Randomised Clinical Trial of Supervised Exercise Therapy vs. Endovascular Revascularisation for Intermittent Claudication Caused by Iliac Artery Obstruction

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RANDOMISED CLINICAL TRIAL

Editor's Choice – Randomised Clinical Trial of Supervised Exercise Therapy *vs.* Endovascular Revascularisation for Intermittent Claudication Caused by Iliac Artery Obstruction: The SUPER study☆

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WHAT THIS PAPER ADDS

This multicentre RCT comparing supervised exercise therapy (SET) and endovascular revascularisation (ER) in patients with intermittent claudication (IC) caused by iliac artery obstruction found no statistically significant differences in maximum walking distance on a treadmill after one year follow up, and a small difference in quality of life in favour of ER. The study is limited because of premature termination, crossovers to ER, and poor compliance with SET, yet it demonstrated no large differences in clinical outcomes, which supports current guidelines to start with SET in patients with mild IC, including when the obstruction is in the iliac arteries.

Objective: International guidelines recommend supervised exercise therapy (SET) as primary treatment for all patients with intermittent claudication (IC), yet primary endovascular revascularisation (ER) might be more effective in patients with iliac artery obstruction.

Methods: This was a multicentre RCT including patients with IC caused by iliac artery stenosis or occlusion (NCT01385774). Patients were allocated randomly to SET or ER stratified for maximum walking distance (MWD) and concomitant SFA disease. Primary endpoints were MWD on a treadmill (3.2 km/h, 10% incline) and disease specific quality of life (VascuQol) after one year. Additional interventions during a mean follow up of 5.5 years were recorded.

Results: Between November 2010 and May 2015, 114 patients were allocated to SET, and 126 to ER. The trial was terminated prematurely after 240 patients were included. Compliance with SET was 57/114 (50%) after six months. Ten patients allocated to ER (8%) did not receive this intervention. One year follow up was complete for 90/114 (79%) SET patients and for 104/126 (83%) ER patients. The mean MWD improved from 187 to 561 m in SET patients and from 196 to 574 m in ER patients ($p = .69$). VascuQol sumscore improved from 4.24 to 5.58 in SET patients, and from 4.28 to 5.88 in ER patients ($p = .048$). Some 33/114 (29%) SET patients had an ER within one year, and 2/114 (2%) surgical revascularisation (SR). Some 10/126 (8%) ER patients had additional ER within one year and 10/126 (8%) SR. After a mean of 5.5 years, 49% of SET patients and 27% of ER patients underwent an additional intervention for IC.

Conclusion: Taking into account the many limitations of the SUPER study, both a strategy of primary SET and primary ER improve MWD on a treadmill and disease specific Qol of patients with IC caused by an iliac artery obstruction. It seems reasonable to start with SET in these patients and accept a 30% failure rate, which, of course, must be discussed with the patient. Patients continue to have interventions beyond one year.

Keywords: Endovascular revascularisation, Intermittent claudication, Randomised controlled trial, Supervised exercise therapy
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† For SUPER Study collaborators, please see Appendix A. Supplementary material.

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INTRODUCTION

Patients with intermittent claudication (IC) caused by peripheral arterial disease (PAD) have leg pain during exertion, which disappears after a short rest. As patients with IC may feel impaired by a limited pain free walking distance (PFWD), treatment is aimed at symptom relief to improve quality of life. Several effective treatment modalities for patients with IC are available including supervised exercise therapy (SET), and endovascular (ER) and surgical revascularisation (SR).

Current international guidelines recommend SET as first line treatment in patients with IC.[1] This recommendation is supported by evidence from 10 randomised controlled trials (RCT) comparing a wide variety of SET programmes with ER in a total of 1 087 patients with IC.[2] Appreciation of this research is hampered by the RCTs including patients with obstructions in both the aorto-iliac and femoropopliteal arteries, comparing SET with ER alone or in various combinations, and using a variety of SET programmes. In addition, the primary endpoints walking distance and quality of life were measured with a variety of exercise tests and questionnaires to assess quality of life (Qol).[2,3]

Superficial femoral artery (SFA) ER has not been proven to confer major benefits over SET.[4,5] As ER of the iliac artery is an intervention with good long term patency, it is generally considered to be the better option for patients with IC. In the only RCT comparing ER and SET in patients with an iliac artery obstruction alone, there was no significant difference in peak walking time on a treadmill, yet patients allocated to ER had better Qol.[6]

The SUPervised exercise therapy *vs.* ER (SUPER) study was conducted to compare the clinical effectiveness of SET and ER as primary treatment in patients with IC caused by an iliac artery obstruction.

METHODS

Design

The SUPER study was a multicentre randomised, parallel group superiority trial conducted in 18 hospitals in The Netherlands and allied physiotherapy practices. The protocol was approved by the medical ethics review board of the Academic Medical Centre (Amsterdam, The Netherlands, MEC 09/285) and by the local site investigators. The SUPER study was registered as NCT01385774 (clinicaltrials.gov) and NTR2776 (Dutch trial registry). Details of the study protocol have been published.[7]

Patients

The detailed inclusion and exclusion criteria for the study are listed in the published protocol.[7] In brief, patients were included if they had disabling IC resulting from > 50% stenosis or occlusion of the common or external iliac artery as seen on colour duplex scanning (CDS), magnetic resonance angiography (MRA), or computed tomography angiography (CTA), graded as TASC A, B, and C. Patients with a concomitant > 50% stenosis or occlusion of the SFA were also included. Included patients could walk at least two minutes on a treadmill at 3.2 km/h and 10% incline, had a maximum walking distance (MWD) on the treadmill between 100 and 300 m, and gave written informed consent.

Exclusion criteria were life expectancy of less than three months, inability to complete self reported questionnaires, contrast agent allergy, pregnancy, contraindication to anticoagulant therapy, symptoms of less than three months, ipsilateral common femoral artery (CFA) stenosis > 50% or occlusion, heart failure or angina pectoris NYHA III or IV, participation in another study, already had SET, and renal insufficiency (serum creatinine > 150 µmol/L).

Randomisation

Patients were randomly allocated in a 1:1 ratio in blocks of variable size to SET or ER using a web based dedicated computer randomisation software program (ALEA v. 2.2, NKI-AVL Amsterdam, The Netherlands) to ensure allocation concealment. Randomisation was stratified for MWD at baseline (< or > 200 m) and for concomitant stenosis or occlusion of the SFA.

Interventions

Supervised exercise therapy. Patients allocated to SET were trained according to the guidelines of the Dutch Society for Physical Therapy.[8] The SET programme included information by the physical therapist (PT) about the training programme and the importance of day to day exercise. At the first meeting the walking speed of the patient was recorded with a six minute walking test (6MWT). Each session lasted 60 minutes. During the first 30 minutes, the patient walked on a treadmill to the American College of Sports Medicine (ACSM) claudication pain rating scale 3 (intense pain) as many times as possible. During the second 30 minutes, the training focused on walking pattern improvement and enhancement of endurance and strength, tailored to the individual physiotherapy practice and the individual needs of the patient. All patients were given homework and set individual goals to stimulate walking. Every four weeks patients received feedback by doing a graded treadmill test (increase of slope of 2% every two minutes), and the PT advised on coping and problems encountered during exercise and homework. The SET programme lasted six months and comprised two sessions per week during the first 12 weeks, one session per week during the next eight weeks and once every two weeks during the last four weeks.

Endovascular revascularisation. ER was performed according to local practice by an experienced interventional radiologist certified by the Dutch Society of Interventional Radiology according to local protocol. Additional insertion of a stent was done for recanalisation of an occlusion, for a residual mean pressure gradient > 10 mmHg over the treated stenosis, or for a > 30% residual stenosis.

Additional treatment. All patients received secondary prevention of cardiovascular events according to the Dutch guidelines for patients with PAD and for cardiovascular risk management, comprising statin and antiplatelet therapy, and treatment of hypertension if necessary to control blood pressure with a target of 140/90 mmHg or 130/80 mmHg in patients with diabetes. All patients were advised to stop smoking. Patients were not treated with cilostazol as this is not approved in The Netherlands for medical treatment of patients with PAD.

Assessments

At baseline and follow up visits the PFWD and MWD on a treadmill with a speed of 3.2 km/h at a 10% incline were recorded by an observer who was unaware of the allocated treatment. PFWD was defined as the distance covered without any pain, and MWD was defined as the maximum distance covered at the treadmill test. For logistical reasons the upper limit of the MWD was set at 800 m (15 minutes) at the three follow up assessments. The ankle brachial index (ABI) was defined as the ratio of the highest systolic pressure of the dorsalis pedis or posterior tibial artery and the highest of both brachial artery systolic pressures and was measured at rest and after the treadmill test.

Health related quality of life (HrQol) and functional outcomes questionnaires were used as patient reported outcome measures (PROMS). Generic Qol was measured with the Short Form 36 (SF-36), disease specific Qol was measured with the Dutch version of the Vascular Quality of Life Questionnaire (VascuQol), and health status was assessed with the EuroQol 5D-3l (EQ-5D-3l) instrument. The VascuQol instrument consists of 25 items in five domains.[9] Each item is rated on a seven point scale, with a score of one representing the worst and a score of seven representing the best score. The score per domain is calculated by dividing the sum of all scores by the number of items in the domain. The VascuQol sumscore is calculated by adding up the scores on all items and dividing by 25. All questionnaires were to be completed by the patients at baseline and one, six, and 12 month follow ups.

Outcomes

Primary endpoints were change in MWD and disease specific Qol (VascuQol) after one year. Secondary endpoints were PFWD, generic Qol (SF-36), health status (EQ-5D), complications of interventions, treatment failures and additional interventions after one year.

In the original protocol the duration of follow up was one year, but permission was granted by all local medical ethics review boards to extend the duration of follow up to record major adverse cardiovascular events (MACE; defined as myocardial infarction, transient ischaemic attack or stroke, and death) and major adverse limb events (MALE; defined as additional endovascular or surgical vascular interventions, and major amputation) from the patient electronic medical records until January 2019. Patients were not invited for a treadmill test or to report PROMS. Survival status on 1 January 2019 was collected from the Dutch municipal personal records database, in which personal details of all people residing in The Netherlands are stored.

Sample size calculation

As little was known about the expected treatment effect that would be revealed on the VascuQol scale, Cohen's effect size *d* was used as the benchmark to assess the relative magnitude of score differences between the treatment groups. A moderate effect was assumed ($d = .4$) on Qol and MWD. A sample size of 180 patients in each group had 90% power to detect a difference in VascuQol score means of 0.377 between the SET and the ER group, at a two sided significance level of 5% (assuming overall VascuQol scores of 4.60 and 4.97 [common standard deviation, SD, 1.1], respectively). Using an unpaired *t* test with a 5% two sided significance level, this sample size also had 90% power to detect a difference in means of 86 m MWD on a treadmill at a speed of 3.2 km/h at 10% incline (SET group mean of 250 m and the ER group mean of 336 m) assuming a common SD of 250 m. Anticipating a maximum dropout rate of 10%, 200 patients needed to be included in each treatment arm.

Analysis

All analyses were performed according to the intention to treat principle by an independent statistician (SvD). Descriptive statistics were presented as mean with standard deviation (SD) or median with interquartile range (IQR) depending on the distribution of the data. To take into account the repeated measurements structure of the data, differences between MWD, VascuQol sumscore, SF-36, and EQ-5D were assessed with a linear mixed model with a Toeplitz covariance structure. Missing data on the five domains of the VascuQol (except the social domain which has only two items) were imputed if at least half of the items of the domain were completed by the patient. Multiple imputation was performed using predictive mean matching with 10 imputation sets. Overall survival and freedom from additional interventions were estimated with Kaplan–Meier survival analysis. Differences in survival between groups were assessed with the log rank test. Assumptions for linear mixed model, log rank test and Kaplan–Meier were checked. All statistical analyses were done with the Statistical Package for the Social Sciences version 22 (SPSS Inc., Armonk, NY, USA). The level of significance was set at a p value $< .050$.

RESULTS

Between November 2010 and May 2015, 240 patients were included in the study (Fig 1). It was not possible to record all patients who were eligible but did not participate in the study. It is known that 52 patients did not satisfy the inclusion criteria or had a preference for ER or SET and did not consent to participate in the trial, but this is very likely to be an underestimation. Unfortunately, the study had to be terminated prematurely because of the slow recruitment

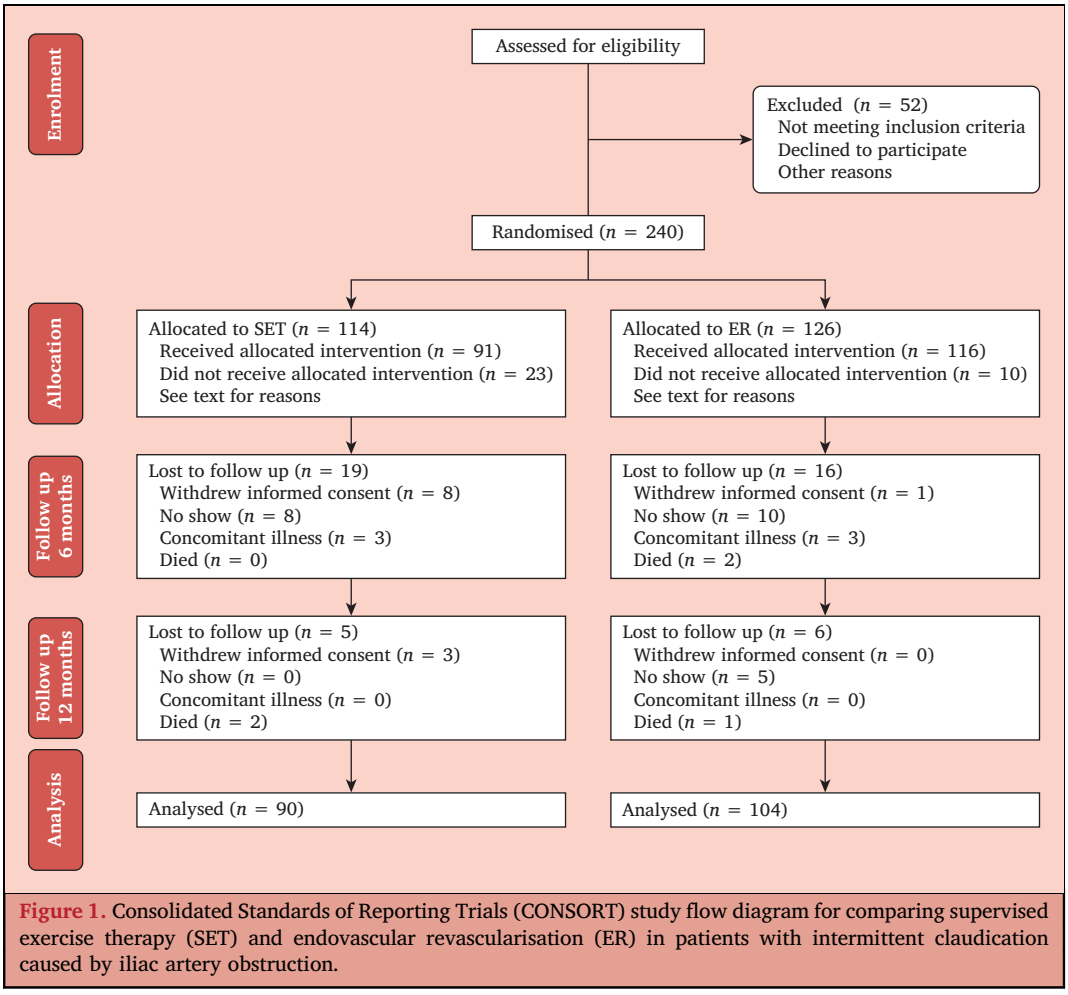

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) study flow diagram for comparing supervised exercise therapy (SET) and endovascular revascularisation (ER) in patients with intermittent claudication caused by iliac artery obstruction.

rate and there were insufficient financial means to continue until all required 400 patients were included.

Table 1 shows the baseline characteristics of the study population. There was a slight imbalance in baseline characteristics, with a higher proportion of men and patients with a history of ischaemic heart disease in the ER group.

Interventions

Compliance of the 114 patients who were allocated to SET was poor. 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 programme as per protocol. There were various reasons for attrition: 11 patients withdrew informed consent after being allocated to SET, 12 patients could not follow SET as it was not reimbursed by their health insurance, 16 patients were not able to complete the programme because of concomitant comorbidity, nine patients could not comply for logistic reasons, seven patients stopped because they had achieved their personal goals, five quit because of a lack of motivation, five patients had immediate crossover to ER, and for 15 patients the reasons for dropout were unclear. There was one serious adverse event in a patient who was admitted to the hospital because she collapsed during SET because of a sinus arrest for which a pacemaker was implanted.

Some 10 (8%) of the 126 patients who were allocated to ER did not receive the intervention. One patient developed severe renal insufficiency and ER was cancelled, two patients had other medical priorities (aortic valve replacement, severe nephrolithiasis), in four patients no significant stenosis was found during the intervention, in one patient ER was not technically feasible, and in two patients the reason was unknown. ER was technically successful in112/116 (97%) of the remaining patients. Details of the interventions are listed in Table 2. The reasons for technical failure in four patients were a residual stenosis $>$ 30% (n = 1), unsuccessful recanalisation (n = 1), and unknown (n = 2). Adjunctive interventions were stent insertion for dissection (n = 2), ER of the contralateral iliac (n = 6), ipsilateral common femoral (n = 2), and superficial femoral arteries (n = 1), and thrombosuction and thrombolysis (n = 1). Procedures were done as day cases (39%) or with one night admission (53%), and some patients (8%) were admitted longer.

ER led to complications in 11 patients (9%). Five patients had spontaneous resolution of a groin haematoma and one of a transient thrombosis of the CFA, one patient had an iliac artery dissection that was treated by repeat angioplasty the next day, in one patient a stent migrated to

the CFA which was resolved with an extra endovascular intervention, one patient needed thrombosuction and thrombolysis for distal embolisation, one patient had CFA occlusion from a closure device for which surgical removal was necessary, and in another patient a closure device migrated to the lower leg arteries and was removed surgically.

Table 1. Baseline characteristics of 240 patients treated with supervised exercise therapy (SET) and endovascular revascularisation (ER) for intermittent claudication caused by iliac artery obstruction

	SET n = 114	ER n = 126
Age	63 ± 8	61 ± 9
Men	63 (55)	83 (66)*
Smoker		
Current	60 (53)	68 (54)
Former	48 (42)	53 (42)
Never	6 (5)	5 (4)
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 revascularisation	10 (9)	13 (10)
Concomitant superficial femoral artery obstruction	58 (51)	59 (47)
Both legs symptomatic	24 (21)	31 (25)
Body mass index – kg/m^2	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)
VascuQol sumscore	4.24 (4.02–4.46)	4.28 (4.11–4.45)
SF-36 score		
Physical component score	34.61 (32.88–36.33)	35.02 (33.24–36.80)
Mental component score	48.15 (45.49–50.81)	48.60 (46.26–50.93)
EQ-5D		
Index score	0.67 (0.63–0.72)	0.71 (0.67–0.75)
VAS	64.99 (61.27–68.70)	67.42 (64.40–70.45)

Data are presented as n (%), mean ± standard deviation or mean (95% confidence interval). COPD = chronic obstructive pulmonary disease; TIA = transient ischaemic attack; SF-36 = Short Form 36; EQ-5D = EuroQol 5D; VAS = visual analogue scale.
* Statistically significant difference.

Table 2. Details of endovascular revascularisation (ER) interventions in 126 patients treated for intermittent claudication caused by iliac artery obstruction

	Left (n = 59)	Right (n = 73)
Location of ER		
Common iliac artery	43 (73)	46 (63)
External iliac artery	10 (17)	13 (18)
Both iliac arteries	6 (10)	14 (19)
Details of intervention		
ER with stent	46 (78)	52 (71)
ER alone	13 (22)	21 (29)

Data are presented as n (%).

Additional interventions

Table 3 lists the additional interventions in both treatment groups. Within one year of follow up 33/114 (29%) patients allocated to SET underwent additional ER of the iliac arteries, and 2/114 (2%) had a surgical revascularisation. Some 10/126 (8%) of the patients allocated to ER underwent additional ER within one year, and another 10 (8%) had an additional surgical revascularisation. These operations comprised aortobifemoral bypass (n = 1), thromboendarterectomy of the iliac (n = 1), common femoral (n = 4), and popliteal arteries (n = 1), and femoropopliteal bypass (n = 6).

Primary outcomes

After one year, follow up was complete for 90/114 (79%) of the patients allocated to SET and for 104/126 (83%) of the patients allocated to ER. The MWD on a treadmill had improved in the SET group from 187 to 561 m and in the ER group from 196 to 574 m, which was not statistically significantly different (Table 4). The mean VascuQol sumscore improved from 4.24 in the SET group to 5.58, and from 4.28 in the ER group to 5.88 after one year, which is a statistically significant difference (Table 4).

Table 3. Details of cumulative additional interventions within one year follow up in 240 patients treated with supervised exercise therapy (SET) and endovascular revascularisation (ER) for intermittent claudication caused by iliac artery obstruction

	SET (n = 114)	ER (n = 126)
Additional ER		
1 mo	5 (4)	3 (2)
6 mo	13 (11)	6 (5)
12 mo	33 (29)	10 (8)
Additional surgical revascularisation		
1 mo	0 (0)	3 (2)
6 mo	1 (1)	8 (6)
12 mo	2 (2)	10 (8)

Data are presented as n (%).

Secondary outcomes

Table 4 details the secondary outcomes after one year and shows that these were significantly better in favour of the ER group for PFWD, SF-36 physical component score, and EQ-5D index score, whereas there were no differences in outcomes on the SF-36 mental component score and the visual analogue rating score of the EQ-5D instrument. Of note, all secondary outcomes were statistically significantly improved compared with baseline scores in both treatment groups.

Long term outcomes

Table 5 details the outcomes after a mean follow up of > 5.5 years. There was no difference in the incidence of MACE during follow up, and mortality after > 5.5 years was 15% for patients allocated to SET and 16% in the ER group (Fig. 2). MALE occurred more often in patients allocated to SET and was solely driven by additional interventions, as there were no major amputations during long term follow up. Eventually, 49% of all patients allocated to SET underwent revascularisation (Table 5). Some 27% of the patients allocated to ER had an additional revascularisation. The details of the additional interventions are listed in

Table 4. Primary and secondary endpoints after one year follow up in 240 patients treated with supervised exercise therapy (SET) and endovascular revascularisation (ER) for intermittent claudication caused by iliac artery obstruction

	SET (n = 114)	ER (n = 126)	p value
Primary endpoints			
Maximum walking distance − m			
Baseline	187 (175–200)	196 (184–208)	
1 mo	411 (360–462)	493 (445–542)	.016
6 mo	528 (475–581)	531 (483–579)	.93
12 mo	561 (507–615)	574 (526–624)	.69
VascuQol sumscore			
Baseline	4.24 (4.02–4.46)	4.28 (4.11–4.45)	
1 mo	4.95 (4.72–5.18)	5.88 (5.67–6.10)	<.001
6 mo	5.22 (4.98–5.47)	5.98 (5.77–6.19)	<.001
12 mo	5.58 (5.32–5.82)	5.88 (5.67–6.09)	.048
Secondary endpoints			
Pain free walking distance − m			
Baseline	83 (75–92)	88 (79–95)	
1 mo	186 (131–242)	347 (294–400)	<.001
6 mo	268 (211–325)	384 (332–436)	.002
12 mo	368 (309–427)	450 (396–503)	.036
SF-36 Physical component score			
Baseline	34.61 (32.88–36.33)	35.02 (33.24–36.80)	
1 mo	38.56 (36.70–40.42)	44.97 (43.23–46.71)	<.001
6 mo	40.27 (38.34–42.20)	45.35 (43.63–47.01)	<.001
12 mo	42.53 (40.50–44.55)	45.62 (43.90–47.35)	.023
SF-36 Mental component score			
Baseline	48.15 (45.49–50.81)	48.60 (46.26–50.93)	
1 mo	48.68 (46.72–50.63)	51.13 (49.30–53.00)	.073
6 mo	49.78 (47.75–51.82)	52.29 (50.47–54.01)	.073
12 mo	49.65 (47.43–51.70)	52.13 (50.31–53.95)	.073
EQ-5D index			
Baseline	0.67 (0.63–0.72)	0.71 (0.67–0.75)	
1 mo	0.71 (0.67–0.75)	0.82 (0.78–0.85)	<.001
6 mo	0.74 (0.70–0.78)	0.82 (0.78–0.85)	.007
12 mo	0.77 (0.73–0.81)	0.84 (0.80–0.87)	.023
EQ-5D VAS			
Baseline	64.99 (61.27–68.70)	67.42 (64.40–70.45)	
1 mo	67.82 (65.91–70.72)	75.72 (73.00–78.45)	<.001
6 mo	71.80 (68.81–74.79)	75.13 (72.47–77.79)	.10
12 mo	73.80 (70.71–76.88)	74.76 (72.03–77.48)	.65

Data are presented as mean (95% confidence interval). SF-36 = Short Form 36; EQ-5D = EuroQol 5D; VAS = visual analogue scale.

Table 5. Outcomes of long term follow up in 240 patients treated with supervised exercise therapy (SET) and endovascular revascularisation (ER) for intermittent claudication caused by iliac artery obstruction

	SET (n = 114)	ER (n = 126)
Follow up – mo	69.2 ± 13.3	69.5 ± 14.1
MACE	30 (26)	30 (24)
Myocardial infarction	7 (6)	6 (5)
TIA or stroke	6 (5)	4 (3)
Mortality	17 (15)	20 (16)
MALE	57 (49)	31 (25)
One additional intervention	57 (49)	31 (25)
ER	51	19
Surgical	2	10
Hybrid	4	2
Two additional interventions	9 (8)	5 (4)
ER	6	5
Surgical	0	0
Hybrid	3	0
Three additional interventions	1 (1)	1 (1)
ER and surgical	1*	0
Surgical	2	1
Major amputation	0	0

Data are presented as n (%) or mean ± standard deviation. MACE = major adverse cardiovascular event; MALE = major adverse limb event

* Patient had seven additional interventions.

supplementary Table S1. The Kaplan–Meier survival analysis shows that most of the additional interventions occurred within the first two years after randomisation (Fig. 3).

DISCUSSION

The SUPER study was conducted with the intention to provide definitive evidence on the relative effectiveness of SET and ER for symptom relief in patients with IC caused by an iliac artery obstruction. Although 240 patients were included, which makes it the largest study in this field, there were many issues that hamper interpretation of the study outcomes. One of the major limitations is the premature termination of the study. Patient accrual was much slower than expected and this put a strain on the budget, which stopped in May 2016. Failure to include the required number of patients obviously limits the scientific validity with regard to the observed outcomes, because the study may be underpowered. Although it is not to be expected that the results would change markedly, if only in precision, the existence of a random low or high difference in outcomes between both groups cannot be excluded. Unfortunately, as only few participating centres registered the eligible patients, it is unknown how many were not included in the study. Although it is known that 52 patients did not participate because they did not satisfy the inclusion criteria or had a preference for ER or SET, it is also known that this has been under reported, and this is a limitation of the external validity of the study.

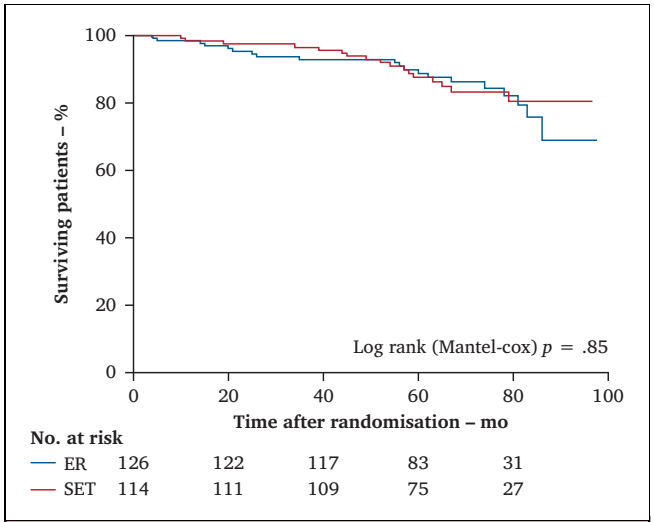

Figure 2. Cumulative Kaplan–Meier estimate of overall survival of patients treated with supervised exercise therapy (SET) and endovascular revascularisation (ER) for intermittent claudication caused by iliac artery obstruction.

There were many crossovers in this study, with 29% of the patients allocated to SET having an iliac artery ER within one year. Some patients who were allocated to SET felt as if they were denied a more effective treatment and immediately demanded to be crossed over to ER or withdrew informed consent after randomisation. The authors were not in a position to withhold these patients from ER and insist on treatment with SET and did not want to exclude the possibility of ER when SET did not lead to satisfactory symptom relief.

A further limitation is that only half of the patients complied with some form of SET, and only one third of the participants had SET according to the study protocol. Unfortunately, during the course of the study the Dutch government stopped reimbursement of SET by health insurance companies. As the authors did not have the financial means to provide SET for patients affected by this measure, some decided to withdraw participation while others continued to participate in the study, albeit without SET. It was noted also that musculoskeletal disorders hampered SET in a substantial number of patients, or that they were happy with SET at a lower intensity.

Although every effort was made to motivate patients to comply with their follow up assessments, these were complete for only 80% of the included patients. Attrition rates were similar for both treatment groups, yet it might be that this influenced the results. It was noted that patients that had crossed over to ER were less inclined to come to follow up assessments, which may overestimate the effect of SET. On the other hand, there were also patients who were dissatisfied with the results of ER and withdrew from the study, which may overestimate the effect of ER.

Finally, it could be argued that walking distance on a treadmill is not an endpoint that captures meaningful clinical improvement, because patients who train regularly on a treadmill become familiar with the device and may have an advantage over those who do not have SET.[10] Moreover, the

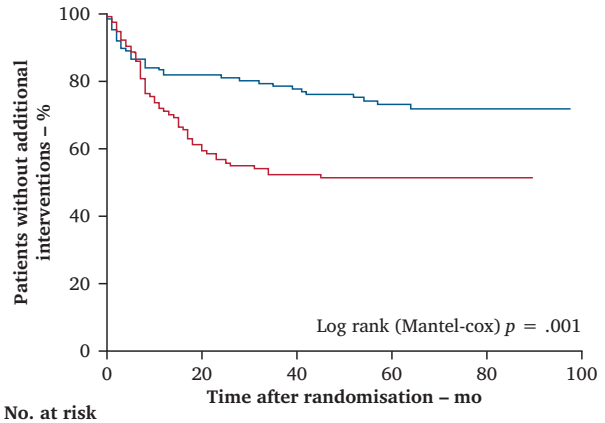

Figure 3. Cumulative Kaplan–Meier estimate of freedom from additional interventions in patients treated with supervised exercise therapy (SET) and endovascular revascularisation (ER) for intermittent claudication caused by iliac artery obstruction.

correlation between MWD on a treadmill and on a corridor is moderate,[11] and also between treadmill testing and the 6MWT, which has recently been advocated as a preferred endpoint for evaluation of interventions for IC.[10]

How then can the results of this study be interpreted, taking into account the many limitations? One can take a pragmatic view and regard the course of the study as a representation of a real world setting, in which not all patients fully comply with SET, have their own preference regarding treatment, and may experience a failed revascularisation attempt. A strategy of SET first would reduce the proportion of iliac ER to 29% within one year, with no difference in MWD on a treadmill, at the cost of a slightly lower health status as measured with the EQ-5D and disease specific Qol. Of note, both treatments conferred an increase in disease specific Qol which was larger than the smallest minimally important difference on the VascuQol mean score, which was derived from a sample of 118 SUPER study participants.[12] This implies that patients in both treatment arms experienced a clinically significant improvement in disease specific Qol. Another advantage of starting off with SET is that possible complications of ER are avoided, also because the need for repeat interventions remains, even after successful ER. The presence of a single iliac artery obstruction does not seem to be a predictor of successful ER. In a post hoc analysis similar outcomes were found for MWD and PFWD as in the primary analysis for patients with and without a concomitant SFA stenosis or occlusion (supplementary Table S2).

One may also take a different point of view and regard the SUPER study as a failed experiment because of the many limitations and conclude that referring patients for SET is cumbersome, because of low patient compliance and motivation and a high likelihood of failure. The absence of big differences in outcomes seems to be an ideal opportunity to discuss the pros and cons of both treatment options and find out with shared decision making which treatment fits best with the preferences of the patient.[13,14] Ultimately, a cost effectiveness analysis may help to further guide policy makers' and guideline committees' decisions regarding the preferred initial treatment.

How do the results of this study relate to previous research? The CLEVER study is the only RCT with a similar comparison of SET and ER in patients with iliac artery obstructions, although patients also received treatment with cilostazol.[6] Follow up at 18 months was complete for 34/43 (79%) patients allocated to SET and for 41/46 (89%) allocated to ER. There was no significant difference in peak walking time on a treadmill, and patients allocated to ER had better Qol in several domains of the peripheral arterial disease questionnaire (PAQ). CLEVER also suffered from slow enrolment and was terminated by the Data Safety Monitoring Board after reviewing interim results. Although there were no crossovers in CLEVER, the outcomes seem similar to those in the present study. In a prospective observational study of patients referred for SET, 18/69 (26%) of patients with iliac artery obstructive disease underwent an ER within six months, which is also in line with the present study.[15]

It was noted that interventions for IC did not stop after one year, but, unfortunately, the impact on MWD and PROMS could not be recorded. After a mean follow up of 69 months, 49% of patients in the SET group had had an intervention for IC, and 27% in the ER group had had an additional intervention. This mirrors the findings of the ERASE study in which 106 patients were treated with SET only and 106 with combination therapy of SET and ER.[16] After a mean of 5.4 years of follow up, a total of 65 additional interventions were done in patients allocated to SET and 149 (including the 106 initial interventions) in the combination therapy group. In ERASE, differences in walking distance and Qol at one year follow up favoured combination therapy but were not sustained after five years, despite a larger number of interventions in this group.[17] The longevity of interventions for IC is also questioned by the long term results of the IRONIC RCT in which patients with IC were allocated to any intervention plus structured exercise therapy (ET) and best medical therapy (BMT) *vs.* ET and BMT alone. The early benefit of revascularisation in Qol and walking capacity lasted for two years but disappeared after five year follow up.[18]

Taking into account the many limitations of the SUPER study, both a strategy of primary SET and primary ER improve MWD on a treadmill and disease specific Qol of patients with IC caused by an iliac artery obstruction. It seems reasonable to start with SET in these patients and accept a 30% failure rate, which must, of course, be discussed with the patient. Patients continue to have interventions beyond one year.

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.2021.09.042.

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