariate analysis showed independent predictors of cardiovascular death were age over 70 years, diabetes mellitus, maximum walking distance, history of coronary revascularization, and completion of training program. The cardiovascular event-free rate was also higher in patients who completed the training program (P=0.048).

Conclusions Supervised exercise training improved cardiovascular mortality and morbidity in patients with PAD, which suggests that exercise training should be considered as a secondary prevention strategy for these patients. (*Circ J* 2009; **73:** 167 – 173)

Key Words: Claudication; Diabetes mellitus; Exercise; Peripheral vascular disease

Patients with lower extremity peripheral arterial disease (PAD) experience substantial functional disability because of claudication, rest pain, and the loss of tissue integrity in the distal limbs.[1,2] Consequently, they have considerable difficulty in carrying out routine daily activities and many affected patients become so deconditioned from lack of exercise that they are housebound or dependent on others.

There is strong evidence to support a central role for exercise training to improve the walking ability of patients with claudication.[3–5] In particular, supervised, hospital-based exercise training is considered effective and is recommended as the initial treatment strategy for patients with claudication. The degree of improvement in walking ability after supervised exercise training was shown to be significantly better than that of home-based training such as "go home and take walks".[6–8]

Regular exercise or improved physical activity is associated with improved blood pressure,[9–11] serum lipid profile,[12,13] glycemic control,[14,15] and reduced central adiposity.[16,17] Exercise-induced improvement in walking ability of PAD patients, if associated with improvements in these cardiovascular risk factors, theoretically reduces the risk of cardiovascular events,[18,19] and thereby could improve the long-term survival of these patients. Although previous studies have examined the potential of exercise training in improving walking ability, its benefits for long-term mortality and morbidity have not been studied.

Accordingly, in the current study we sought to determine whether performing supervised exercise training would have a favorable impact on the long-term mortality and morbidity of PAD patients presenting with claudication.

Methods

Study Population

Results for a maximum of 13 years' longitudinal follow-up initiated in 1992 are presented. Between December 1992 and April 2005, a total of 126 patients with a clinical diagnosis of Fontaine stage II PAD (ie, intermittent claudication upon ambulation) and who lived close enough to return to the clinic on a regular basis were enrolled to participate in a supervised exercise training program. The diagnosis of PAD was based on the evidence of functional limitation because of intermittent claudication during a screening treadmill test, and a resting ankle–brachial pressure index (ABPI) <0.9. Exclusion criteria were Fontaine stage I PAD (ambulation not limited by claudication), Fontaine stage III–IV PAD (rest pain, skin ulcer or gangrene), exercise tolerance limited by symptoms of congestive heart failure or chronic obstructive pulmonary disease, exercise-induced myocardial ischemia, and leg pain of nonvascular origin. Patients with untreated diabetes mellitus (DM) were also excluded because the degree of glycemic control might

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*Department of Cardiology, National Cardiovascular Center, Suita, *Department of Health Economics and Epidemiology Research, Graduate School of Medicine, University of Tokyo, Tokyo and **Department of Cardiology & Catheterization Laboratory, Shonan Kamakura General Hospital, Kamakura, Japan*
Mailing address: Satoshi Takeshita, MD, Department of Cardiology & Catheterization Laboratory, Shonan Kamakura General Hospital, 1202-1 Yamazaki, Kamakura 247-8533, Japan. E-mail: stake@muse.ocn.ne.jp

Table 1 Clinical Characteristics

	Exercise training completers (n=64)	Exercise training non-completers (n=54)	P value
Basic characteristics			
Age, years	69±8	67±10	0.122
Male sex	58 (90.6)	44 (81.5)	0.148
Hypertension	55 (85.9)	49 (90.7)	0.421
Hypercholesterolemia	36 (56.3)	33 (61.1)	0.593
Diabetes mellitus	34 (53.1)	29 (53.7)	0.950
Smoker	59 (92.2)	49 (90.7)	0.779
Body mass index, kg/m^2	22.1±2.6	22.4±3.2	0.523
History of myocardial infarction	5 (7.8)	6 (11.1)	0.539
History of coronary revascularization	6 (9.4)	8 (14.8)	0.363
History of stroke	11 (17.2)	10 (18.5)	0.851
Ankle brachial pressure index	0.55±0.19	0.53±0.17	0.517
Maximum walking distance, m	475.0±369.0	332.8±251.8	0.018
Site of stenosis			
Iliac artery	25 (39.1)	29 (53.7)	0.122
Femoral artery	40 (62.5)	37 (68.5)	0.584
Below the knee arteries	13 (20.3)	15 (27.8)	0.380
Medications			
Aspirin	32 (50.0)	31 (57.4)	0.422
Other antiplatelet drugs	51 (79.7)	46 (85.2)	0.437
Statins	16 (25.0)	18 (33.3)	0.415
β-blockers	5 (7.8)	12 (22.2)	0.061
ACEI/ARB	19 (29.7)	26 (48.1)	0.851

Values are mean±SD or number (%) of subjects
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.

affect their response to exercise training.

After enrollment, patients underwent supervised exercise training and were invited to return for annual follow-up examinations. Patient's characteristics, medical history, and cardiovascular risk factors were collected at the time of enrollment into the exercise training program.

Training Protocol

Patients underwent an exercise training program that comprised 12 weeks (3 days per week) of supervised treadmill walking. Exercise training began with a 10-min warm-up and ended with a 10 min cool-down. Exercise intensity started from a constant pace of 2.4 km/h at 5% grade. The severity of claudication pain was graded on a scale of 1–10: 0 = no pain, 1 = onset of claudication, 5 = moderate pain, 8 = severe pain, and 10 = maximal claudication pain. During each session, patients were instructed to walk to the point of severe pain (score 8), and then rest by sitting on a chair. As soon as the claudication pain subsided, they resumed walking. The exercise–rest–exercise cycle was repeated several times during the hour of supervision. If the patients could walk for 10 min with a claudication pain score of less than 8, the walking speed was increased in subsequent sessions by 0.3 km/h up to a maximum of 4.2 km/h. If the patient reached 4.2 km/h, the grade was increased each time by 1%. Both the claudication pain score and maximum walking distance (distance walked before reaching claudication pain score of 10) were measured at the final training session of the day. If the patient did not complete the 12-week training program, the reason for discontinuation was documented.

The exercise training program also included weekly health education lectures addressing risk factors for atherosclerosis, including smoking. All patients were encouraged to continue home-based exercise training irrespective of whether they completed the 12-week supervised exercise training.

Long-Term Outcome

The clinical outcome was assessed from hospital records or telephone questionnaires under the auspices of the institutional cardiovascular outcome monitoring program after a minimum interval of 6 months from the termination of the exercise training. The primary endpoint was cardiovascular death, which included cardiac, cerebrovascular, vascular and sudden death. The secondary endpoint was cardiovascular events, which included cardiovascular death, cardiac events (nonfatal myocardial infarction and coronary artery revascularization), cerebrovascular events (nonfatal ischemic stroke, transient ischemic attack, and carotid artery revascularization), vascular events (rupture, dissection, or thrombosis of major arteries), and major amputation.

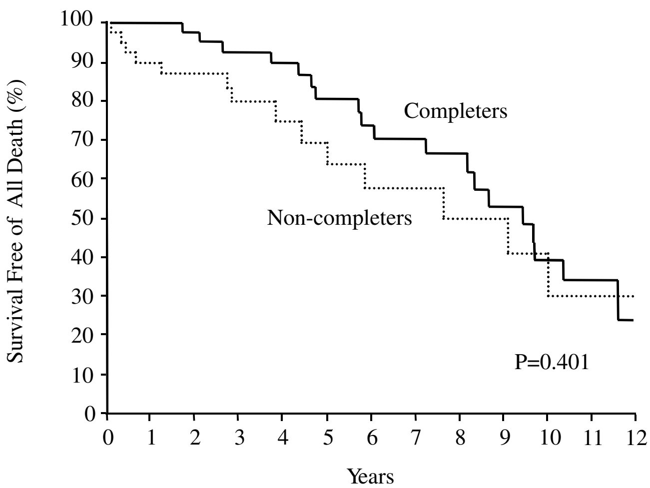
Statistical Analyses

SPSS version 11.0 was used for all statistical analyses (Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation (SD), and comparisons between groups were performed using Student's t-test. Age, body mass index (BMI), ABPI, and maximum walking distance were treated as continuous variables. We used the chi-square test for 2×2 tables to compare categorical data. Event-free survival was estimated using the Kaplan-Meier survival method with log-rank statistics. For the cardiovascular mortality analysis, survival time was defined as the time from initiation of exercise training to the time of cardiovascular death. The patients who died of noncardiovascular causes were censored at the time of death. Patients with cardiovascular events were included up to the time of their event and then censored. Among the variables listed in **Table 1**, 6 (ie, age >70 years, DM, BMI, maximum walking distance, history of coronary revascularization, and completion of supervised exercise training) satisfied the proportional hazards assumption checked by the graphical technique, and were included in the multiple Cox proportional hazards model.

Table 2 Clinical Outcomes

Outcome	*All (n=118)*	*Exercise training completers (n=64)*	*Exercise training non-completers (n=54)*
Cardiac death	*8 (6.8)*	*3 (4.7)*	*5 (9.3)*
Cerebrovascular death	*1 (0.8)*	*0*	*1 (1.9)*
Vascular death	*3 (2.5)*	*1 (1.6)*	*2 (3.7)*
Sudden death	*4 (3.4)*	*2 (3.1)*	*2 (3.7)*
Noncardiovascular death	*17 (14.4)*	*13 (20.3)*	*4 (7.4)*
Nonfatal myocardial infarction	*1 (0.8)*	*1 (1.6)*	*0*
Coronary artery revascularization	*13 (11.0)*	*5 (7.8)*	*8 (14.8)*
Nonfatal ischemic stroke	*11 (9.3)*	*8 (12.5)*	*3 (5.6)*
Transient ischemic attack	*2 (1.7)*	*2 (3.1)*	*0*
Carotid artery revascularization	*2 (1.7)*	*2 (3.1)*	*0*
Ischemic vascular events	*1 (0.8)*	*0*	*1 (1.9)*
Major amputation	*5 (4.2)*	*2 (3.1)*	*3 (5.6)*

Values are number (%) of subjects.



Patients at Risk

Completers	64	64	55	46	43	37	33	28	25	20	17	11	6
Non-completers	54	49	38	33	22	19	16	12	11	10	6	6	5

Fig 1. Kaplan-Meier survival curve free from all-cause death. The estimated survival free from all-cause death in patients who completed the exercise (solid line) and those who did not (broken line) was 94.6% vs 85.3% at 3 years; 85.7% vs 77.7% at 5 years; and 55.9% vs 49.0% at 10 years, respectively.

Ethics and Study Integrity

The institutional review board approved the study protocol and the patients gave written informed consent before participation. The authors had full access to, and take full responsibility for, the integrity of the data. All authors read and agreed to the manuscript as presented.

Results

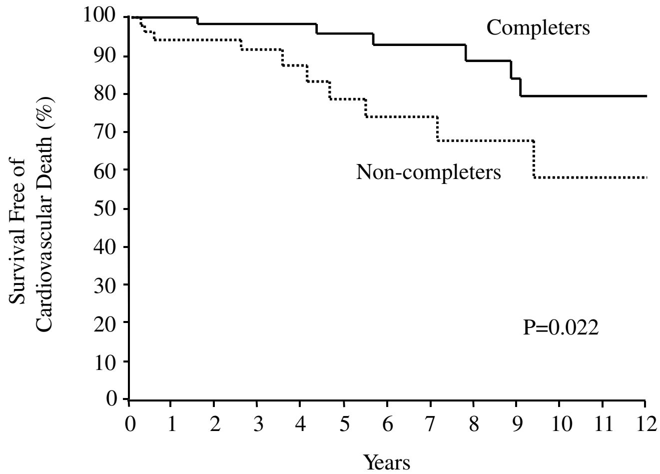
Patient Characteristics

Follow-up contact was possible for 118 of the 126 eligible patients (93.7%). Mean follow-up was 5.7±3.9 years (range 0.2–13.4). The mean age was 68±9 years (range 40–86), and 102 patients (86.4%) were male. Among the 118 participants, 64 (54.2%) completed the supervised exercise program and 54 (45.8%) did not. Mean term to dropout from the commencement of exercise training was 20.6±18.7 days (range 1.0–73.0). The reasons for discontinuation of exercise were loss of motivation in 33 (61.1%), transportation factors in 12 (22.2%), job factors in 5 (9.3%), medical reasons unrelated to cardiovascular events in 3 (5.6%), and early satisfactory improvement in walking ability in 1 (1.9%). Except for the maximum walking distance at baseline, there were no significant differences in the clinical characteristics of the patients who completed the exercise training program vs those who did not (**Table 1**). It should be mentioned that, because patients who completed the exercise training program showed significantly longer walking distance at baseline, we considered the possibility of an interaction between maximum walking distance at baseline and completion of exercise training program. However, statistical analysis revealed no such interactions between these 2 factors.

Clinical Outcomes

During the exercise training, no cardiovascular events occurred. At the end of the exercise training, smoking cessation was achieved in 35 (54.7%) patients who completed the exercise training vs 28 (51.9%) who did not (P=0.73). Patients who completed the training achieved a significant improvement in walking ability. The maximum walking distance improved by 108%, from 475.0±369.0 m at baseline to 987.5±615.5 m at the end of the training (P<0.001).

Overall clinical outcomes are shown in **Table 2**. For the primary endpoint analysis, a total of 16 cardiovascular deaths (13.6%) occurred among the 118 patients, which included 8 cardiac deaths (3 myocardial infarctions, 5 heart failures), 1 cerebrovascular death, 3 vascular deaths, and 4 sudden



Patients at Risk

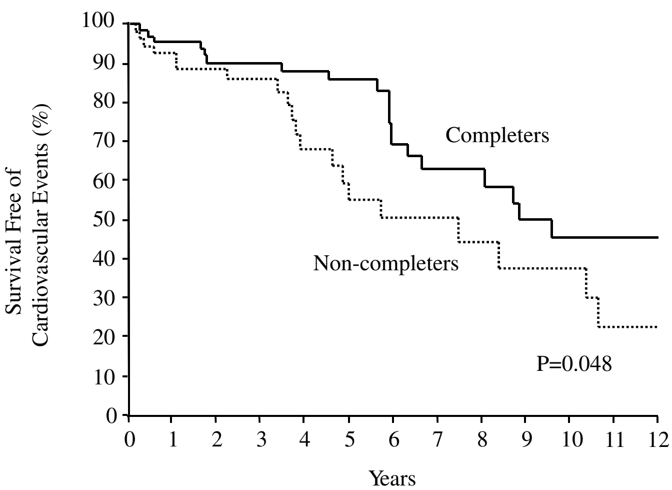
Completers	64	64	56	46	43	37	33	28	25	20	17	11	6
Non-completers	54	49	38	33	22	19	16	12	11	10	6	6	5

Fig 2. Kaplan-Meier survival curve free from cardiovascular death. The estimated survival free from cardiovascular death in patients who completed supervised exercise training (solid line) and those who did not (broken line) was 98.3% vs 91.5% at 3 years; 95.9% vs 83.4% at 5 years; and 79.9% vs 58.4% at 10 years, respectively.

Table 3 Multivariate Analysis for Predictors of Cardiovascular Death

	RR (95%CI)	*P value*
Age >70 years	*11.2 (2.59–48.2)*	*0.001*
Diabetes mellitus	*22.1 (3.56–137.8)*	*0.001*
Maximum walking distance	*0.99 (0.99–1.00)*	*0.012*
History of coronary revascularization	*5.23 (1.26–21.7)*	*0.023*
Completion of exercise training program	*0.16 (0.05–0.54)*	*0.003*

RR, risk ratio; CI, confidence interval.



Patients at Risk

Completers	64	61	51	44	40	34	30	19	18	13	10	7	4
Non-completers	54	48	36	32	19	15	11	8	7	6	5	3	3

Fig 3. Kaplan-Meier survival curve free from cardiovascular events. The estimated survival free from cardiovascular events in patients who completed supervised exercise training (solid line) and those who did not (broken line) was 90.2% vs 85.8% at 3 years; 85.7% vs 63.7% at 5 years; and 45.7% vs 38.0% at 10 years, respectively.

deaths. Noncardiovascular death occurred in an additional 17 (14.4%) patients, 10 of which (58.8%) were from cancer. For the secondary endpoint analysis, a total of 51 cardiovascular events occurred among 40 (33.9%) patients. There were no gender differences in either endpoint.

Predictors of Cardiovascular Deaths and Events

The estimated survival free from all-cause death in patients who completed the exercise and those who did not (broken line) was 94.6% vs 85.3% at 3 years, 85.7% vs 77.7% at 5 years, and 55.9% vs 49.0% at 10 years, respectively (**Fig 1**). No statistically significant differences were observed between the 2 groups.

For the primary endpoint, the cardiovascular death-free rate was significantly higher in patients who completed the exercise program than in those who did not (79.9% vs 58.4%, P=0.022) (**Fig 2**). The cardiovascular death-free rates of the 2 groups of patients were estimated to be 98.3% vs 91.5% at 3 years, 95.9% vs 83.4% at 5 year, and 79.9% vs 58.4% at 10 years, respectively. Multivariate analysis revealed independent predictors of cardiovascular deaths to be age over 70 years, DM, maximum walking distance, history of coronary revascularization, and completion of exercise training program (**Table 3**).

For the secondary endpoint, the cardiovascular event-free rate was also higher in patients who completed exercise training than in those who did not (45.7% vs 22.8%, P=0.048) (**Fig 3**). Cardiovascular event-free rates of completers and non-completers were estimated to be 90.2% vs 85.8% at 3 years; 85.7% vs 63.7% at 5 years; and 45.7% vs 38.0% at 10 years, respectively.

Discussion

This retrospective cohort study with a maximum of 13 years of follow-up demonstrated that undergoing a 12-week supervised exercise training program reduced overall cardiovascular mortality by 52% and morbidity by 30%. To our knowledge, this is the first report to document that exercise training provides a significant reduction in the cardiovascular mortality and morbidity of patients with PAD.

Despite disparity in patient selection, previous studies have consistently documented some degree of agreement with respect to increased overall mortality of patients with claudication, approximately 30% at 5 years, and 50% at 10 years.[20] This increased risk of dying is attributable to the increase in cardiovascular mortality of patients with PAD. Criqui et al, for example, reported that all-cause mortality of claudication patients was increased by 3.1-fold, cardiovascular mortality by 5.9-fold, and coronary artery disease mortality by 6.6-fold.[21] Similarly, Dormandy et al showed that 40–60% of deaths of PAD patients were associated with coronary artery disease, 10–20% with cerebrovascular disease, and 10% with other vascular diseases.[22] In the current study, we also observed an increased risk of all-cause death, as well as cardiovascular death, in patients with claudication. The overall mortality from all-cause death at the 5- and 10-year follow-up was estimated to be approximately 20% and 50%, respectively, and cardiovascular death approximately 10% and 30%, respectively. In addition, approximately 50% of cardiovascular deaths was found to be attributable to cardiac death, 6% to cerebrovascular death, and 19% to other vascular deaths, consistent with previous observations by other investigators. However, it should be noted that, at the time of enrollment for exercise training, we excluded patients who showed exercise-induced myocardial ischemia. In this regard, it is possible that the risk for future cardiovascular deaths and events documented in the current study was underestimated compared with the general PAD population.

Supervised exercise training is a primary efficacious treatment modality to alleviate the claudication symptoms of patients with PAD.[3–6,23–25] The potential of exercise training improve the walking ability of patients with claudication has been established by several previous studies.[3–5] A meta-analysis performed by Gardner and Poehlman, for example, demonstrated that supervised exercise training of patients with claudication improved pain-free walking time by an average of 180% and maximal walking time increased by 120%.[3] Exercise-induced improvements in walking ability have also been shown to translate into increases in routine daily activity.[26,27] Gardner et al reported that 6 months of exercise training improved treadmill walking ability, accompanied by a 31% increase in routine daily activity as measured by accelerometry.[27] Moreover, self-reported physical activity improved by 62%, suggesting that patients themselves appreciated this functional improvement. It should also be pointed out that increased physical activity reduces cardiovascular events in patients with PAD.[28–30] The present study extended those previous observations by demonstrating that completion of a supervised exercise training program ultimately results in a net reduction in cardiovascular mortality and morbidity in PAD patients presenting with claudication.

The mechanisms whereby exercise training improves cardiovascular mortality and morbidity in patients with PAD remain undetermined in this study, but there are several potential explanations. First, increased walking ability or physical activity after exercise training lasts for a certain time period and such increases would be associated with improvements in blood pressure, serum lipid profile and glycemic control, as well as reduced central adiposity,[9–17] which theoretically has the potential to reduce the risk of cardiovascular ischemic events[18,19] and thereby improve long-term survival. Second, PAD patients have decreased endothelial function compared with non-PAD patients.[31] A study performed by Brendle et al demonstrated that 6 months of exercise training increased endothelial-dependent vasodilation of the peripheral vessels by 61%.[32] Such a favorable effect of exercise training on endothelial function has been shown previously in the epicardial coronary vessels and in the resistance vessels of patients with coronary artery disease.[33] It is possible that improved endothelium-dependent vasodilation of the coronary arteries contributed to the reduction in coronary events in the present patients.[34] Third, exercise training improves abnormal hemorheology in patients with claudication, and thereby facilitates systemic oxygen delivery.[23] Ernst and Matrai, for example, reported that 2 months of exercise training improved blood and plasma viscosity to a level similar to that seen with medications such as pentoxifylline.[35] Improved hemorheology after exercise training has also been shown in PAD patients.[36] The possibility that such an effect of exercise training contributed to the improvement in the long-term outcome of the present patients cannot be ignored.

Exercise capacity is a well-established predictor of cardiovascular and overall mortality.[29] PAD patients with higher physical activity have reduced mortality and cardiovascular events than those with lower physical activity.[28] In the current study, we found that the maximum walking distance was a significant predictor of cardiovascular mortality in patients with claudication. Poor walking ability is a modifiable risk factor, and improvement in walking ability over time may achieve improvements in the mortality of PAD patients presenting with claudication. In fact, improvement in fitness over time have been shown to improve the mortality of healthy men and women.[37] Myers et al also reported that every 1-MET increase in treadmill performance was associated with a 12% improvement in survival among men referred for exercise testing.[29] Similarly, studies from the National Exercise and Heart Disease Project in patients who had had a myocardial infarction demonstrated that every 1-MET increase in exercise capacity after a training period was associated with a reduction in all-cause mortality ranging from 8% to 14% over the course of 19 years of follow-up.[38] Whether similar relationships exist between improvement in walking ability after exercise training and survival in PAD patients with claudication remains to be determined in future studies.

The observation that DM is another independent contributor to cardiovascular mortality was not surprising. Previous studies consistently identify DM as a key risk factor for developing PAD.[39–43] The extent to which DM contributes to progression to disability and/or premature mortality in individuals with PAD has also been demonstrated by several investigators. Barzilay et al, for example, found an increased risk (>40%) of death for individuals with both lower extremity arterial disease and DM compared with those with lower extremity arterial disease alone.[44] Leibson et al reported an even higher risk ratio of death for such patients; in their study, the risk of death for PAD patients with DM was 2.2-fold that of those without DM.[45] Considering the fact that we excluded patients with untreated DM from the exercise training program, its actual contribution to the poor prognosis of PAD patients may be more robust than the results described here.

Finally, patients were selected if considered most likely to benefit from an exercise program; that is, if they had no complicating comorbidities that would interfere with exercising, such as arthritis, chronic obstructive pulmonary disease or coronary artery disease. How this information applies to the more general population of patients with claudication that we see in practice, or to those with multiple comorbidities, remains to be determined.

Study Limitations

First, the results of the current study were based on a retrospective and nonrandomized analysis. In addition, the number of study patients was relatively small. Second, longitudinal follow-up of cardiovascular risk factors was not performed. Therefore, the effect of improved physical activity after exercise training on cardiovascular risk factors remains undetermined. Future prospective studies are required to prove the efficacy of exercise training on the long-term outcome of patients with PAD.

Conclusions

Performance of supervised exercise training was associated with a significant reduction in cardiovascular mortality and morbidity. Exercise training for PAD patients with claudication may be upgraded from a symptomatic intervention to a preventive strategy with long-term prognostic benefits.

Acknowledgments

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