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Cost-effectiveness of Exercise Therapy in Patients with Intermittent Claudication: Supervised Exercise Therapy versus a 'Go Home and Walk' Advice

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Abstract *Objectives:* The Exercise Therapy in Peripheral Arterial Disease (EXITPAD) study has shown supervised exercise therapy (SET) to be more effective regarding walking distance and quality of life than a 'go home and walk' advice (WA) for patients with intermittent claudication. The present study aims to assess the cost-effectiveness of SET versus WA.
Patients and methods: Data from the EXITPAD study, a 12-month randomised controlled trial in 304 patients with claudication, was used to study the proportion of costs to walking distance and quality of life. Two different incremental cost-effectiveness ratios (ICERs) were calculated for SET versus WA: costs per extra metre on the treadmill test, and costs per quality-adjusted life year (QALY). QALYs were based on utilities derived from the EuroQoL-5 dimensions (EQ-5D).
Results: Mean total costs were higher for SET than for WA (3407 versus 2304 Euros), mainly caused by the costs of exercise therapy. The median walking distance was 620 m for SET

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and 400 m for WA. QALYs were 0.71 for SET and 0.67 for WA. All differences were statistically significant. The ICER for cost per extra metre on the 12-month treadmill test was € 4.08. For cost per QALY, the ICER was € 28693.
Conclusion: At a willingness-to-pay threshold of € 40 000 per QALY, SET likely is a cost-effective therapeutic option for patients with claudication.

Introduction

Intermittent claudication (IC) is defined as atherosclerotic disease of the arteries of the legs, causing walking impairment due to muscular pain. Although IC is not directly life threatening, it implies that the patient has a very serious vascular disease. Moreover, IC has been found to be associated with a significantly lowered quality of life, which can be improved with therapy.[1] Exercise therapy is considered to be the main conservative treatment for patients with IC. However, compliance with unsupervised exercise therapy is reported to be low.[2] In the Exercise Therapy in Peripheral Arterial Disease (EXITPAD) study, a multicentre randomised trial, Nicolaï et al.[3] have shown that supervised exercise therapy (SET) is more effective than an (unsupervised) walking advice (WA) when it concerns walking distance, score on the Walking Impairment Questionnaire (WIQ)[4] and Quality of Life as measured with the short form 36 health survey (SF-36) questionnaire.[5] Because supervision obviously means an investment, in the present study, a cost-effectiveness analysis is performed to answer the question whether supervised exercise therapy is value for money compared with a 'go home and walk' advice.

Materials and Methods

Patients and interventions

From the 11 participating outpatient vascular surgery clinics, 304 patients with peripheral arterial disease, stage II according to Fontaine and eligible for conservative treatment, were enrolled in the EXITPAD study. Inclusion criteria were an ankle-brachial index (ABI) less than 0.9 and an absolute claudication distance (ACD) below 500 m. Exclusion criteria included a prior supervised exercise therapy programme for intermittent claudication, previous peripheral vascular intervention, insufficient command of the Dutch language, serious cardiopulmonary limitations (New York Heart Association (NYHA) 3–4), previous lower-limb amputation, psychiatric instability and other serious co-morbidity which may hinder physical training. Patients were randomised to one of three possible interventions: WA, SET or SET with feedback. Patients in the WA group received an oral walking advice, together with a brochure. They were instructed to complete three training sessions per day. In each session, maximum pain level should be reached three times. Patients in the SET groups were referred to a local physical therapist. The main goal of the physical therapy was to increase the patient's walking distance by interval training up to maximal pain with short walking intervals, in combination with walking pattern improvement and enhancement of endurance and strength. The frequency of therapy was two to three sessions of 30 min per week. During the treatment year, this frequency could be adjusted depending on the individual need of the patient.

In addition to physical therapy, patients in the SET with feedback group received an accelerometer (Personal Activity Meter (PAM), PAM B.V., Doorwerth, the Netherlands), which assesses physical activity during daily routine. Patients were instructed to wear the PAM during the whole treatment year, and record the score on a daily basis. The physical therapist used the PAM score for feedback on the patient's walking efforts outside the therapy setting. Of the 304 patients, 102 were randomised to the WA group, 109 to the SET group, and 93 to the SET with feedback group. Follow-up was for 1 year. Patients who did not perform a 12-month treadmill test were treated in conformity with the clinical trial, which applied a modified intention-to-treat method and did not include those patients in the analysis. This left 83 patients in the WA group for analysis, and 169 in the SET group (76 with and 93 without feedback). For a detailed overview of the methods of the EXTIPAD trial, see Nicolaï et al.[3]

Outcome measurements

In the economic evaluation, two outcome measurements were considered. The first was the walking distance, or the absolute claudication distance, in metres, on the treadmill assessment at the end of the treatment year. The second was the Quality of Life (QoL) as assessed with the EuroQoL-5 dimensions (EQ-5D), which was filled out by the patients at baseline and at the 3-, 6-, 9- and 12-month-assessments. The EQ-5D instrument,[6] a self-report measure, is a descriptive system with five questions, each representing one dimension of Health-related Quality of Life (HRQoL), which are mobility, self-care, daily activities, pain/discomfort and depression/anxiety. Each dimension can be rated at three levels: no problems, some problems and major problems, and together classify persons into 1 of 243 possible health states. Based on preferences elicited from a general UK population,[7] EQ-5D health states can be converted into utility scores, ranging from −0.59 (worst imaginable health state) to 1 (best imaginable health state). A quality-adjusted life year (QALY) is calculated by multiplying the utility score with the time that the patient was experiencing that utility. When a patient was in the best imaginable health state for 1 year that would lead to 1 QALY. With a utility score of 0.8 over 2 years, the number of QALYs would be 1.6.

Costs

The analysis took a societal perspective, which implies that all relevant costs, inside and outside the health-care sector, were taken into account. Cost data for all patients were gathered by means of a retrospective cost questionnaire with a 3-month recall period, which took place at baseline and at the 3-, 6-, 9- and 12-month assessments. For calculation of cost-effectiveness, only costs after baseline were considered. The cost questionnaire contained items on general physician (GP) contacts, outpatient visits, visits to the emergency room (ER), hospital admissions, therapy sessions at the physical therapist, contacts with the company doctor, home care and informal care, prescribed and over-the-counter (OTC) medication, devices such as special shoes or a treadmill and lost productivity because of absence from both paid and unpaid work. Further, for all visits to health-care providers, patients were asked to report their means of transportation, to be able to compute travel costs. Per type of health-care provider, a mean travel distance was applied, based on the number of available practices per square kilometre in the Netherlands. Furthermore, for patients included in the Atrium MC in Heerlen, which was a subsample of 123 patients, costs of hospital procedures, related to both outpatient visits as well as hospital admission, were collected from the hospital databases. When possible, standard prices from the Dutch manual for cost research were used.[8] For hospital procedures, prices from the financial department of the Atrium MC were applied. Prices for medication were derived from the Dutch Pharmacotherapeutic Compass.[9] When necessary, prices were converted to the price level of 2008 by means of national price index figures.[10] The costs of the PAM, which were € 79, were not included in the analysis. This cost would only apply to the patients who were in the SET plus feedback condition, which is part of the total SET group. As the clinical trial already found that PAM did not add to the effectiveness of standard SET, we decided to calculate the cost-effectiveness of SET versus WA excluding the cost of PAM, as this, in our opinion, best reflects the cost-effectiveness of supervised exercise therapy.

Cost-effectiveness

The costs and outcomes were combined into two Incremental Cost-Effectiveness Ratios (ICERs), which divide the difference in costs between the two strategies by the difference in effect between the strategies. An ICER can be interpreted as the extra costs for the experimental intervention that have to be invested to gain one extra unit of effect. The first ICER is the cost per extra metre on the treadmill test after 1 year, with the difference in effect calculated as mean walking distance in the intervention group minus the mean walking distance in the control group, and the second is the cost per QALY.

Data analysis

Missing items were imputed with the overall mean for the respective variable. As cost data are generally highly skewed, and not distributed normally, we used non-parametric bootstrap simulations performed in Microsoft Excel with 1000 replications to estimate uncertainty intervals around the ICERs.[11,12] The uncertainty interval is represented by the 2.5th and 97.5th percentiles. When a difference has an uncertainty interval which does not include zero, it is statistically significant. The results of ICER bootstraps are presented in cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).[13] Cost-effectiveness planes show differences in costs on the vertical axis and differences in effect on the horizontal axis. Bootstrapped cost-effectiveness pairs located in the northwest quadrant indicate SET to be inferior to WA (more costly and less effective than WA). Cost-effectiveness pairs located in the southeast quadrant show SET to be dominant over WA (more effective and less costly than WA). With respect to the other two quadrants (higher costs for better effectiveness and lower costs for lower effectiveness), the preference for an intervention depends on the threshold value, that is, what society is prepared to pay for an effectiveness gain, or willing to accept as savings for effectiveness loss. The CEAC represents the probability that, given a certain threshold for the willingness to pay for a QALY or for extra metre on the treadmill test, the intervention is cost-effective. A CEAC is constructed by taking a certain threshold (e.g., € 20 000 per QALY) and calculating the percentage of the 1000 bootstrapped ICERs that are below that threshold, and therefore cost-effective, given that threshold. By repeating this procedure for various thresholds, a curve is generated, with threshold on the *x*-axis and probability of the intervention being cost-effective on the *y*-axis.

Results

Walking distance

At baseline, both groups walked a median distance of 260 m, with comparable interquartile ranges (160—370 for WA and 165—370 for SET). At the 12-month treadmill test,

Table 1 Mean (SD) EQ-5D utility scores per measurement and total mean QALYs.

	WA	SET	*P*-value (Mann—Whitney)
T0	0.62 (0.23)	0.66 (0.20)	0.51
T3	0.68 (0.23)	0.69 (0.21)	0.50
T6	0.69 (0.19)	0.72 (0.17)	0.40
T9	0.68 (0.23)	0.73 (0.21)	0.03
T12	0.66 (0.26)	0.74 (0.20)	0.03
			Difference (bootstrapped 2.5th—97.5th perc)
QALY	0.67	0.71	0.038 (0.0003—0.0796)

Table 2 Mean volumes (SD) and costs (SD), and mean difference in costs with bootstrapped 2.5th and 97.5th percentiles. Significant differences (where zero is not included in the confidence interval between the 2.5th and 97.5th percentile) are shown in bold.

Cost category	Unit price		WA		SET		Difference (SET−WA)
			Volume (SD)	Cost (SD)	Volume (SD)	Cost (SD)	Cost (2.5th–97.5th perc)
Exercise therapy[a]	€ 24.67 per session		5.68 (10.33)	€ 148.87 (270)	59.62 (31.93)	€ 1573.85 (844)	€ **1424.98 (1296–1561)**
Hospital days	€ 387 per day		0.19 (0.75)	€ 74.09 (288)	0.24 (1.26)	€ 91.57 (487)	€ 17.49 (−75.11–126.01)
Hospital procedures	NA, various prices		55.82 (30.18)	€ 1458.53 (1512)	52.99 (39.31)	€ 1249.83 (1235)	−€ 208.71 (−600–124)
Outpatient visits[a]	€ 67		1.27 (2.04)	€ 88.12 (142)	1.67 (2.51)	€ 116.23 (174)	€ 28.11 (−11.76–65.11)
GP contacts[a]	At practice	€ 21.91	1.50 (2.61)	€ 31.37 (50.11)	1.75 (3.29)	€ 41.12 (84.97)	€ 9.75 (−6.24–27.15)
	At home	€ 43.81					
	Telephone	€ 10.95					
GP night/ER[a]	At practice	€ 21.91	0.11 (0.61)	€ 13.13 (58.45)	0.07 (0.26)	€ 7.60 (31.49)	−€ 5.54 (−19.29–6.96)
	At home	€ 43.81					
	Telephone	€ 10.95					
	ER	€ 150.75					
Company doctor[a]	€ 70		0.02 (0.11)	€ 1.66 (8.44)	0.07 (0.71)	€ 5.24 (52.20)	€ 3.58 (−2.03–12.38)
Home care/informal care	€ 36.98 (Home care)		15.47 (48.32)	€ 334.22 (1193)	12.62 (47.48)	€ 228.46 (797)	−€ 105.76 (−393–155)
	€ 9.00 (Inf care)						
Medication/Out-of-pocket	NA			€ 5.80 (24.41)		€ 2.47 (12.70)	−€ 3.33 (−9.44–1.74)
Unpaid productivity	per hour		3.92 (12.66)	€ 35.26 (113.92)	7.67 (31.25)	€ 69.06 (281)	€ 33.80 (−12.76–83.91)
Paid productivity	per hour		0.37 (112.86)	€ 112.86 (652)	0.07 (0.65)	€ 22.07 (197)	−€ 90.79 (−252.38–18.24)
Total costs				€ 2304 (2228)		€ 3407 (2071)	€ **1104 (528–1647)**

[a] Costs do not match exactly with unit price × volume because travel costs (dependent on distance and means of transportation) are included.

the patients in the SET groups scored significantly better on walking distance than the patients in the WA group; the median walking distance of the SET patients was 600 m (interquartile range 435—1040) as opposed to 400 m (230—590) for the WA-patients (p-value < 0.001).[3]

Quality of Life

Table 1 shows mean EQ-5D utility scores for all assessments. At baseline, the difference in utility scores is not statistically significant. At 9 and 12 months, the SET group has significantly higher scores than the WA group. This also translates to the mean QALYs, which are 0.67 and 0.71 for WA and SET, respectively. The difference between the groups is 0.038, with a bootstrapped 2.5th percentile of 0.0003 and a 97.5th percentile of 0.0796, indicating a significant gain in quality of life, as zero is not included in the uncertainty interval.

Costs

Volumes and costs of cost categories are shown in Table 2. Total costs for the SET group are statistically significantly higher, as expected. The difference is caused mainly by the costs of exercise therapy. The other cost categories are more or less comparable between the groups, except for the productivity costs for paid work, which seem to be higher for the WA group, and the costs of home care and informal care, which seem to be higher for the SET group. However, the bootstrapped 95% uncertainty intervals for these categories, which consist of the 2.5th and 97.5th percentile, indicate that these differences are not statistically significant.

Cost-effectiveness

The ICER for cost per extra metre on the 12-month treadmill test is € 4.08. For cost per QALY, the ICER is € 28693. The incremental cost-effectiveness plane of the 1000 bootstrap replications for cost per QALY is shown in Fig. 1. Most of the cost-effectiveness pairs are located in the upper-right quadrant, where SET is more costly than WA, but also more effective. A minority of replications is situated in the upper-left quadrant, where SET is more costly and less effective than WA. The fact that the replications are divided over the upper two quadrants indicates there is some uncertainty concerning the effectiveness of SET regarding QALYs. However, considering that only two 24 replications (less than 2.5%) are in the upper-left quadrant, this uncertainty is very minor. The fact that there are no replications in the lower quadrants indicates that there is no uncertainty regarding costs.

Fig. 2 shows the incremental cost-effectiveness plane for cost per metre on the 12-month treadmill test. All 1000 replications are in the upper-right quadrant, indicating that there is no uncertainty whatsoever; SET is more costly and more effective than WA when it concerns walking distance.

Because, for both outcome measures, SET is more costly and more effective, the probability of SET being cost-effective depends on the amount society is willing to pay to gain a QALY or an extra metre. Cost-effectiveness acceptability curves show that probability in relation to this so-called willingness to pay, or cost-effectiveness threshold. For cost per QALY (Fig. 3), when for instance the cost-effectiveness threshold is € 40 000, the probability of SET being cost-effective compared with WA is almost 64%. For cost per metre (Fig. 4), a very high probability (85%) is already reached at a cost-effectiveness threshold of € 6.

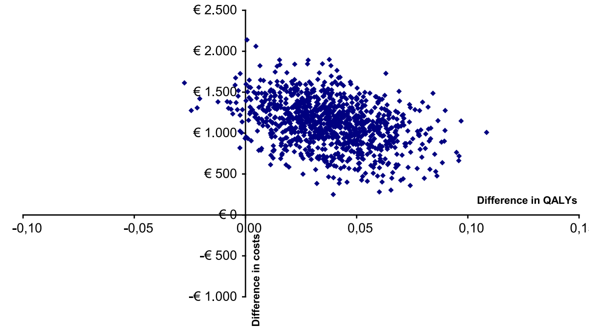

Figure 1 Incremental cost-effectiveness plane for cost per QALY (SET versus WA), showing all 1000 bootstrapped cost-effectiveness pairs. The cost-effectiveness plane consists of four quadrants. Dots in the upper quadrants indicate higher costs for SET, whereas dots in the lower quadrants represent higher costs for WA. Dots to the right of the *Y*-axis indicate better effects (more QALYs) for SET, and dots to the left of the *Y*-axis mean better effects for WA. The northwest quadrant contains cost-effectiveness pairs which are both more effective and less costly (i.e., dominant) for SET, the southeast quadrant means dominancy for WA. As most of the bootstrapped pairs are in the northeast quadrant, this means that SET is more effective in terms of QALYs, but at a certain price.

Discussion

The cost-effectiveness analysis of the EXITPAD study showed that SET was more costly and more effective than WA, for both QALYs and walking distance. The probability of SET being cost-effective therefore depends on the cost-effectiveness threshold that is applied. For cost per metre, this is a very difficult issue, as there is no previous information, and therefore no frame of reference, on cost-

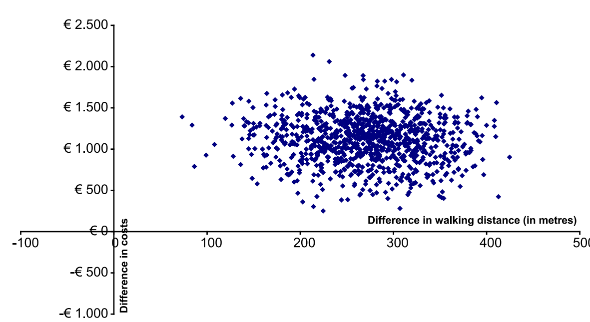

Figure 2 Incremental cost-effectiveness plane for cost per metre walking distance (SET versus WA). All cost-effectiveness pairs are situated in the northeast quadrant, implying that SET is more effective in terms of walking distance, but also more expensive.

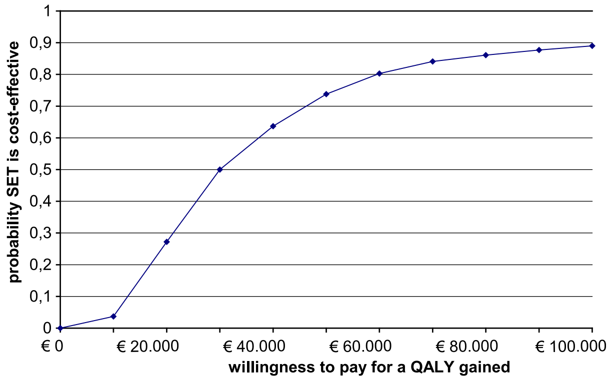

Figure 3 Cost-effectiveness acceptability curve for cost per QALY. The curve indicates the probability that SET is cost-effective, given the societal willingness to pay (threshold value) for one QALY gained.

effectiveness concerning this outcome parameter. The point where the probability of SET being cost-effective exceeds 50%, therefore, where the probability that SET is more cost-effective than WA is higher than the probability that WA is more cost-effective than SET, is reached at about € 4.15 per extra metre.

For cost per QALY, many formal and informal thresholds are being used. There is no clear consensus in the literature about what is considered a reasonable amount to pay for a QALY gained. For instance, Laupacis suggested a range between € 12 000 and € 60 000 for the Ontario guidelines.[14] Although the stated threshold of the British National Institute for Clinical Excellence (NICE) threshold is £ 30 000 (about € 34 000), their revealed threshold, that is, the threshold that can be derived on the basis of the interventions that are included in the insurance package, is £ 55 000 (almost € 63 000), nearly twice as high. In the Netherlands, recently, the suggestion has been made to include burden of disease into the cost-effectiveness threshold.[15] With the burden of disease varying from 0 to 1, with a higher number indicating a higher burden, the threshold would be € 80 000 per QALY for a highly burdensome disease (score 1), while treatment of diseases with a burden of less than 0.10 should not be in the insurance package at all; therefore, there the threshold is zero. For claudication, the burden of disease is not known; however, for heart- and peripheral arterial disease, it is 0.55 and for hip arthrosis, it is 0.42. As claudication falls into the same range of complaints, one could assume that the burden of disease for claudication is 0.50. The threshold for a disease burden of 0.5 as advised by the Dutch Council for Public Health and Health Care is about € 40 000, which corresponds with a probability of SET being cost-effective of 64%.

The incremental cost-effectiveness as studied in the EXITPAD study concerns SET versus WA. Another frequently performed intervention in claudication patients is a percutaneous vascular intervention (PVI) for revascularisation. Spronk et al.[16] compared the cost-effectiveness of a PVI versus hospital-based exercise therapy and concluded that, as there was not a significant difference in effectiveness, but revascularisation is much more costly, exercise was the preferred therapy. However, two studies investigating the effectiveness of a PVI versus SET on walking distance showed conflicting results.[17,18] It is clear that, of the three options, PVI is the most costly and WA is the most economical. Moreover, exercise therapy is a safe option compared with a PVI, which, being an invasive procedure, carries the risk of complications.[19]

A major strength of the present study was that it collected patient-level cost data for all relevant cost categories. For the devices and medication, however, these cost data might have been less reliable than for the other categories as the frequency and length of use of medication was not recorded, and for the devices as well as for the OTC drugs, patients reported such an enormous variety of products (from vitamin pills to Nordic walking sticks and health resorts) that it was difficult to assign a realistic price to all items. Moreover, it is questionable whether all patients interpreted the question on the out-of-pocket costs in the same way. However, as can be read from Table 2, the per-patient cost for this category is very modest. Nevertheless, an additional analysis was performed, excluding this specific cost category, leading to results that were very comparable with the results of the main analysis (i.e., € 2298 and € 3405 for WA and SET, respectively). Hence, even if these cost items were unreliable, this could not impact the results and conclusions.

Summarising, for cost per extra metre on the treadmill, with great certainty (85%) SET is cost-effective at € 6 per metre. There is, however, no frame of reference for the willingness to pay for lengthening the maximum walking distance. For cost per QALY, assumed that € 40 000 is an acceptable price to pay for a QALY; SET has a higher probability than WA to be cost-effective. In conclusion, the present economic evaluation shows that SET is likely a cost-effective therapeutic option for patients with claudication.

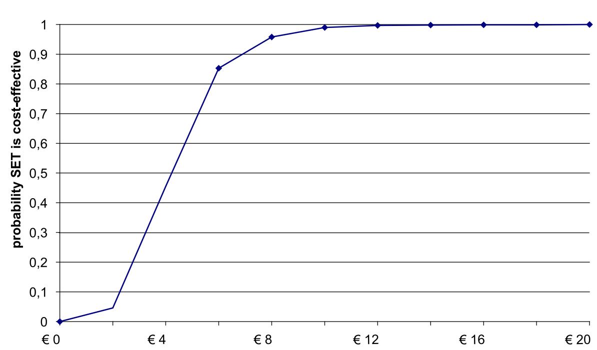

Figure 4 Cost-effectiveness acceptability curve for cost per metre. The curve indicates the probability that SET is cost-effective, given the societal willingness to pay for one extra metre on the treadmill test.

Conflict of Interest

None.

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