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Cost Effectiveness of Endovascular Revascularisation *vs.* Exercise Therapy for Intermittent Claudication Due to Iliac Artery Obstruction

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WHAT THIS PAPER ADDS

Current guidelines advise supervised exercise therapy (SET) as primary treatment for patients with intermittent claudication (IC) and refer to endovascular revascularisation (ER) when SET fails. ER as primary treatment of an iliac artery obstruction remains ambiguous due to a lack of evidence. This cost effectiveness analysis shows that ER is slightly more effective and more costly than SET as a primary treatment for IC due to an iliac artery obstruction. The difference in effectiveness, however, is not clinically relevant. The results of the analysis support current guideline recommendations also to start with SET in patients with IC, if caused by an iliac artery obstruction.

Objective: To compare cost effectiveness of endovascular revascularisation (ER) and supervised exercise therapy (SET) as primary treatment for patients with intermittent claudication (IC) due to iliac artery obstruction.
Methods: Cost utility analysis from a restricted societal perspective and time horizon of 12 months. Patients were included in a multicentre randomised controlled trial (SUPER study, NCT01385774, NTR2648) which compared effectiveness of ER and SET. Health status and health related quality of life (HRQOL) were measured using the Euroqol 5 dimensions 3 levels (EQ5D-3L) and VascuQol-25-NL. Incremental costs were determined per allocated treatment and use of healthcare during follow up. Effectiveness of treatment was determined in quality adjusted life years (QALYs). The difference between treatment groups was calculated by an incremental cost utility ratio (ICER).
Results: Some 240 patients were included, and complete follow up was available for 206 patients (ER 111 , SET 95). The mean costs for patients allocated to ER were €4 031 and €2 179 for SET, a mean difference of €1 852 (95% bias corrected and accelerated [bca] bootstrap confidence interval 1 185 — 2 646). The difference in QALYs during follow up was 0.09 (95% bcaCI 0.04 — 0.13) in favour of ER. The ICER per QALY was €20 805 (95% bcaCI 11 053 — 45 561). The difference in VascuQol sumscore was 0.64 (95% bcaCI 0.39 — 0.91), again in favour of ER.
Conclusion: ER as a primary treatment, results in slightly better health outcome and higher QALYs and HRQOL during 12 months of follow up. Although these differences are statistically significant, clinical relevance must be discussed due to the small differences and relatively high cost of ER as primary treatment.

Keywords: Cost—Benefit analysis, Exercise therapy, Intermittent claudication, Health status, Peripheral arterial disease
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INTRODUCTION

Treatment of patients with intermittent claudication (IC) due to peripheral arterial disease (PAD) is aimed at improvement of pain free and maximum walking distance and quality of life. International guidelines advise supervised exercise therapy (SET) as primary treatment, regardless of the anatomical level of arterial obstruction, and refer to endovascular revascularisation (ER) when SET fails.[1,2] The evidence base for this recommendation comes from

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randomised controlled trials (RCTs) comparing both treatments or a combination thereof in patients with obstructions in the iliac and superficial femoral arteries.[3–11]

As results of ER in the iliac arteries are durable, physicians may hesitate to offer SET to patients with IC due to arterial obstructions at this level. Yet, in the CLEVER RCT patients with iliac artery obstructions who were allocated to stenting showed improvement in walking time at 18 months of follow up similar to those treated with SET. ER conferred more improvement in health status and quality of life, although at higher cost.[3,12,13] However, since the CLEVER study was terminated prematurely and only 32 patients in both groups had treadmill testing at the end of follow up, there is no strong evidence for superiority of one treatment over the other. This might result in the situation that still a significant volume of patients with IC due to an iliac artery obstruction are primarily treated invasively, even when a sufficient infrastructure for SET, as in The Netherlands, is present.[14]

It is estimated that around 20 to 40 million people globally have IC, of which a substantial number have an iliac artery obstruction.[15] This confirms the necessity for policy makers and vascular surgeons to determine the cost effectiveness of primary treatment of iliac artery obstruction in patients with IC. The aim of the current study was to determine the cost and effectiveness of ER and SET as primary treatment for patients with IC due to an iliac artery obstruction after one year of follow up.

MATERIALS AND METHODS

This economic evaluation is reported in concurrence with the Consolidated Health Economic Evaluation Reporting Standards elements; the full checklist is enclosed in the supplementary material.[16]

For this analysis, data from the SUPervised exercise or Endovascular Revascularisation for intermittent claudication due to an iliac artery obstruction (SUPER) study (NCT01385774, NTR2648) were used. In summary, this was a multicentre randomised controlled, parallel superiority trial conducted in 18 hospitals and allied physiotherapy practices in The Netherlands. Patients were eligible if they had disabling IC, with a maximum walking distance between 100 and 300 metres on a treadmill, a significant stenosis or occlusion of the common or external iliac artery on imaging and an ankle brachial index (ABI) < 0.9, or > 0.15 drop in ABI after a standardised exercise test.

After signed informed consent patients were randomly allocated to SET or ER. SET was given according to the Royal Dutch Society for Physical Therapy guidelines.[17] The exercise programme had a duration of six months, with two sessions per week during the first 12 weeks and one session per week during the following eight weeks, and finally once every two weeks. ER was performed according to local practice by an experienced interventional radiologist certified by the Dutch Society of Interventional Radiology according to local protocol. Additionally, insertion of a stent was performed for recanalisation of an occlusion, for a residual mean pressure gradient $>$ 10 mmHg over the treated stenosis, or for a $>$ 30% residual stenosis. Both treatment arms received best medical treatment and were advised to stop smoking. The study was approved by the Medical Ethics Committee of the Academic Medical Centre in Amsterdam (MEC 2009_285). The full study protocol has been published previously.[18]

Cost analysis

The cost of treatment was expressed in euros, and unit costs of allocated treatment and additional treatment during follow up were taken from the Dutch Cost Manual, and if not available, from the Dutch Care Products Manual of The Netherland Care Institute or the Amsterdam University Medical Centre hospital ledger.[19,20] These tariffs are shown in Table 1. Additional invasive treatment during follow up comprised either ER, without or with insertion of stents, or surgical revascularisation, which was defined as any surgical intervention attributable to the primarily affected limb(s) and requiring intervention in a surgical theatre. Travel costs were based on distance between the patients' home address and hospital or physiotherapy practice. The unit costs are expressed for the base year 2015; costs derived from different calendar years were price indexed with general consumer price index figures for The Netherlands.

Treatment effectiveness

For the cost utility analysis (CUA) and effectiveness of treatment, which is expressed in quality adjusted life years

Table 1. Costs and source for diagnostics and treatment of intermittent claudication in The Netherlands

	Unit costs – €	Source
Invasive treatment		
ER without stent	1 595	DCPM
ER with one stent	2 910	DCPM
ER with two stents	4 225	DCPM
Surgical revascularisation	8 780	DCPM
Admissions		
Admission per day on surgical ward	409	DCM
ICU admission per day	2 035	DCM
Diagnostic imaging		
MRI scan	344	DCM
CT scan	141	DCM
Duplex	196	HL
Outpatient care		
Outpatient visit	74	DCM
Physiotherapy per session	33	DCM
Out of pocket expenses		
Travel costs per kilometre	0.19	DCM
Parking fee	3	DCM

ER = endovascular revascularisation; ICU = intensive care unit; MRI = magnetic resonance imaging; CT = computed tomography; DCM = Dutch Costing Manual 2014; DCPM = Dutch Care Products Manual of the Dutch Care Institute, 2015; HL = Hospital Ledger Academic Medical Centre Amsterdam, 2015.

(QALYs), the Euroqol 5 dimensions 3 levels (EQ5D-3L) questionnaire was used.[21] Missing data from the EQ5D-3L were imputed using predictive mean matching with single imputation of other follow up questionnaires if at least one measurement was present. If these data were not available, patients were excluded from the CUA. Reference data on the EQ5D-3L from the Dutch population were used to determine QALYs.[22] QALYs were estimated by linear interpolation between successive time points.

In order to present a more distinct result for clinical practice the disease specific VascuQol-25-NL questionnaire was also recorded during follow up. This questionnaire with 25 questions was developed for patients with chronic lower limb ischaemia and comprises five domains: pain, symptoms, activities, social wellbeing, and emotional wellbeing. The answers on questions range from 1 (worst possible) to 7 (best possible), culminating in an average sumscore ranging from 1 to 7.[23] The Dutch version of the VascuQol has been validated in patients with IC.[24] Patients were asked to complete questionnaires at baseline and one, six, and 12 months after randomisation.

Statistical analyses

The health economic analyses were performed on an intention to treat basis, in order to present results of both therapies in line with everyday practice. Continuous variables were presented as means with standard deviation (SD) or medians with interquartile range (IQR) depending on the distribution of the data. Statistical analyses were performed using R.[25] A p value $< .050$ was considered statistically significant. Estimated mean costs for both treatments were calculated using an independent samples t test, with their bias corrected and accelerated (bca) 95% confidence interval (CI) after bootstrapping, drawing 1 000 samples of the same size as the original samples and with replacement. Bootstrapping was stratified by randomisation group.

The economic evaluation was performed as a cost effectiveness analysis (CEA) with the costs per patient. The analyses were performed from a restricted societal perspective with a time horizon of 12 months, therefore no discounting of costs and effects was performed. Additionally, two CUAs were performed with the costs per QALY gained and the cost per additional point improvement on the VascuQol sumscore. To compare cost and effectiveness of treatment, results were presented as an incremental cost effectiveness ratio (ICER), for which the difference in costs are divided by the difference in QALY or VascuQol. Furthermore, the cost per minimally clinically important difference (MCID) between treatment groups on the VascuQol sumscore was calculated. The sample size calculation for this trial (200 patients in each arm) used Cohen's effect size d to determine a moderate effect ($d = 0.4$) between treatment groups. This translates into a difference of 86 metres on a standard treadmill test (3.2 km/h, 10% incline) and a difference of 0.377 on the VascuQol questionnaire in favour of ER. However, during the course of the study the MCID for patients with IC on this questionnaire was determined in a sample of 118 SUPER study participants by three different methods, resulting in an MCID ranging from 1.19 to 1.66.[26] Since the appropriate method of determining a MCID is still subject to debate the range of MCID values has been presented instead of the result of a single value.

A cost effectiveness acceptability curve was drawn to show the probability of ER being more efficient in terms of QALYs than SET treatment for different levels of willingness to pay. Results are displayed graphically with a cost effectiveness plane based on 1 000 bootstrap samples and a cost effectiveness acceptability curve.

RESULTS

Two hundred and forty patients were included in the SUPER study between November 2010 and May 2015. The study aimed to include 400 patients but was terminated prematurely because accrual was slow and funds ran out. Some 126 patients were allocated to ER and 114 to SET. Baseline characteristics of the groups are shown in Table 2. These characteristics were balanced, with the exception of the proportion of males and patients with a history of ischaemic heart disease. Complete health status and quality of life outcomes were retrievable in 206 patients, 111 patients allocated to ER and 95 allocated to SET. The baseline characteristics of patients with and without health status and quality of life data are shown in the supplementary material. Besides a small difference in age and the presence of a previous endovascular intervention, there were no distinct differences between these two groups.

Cost of treatment

Table 3 shows the volume and healthcare costs of the allocated treatment and during one year follow up for both groups. The mean cost of SET was €2 179 (95% bcaCI 1 752 − 2 723). As expected, mean costs of ER were higher with a mean of €4 031 (95% bcaCI 3 604 − 4 666) per patient. This difference is mainly due to allocated treatment and concomitant days of admission on a surgical ward. The mean difference in cost between treatment strategies was €1 852 (95% bcaCI 541 − 2 181).

Health outcomes and quality of life

Both treatments improved health status compared with baseline, resulting in a mean QALY during follow up of 0.82 (95% bcaCI 0.79 − 0.85) for ER and 0.73 (95% bcaCI 0.70 − 0.76) for SET. The difference between treatment groups was 0.09 (95% bcaCI 0.04 − 0.13) in favour of ER (Table 4).

The VascuQol sumscore during follow up was 5.76 (95% bcaCI 5.58 − 5.91) in the ER group and 5.11 (95% CI 4.91 − 5.32) in the SET group, which is a difference of 0.64 (95% bcaCI 0.39 − 0.91) in favour of ER (Table 4). This difference,

Table 2. Baseline characteristics of 240 patients with intermittent claudication due to iliac artery obstruction

	SET (n = 114)	ER (n = 126)
Age – y	63 ± 8	61 ± 9
Sex	63 (55)	83 (66)
Smoker		
Current	60 (53)	68 (54)
Former	48 (42)	53 (42)
Comorbidity		
Hypertension	54 (47)	60 (48)
Hypercholesterolaemia	64 (56)	82 (65)
Diabetes	19 (17)	26 (21)
Ischaemic heart disease	23 (20)	41 (33)
Cerebrovascular disease		
TIA	6 (5)	8 (6)
Stroke	4 (4)	5 (4)
COPD		
Mild	19 (17)	25 (20)
Severe	1 (1)	1 (1)
Concomitant musculoskeletal disorders		
Previous	13 (11)	7 (6)
Current	6 (5)	5 (4)
Previous endovascular intervention	10 (9)	13 (10)
Concomitant superficial femoral artery obstruction	58 (51)	59 (47)
Both legs symptomatic	24 (21)	31 (25)
Body mass index	25.8 ± 4.6	25.7 ± 3.8
Pain free walking distance – m	83 ± 46	88 ± 55
Maximum walking distance – m	187 ± 66	196 ± 68
Ankle brachial index at rest		
Left	0.80 ± 0.21	0.83 ± 0.20
Right	0.80 ± 0.19	0.82 ± 0.19
Ankle brachial index after treadmill test		
Left	0.55 ± 0.35	0.56 ± 0.34
Right	0.45 ± 0.31	0.51 ± 0.32
Medication		
Platelet aggregation inhibitor	91 (80)	112 (89)
Statin	74 (65)	96 (76)
ACE inhibitor	26 (23)	39 (31)
Diuretic	20 (18)	28 (22)
Beta blocker	33 (29)	37 (29)
Insulin	7 (5)	7 (6)
Oral antidiabetic medication	13 (11)	19 (15)

Data are presented as n (%) or mean ± standard deviation. TIA = transient ischaemic attack; COPD = chronic obstructive pulmonary disease; ACE = angiotensin converting enzyme.

however, is smaller than any of the previously mentioned MCID values, which ranged from 1.19 to 1.66.

Incremental cost effectiveness and cost utility analyses

The CUAs are shown in Fig. 1A and B. Fig. 1A shows the cost effectiveness plane for the difference in mean costs and the difference in effect, i.e., QALYs between the two treatment groups. The ICER per QALY was €20 805 (95% bcaCI 11 053 – 45 561).

Fig. 1B shows the cost effectiveness plane for the difference in mean costs and the difference in VascuQol sumscore for ER minus SET. The ICER was €2 877 (95% bcaCI 1 588 – 5 347) for a point increase on the VascuQol sumscore. Table 4 shows the cost per MCID on the VascuQol sumscore, which ranged between €3 423 (95% bcaCI 1 893 – 6 637) for a MCID for 1.19 and €4 775 (95% bcaCI 2 640 – 9 258) for a MCID of 1.66

Willingness to pay

The cost effectiveness acceptability curve is shown in Fig. 2. The Dutch government maintains different values for the amount society is allowed to spend for an increase in QALYs depending on the influence the disease has on health status according to the proportional shortfall method.[27,28] This amount ranges from €20 000 to €80 000 per QALY. Dutch society is allowed to spend €20 000 if there is a burden of disease, i.e., loss of QALYs of up to 0.4, which is applicable for patients in this study. At this price level there is a 40% probability that ER is a cost effective treatment compared with SET as is shown in Fig. 2.

DISCUSSION

This CEA shows that ER confers a small benefit in QALYs and health related quality of life (HRQOL) over SET for patients with IC due to an iliac artery obstruction, yet at a higher cost. Although HRQOL was slightly higher in patients treated with ER, this difference between treatment groups was below the MCID of the VascuQol sumscore during 12 months of follow up. Therefore, the clinical relevance of this modest benefit *vs.* the additional costs needs to be discussed.

The result of this study is based upon the largest RCT comparing ER and SET for patients with IC due to an iliac artery obstruction and is in concurrence with previously conducted cost effective analyses of these treatments. These studies, all but one without regard to the anatomic level of stenosis, also showed a small or even no benefit for ER, with an ICER ranging from about €38 000 to €380 000.[13,29–31] The current study therefore presents the smallest difference between treatments in terms of ICER per QALY. Nonetheless, it shows that even with an iliac artery obstruction ER is only slightly better but certainly more costly.

Limitations

During the course of this trial the lack of adherence to SET was substantial. After one month 75/114 (66%) patients attended the programme which declined further to 68/114 (60%) after three months and to 57/114 (50%) after six months. Only 33/114 (29%) patients followed the complete SET program as per protocol. Additionally, five patients had a direct crossover from SET to ER. This was mostly as a result of comorbidities or logistic problems for patients, but also partly due to reimbursement issues. During the conduction of the SUPER study, the Dutch Ministry of Health, Welfare and Sports decided that SET was no longer covered in basic health insurance. As there was no budget to pay for SET as study treatment, this led to termination of participation in the study, termination of SET, or crossover to ER. Twelve patients allocated to SET could not participate in the exercise programme because their health insurance did not

Table 3. Cost of allocated treatment and during follow up of 240 patients with intermittent claudication due to iliac artery obstruction, treated with supervised exercise therapy (SET) or endovascular recanalisation (ER) in The Netherlands

	SET (n = 95)		ER (n = 111)	
	Volume	Total costs – €	Volume	Total costs – €
Allocated endovascular treatment				
ER without stent	NA		62	180 420
ER with one stent	NA		30	47 850
ER with two stents	NA		13	54 925
Physiotherapy per session	1 940	64 020	NA	
Additional interventions				
ER without stent	8	29 100	4	11 640
ER with one stent	10	12 760	3	4 785
ER with two stents	13	54 925	0	0
Surgical revascularisation	1	8 780	5	43 900
Diagnostic imaging				
MRI scan	6	2 064	3	1 032
CT scan	4	564	3	423
Duplex ultrasound	8	1 568	10	1 960
Hospital care				
Admission per day on surgical ward	64	26 176	243	99 387
ICU admission per day	2	4 070	0	0
Outpatient care				
Outpatient visit	12	888	6	444
Out of pocket expenses				
Travel costs	9 082	2 056	1 638	662
Total healthcare costs		206 971		447 428
Mean cost per patient (95% bcaCI) – €	2 179 (1 752–2 723)		4 031 (3 604–4 666)	
Mean difference ER SET (95% bcaCI) – €	1 852 (1 185–2 646)			

NA = not available; MRI = magnetic resonance imaging; CT = computed tomography; ICU = intensive care unit; bcaCI= bias corrected and accelerated confidence interval.

reimburse therapy. In 2017 this decision was revoked, and since then SET is reimbursed for all patients with IC.[32] Taking non-adherence to SET and crossovers into account as it skews the results, intention to treat analysis was regarded to be in line with the actual effect of the therapy, better than with a per protocol analysis. However, the benefit of ER might be underestimated due to a diluting effect of crossovers in the SET group, or the effect of SET might be underestimated due to non-adherence of SET, which both have to be taken into account. Putting it all together, the outcomes of the study may be interpreted as a comparison of ER *vs.* deferred ER in case of non-successful SET for whatever reason.

A further limitation is that the SUPER study was stopped before the desired number of 400 patients could be included because of slow accrual and termination of funding. As such, observed findings might reflect a random high or low difference, and statistical significance may not have been reached because the number of included patients was lower than determined.

Insight was gained in overall costs by using the Dutch Cost Manual. However, not all cost components were available in this manual and were for this reason completed with the Dutch Care Products Manual of The Netherland Care Institute and the University Medical Centre Amsterdam hospital ledger (Table 1). Therefore,

Table 4. Quality adjusted life years (QALYs) and VascuQol outcomes in 240 patients with intermittent claudication due to iliac artery obstruction treated with supervised exercise therapy (SET) or endovascular revascularisation (ER)

	SET (n = 95)		ER (n = 111)
Mean EQ5D-3L	0.77 (0.73–0.81)		0.84 (0.80–0.87)
Mean QALY	0.73 (0.70–0.76)		0.82 (0.79– 0.85)
Difference QALY		0.09 (0.04–0.13)	
VascuQol sumscore during follow up	5.11 (4.91–5.32)		5.76 (5.58–5.91)
Difference on VascuQol sumscore		0.64 (0.39–0.91)	
Cost per MCID on VascuQol sumscore 1.19 – €		3 423 (1 893–6 637)	
Cost per MCID on VascuQol sumscore 1.66 – €		4 775 (2 640–9 258)	

Data are presented with (95% confidence intervals). EQ5D-3L = the Euroqol 5 dimensions 3 levels; MCDI = minimally clinically important difference.

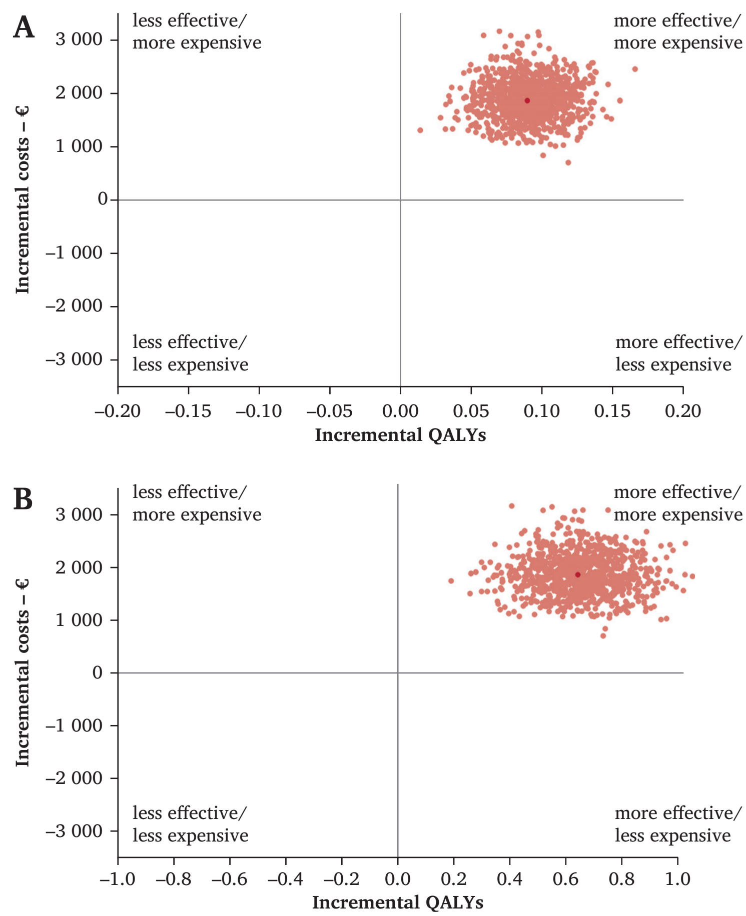

Figure 1. Cost effectiveness plane showing (A) the difference in mean costs and the difference in effect i.e. quality adjusted life years (QALYs) and (B) the difference in mean costs and the difference in effect (endovascular revascularisation [ER] minus supervised exercise therapy [SET]) on VascuQol sumscore during 12 months follow up between the two treatment groups of ER and SET for 240 patients with intermittent claudication (IC) due to iliac artery obstruction. Each dot refers to the result of a single bootstrap with a total of 1 000 bootstraps. The upper right quadrant represents a more effective yet more costly treatment.

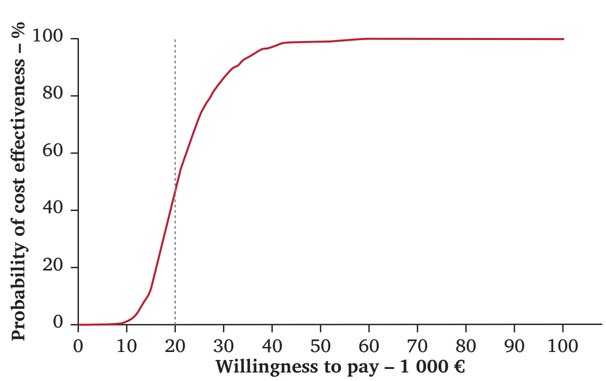

Figure 2. Cost effectiveness acceptability curve showing the probability of endovascular revascularisation (ER) being cost effective on the vertical axis and the different values society is willing to pay on the horizontal axis per quality adjusted life years quality adjusted life year (QALY) gained in 240 patients with intermittent claudication due to iliac artery obstruction.

this presents the best available approximation of costs of treatment in patients with IC. On the other hand, a strength of this economic analysis is that most cost components were collected on an individual patient level and not estimated.

Furthermore, the societal scope of this analysis is restricted since the only information about costs for patients and family consisted of travel cost and parking fees. For example, the time spent on the intervention was not available, and in addition other sectors such as productivity cost were also not taken into account. Lastly, the trial data used limited the time horizon to 12 months, which makes it impossible to state anything about long term cost effectiveness.

Perspectives

Although ER is slightly more effective for patients with IC due to an iliac artery obstruction than SET, this benefit is below the MCID on the VascuQol sumscore. Moreover, the clinical relevance of the small difference of 0.09 in QALYs between treatment groups is debatable. Therefore, the question remains whether society is willing to pay for this arguable benefit in outcome compared with the additional treatment cost. As shown, this would not be feasible under current regulations in The Netherlands. Notwithstanding, this willingness to pay by policymakers will be different across countries.

Moreover, invasive treatment is relatively safe but not without risks. A Cochrane review on the comparison of ER *vs.* SET showed a procedure related minor complication rate of 8%, and a small number of major complications.[33] These risks have to be discussed with patients when deciding on treatment and could present an argument to refer patients to SET.

Nonetheless, in order to improve the access to SET, which can be challenging in some countries, an infrastructure of physiotherapists is needed.[34] The results of this study could present an additional argument to implement such infrastructure.

Even though it is shown that SET is an excellent treatment option for patients with IC due to an iliac artery obstruction, not all patients are eligible due to comorbidity or personal preferences.[35] Treating physicians therefore need to maintain a patient tailored approach in referring them to SET and need to discuss the harms and benefits of both treatment options.

Conclusion

Endovascular revascularisation in patients with IC due to an iliac artery obstruction improves QALYs and HRQOL more than SET, but the difference is not clinically relevant and comes at additional costs. In the authors' opinion the results support current guidelines in which SET is advised as primary treatment for patients with intermittent claudication, including when this is caused by an iliac artery obstruction.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2021.10.048.

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