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Percutaneous Coronary Angioplasty Compared With Exercise Training in Patients With Stable Coronary Artery Disease: A Randomized Trial

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Percutaneous Coronary Angioplasty Compared With Exercise Training in Patients With Stable Coronary Artery Disease

A Randomized Trial

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Background—Regular exercise in patients with stable coronary artery disease has been shown to improve myocardial perfusion and to retard disease progression. We therefore conducted a randomized study to compare the effects of exercise training versus standard percutaneous coronary intervention (PCI) with stenting on clinical symptoms, angina-free exercise capacity, myocardial perfusion, cost-effectiveness, and frequency of a combined clinical end point (death of cardiac cause, stroke, CABG, angioplasty, acute myocardial infarction, and worsening angina with objective evidence resulting in hospitalization).

Methods and Results—A total of 101 male patients aged ≤70 years were recruited after routine coronary angiography and randomized to 12 months of exercise training (20 minutes of bicycle ergometry per day) or to PCI. Cost efficiency was calculated as the average expense (in US dollars) needed to improve the Canadian Cardiovascular Society class by 1 class. Exercise training was associated with a higher event-free survival (88% versus 70% in the PCI group, $P=0.023$) and increased maximal oxygen uptake ($+16\%$, from 22.7 ± 0.7 to 26.2 ± 0.8 mL O_2/kg, $P<0.001$ versus baseline, $P<0.001$ versus PCI group after 12 months). To gain 1 Canadian Cardiovascular Society class, $6956 was spent in the PCI group versus $3429 in the training group ($P<0.001$).

Conclusions—Compared with PCI, a 12-month program of regular physical exercise in selected patients with stable coronary artery disease resulted in superior event-free survival and exercise capacity at lower costs, notably owing to reduced rehospitalizations and repeat revascularizations. (***Circulation***. 2004;109:1371-1378.)

Key Words: coronary disease ■ exercise ■ angina ■ angioplasty ■ cost-benefit analysis

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The technical advances in percutaneous coronary interventions (PCI) with intracoronary stent implantation have made it the therapy of choice in patients with significant coronary artery disease (CAD), even in stable clinical conditions. Although the benefits of rescue coronary interventions in myocardial infarction and acute coronary syndromes are well established,[1,2] the risk-benefit ratio is less clear in the stable patient with only exercised-induced angina pectoris. Despite their frequent use, percutaneous coronary interventions still carry a significant risk of acute periprocedural complications and follow-up reinterventions due to restenosis compared with medical therapy.[3–5]

We have previously reported that regular physical exercise as part of a multifactorial intervention improves symptom-free exercise tolerance and myocardial perfusion in patients with stable CAD and retards the progression of CAD over time.[6,7] Because no net regression of epicardial coronary stenoses was observed in the majority of patients, improved endothelium-dependent vasodilation may represent the most important mechanism to explain the marked reduction of myocardial ischemia.[8,9] Single-center randomized clinical studies confirmed the effect of exercise training on clinical symptoms and indicated a reduced event rate in patients with stable CAD.[10,11] In a large meta-analysis that included 8440 patients in 32 trials, exercise training as part of coronary rehabilitation programs was associated with a 31% reduction in the mortality rate in patients with stable CAD/myocardial infarction.[12]

On the basis of these results, we initiated the present randomized trial comparing exercise training with medical therapy as the first-line treatment strategy with standard PCI in patients with stable CAD. The aim of this study was to

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compare the effects of both therapeutic strategies on clinical symptoms, angina-free exercise capacity, myocardial perfusion, cost-effectiveness, and frequency of a combined clinical end point (death of cardiac cause, stroke, CABG, angioplasty, acute myocardial infarction, and worsening angina with objective evidence resulting in hospitalization).

Methods

Patient Selection and Assignment

A total of 101 male patients aged ≤70 years with stable CAD and 1 native coronary artery stenosis of ≥75% by visual assessment amenable to PCI were recruited for this study. Eligible patients had class I to III angina pectoris (classified according to the Canadian Cardiovascular Society [CCS]) with documented myocardial ischemia during stress ECG and/or ^{99m}Tc scintigraphy. Exclusion criteria were acute coronary syndromes or recent myocardial infarction (<2 months), left main coronary artery stenosis >25% or high-grade proximal left anterior descending artery stenosis, reduced left ventricular function (ejection fraction <40%), significant valvular heart disease, insulin-dependent diabetes mellitus, smoking, and occupational, orthopedic, and other conditions that precluded regular exercise. Patients after previous CABG or PCI within the last 12 months were also excluded. For practical reasons (participation in group training sessions), only patients living within a 25-km radius of our institution were recruited.

Patients were randomly assigned to either stent angioplasty or exercise training by drawing an envelope with the treatment assignment enclosed. Medical treatment was adjusted according to current clinical guidelines and was continued by the patients' private physicians. The investigational protocol was approved by the ethics committee for human studies at the University of Leipzig.

Follow-up began after randomization on an intention-to-treat basis. The mean interval between randomization and PCI was 14.8±3.3 days, and the interval between randomization and initiation of training therapy was 21.3±2.6 days (P=NS).

Assessment of Clinical Status and Exercise Testing

Initially and after 12 months, the angina pectoris status of all patients was classified according to CCS class by a physician blinded for patient assignment, and a symptom-limited ergospirometry was performed.[13]

Myocardial Scintigraphy

Myocardial perfusion studies were performed by use of a 2-day stress-rest protocol with 400 MBq of ^{99m}Tc-labeled tetrofosmin. Before ergometer stress testing, medication with β-blockers was withdrawn for 48 hours and medication with nitrates was withdrawn for at least 12 hours. Ergometry by stepwise increase in workload was discontinued at each patient's maximal exercise level limited by fatigue, dyspnea, or angina. The radiopharmaceutical agent was injected at the maximal symptom-limited exercise level. Follow-up scintigraphy after 12 months was performed at the same rate-pressure product as the initial study to compare myocardial perfusion at the same cardiac oxygen consumption. For single-photon emission computed tomography (SPECT) acquisition, a dual-head camera with detectors positioned at an angle of 90° (ADAC Laboratories, Vertex) and with ultra-high-resolution collimators was used.[14]

Cardiac Catheterization

Coronary angiography was performed with 6F catheters (Cordis Inc) at baseline and after 12 months after intracoronary application of 200 μg of nitroglycerine to rule out coronary spasms. Quantitative computed analysis was performed by a cardiologist blinded for patient identity and assignment with a validated image-processing algorithm (Cardiovascular Measurement System version 3.0, MEDIS Inc) as described previously.[8] The standard deviation between consecutive measurements of percentage diameter reduction was <5%.[8] Restenosis was defined as >50% diameter stenosis at follow-up.[15] Repeat coronary angiography was performed to assess the long-term result of the coronary intervention in the PCI group and to monitor the progression of coronary atherosclerosis in both groups.

Scoring System for Quantification of Disease Progression

Stenoses with <10% change in diameter reduction were classified as unchanged (±0). A difference ≥10% between baseline and follow-up was graded as progression (+1), and a negative difference ≥10% was graded as regression (−1). Any lesion that necessitated intervention by PCI or bypass surgery was assigned a grade of +3. Progression from subtotal occlusion to total occlusion (99% to 100%) and spontaneous recanalization of previously occluded coronary arteries were not classified as progression or regression, respectively.

In the culprit lesion, an asymptomatic in-stent restenosis <50% was calculated as no change (±0). An in-stent restenosis ≥50% was rated as progression (+1). An in-stent restenosis ≥50% that required an intervention was also classified as a progression (+3). A single variable was calculated per patient by adding the grades assigned to the separate stenoses as reported previously.[6]

Percutaneous Coronary Stent Angioplasty

In patients randomized to stent angioplasty, the target lesion was treated with PCI after a bolus of 10 000 IU of heparin with a 6F guiding catheter. All patients were given acetylsalicylic acid 100 mg/d and clopidogrel 300 mg/d on the day before the procedure. Acetylsalicylic acid 100 mg/d was continued throughout the study period, and clopidogrel 75 mg/d was continued for 4 weeks. Revascularization was technically unsuccessful in 1 patient with a subtotal proximal type C lesion of a prominent diagonal branch. This patient remained clinically stable with conservative treatment and was followed up on an intention-to-treat basis.

Exercise Training Program

During the first 2 weeks, patients exercised in the hospital 6 times per day for 10 minutes on a bicycle ergometer at 70% of the symptom-limited maximal heart rate. Before discharge from the hospital, a maximal symptom-limited ergospirometry was performed to calculate the target heart rate for home training, which was defined as 70% of the maximal heart rate during symptom-limited exercise. Patients were asked to exercise on their bicycle ergometer close to the target heart rate for 20 minutes per day and to participate in one 60-minute group training session of aerobic exercise per week.

Statistical Analysis

Parametric parameters were calculated as mean±SE. The 2-tailed Student's unpaired t test was used for comparisons between groups. Fisher's exact test or the χ^2 test was used for categorical variables with nominal scales and the Wilcoxon or Mann-Whitney rank sum test for those with ordinal scales (SigmaStat 2.03, version 2.0 SPSS Inc). A multivariate analysis was performed to confirm that the composite end point was only influenced by the intervention and not by other baseline parameters (age, maximal oxygen uptake, number of diseased vessels, Gensini score, and lesion type). A probability value <0.05 was considered statistically significant.

The calculation of cost-effectiveness was based on the total costs of treatment, including hospital charges, expenses for supervised training sessions, and the individual bicycle ergometer, and costs of all interventions, coronary angiographies, and rehospitalizations within the follow-up period of 1 year.

In line with the Atorvastatin Versus Revascularization Treatments (AVERT) and Randomised Intervention Treatment of Angina (RITA-2) studies,[4,5] we defined an ischemic event as 1 of the following: death of cardiac cause, stroke, resuscitation after cardiac arrest, CABG, angioplasty, and worsening angina with objective evidence that resulted in hospitalization. Kaplan-Meier survival statistics were used to examine the time to a first ischemic event, and a log-rank test was applied to compare

TABLE 1. Clinical Characteristics

	Training Group (n=51)	PCI Group (n=50)	P
Age, y	62±1	60±1	0.66
Body mass index, kg/m^2	27.2±0.4	28.0±0.5	0.35
LVEF (ventriculography), %	64±1	62±2	0.32
LVEDD, mm	52±2	52±2	0.89
Mean No. of risk factors	1.9±0.2	1.8±0.1	0.71
Cardiovascular risk factors, No. of patients (%)			
Current smoking	9 (18)	8 (16)	0.69
Hyperlipidemia*	39 (77)	43 (86)	0.22
Hypertension†	42 (82)	35(70%)	0.15
Diabetes mellitus	12 (23)	11 (22)	0.86
LDL, mmol/L	3.2±0.2	3.2±0.2	0.91
HDL, mmol/L	1.3±0.1	1.3±0.1	0.88
Concurrent medication, No. of patients (%)			
ACE inhibitors/ AT1-receptor antagonists	38 (74)	44 (88)	0.13
β-HMG-CoA reductase inhibitors	36 (72)	40 (80)	0.27
β-Receptor antagonists	45 (88)	43 (86)	0.74
Acetylsalicylic acid	50 (98)	49 (98)	0.98
CCS classification of angina, No. of patients (%)			
Class I	21 (41)	15 (30)	. . .
Class II	27 (53)	33 (66)	. . .
Class III	3 (6)	2 (4)	0.41
Nature of CAD, No. of patients (%)			
Single vessel	29 (57)	30 (60)	. . .
Double vessel	13 (26)	14 (28)	. . .
Triple vessel	9 (18)	6 (12)	0.72
Location of target lesion, No. of patients (%)			
Left anterior descending CA	11 (22)	9 (18)	. . .
Left circumflex CA	22 (43)	25 (50)	. . .
Right CA	18 (35)	16 (32)	0.78
Lesion type, No. of patients (%)			
Type A	11 (22)	10 (20)	. . .
Type B	34 (67)	34 (68)	. . .
Type C	6 (14)	6 (12)	0.98
Lesion length, mm	9.5±3.4	10.3±3.3	0.12
Myocardial infarction‡	26 (52)	20 (39)	0.27
Gensini score	13.8±2	13.2±2	0.64

LVEF indicates left ventricular ejection fraction assessed by angiography; LVEDD, left ventricular end-diastolic dimension assessed by echocardiography; AT, angiotensin; and CA, coronary artery. Data presented are mean±SEM or number of patients.

*Hyperlipidemia was defined as LDL >3.5 mmol/L.

†Hypertension was defined as systolic RR >140 mm Hg or diastolic RR >90 mm Hg.

‡Myocardial infarction did not occur within 2 months before the screening visit.

event-free survival between intervention groups. The sample size of 101 patients provided the study with 80% power and a 2-sided level of significance of 5% to detect a difference of 15% in the rate of ischemic events between the treatment groups presuming a 10% loss to follow-up in both groups. On the basis of data published in the AVERT and RITA-2 studies,[4,5] an event rate of 30% was expected in the PCI group. An accrual period of 4 years was estimated, with 50% of the enrollment being completed after 2 years.

Results

Baseline Characteristics

One hundred one patients were prospectively randomized to either PCI or to a conservative strategy with exercise training between March 1997 and March 2001. Both groups were comparable with regard to baseline characteristics and medical therapy (Table 1), which remained unchanged during
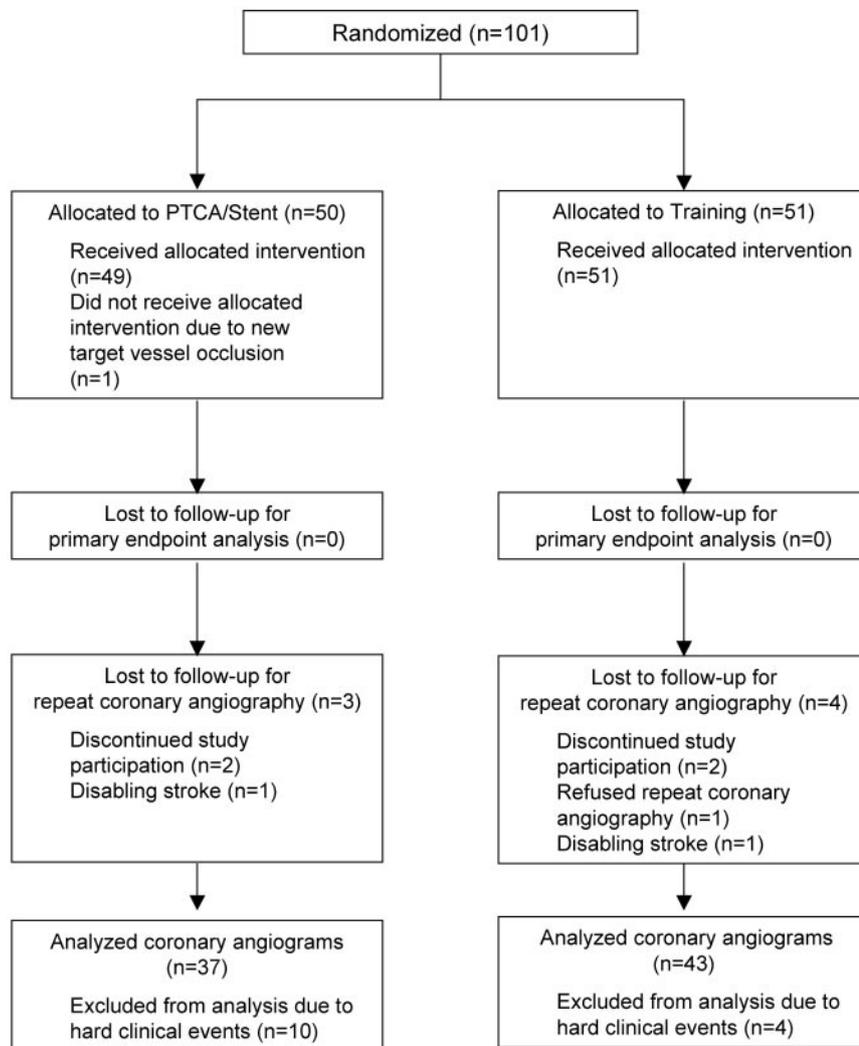
Figure 1. Patient flow diagram of events and dropouts during clinical phases of present randomized trial.

follow-up. LDL cholesterol levels remained unchanged during the study period. HDL serum levels were significantly increased in the training group after 12 months (from 1.3 ± 0.1 to 1.4 ± 0.1 mmol/L, $P<0.01$ versus PCI group for change), whereas they declined further in the control group (from 1.4 ± 0.1 to 1.2 ± 0.1 mmol/L, $P<0.05$ versus baseline).

Dropouts and Clinical Events
Among the 51 training patients and 50 PCI patients, 2 patients in each group terminated their study participation before the final examinations were completed. All dropout patients were followed up on an intention-to-treat basis for clinical events and were contacted by phone. In remaining 49 training patients, compliance with the prescribed training protocol remained high throughout the study period ($70 \pm 2\%$). One additional patient in each group did not receive a control coronary angiography because of a disabling stroke. One patient in the training group declined repeat coronary angiography but completed the clinical follow-up examinations. In total, 47 training patients and 47 PCI patients completed both the initial and follow-up coronary angiograms. Of these, the angiograms of 10 patients in the PCI group and 4 in the training group were excluded from quantitative coronary

angiography owing to hard clinical events (stroke, target-vessel revascularization, PCI of a de novo lesion, or CABG) during follow-up. In total, angiographic follow-up was complete for 43 patients in the training group and 37 in the PCI group (Figure 1).

In parallel, patients with clinical events were excluded from the analysis of clinical symptoms and exercise capacity because the result may not reflect the effect of the primary intervention. Clinical follow-up was complete for 43 training patients (with 2 dropouts and 6 patients with clinical events) and 33 PCI patients (2 dropouts and 15 patients with clinical events).

Within the study period of 12 months, a total of 21 events were documented in 15 patients in the PCI group (Table 2), for an event-free survival of 70% in the PCI group. Six events were documented in 6 patients in the exercise training group (Table 2), which resulted in an event-free survival of 88% in the training group; this was significantly higher than in the PCI group (OR 0.33, 95% CI 0.12 to 0.90, $P=0.023$; Figure 2). No adverse events were observed during the training sessions in any patient. In the multivariate analysis, only the training intervention was found to influence the rate of ischemic events ($P=0.009$). Age, ejection fraction, $\dot{V}O_2$ max,

TABLE 2. Ischemic Events

	Exercise Training Group (n=51)		PCI Group (n=50)	
	No. of Patients for Whom the Event Was the First	Total No. of Patients With Event	No. of Patients for Whom the Event Was the First	Total No. of Patients With Event
Death of cardiac causes	0	0	0	0
Resuscitation after cardiac arrest	0	0	0	0
Nonfatal myocardial infarction	0	0	1	1
Cerebrovascular accident	2	2	1	3
CABG	0	0	1	1
PTCA of target lesion as event	2	2	2	2
PTCA of other coronary segments as event	1	1	4	7
Hospitalization and coronary angiography owing to worsening angina	1	1	6	7
Major ischemic events (cerebrovascular accidents, CABG, and PTCA owing to unstable angina pectoris)	5	5	9	14
Any ischemic event	6	6	15	21

number of diseased vessels, lesion type, and Gensini score did not affect the event rate.

Clinical Symptoms and Exercise Tolerance

In both groups, clinical symptoms improved significantly during the study period. In the exercise training group, average CCS class decreased from 1.5 ± 0.1 at baseline to 0.4 ± 0.1 after 12 months ($P<0.001$ versus baseline). In the PCI group, mean CCS score was reduced from 1.7 ± 0.1 to 0.7 ± 0.1 ($P<0.001$ versus baseline).

After 12 months of exercise training, maximal exercise tolerance was increased significantly by 20% (from 133 ± 5 to 159 ± 5 W, $P<0.001$ versus baseline and versus PCI), and the ischemic threshold was elevated by 30% (from 98 ± 6 to 127 ± 8 W, $P=0.03$ versus baseline). In the PCI group, only the ischemic threshold showed a significant increase after 12

months (Table 3). Exercise training was associated with a 16% increase in maximal oxygen uptake (from 22.7 ± 0.7 to 26.2 ± 0.8 mL O_2/kg, $P<0.001$ versus baseline, $P=0.008$ versus PCI group after 12 months).

Angiographic and Scintigraphic Follow-Up

Patients with ischemic events were excluded from analysis of follow-up angiograms and scintigraphies. As expected, relative target-lesion stenosis was reduced significantly in the PCI group immediately after the intervention (from $81\pm1\%$ to $12\pm1\%$, $P<0.001$; Table 4). Owing to restenosis, a mean late lumen loss of 0.67 ± 0.07 mm was observed in the target lesion after 12 months, associated with a mean target-lesion stenosis of $31\pm2\%$ ($P<0.001$ versus baseline and versus the training group). When restenosis of 50% was used as a binary cutoff value, 7 (15%) of the 47 patients with control angiog-
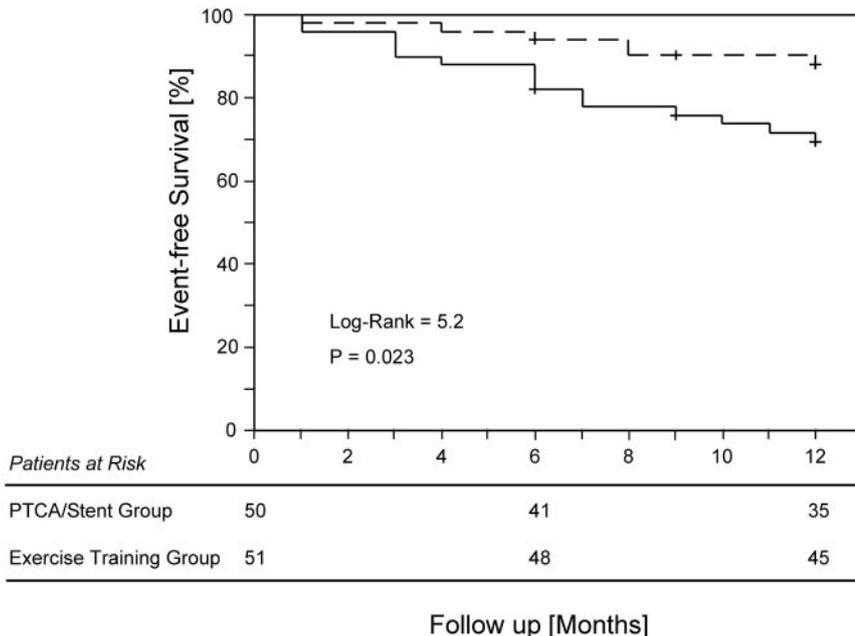

Figure 2. Event-free survival after 12 months was significantly superior in exercise training group versus PCI group ($P=0.023$ by log-rank test).

Log-Rank = 5.2
P = 0.023

Patients at Risk

	0	6	12
PTCA/Stent Group	50	41	35
Exercise Training Group	51	48	45

Follow up [Months]

TABLE 3. Ergospirometry Results

	Exercise Training Group (n=43)		PCI Group (n=33)	
	Baseline	End of Study	Baseline	End of Study
Resting heart rate, bpm	71±2	65±1*†	70±2	70±1
Ischemic threshold, W	98±6	127±8‡	99±5	119±7‡
Maximal heart rate, bpm	131±3	137±3*	132±3	133±3
Physical work capacity, W	133±5	159±5§	130±5	130±5
$\dot{V}o_2$ max, mL · kg^{-1} · min^{-1}	22.6±0.7	26.2±0.8†	22.3±0.6	22.8±0.9

$\dot{V}o_2$ max indicates oxygen uptake at peak exercise; ischemic threshold, first occurrence of angina pectoris and/or ST-segment depression during stress test.

In the training group of 51 patients, 6 patients with clinical events and 2 dropouts were excluded; in the PCI group of 50 patients, 15 patients with clinical events and 2 dropouts were excluded. Data are mean±SEM.

*$P<0.01$, significantly different, 12 months vs baseline.

†$P<0.01$, significantly different, exercise training vs PCI.

‡$P<0.05$, significantly different, 12 months vs baseline.

§$P<0.001$, significantly different, exercise training vs PCI.

raphy in the PCI group developed a significant target-vessel restenosis during follow-up, which required reinterventions in 2 cases. No significant change in the average degree of target-lesion stenosis was observed in the exercise training group (78±2% at study baseline versus 77±2% at 12 months; Table 4).

When total progression of CAD was classified according to the grading system, patients in the exercise training group showed a mean progression of 0.30±0.14 versus 0.81±0.20 in the PCI group ($P=0.035$). In other words, 15 (32%) of 47 exercise training patients with control angiography but 21 (45%) of 47 of the PCI patients had progression of CAD during follow-up.

The ^{99m}Tc scintigraphy documented improved myocardial perfusion distal to the target lesion in patients in the PCI group (^{99m}Tc uptake 77.8±2.4% after 12 months versus 65.1±2.2% at baseline, $P=0.003$ versus baseline). Although the coronary target lesion in the training group remained virtually unchanged, improved ^{99m}Tc uptake distal to the target lesion was observed in the majority of patients after 12 months (76.6±1.9% after 12 months versus 68.1±1.8% at baseline, $P<0.001$ versus baseline).

Cost-Effectiveness

On average, the expenses for 1 year of exercise training amounted to $3708±156 compared with $6086±370 per PCI patient ($P<0.001$ for comparison between groups). These calculations include all expenses caused by rehospitalizations, need for repeat revascularization, or any other cardiovascular event and costs for the infrastructure needed to initiate and maintain a daily exercise training program (eg, cycle ergometers, training facilities, and supervising staff). To gain 1 CCS class, $6956 was spent in the PCI group compared with $3429 in the exercise training group ($P<0.001$ for comparison between groups).

Discussion

In the present study, we found that in patients with stable CAD and an angiographically documented stenosis amenable for PTCA, a 12-month exercise training program resulted in a higher event-free survival rate than with standard PCI intervention. Both PCI and exercise training were equally effective in improving symptom-free exercise tolerance (CCS class). However, the training intervention was associated with higher exercise capacity and maximal oxygen uptake after 12 months than in the PCI group. In addition, the training intervention was significantly more cost-effective: It achieved a clinical improvement of 1 CCS class at approximately half the total cost of an interventional strategy. This observation results from the higher initial expenses of the PCI

TABLE 4. Angiographic Findings: Target-Lesion Follow-Up for Patients Without Events

	Exercise Training Group (n=43)		PCI Group (n=37)		
	Baseline	12 Months	Baseline	Post-PTCA	12 Months
Reference diameter, mm	h2.91±0.09	2.85±0.09	2.75±0.05	2.92±0.06	2.76±0.06*
Minimal lumen diameter, mm	0.66±0.06	0.69±0.08	0.53±0.04	2.57±0.05†	1.91±0.00.07*†
Relative stenosis diameter, %	77.9±1.7	76.5±2.4	80.7±1.5	11.8±0.9†	31.3±2.0*†
Late lumen loss, mm	...	...	...	...	0.67±0.00.07
Binary restenosis‡	...	...	...	...	7 (15%)

Data are mean±SEM.

*$P<0.001$, significantly different, 12 months vs post-PTCA within the angioplasty group.

†$P<0.001$, significantly different, exercise training vs angioplasty.

‡For calculation of the binary restenosis rate, all patients with follow-up angiography were included (n=47 in PCI group). Two patients received target-vessel revascularization by PTCA owing to restenosis (counted as events).

procedure and the more frequent rehospitalizations and coronary reinterventions.

As stated in the American Heart Association/American College of Cardiology clinical guidelines for the management of chronic ischemic heart disease, the uncertainty about which patients benefit from PCI and which do not is complicated by the lack of data identifying patients in whom PTCA confers a survival advantage.[16,17] Most of the patients in the present study had only mild exercise-induced clinical symptoms and a preserved left ventricular systolic function and would therefore be predicted to be at low cardiovascular risk.[18,19] In stable CAD, revascularization is recommended only in patients with high-grade proximal left anterior descending artery stenosis. In all other groups, the risk-benefit ratio of coronary interventions remains controversial, especially because coronary interventions must be regarded as a palliative therapy with regard to the underlying process of atherosclerosis.

The results of the present study are consistent with previous clinical trials comparing interventional and conservative strategies in stable CAD. In essence, they support the notion that the interventional approach yields more rapid relief from the symptoms of exercise-induced angina pectoris.[3,4,20] The overall cardiovascular event rate, however, was significantly higher after a PCI as a consequence of periprocedural and postprocedural complications and more frequent repeat coronary angiographies of patients on the interventional track.[3,4,20] In the RITA-2 study,[4] for example, PTCA was associated with a nearly 2-fold increase in the rate of death or definite myocardial infarction. The imbalance between symptomatic improvement and increased risk of additional revascularization interventions in PTCA patients with stable CAD was also evident in a recent meta-analysis.[21]

The potential benefits of a conservative treatment strategy in patients with stable CAD have become even more apparent in light of the recent AVERT study. In 341 patients with stable CAD randomized to either PTCA and stent implantation when necessary or to medical treatment that included 80 mg of atorvastatin per day, the conservative therapy was associated with a 36% reduced risk for any ischemic event.[5]

The event-free survival rate of 70% in the PCI group compares favorably with the control arm of the RAVEL study (RAndomized study with the sirolimus-eluting Bx VELocity balloon-expandable stent [Cypher]),[22] which reported a 71% event-free survival at 1-year follow-up. In the RAVEL study, the cumulative incidence of relevant in-stent restenosis (>50%) was reported to be 27%, compared with only 15% in the present study. The high interventional success rate in the present study and the absence of major periprocedural complications (acute myocardial infarction and death) may be related to the fact that in contrast to the RAVEL study, patients with increased rates of adverse outcomes after coronary interventions (patients with unstable angina/non–ST-segment elevation myocardial infarction and diabetic patients) were excluded. Given the higher event rates with PCI, the value of PCI in terms of more rapid relief of symptoms must be critically weighed against the inherent risks and greater total costs of the procedure.

With the introduction of drug-eluting stents into clinical practice, it may be argued that the outcome of the present study would have been different if drug-eluting stents had been used. However, this is not the case. If one assumes a 0% binary in-stent restenosis rate in the PCI group, as might have been expected if drug-eluting stents had been used, the difference in event-free survival would still be significant (88% in the training group versus 72% in the PCI group, $P=0.039$). This result is not surprising considering that any coronary intervention can only treat a short segment of the coronary tree, without affecting the progression of coronary atherosclerosis in the remaining vessels. Training with increased shear stress, on the other side, exerts beneficial effects on endothelial function and disease progression in the whole arterial bed.

After 12 months, CCS class and myocardial perfusion were improved to a similar degree in both the exercise training and the PCI groups, but only patients in the training group had a significant gain in maximal exercise capacity. This result reflects the issue that the majority of CAD patients lead a sedentary lifestyle, which was not necessarily changed by a coronary intervention alone. Therefore, patients in the PCI group did not recruit the improved myocardial perfusion to increase their overall exercise capacity. In the exercise training group, on the other hand, patients had a higher maximal exercise tolerance as a result of regular prescribed physical activity, which improved both myocardial perfusion (most likely as a result of enhanced coronary endothelial function and collateralization) [23] and peripheral muscle mass/function. However, one needs to remember that the ischemic threshold was comparatively high at baseline (≈ 100 W). In patients with lower symptom-free exercise tolerance, PTCA has been documented to improve overall exercise capacity.[24]

Although the statistical analysis yielded a significant difference in event-free survival, we are aware that the number of patients enrolled in the present trial is too small to support a general recommendation. Therefore, our finding of a reduced event rate needs to be confirmed in a larger, multicenter study.

The present study adds an important piece of evidence to the rationale for exercise training interventions in patients with stable CAD: it documents that an optimized medical therapy together with exercise training as a lifestyle intervention can be an alternative approach to an interventional strategy in selected motivated patients with stable CAD. In the majority of patients with stable CAD, PCI will remain the therapy of choice but should be combined with a more aggressive lifestyle intervention, including daily physical exercise. In this sense, PCI without comprehensive risk factor modification should be viewed as a suboptimal therapeutic strategy.

Acknowledgment

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