Cost-effectiveness of endovascular revascularization compared to supervised hospital-based exercise training in patients with intermittent claudication: A randomized controlled trial

Sandra Spronk, PhD,[a,b,c] Johanna L. Bosch, PhD,[a,b] Pieter T. den Hoed, MD, PhD,[c] Hermanus F. Veen, MD, PhD,[c] Peter M.T. Pattynama, MD, PhD,[b] and **M.G. Myriam Hunink, MD, PhD,[a,b,d]** *Rotterdam, The Netherlands; and Boston, Mass*

Background: **The optimal first-line treatment for intermittent claudication is currently unclear.**
Objective: **To compare the cost-effectiveness of endovascular revascularization vs supervised hospital-based exercise in patients with intermittent claudication during a 12-month follow-up period.**
Design: **Randomized controlled trial with patient recruitment between September 2002-September 2006 and a 12-month follow-up per patient.**
Setting: **A large community hospital.**
Participants: **Patients with symptoms of intermittent claudication due to an iliac or femoro-popliteal arterial lesion (293) who fulfilled the inclusion criteria (151) were recruited. Excluded were, for example, patients with lesions unsuitable for revascularization (iliac or femoropopliteal TASC-type D and some TASC type-B/C.**
Intervention: **Participants were randomly assigned to endovascular revascularization (76 patients) or supervised hospital-based exercise (75 patients).**
Measurements: **Mean improvement of health-related quality-of-life and functional capacity over a 12-month period, cumulative 12-month costs, and incremental costs per quality-adjusted life year (QALY) were assessed from the societal perspective.**
Results: **In the endovascular revascularization group, 73% (55 patients) had iliac disease vs 27% (20 patients) femoral disease. Stents were used in 46/71 iliac lesions (34 patients) and in 20/40 femoral lesions (16 patients). In the supervised hospital-based exercise group, 68% (51 patients) had iliac disease vs 32% (24 patients) with femoral disease. There was a non-significant difference in the adjusted 6- and 12-month EuroQol, rating scale, and SF36-physical functioning values between the treatment groups. The gain in total mean QALYs accumulated during 12 months, adjusted for baseline values, was not statistically different between the groups (mean difference revascularization versus exercise 0.01; 99% CI −0.05, 0.07; $P = .73$). The total mean cumulative costs per patient was significantly higher in the revascularization group (mean difference €2318; 99% CI €2130, € 2506; $P < .001$) and the incremental cost per QALY was 231 800 €/QALY adjusted for the baseline variables. One-way sensitivity analysis demonstrated improved effectiveness after revascularization (mean difference 0.03; CI 0.02, 0.05; $P < .001$), making the incremental costs 75 208 €/QALY.**
Conclusion: **In conclusion, there was no significant difference in effectiveness between endovascular revascularization compared to supervised hospital-based exercise during 12-months follow-up, any gains with endovascular revascularization found were non-significant, and endovascular revascularization costs more than the generally accepted threshold willingness-to-pay value, which favors exercise. (J Vasc Surg 2008;48:1472-80.)**

Intermittent claudication is the mildest manifestation (ie, Rutherford category 1, 2, or 3) of peripheral arterial disease (PAD), with a prevalence around 5% in men older than 50 years.[1,2] As the incidence of intermittent claudication will increase over the next decades due to the aging population in Western societies, the economic impact of intermittent claudication is expected to be substantial.[3]

The treatment goal for intermittent claudication is to improve health-related quality-of-life. The general consensus is to initially treat with exercise training, but endovascular revascularization is increasingly performed because of its technical innovations, immediate success, and low risks of periprocedural mortality and morbidity, which makes it attractive for both the physician and the patient.[4] In addition to effectiveness, however, one needs to consider costs and cost-effectiveness. Initial hospital costs for endovascular revascularization are likely higher than those for exercise training. Besides these initial hospital costs, the cost of follow-ups are important to take into account, such as the

From the Department of Epidemiology,[a] Department of Radiology,[b] Erasmus Medical Center, Department of Surgery, Ikazia Hospital,[c] and Department of Health Policy and Management, Harvard School of Public Health.[d]
Competition of interest: none.
Reprint requests: Sandra Spronk, PhD, Department of Epidemiology & Radiology, Room Ee 21-40b, Erasmus Medical Center, Dr. Molenwaterplein 40, 3015 GD, PO Box 2040, 3000 CA, Rotterdam, The Netherlands (e-mail: s.spronk@erasmusmc.nl).
0741-5214/$34.00

doi:10.1016/j.jvs.2008.06.016

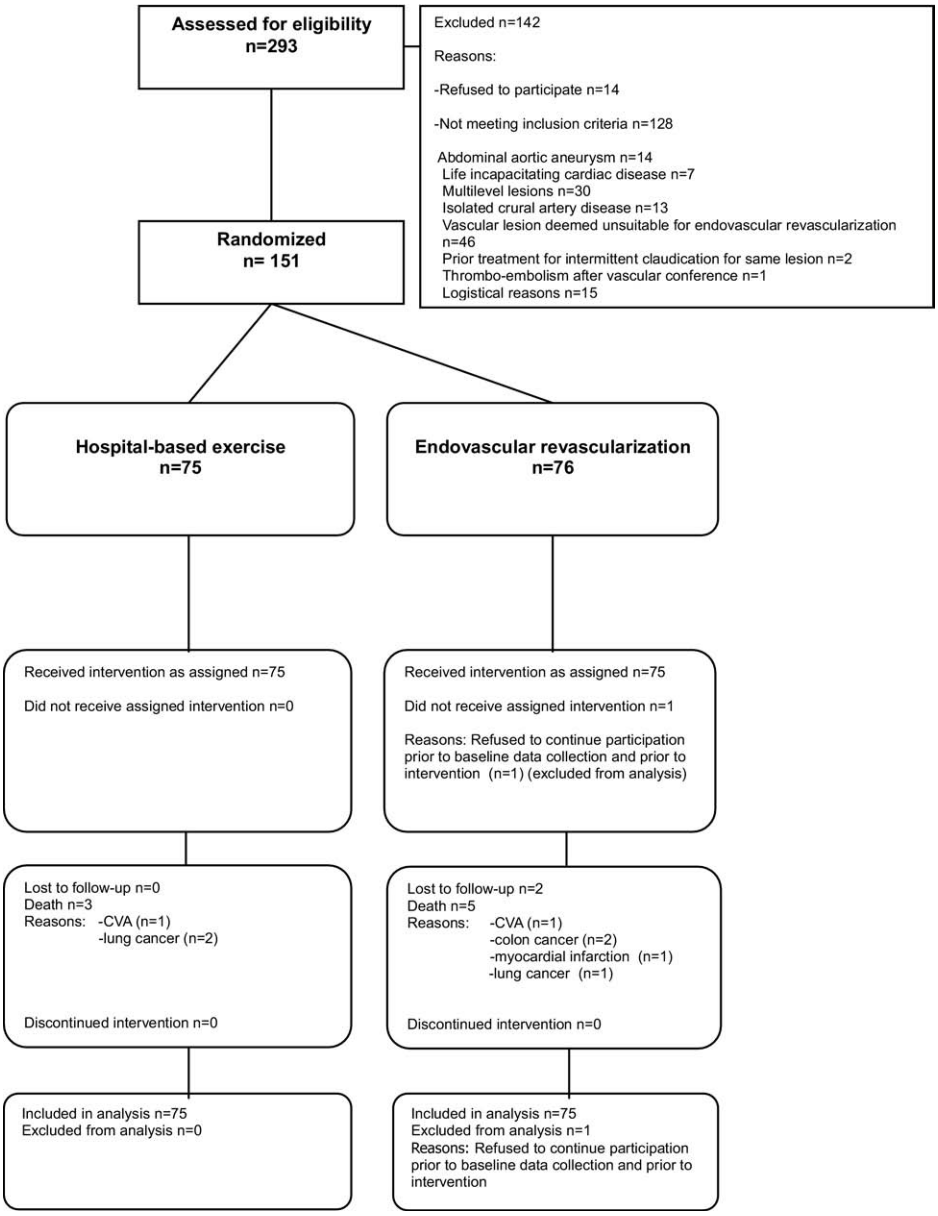

Fig 1. Flow diagram of study (according to CONSORT statement). Diagram illustrates reasons for exclusion, random assignment to endovascular revascularization and supervised hospital-based exercise training and the treatment actually received, including 6- and 12-months follow-up.

costs of diagnostic tests for recurrent symptoms and costs of re-interventions.

This randomized controlled trial (RCT) compared endovascular revascularization vs supervised exercise training as first-line treatment of intermittent claudication, with regard to cost-effectiveness during 12-month follow-up.

METHODS

Study design and patients. The study was an RCT comparing endovascular revascularization to supervised hospital-based exercise in patients with symptoms of intermittent claudication (Rutherford category 1, 2, or 3). The study was performed following good clinical practice and was registered (ISRCTN 64443682).[5] Data were analyzed and reported according to CONSORT guidelines.[6] Institutional review board approval was obtained and all patients gave written informed consent.

All patients referred to the Department of Vascular Surgery with intermittent claudication from September 2002–September 2005 were considered for recruitment (Fig 1). Inclusion criteria were: (1) Rutherford category 1, 2, or 3 $\geq$3 months; (2) maximum pain-free walking dis-

tance of <350 m during a treadmill test; (3) ankle-brachial index (ABI) <0.9 at rest ABI with a decrease of >0.15 after the treadmill test; (4) vascular stenoses of >50% diameter reduction at the iliac or femoro-popliteal level; (5) informed consent. Exclusion criteria were: (1) abdominal aortic aneurysm; (2) life-incapacitating cardiac disease (NYHA classification III and higher (ie, patients had marked limitation of physical activity, comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea);[7] (3) multilevel disease, which would have made multiple revascularization (endovascular and/or surgical) procedures necessary (ie, same-side stenoses at both the iliac and femoral levels, requiring multiple revascularization procedures); (4) isolated tibial artery disease; (5) lesions deemed unsuitable for revascularization (iliac or femoro-popliteal TASC-type D and some TASC type-B/C lesions);[8] (6) prior treatment for the same lesion (including exercise training).

Indication for treatment and exclusion criteria were assessed at the vascular conference by consensus between the vascular surgeons and interventional radiologists. An independent statistician prepared a computer-generated randomization list with a block size of 16. Study personnel dealing with bias-sensitive data were blinded to the assigned treatment and block size.

PROCEDURES

Endovascular revascularization was performed using a 10% oversized balloon (Powerflex or Opta-Pro; Cordis Johnson & Johnson, Miami, Fla). For iliac revascularization, the initial balloon angioplasty was considered technically successful if the pressure gradient across the treated arterial segment was <10 mm Hg at rest. If balloon dilatation was inadequate, a 9 mm diameter, self-expanding, nitinol stent (Luminexx, Bard, Tempe, Ariz) was placed. For femoral revascularization, the decision to place an additional 6-mm diameter, self-expanding, nitinol stent was based on the post-balloon angioplasty angiogram.

Hospital-based exercise was conducted on a walking treadmill for 30 minutes/session, twice weekly, during 24 weeks, which is consistent with a systematic review of the literature of supervised exercise regimens[9] and was considered the maximum attainable in our setting. Each session was supervised by a vascular technologist and began at 3.5 km/hour without incline, and workload was increased (speed or incline as tolerated) until a severe level of claudication pain was reached. The workload was lowered to 1 km/hour until the pain abated, and to avoid that patients were walking with an ischemic leg the whole time. After the pain had been abated, the patient resumed walking at higher workload. This process was repeated for 30 minutes. In addition, all patients were instructed to walk at home for at least 30 minutes 3 times weekly. Feedback and evaluation of these home-based exercise hours were also reported. After the 24-week period, patients were advised to continue exercise at home.

Before randomization, all patients underwent management of risk-factors, including hypertension, serum glucose, cholesterol, lipid profile, and homocysteinemia (if age <50 years), and all were prescribed aspirin therapy (100 mg/day).

OUTCOMES

The outcomes were effectiveness expressed as mean improvement of health-related quality-of-life and functional capacity over the 12-month period and cumulative 12-month costs. Quality-of-life was assessed using a self-administered questionnaire. Costs were assessed from the societal perspective, according to national guidelines for cost-analyses.[10] In addition, clinical success was also assessed but is reported separately in a manuscript focusing on the clinical outcomes.

The questionnaire consisted of the EuroQol-5D (EQ-5D) rating scale, and the dimension "physical functioning" of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). The EQ-5D is a multi-attribute utility instrument that assesses quality-of-life values from the societal perspective and classifies patients into a health-state.[11] For each health-state, a value was calculated using the Dutch scoring algorithm, which was derived from the general population:[12] 0 equates to death and 100 equates to maximum health. The rating scale required the respondent to rate their overall health on a scale from 0-100, where 0 represents death and 100 perfect health.[13] The SF-36 was developed to evaluate physical, social, and physical-role functioning of patients, and it elicits their perceptions of their general health and well-being in eight different health dimensions.[14] "Physical functioning" is most relevant to PAD, and we restricted this analysis to it.[15] The SF-36 was valued on a 100-point scale: 0 means worst health and 100 indicated maximum health. Quality-adjusted life years (QALYs) accumulated during the 12-month follow-up period were based on the EQ-5D values at baseline, 6-months, and 12-months. Functional capacity was expressed as maximum pain-free walking distance and maximum walking distance and measured following treadmill walking (speed 3.5 km/hour, without a graded incline).

Costs (health care costs and non-health care costs) of all relevant items used during the entire trial were collected. Health care costs included costs of all therapeutic procedures, personnel, materials, equipment, additional associated diagnostic or therapeutic procedures, and associated mean hospital admissions during 12-month follow-up. Personnel costs were computed by multiplying time spent with the mean wage rate of the appropriate personnel-category and adding 37% Social Security.[10] Costs of materials were summed cost prices. Equipment costs were calculated as: (time spent on a procedure) × (hourly cost). The annuitized hourly costs of equipment were summed with servicing costs and divided by the proportion of total available room time (33% of a 40-hour work-week for endovascular revascularization and 80% of a 40-hour work-week for supervised exercise).[10]

Non-health care costs included costs of supporting departments, housing, overhead, transportation costs, and patient time costs. The costs of supporting departments were obtained from records of our financial department;

housing and overhead were estimated at 45% of direct assignable costs.[10] Transportation costs included parking costs and mean estimated gasoline costs. Patient-time costs were (hourly wage rate) × (number of hours in-hospital). The hourly wage rate was estimated with the published mean hourly wage rate for Dutch men and women given for different age categories (25-44, 45-54, 55-64, >65). The time required for treatment was based on the mean length of hospitalization, which was estimated from the records of patients undergoing revascularization (8 hours) and/or the exercise program (30 minutes/session). In addition, time invested in unsupervised exercise at home was reported and included in the patient-time cost analysis. Productivity losses were not included as most patients were retired and among the patients who did work, no patient lost his/her job due to claudication.

Costs were discounted at a rate of 3% per annum.[16] All costs are reported in 2005 euros using the consumer price indices of the Central Bureau of Statistics, The Netherlands.[17,18]

Data analysis. Previous studies have shown that the SF-36 dimension "physical functioning" was the most responsive for measuring changes in quality-of-life after adequate treatment of patients with PAD.[15,19,20] Based on these studies, 40-50% of patients were expected to have a substantial improvement of their symptoms after 6 months as measured by the dimension "physical functioning" on the SF-36. A percentage difference of 20-25% between the treatment groups was considered clinically relevant.[21] With these assumptions, 68 patients were required in each trial arm for a power of 80% and a 5% significance level. Anticipating a 5-10% loss to follow-up, we recruited 15 extra patients.

Results were analyzed according to the intention-to-treat principle: we analyzed all patients according to their allocated intervention irrespective of cross-over to the other strategy or completion of follow-up. The only patients excluded from the analysis were those for whom no data was available as they refused further participation immediately following randomization. In addition, results were analyzed with imputation of mean values for quality-of-life at 6- and 12-month follow-up for patients who died of causes other than PAD and for patients who refused a follow-up visit.[22] There were no patients who died of PAD, and there were no missing cost values.

QALY improvement accumulated during the 12-month follow-up period was calculated per patient as the integral under the EQ-5D graph as a function of time adjusted for the baseline value. Since interpolating between the baseline and 6-month value may underestimate the integral under the EQ-5D, we imputed values at 1 week. In patients with a clinical success at 1 week, the 1 week EQ-5D value was assumed equal to the mean EQ-5D value in patients with a clinical success at 6 months. In patients who were negative for clinical success at 1 week, we used the baseline EQ-5D value. In a one-way sensitivity analysis we assumed that the EQ-5D value in the revascularization group would increase immediately after the last intervention to the 6-month value (generating a larger integral under the EQ-5D, which means a larger and more immediate effect), whereas in the exercise group we interpolated between the baseline value and the 6-month value to account for the gradual improvement during the course of the 24-week exercise program. In addition, we calculated the incremental cost-effectiveness ratio as the difference in mean cumulative total costs divided by the difference in mean QALY improvements accumulated during 12 months for the revascularization group compared to the exercise group.

To adjust outcomes for potential imbalances of baseline values and characteristics between the treatment groups, we adjusted for covariates using multivariable regression analyses. We adjusted for baseline scores, age, gender, diabetes mellitus, smoking, hypertension, hyperlipidemia, and disease severity (mild/moderate claudication vs severe claudication). The variables were selected based on the TASC-II report and on clinical judgment.[23]

Significance of differences between group means was assessed with the unpaired *t* test or the Mann-Whitney *U* test, as appropriate, whereas significance of dichotomous outcomes was assessed with the χ^2 test. To adjust for multiple comparisons, a significance level of 0.01 (two-tailed) was used. Ninety-nine percent confidence intervals of the mean cost differences and the mean differences in QALY improvement were calculated with the bootstrap resample method drawing 100,000 samples.[24] Cost-effectiveness outcomes were combined in one outcome: net monetary benefit[25] expressed as the monetary equivalent of effectiveness, which is QALY times the threshold willingness-to-pay (50,000 €/QALY) minus the costs. We determined the probability that revascularization would be cost-effective compared to exercise for varying willingness-to-pay values (acceptability curve).

In value of information analysis, we determined the expected value of obtaining more information from future research.[26] The expected value of perfect information per patient was calculated as[27] the mean of the net monetary benefit of the optimal treatment per bootstrap sample (ie, the expected net monetary benefit with perfect information) minus the mean net monetary benefit with current information from the primary analysis. Next, we estimated the population expected value of perfect information, which was the total expected value of perfect information per patient multiplied by the total number of patients that could benefit from the decision (290,000 annually in the European Union (E.U.) and 190,000 in the United States (U.S.)[28] over the lifetime of the technology (5 years)[28] with a discount rate of 3% per year.

Calculations were performed with SPSS 14.0 for Windows (SPSS Inc., Chicago, Ill), and R version 2.5 (R Foundation, Vienna, Austria).

RESULTS

Patients. Fig 1 shows the flow diagram of patients entering the RCT, including the actual treatments received and patients who were lost to follow-up. One patient who

Table I. Baseline characteristics of the study participants*

	Endovascular Revascularization (n = 75)	*Hospital-based Exercise (n = 75)*	P *value***
Age (y)	65 (+/−11)	66 (+/−9)	.34
Male gender, %	44 (59)	39 (53)	.62
Arterial hypertension, %	32 (43)	28 (38)	.87
Diabetes mellitus, %	11 (16)	15 (24)	.83
Hyperlipidemia, %	40 (53)	38 (51))	.87
History of ischemic heart disease, %	14 (19)	21 (28)	.19
Pulmonary disease, %	7 (9)	9 (12)	.50
Osteoarthritis of the lower limb, %	7 (9)	5 (6)	.66
Renal insufficiency, %	1(1)	3 (4)	.35
History of cerebrovascular disease, %	8 (11)	4 (5)	.32
Smoking, %			
current	12 (16)	17 (23)	.87
ever	40 (53)	32 (43)	
never	23 (31)	25 (34)	
Body mass index	26 (+/−4)	25 (+/−5)	.88
Ankle-brachial index†			
at rest	0.62 (+/−0.18)	0.63 (+/−0.17)	.62
after exercise	0.41 (+/−0.22)	0.42 (+/−0.21)	.60
Pain-free walking distance (m)	82 (+/−48)	104 (+/−65)	.04
Maximum walking distance (m)	174 (+/−76)	186 (+/−97)	.62
Rutherford classification‡, %			
I & II	57 (76)	57 (76)	.87
III	18 (24)	18 (24)	.87
Iliac disease, %	73 (55)	68 (51)	.47
Femoral disease, %	27 (20)	32 (24)	.47
Quality of life			
EuroQol-5D§	0.66 (+/−0.20)	0.69 (+/−0.21)	.22
Rating scale‖	62 (+/−17)	65 (+/−18)	.47
SF-36 Physical functioning	42 (+/−26)	49 (+/−20)	.11

SF-36 Dimension scores = 0-100 (worst-best) scale.
*Mean +/− standard deviation in parentheses, unless otherwise indicated.
†Minimum of right – left.
‡Most severe classification per person.
§EuroQol-5D with Dutch algorithm was used; EuroQol-5D value = 0-1 (death-maximum health) scale.
‖rating scale = 0-100 (worst-best) scale.
**Considering multiple statistical tests, a *P* value of ≤ .01 was considered to be statistically significant.

refused further participation before baseline data was collected, was excluded from the analysis. Thus, 150 patients were analyzed for quality-of-life and costs (Fig 1). In the revascularization group, 4 patients technically failed initial treatment. Two were advised home-based exercise, and 2 underwent surgical intervention (Fig 1). The baseline characteristics of the study participants did not differ significantly between the groups (Table I). Ninety-two percent (69 of 75) of revascularization patients responded to the questionnaires at 6 months and 89% (67 of 75) at 12 months. Among exercise patients, 99% (74 of 75) responded at 6 months, and 96% (72 of 75) at 12 months. During follow-up, 10 patients in the revascularization group and 11 patients in the exercise group underwent additional treatment (Table II). Eight patients in the exercise group underwent endovascular revascularization whereas 3 patients in the revascularization group started home-based exercise.

OUTCOMES

In both the revascularization group and the exercise group improvement in the adjusted 6- and 12-months EuroQol, rating scale, and SF36 physical functioning was demonstrated, but the differences between the groups were not statistically significant (Table III). Whereas in the endovascularization group all quality-of-life measures showed a non-significant decrease in quality of life from 6 to 12 months, in the exercise group there was an increase in two of the three measures (Table III). After adjustment for baseline variables, the QALY improvement accumulated during 12-month follow-up was not significantly different between the groups (mean difference 0.01; 99% CI, −0.05, 0.07; $P = 0.73$) (Table III). At 6- and 12-months, both revascularization and exercise patients improved their maximum pain-free walking distance and their maximum walking distance (Table III). After adjustment for the baseline variables, there were no significant differences in functional capacity between the two groups at 6- or 12-month follow-up.

After adjustment for the baseline variables, the total mean cumulative costs per patient during 12 months were higher following revascularization than following exercise (mean difference €2,318; 99% CI, €2,130, € 2,506; $P <$ .001) and the mean incremental cost-effectiveness ratio was 231,800 €/QALY (Table IV). The sensitivity analysis demonstrated a larger gain in effectiveness following revascular-

Table II. Additional treatment during follow-up

	Endovascular revascularization (n = 75)		*Supervised hospital-based exercise (n = 75)*	
Additional treatment	*0-6 months (n)*	*6-12 months (n)*	*0-6 months (n)*	*6-12 months (n)*
Home-based exercise	3	0	0	0
Endovascular revascularization with or without stent placement				
Common iliac artery	0	1	2	3
Femoral artery	0	1	2	1
Surgical intervention				
Aorto-bifurcation graft	2	0	1	0
Femoral-femoral cross-over graft	1	0	0	0
Femoro-popliteal bypass	0	0	2	0
Patch plasty of common femoral artery	2	0	0	0

Table III. Mean improvement in different measures of quality of life and functional capacity compared to baseline and differences between the groups (endovascular revascularization compared to supervised hospital-based exercise*)[$]

	*Mean score improvement (99% CI)**			
	Endovascular revascularization (n = 75)	*Hospital-based exercise (n=75)*	*Adjusted mean difference (99% CI)*†*	*Adjusted P-value‖*
EQ-5D 6 months[‡]	0.16 (0.10, 0.21)	0.09 (0.03, 0.15)	0.02 (−0.07, 0.10)	.59
EQ-5D 12 months	0.11 (0.04, 0.18)	0.07 (0.02, 0.13)	0.02 (−0.09, 0.12)	.63
Quality-adjusted life years accumulated during 12 months	(0.15, 0.24)	0.17 (0.14, 0.22)	0.01 (−0.05, 0.07)	.73
Maximum pain-free walking distance 6 months (m)	679 (519, 837)	899 (743, 1054)	−16 (−32, 2)	.02
Maximum pain-free walking distance 12 months (m)	806 (646, 960)	943 (786, 1099)	24 (−42, 91)	.34
Maximum walking distance 6 months (m)	755 (600, 909)	1138 (1006, 1270)	16 (−60, 93)	.58
Maximum walking distance 12 months (m)	826 (680, 970)	1034 (896, 1170)	24 (−42, 91)	.34

*Positive difference indicates endovascular revascularization has a better outcome; negative number indicates supervised hospital-based exercise has a better outcome.

†Adjusted for baseline quality-of-life scores or functional capacity scores, age, gender, severity of disease (mild/moderate vs severe), smoking, hypertension, hyperlipidemia, and diabetes mellitus.

‡EuroQol-5D with Dutch algorithm was used; EuroQol-5D value = 0-100 (death-maximum health) scale.

§Rating scale and SF-36 Dimension scores = 0-100 (worst-best) scale.

‖Considering multiple statistical tests, a *P* -value of ≤ .01 was considered to be statistically significant.

ization (mean difference 0.03; 99% CI, 0.02, 0.05; $P < .001$), making the incremental cost-effectiveness ratio smaller (75,208 €/QALY) (Table IV). Combining QALYs and costs using a willingness-to-pay of 50,000 €/QALY resulted in a higher mean net monetary benefit per patient for the exercise group (€6,891; 99% CI, 5,128, 8,656) compared to the revascularization group (€3,639 99% CI, 2,214, 5,064). Using a willingness-to-pay value of 50,000 €/QALY, revascularization would be the optimal first-line treatment in 5% of bootstrap samples (Fig 2a), whereas in the sensitivity analysis this would be the case in 10% (Fig 2b). The total expected value of perfect information expressed in net monetary benefit was €30 per patient and the population expected value of perfect information was €39 million for the E.U. and €26 million for the U.S (Table V).

DISCUSSION

In this prospective RCT, the cost-effectiveness of endovascular revascularization was compared to supervised hospital-based exercise in patients with intermittent claudication after 12-month follow-up. There was no significant difference in the 6- and 12-month EuroQol rating scale, SF36 physical functioning, and QALYs between the treatment groups and revascularization was significantly more expensive, which favors exercise. Furthermore, the small gain achieved with endovascular revascularization was non-significant and the incremental cost/QALY gained by revascularization compared to exercise was higher than the generally-accepted willingness-to-pay threshold of 50,000 €/QALY. The large population expected value of perfect information suggests that a substantial investment in future research would be justified.

Prior to the current RCT, there was no level-I evidence with respect to the effectiveness and costs of treatment for intermittent claudication. In the published literature about intermittent claudication, one previous study compared quality-of-life and costs for percutaneous transluminal angioplasty, bypass surgery, or exercise using a Markov deci-

Table IV. Total mean cumulative costs per patient during 12 months of follow-up after endovascular revascularization and supervised hospital-based exercise

	Endovascular revascularization (n = 75)	*Hospital-based exercise (n = 75)*	*Adjusted mean difference (99% CI)**	*Adjusted P-value‡*
Procedure				
Material costs	€ 1444	€ 1		
Personnel costs	€ 441	€ 433		
Equipment costs	€ 76	€ 51		
Associated admission costs	€ 217	€ 0		
Total mean cumulative procedure costs	€ 2178 (1949, 2419)	€ 485 (454, 515)	€ 1035 (903, 1167)	<.001
Patient				
Transportation costs	€ 13	€ 164		
Productivity losses	€ 552	€ 941		
Total mean cumulative patient costs	€ 565 (519, 612)	€ 1104 (1021, 1189)	€ 504 (463, 546)	<.001
Follow-up				
Associated outpatient visits and ABI measurements	€ 86	€ 0		
Additional imaging costs	€ 65	€ 92		
Additional therapeutic costs	€ 657	€ 532		
Additional admission costs†	€ 2578	€ 339		
Total mean cumulative follow-up costs	€ 3401 (865, 7018)	€ 958 (333, 1769)	€ 205 (187, 223)	<.001
Total mean cumulative housing/supporting departments/overhead costs	€ 793 (767, 818)	€ 207 (203, 211)	€ 586 (560, 611)	<.001
Total mean cumulative costs	€ 7031 (4522, 10556)	€ 2771 (2158, 3591)	€ 2318 (2130, 2506)	<.001

ABI, Ankle brachial index; *95% CI,* 95% confidence interval determined with the bootstrap resample method.

*Adjusted for age, gender, severity of disease (mild/moderate vs severe), smoking, hypertension, hyperlipidemia, and diabetes mellitus.

†In the endovascular revascularization group, the additional admission costs were due to surgical interventions (n = 5) and secondary endovascular revascularizations (n = 2). In the supervised hospital-based exercise group, the additional admission costs were due to surgical interventions (n = 3) and endovascular revascularizations (n = 8).

‡Considering multiple statistical tests, a *P* value of ≤ .01 was considered to be statistically significant.

sion analysis and data from cohort studies.[29] The previous study showed that QALYs increased only slightly with vascular interventions compared to exercise, and that any small gain in QALYs that is obtained through vascular intervention is done so at a high cost ($311,000/QALY). The current study supports these findings and found a similar incremental cost-effectiveness ratio (230,000 €/QALY = $330,000/QALY).

Revascularization has higher initial costs than exercise. Besides the higher initial costs, we also found higher follow-up costs as revascularization patients had more surgical interventions than exercise patients, who tended to get a (less-expensive)[30] endovascular revascularization if secondary treatment was needed. This difference in secondary treatment arose because three arterial lesions were not suitable for endovascular (re-)intervention after prior failure and because of surgeon preference in 2 patients. Whatever the treatment considered, if the initial procedure failed, total costs during 12-month follow-up are 2- to 4-fold higher than if the initial procedure was successful.[30]

Our study may have lacked power as it was designed to demonstrate clinically-relevant differences, rather than equivalences, in quality-of-life. The differences in the 6- and 12-month quality-of-life results were small and non-significant. Furthermore, it should be noted that quality-of-life is a subjective outcome which may be influenced by the perception of individual subjects. Patients in the exercise group may have underestimated their quality-of-life since improvement in symptoms occurs slowly during an exercise program and may, therefore, have been less noticeable. Conversely, the revascularization group may have overestimated their quality-of-life since their improvement after treatment was immediate and, therefore, would have contrasted with the pre-intervention state. This may indicate that the difference in quality-of-life between the treatment groups may in fact have been in favor of exercise. Furthermore, we had limited follow-up time-points and our 1-week quality-of-life value was based on the clinical success rather than a direct measurement of quality-of-life. In a sensitivity analysis using a fairly extreme assumption favoring revascularization, however, the conclusions remained the same. Another limitation could be that our study took place in a single center and with adherence to strict in- and exclusion criteria. Consequently, there were patients excluded based on anatomic reasons and considered to be unsuitable for revascularization. In clinical practice some patients may be good candidates for exercise therapy and poor candidates for revascularization and vice versa, which affects the generalizability of our results and emphasizes the importance of patient-tailored decision making. The advantage of our single center study and adhering to strict in- and exclusion criteria is the homogeneous group of study participants, as illustrated by the baseline characteristics. Another limitation of our study is that bias towards exercise may have occurred in patients with bilateral symptoms, as walking inherently treats both

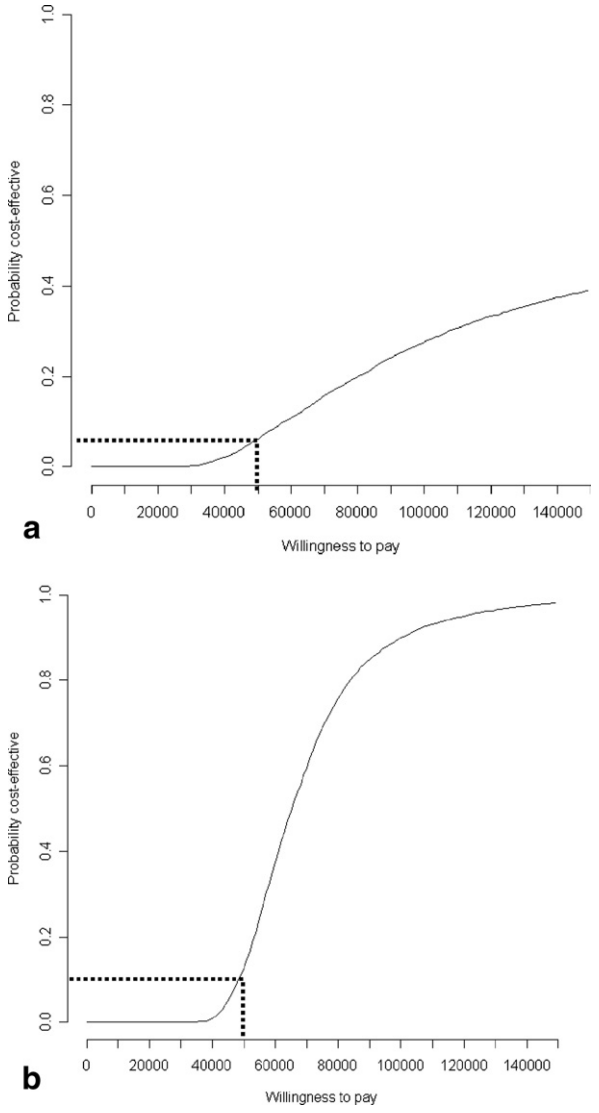

Fig 2. a, Cost-effectiveness acceptability curve for revascularization versus exercise for the baseline analysis. **b,** Cost-effectiveness acceptability curve for revascularization versus exercise for the sensitivity analysis.

limbs. To be consistent, patients with bilateral symptomatic lesions in the endovascular revascularization group were treated on both sides. The severity of ipsilateral symptoms at baseline, however, may have disguised latent contralateral symptoms in some patients. After endovascular revascularization, increased mobility would encourage the discovery of the latent contralateral symptoms. Since peripheral arterial disease is a two-limb problem we chose for a patient-based approach to treatment and analysis of the trial results.

As with every randomized trial, we could only evaluate a limited number of strategies. In addition to revascularization and exercise training, other treatment strategies are of interest, for example, optimal medical treatment in combination with home-based exercise or optimal medical treatment combined with angioplasty, which have been compared in a previous RCT.[31] Other interesting treatment arms could be revascularization plus supervised exercise training or revascularization plus pharmacologic therapy. Since the recently performed RCT costs less than €1 million and our estimated population expected value of perfect information was well over €1million for the E.U. or U.S. populations, further clinical studies in this area are expected to be worth the cost.

Table V. Adjusted difference in mean cumulative total costs, mean QALY improvement, incremental cost-effectiveness ratios, and net monetary benefit per patient during 12 months of follow-up after endovascular revascularization compared to supervised hospital-based exercise for the baseline analysis and sensitivity analysis[¶]

	Adjusted[†‖] (99% CI)*
Difference in cumulative mean total costs	€ 2318 (2130, 2506)
Baseline analysis[‡]**	
Difference in QALY improvement accumulated during 12 months	0.01 (−0.05, 0.07)
Incremental cost-effectiveness ratio*	231 800 €/QALY[§]
Difference in net monetary benefit*	−€ 3253 (− 6270, −235)

99% CI, 99% confidence interval determined with the bootstrap resample method; *QALY,* quality-adjusted life year.
*Endovascular revascularization compared to hospital-based exercise.
†Adjusted for baseline EuroQol, age, gender, severity of disease (mild/moderate vs severe), smoking, hypertension, hyperlipidemia, and diabetes mellitus.
‡Baseline analysis used imputed EQ-5D values at 1 week based on clinical success at 1 week.
§Confidence intervals around ICERs are not reported because they are ambiguous in interpretation.
‖Considering multiple statistical tests, a *P* value of ≤ .01 was considered to be statistically significant.
¶Sensitivity analysis was based on the assumption that the EQ-5D value in the revascularization group would increase immediately after the last intervention to the 6-month value, whereas in the exercise group we interpolated between the baseline value and the 6-month value to account for the gradual improvement during the course of the 24-week exercise program.
**Using a threshold willingness-to-pay of 50,000 €/QALY.

CONCLUSIONS

In conclusion, there was no significant difference in effectiveness between endovascular revascularization compared to supervised hospital-based exercise during 12-month follow-up, any gains with endovascular revascularization found were non-significant, and endovascular revascularization costs more than the generally accepted threshold willingness-to-pay value, which favors exercise.

AUTHOR CONTRIBUTIONS

Conception and design: SS, JB, PdH, HV, PP, MH
Analysis and interpretation: SS
Data collection: SS, PdH, HV

Writing the article: SS, JB, MH
Critical revision of the article: JB, PP, MH
Final approval of the article: SS, JB, PdH, HV, PP, MH
Statistical analysis: SS, MH
Obtained funding: Not applicable
Overall responsibility: SS, MH

REFERENCES

1. Dormandy J, Mahir M, Ascady G, Balsano F, De Leeuw P, Blombery P, et al. Fate of the patient with chronic leg ischaemia. A review article. J Cardiovasc Surg (Torino) 1989;30:50-7.
2. Balkau B, Vray M, Eschwege E. Epidemiology of peripheral arterial disease. J Cardiovasc Pharmacol 1994;23(Suppl 3):S8-16.
3. Rose G, McGartner P, Reid DD. Self-administration of a questionnaire on chest pain and intermittent claudication. Brit J Prevent Soc Med 1977;31:42-8.
4. Isner JM, Rosenfield K. Redefining the treatment of peripheral artery disease. Role of percutaneous revascularization. Circulation Oct 1993; 88(4 Pt 1):1534-57.
5. Registration T. http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=199. Accessed 2006.
6. Moher D, Pham B, Klassen TP, Schulz KF, Berlin JA, Jadad AR, Liberati A. What contributions do languages other than English make on the results of meta-analyses? J Clin Epidemiol 2000;53:964-72.
7. NYHA c. Accessed 2006.
8. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Concensus (TASC). J Vasc Surg 2000;31(1 Pt 2):S1-296.
9. Wind J, Koelemay MJ. Exercise therapy and the additional effect of supervision on exercise therapy in patients with intermittent claudication. Systematic review of randomised controlled trials. Eur J Vasc Endovasc Surg 2007;34:1-9.
10. Oostenbrink J, Koopmanschap M, Rutten F. Standardisation of costs: the Dutch manual for costing in economic evaluations. Pharmacoeconomics 2002;20:443-54.
11. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095-108.
12. Busschbach J. http://www.xs4all.nl/~jannetvb/busschbach/faq_qoL&euroqol.htm. Accessed 2006.
13. Froberg DG, Kane RL. Methodology for measuring health-state preferences–II: scaling methods. J Clin Epidemiol 1989;42:459-71.
14. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
15. Bosch JL, van der Graaf Y, Hunink MG. Health-related quality of life after angioplasty and stent placement in patients with iliac artery occlusive disease: results of a randomized controlled clinical trial. The Dutch Iliac Stent Trial Study Group. Circulation 1999;99:3155-60.
16. Gold M. Panel on cost-effectiveness in health and medicine. Med Care 1996;34(12 Suppl):DS197-9.
17. Eurostata. http://epp.eurostat.ec.europa.eu/portal/page?_pageid=1996,39140985&_dad=portal&_schema=PORTAL&screen=detailref&language=en&product=EU_shorties&root=EU_shorties/shorties/euro_cp/cp000. Updated daily. Accessed November 6, 2006.
18. Central Bureau of Statistics The Netherlands. http://www.cbs.nl/. Accessed 2006.
19. Spronk S, Bosch JL, Veen HF, den Hoed PT, Hunink MG. Intermittent claudication: functional capacity and quality of life after exercise training or percutaneous transluminal angioplasty--systematic review. Radiology 2005;235:833-42.
20. Mehta T, Venkata Subramaniam A, Chetter I, McCollum P. Assessing the validity and responsiveness of disease-specific quality of life instruments in intermittent claudication. Eur J Vasc Endovasc Surg 2006;31: 46-52.
21. Bosch JL, Hunink MG. The relationship between descriptive and valuational quality-of-life measures in patients with intermittent claudication. Med Decis Making 1996;16:217-25.
22. van der Heijden GJ, Donders AR, Stijnen T, Moons KG. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. J Clin Epidemiol 2006;59:1102-9.
23. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45(1 Suppl):S5-67.
24. Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. Stat Med 2000;19: 3219-36.
25. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making 1998;18(2 Suppl):S68-80.
26. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute For Clinical Excellence (NICE). Lancet 2002;360:711-5.
27. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. J Health Econ 1999;18:341-64.
28. Meijer WT, Cost B, Bernsen RM, Hoes AW. Incidence and management of intermittent claudication in primary care in The Netherlands. Scand J Prim Health Care 2002;20:33-4.
29. de Vries SO, Visser K, de Vries JA, Wong JB, Donaldson MC, Hunink MG. Intermittent claudication: cost-effectiveness of revascularization versus exercise therapy. Radiology 2002;222:25-36.
30. Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet 2005;366:1925-34.
31. Nylaende M, Abdelnoor M, Stranden E, Morken B, Sandbaek G, Risum Ø, et al. The Oslo balloon angioplasty versus conservative treatment study (OBACT)–the 2-years results of a single centre, prospective, randomised study in patients with intermittent claudication. Eur J Vasc Endovasc Surg 2007;33:3-12.

Submitted Mar 26, 2008; accepted Jun 4, 2008.