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The Effect of Arterial Disease Level on Outcomes of Supervised Exercise Therapy for Intermittent Claudication

A Prospective Cohort Study

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Objective: To assess whether level of arterial obstruction determines the effectiveness of SET in patients with IC.

Background Data: Guidelines advocate SET before invasive treatment for IC, but early revascularization remains widespread, especially in patients with aortoiliac disease.

Methods: Patients were recruited from 10 Dutch centers between October 2017 and October 2018. Participants received SET first, followed by endovascular or open revascularization in case of insufficient effect. They were grouped according to level of stenosis (aortoiliac, femoropopliteal, multilevel, or rest group with no significant stenosis). Changes from baseline walking performance (maximal and functional walking distance on a treadmill test, 6-minute walk test) and vascular quality of life questionnaire-6 at 3 and 6 months were compared, after multivariate adjustment for possible confounders. Freedom from revascularization was estimated with Kaplan-Meier analysis.

Results: Some 267 patients were eligible for analysis (aortoiliac n = 70, 26%; femoropopliteal n = 115, 43%; multilevel n = 69, 26%; rest n = 13, 5%). No between group differences in walking performance or vascular quality of life questionnaire-6 were found. Mean improvement in maximal walking distance after 6 months was 439 m [99% confidence interval (CI) 297–581], 466 m (99% CI 359–574), 353 m (99% CI 210–496), and 403 m (99% CI 58–749), respectively ($P = 0.40$). Freedom from intervention was 73.9% for aortoiliac disease and 88.6% for femoropopliteal disease (hazard ratio 2.46, 99% CI 0.96 – 6.30, $P = 0.013$).

Conclusions: Short-term effectiveness of SET for IC is not determined by the location of stenosis. Although aortoiliac disease patients improved walking performance and health-related quality of life similarly compared to other arterial disease level groups, they underwent revascularization more often.

Keywords: endovascular revascularization, exercise, intermittent claudication, peripheral arterial disease

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Patients with intermittent claudication (IC) due to peripheral arterial disease (PAD) are first treated with supervised exercise therapy (SET). Invasive open or endovascular revascularization (OR, ER) is considered if SET fails to satisfactorily relieve symptoms.[1] With this approach the majority of patients do not require any intervention at all,[2] even after 7 years of follow-up.[3] Revascularization as initial treatment, thus unnecessary in most, leads to higher costs,[4] considerable re-intervention rates,[5] and more amputations.[6]

ER of aortoiliac stenoses is associated with more favorable procedural results and patency rates compared to revascularization in more distal disease.[1] Nonetheless, SET remains the guideline-advocated treatment of choice in all IC patients. Three randomized controlled trials compared SET with ER for aortoiliac stenoses and reported no important differences regarding walking performance or health-related quality of life).[7–9] Even so, IC patients with aortoiliac disease are 4 times more often referred for early revascularization.[10] This discrepancy is probably related to optimal safety and efficacy of ER in aortoiliac disease compared to femoropopliteal disease, but may also suggest that some vascular surgeons consider these patients less responsive to SET. Proximal and distal PAD indeed are different entities, associated with distinct risk factor profiles[11,12] and general prognosis.[13,14] Nevertheless, the effect of arterial disease level on outcomes of SET is unknown.

The current study compared the effectiveness of SET in patients with IC according to the location of stenosis (aortoiliac, femoropopliteal, or multilevel disease) regarding walking performance, health-related quality of life, and clinical outcome.

METHODS

Study Design

The ELECT registry is a multi-center prospective observational study ("Netherlands Trial Register" registration number: NTR732). Participants were included between October 2017 and October 2018 in 10 vascular surgery centers across the Netherlands. A detailed account of the study methods is found in a previously published study protocol.[15] In summary, all patients diagnosed with IC (PAD Fontaine II/Rutherford 1–3) who were considered candidates for SET as primary treatment by their physicians were eligible. Patients were excluded in case of advanced stage of PAD (ischemic rest pain and/or ulcers: Fontaine >II, Rutherford 4–6), vascular intervention as primary treatment, prior PAD treatment (SET or revascularization) <12 months before inclusion, or co-morbidity limiting proper ambulation.

This study used diagnostic and outcome measures that were recorded as part of the standard of care, supplemented by a set of questionnaires and imaging of the aortoiliac and femoropopliteal tract [color duplex ultrasound scanning (DUS), magnetic resonance

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angiography (MRA), or computed tomography angiography (CTA)]. Functional outcomes regarding walking performance and health-related quality of life were collected by the physical therapist responsible for SET and were extracted from the standardized feedback letter that is sent to the referring vascular surgeon. The participant's hospital electronic health record was used to document baseline characteristics, vascular laboratory, and imaging data. The ELECT registry was exempted from formal medical ethical approval by the Medical Research Ethics Committees United (reference number W17.071). All participants provided formal written informed consent.

Treatment of Subjects

All participants were treated according to current guideline recommendations.[1] In short, they received a standard regimen of SET, which entails treadmill-based or track-based exercise and lifestyle coaching. SET was provided by qualified physical therapists participating in the nationwide network ClaudicatioNet[16] and following usual practice as specified in the physical therapy guidelines.[17] After 3 to 6 months, a follow-up evaluation by the vascular surgeon was scheduled. During these visits, the decision to either continue conservative management or treat invasively (ER or OR) was made in a shared decision-making environment.

Determination of Arterial Disease Level

The choice of vascular imaging modality was left to the discretion of the treating vascular surgeon. Execution of imaging, mandatorily as part of the ELECT Registry, occurred ≤3 months before or after inclusion. MRA and CTA were interpreted by experienced radiologists in the participating centers, as per usual care. A >50% stenosis on MRA or CTA was considered significant. In some centers DUS, was performed, by accredited vascular technicians. A lesion was considered significant if either a peak systolic velocity ratio of ≥2.5 or an end diastolic velocity of ≥0.6 m/s was observed, or if flow was absent (occlusion).

A team of physicians including 1 vascular surgeon (JT) and 2 MDs (PhD candidates; MH, SJ) independently assessed all DUS and MRA or CTA scans readings and radiologist reports. Based on these assessments, participants were divided into 4 groups:

1. Aortoiliac disease: significant stenoses or occlusions in the common iliac artery, external iliac artery, and/or internal iliac artery.
2. Femoropopliteal disease: significant stenoses or occlusions in the common femoral artery, superficial femoral artery, and/or popliteal artery.
3. Multilevel disease: significant stenoses at both the aortoiliac and femoropopliteal level.
4. No disease: no significant stenoses in the aortoiliac and femoropopliteal tract. Notably, this does not rule out undetected infrageniculate disease distally from the area scanned with DUS.

Each significant lesion was classified according to TransAtlantic Inter-Society Consensus (TASC).[18] It must be appreciated that the inter-observer agreement of this classification is poor.[19,20] If required, disagreement was solved by discussion and consultation of a fourth observer (vascular surgeon, MS).

Study End Points

The primary objective was to compare outcomes of SET in patients with aortoiliac disease compared with femoropopliteal disease with respect to change in maximal and functional walking distance (MWD, FWD) on a standardized treadmill test. The standardized Gardner Skinner protocol,[21] set at a walking speed of 3.2 km/h, was advocated in the study protocol. Nevertheless, a small portion of physical therapists deviated from this suggested protocol and adjusted the speed to the comfort of the patient (either 2 km/u or 4.2 km/u). As no significant difference in set speed was identified between groups (Supplemental Table 1, Supplemental Digital Content, http://links.lww.com/SLA/C255), this factor was not considered in the primary analysis.

Secondary endpoints were changes in 6-minute walk test (6MWT) performance and vascular quality of life questionnaire-6 (VascuQoL-6), freedom from vascular interventions for the lower extremities, and achievement of the main treatment goal as drafted by the physical therapist and patient at the start of the SET program. All outcomes were also compared for patients with aortoiliac disease, femoropopliteal disease, multilevel disease, and the no disease group.

Sample Size

We hypothesized that there is no clinically relevant difference in change in MWD between subjects with aortoiliac and femoropopliteal disease after 6 months. In an equivalence study design, to exclude a mean difference between groups of >150 m change with a standard deviation (SD) of 300 m, an α of 0.01, and a power of 80%, enrollment of 96 patients per arterial disease level group was projected.

Statistical Analysis

Statistical analysis was performed with SPSS version 22 (IBM Corporation, Armonk, NY). Categorical variables were presented as numbers with percentages and compared using χ^2 or Fisher exact test. Continuous variables were reported as means ± SD or as medians with interquartile range. They were compared using 1-way analysis of variance or Kruskall-Wallis rank sum tests for the 4 groups, and Tukey Honest Significant Difference test or Man-Whitney U test for the comparison between aortoiliac and femoropopliteal disease, as appropriate. To account for multiple comparisons, only the 2 a priori formulated comparisons were conducted throughout the study (between the 4 groups overall and between aortoiliac and femoropopliteal disease specifically). Furthermore, a strict significance level of 0.01 was used. Missing continuous outcome and predictor data were imputed using multivariate imputation by chained equation.

Changes from baseline walking performance (FWD, MWD, 6MWT) and Vascuqol-6 sum scores at 3- and 6-months follow-up were compared between groups after multivariate adjustment. To this end, a general linear model was used with disease level as the independent variable. Covariates used for this adjustment were selected in univariable and multivariable methods. Effects with a P-value of less than 0.2 were considered significant. First, baseline variables displaying a significant difference between aortoiliac and femoropopliteal groups were entered in the multivariable model. Then, covariates were selected using backwards elimination in the multivariable analysis to keep only factors significantly affecting change in MWD in the model. Sex, age, and body-mass index were included regardless of P-value, as the literature considers these parameters as predictors of walking performance.[22–24] Walking performance data are generally nonnormally distributed, thus for the general linear model the assumption of normality of the residuals was confirmed. A detailed account on the effect of various baseline measures on the different outcome measures in the ELECT Registry will be published separately.

Freedom from intervention between groups was estimated using Kaplan-Meier survival analysis and compared with log rank tests. Cox proportional hazard analysis was used to correct for the effect of several unevenly distributed potential confounders ($P < 0.05$, and $P < 0.2$) between disease level groups at baseline. The time to attainment of the main treatment goal was not exactly measured, but rather determined at fixed intervals (3 and 6 months). Thus,

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instead of the pre-planned Kaplan-Meier survival analysis for this outcome, rates for attainment of the treatment goal were compared between groups using χ^2 at 3 months and 6 months follow-up.

Sensitivity Analysis

Several sensitivity analyses assessed the impact of methodological decisions on the conclusions. First, we conducted an analysis without imputation (complete-case analysis). Second, we performed a ‘‘per protocol’’ analysis were all patients who underwent an intervention were excluded. Third, a supplemental analysis redefining disease level to ‘‘inflow’’ lesions (aortoiliac and multilevel disease) versus ‘‘outflow’’ lesions (no evidence of aortoiliac disease).

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RESULTS

During the 1-year inclusion period, 493 patients were evaluated and 343 patients were willing to participate in the ELECT registry. As 46 were excluded for reasons listed in Figure 1, a total of 297 patients participated in the study. Data were missing or incomplete in 30; therefore, 267 patients were eligible for the primary analysis (aortoiliac disease n = 70, 26%; femoropopliteal disease n = 115, 43%; multilevel disease n = 69, 26%; no significant stenosis in either tract n = 13, 5%).

Baseline characteristics per group are compared in Table 1. In general, participants with aortoiliac disease were on average 7 years younger, had diabetes mellitus over 3 times less often, and had higher ankle brachial index (ABI) values and less severe TASC scores compared to participants with femoropopliteal disease. Participants had completed a mean number of 17 ± 5 (n = 204) SET sessions after 3 months, and 26 ± 6 (n = 171) after 6 months. The mean number of SET sessions were not different between the aortoiliac, femoropopliteal, multilevel, and no disease group at 3 months (17 ± 5, 17 ± 5, 20 ± 4, 17 ± 5, respectively; $P = 0.27$) and 6 months follow-up (26 ± 6, 26 ± 6, 26 ± 7, 29 ± 6, respectively; $P = 0.64$).

Walking Performance and Health-related Quality of Life

Unadjusted changes from baseline after 3 and 6 months of SET are shown in Table 2. Patients with aortoiliac, femoropopliteal, or multilevel stenoses all showed significant improvements in MWD, FWD, 6MWD, and Vascuqol-6 sum scores. Participants in the ‘‘no disease group’’ did not improve in Vascuqol-6 and 6MWT. No statistically significant differences in outcomes between overall disease level groups and between patients with femoropopliteal and aortoiliac disease were found.

Table 3 shows changes in outcome parameters following correction for age, sex, body-mass index, comorbid chronic obstructive pulmonary disease, prior ER, and TASC score. Selection of these covariates is summarized in Supplemental Table 2 in the Supplemental Digital Content, http://links.lww.com/SLA/C255. Again, between-group differences were absent. The adjusted difference between aortoiliac and femoropopliteal disease patients regarding change in MWD after 3 months was −112 m [99% confidence interval (CI) −274 to 50, $P = 0.093$], after 6 months −27 m (99% CI −211 to 157, $P = 0.63$). For change in FWD after 3 months this was −73 m (99% CI −241 to 94, $P = 0.28$), after 6 months −12 m (99% CI −199 to 175, $P = 0.60$). Regarding change in 6MWT after 3 months this was 10 m (99% CI −27 to 46, $P = 0.52$), after 6 months 29 m (99% CI −28 to 86, $P = 0.23$). For Vascuqol-6 sum scores after 3 months this was −1.4 (99% CI −3.2 to 0.5, $P = 0.072$), after 6 months −0.6 (99% CI −2.4 to 1.3, $P = 0.46$). The various sensitivity analyses (Supplemental Tables 3–6, Supplemental Digital Content, http://links.lww.com/SLA/C255) did not lead to different conclusions.

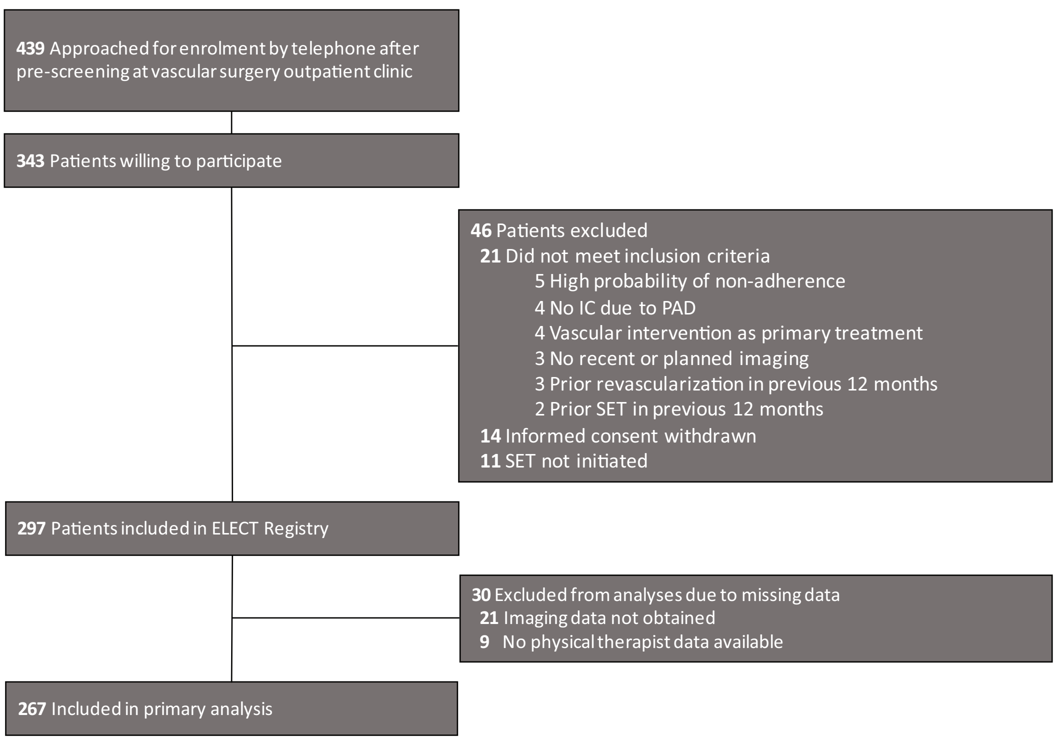

FIGURE 1. Flow chart of the inclusion process.

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TABLE 1. Baseline Population Characteristics by Disease Level (n = 267)

	Aortoiliac Disease (n = 70)	Femoro-popliteal Disease (n = 115)	Multilevel Disease (n = 69)	No Disease (n = 13)	Overall *P*-value	AoI Versus FP *P*-value
Age, y	63.7 ± 8.9	70.6 ± 8.8	68.8 ± 8.2	67.5 ± 10.8	<0.001	<0.001
Female sex, n (%)	36 (51.4)	43 (37.4)	20 (29)	4 (30.8)	0.045	0.068
BMI	26.4 (6)	25.9 (4)	26.8 (5)	28 (6)	0.105	—
Smoking						
Current, n (%)	37 (52.9)	40 (34.8)	34 (49.3)	4 (30.8)	0.039	0.011
Former, n (%)	28 (38.6)	48 (41.7)	28 (40.6)	6 (46.2)		
Comorbidity, n (%)						
Diabetes	8 (11.4)	40 (34.8)	17 (24.6)	4 (30.8)	0.003	<0.001
Dyslipidemia	32 (45.7)	54 (47)	46 (66.7)	10 (76.9)	0.009	0.88
Hypertension	36 (51.4)	70 (60.9)	47 (68.1)	10 (76.9)	0.138	—
Kidney disease	3 (4.3)	10 (8.7)	16 (23.2)	0	0.002	0.376
Cerebrovascular disease	3 (4.3)	13 (11.3)	15 (21.7)	1 (7.7)	0.015	0.114
Ischemic heart disease	15 (21.4)	26 (22.6)	15 (21.7)	3 (23.1)	1.0	—
Heart failure	1 (1.4)	6 (5.2)	7 (10.1)	1 (7.7)	0.11	—
COPD	17 (24.3)	16 (13.9)	17 (24.6)	0	0.045	0.079
Musculoskeletal disease legs	8 (11.4)	16 (13.9)	14 (20.3)	2 (15.4)	0.515	—
Prior CVD intervention, n (%)						
CABG	4 (5.7)	10 (8.7)	7 (10.1)	1 (7.7)	0.769	—
PCI	9 (12.9)	13 (11.3)	7 (10.1)	2 (15.4)	0.887	—
EVAR or open AAA repair	2 (2.8)	1 (0.9)	3 (4.3)	0	0.395	—
Previous IC treatment, n (%)						
ER	12 (17.1)	13 (11.3)	18 (26.1)	4 (30.8)	0.034	0.275
OR	0	7 (6.1)	5 (7.2)	1 (7.7)	0.074	—
SET	6 (7.1)	13 (11.3)	6 (8.7)	2 (15.4)	0.584	—
Symptomatic leg, n (%)						
Left	16 (22.9)	33 (28.7)	13 (18.8)	1 (7.7)	0.002	0.665
Right	22 (31.4)	32 (27.8)	8 (11.6)	7 (53.8)		
Both	32 (45.7)	50 (43.5)	48 (69.6)	5 (38.5)		
ABI in rest	0.72 (0.21)	0.58 (0.23)	0.55 (0.24)	0.79 (0.33)	<0.001	<0.001
ABI after exercise	0.39 (0.31)	0.3 (0.23)	0.22 (0.15)	0.5 (0.25)	<0.001	0.031
FWD, m	280 (258)	284 (304)	195 (214)	220 (450)	0.026	0.407
MWD, m	443 (378)	450 (432)	335 (250)	377 (422)	0.007	0.901
6-min walking test, m	396 ± 114	383 ± 86	327 ± 117	412 ± 126	<0.001	0.863
Vascuqol-6 sumscore	16 (6)	16 (6)	14 (7)	15 (7)	0.353	—
TASC score, n (%)						
TASC A	47 (67.1)	44 (38.3)	15 (21.7)*	n/a	<0.001	<0.001
TASC B	17 (24.3)	46 (40)	27 (39.1)*	n/a		
TASC C	1 (1.4)	16 (13.9)	16 (23.2)*	n/a		
TASC D	4 (5.7)	7 (6.1)	10 (14.5)*	n/a		
Unknown	1 (1.4)	2 (1.7)	1 (1.4)	n/a		

Presented are numbers with percentages, means ± standard deviations, and median (interquartile range).
P-values are added for comparison between groups overall and between aortoiliac and femoropopliteal disease specifically in case of $P < 0.05$ for the overall comparison.
*Based on disease level with highest score.
AAA indicates abdominal aortic aneurysm; ABI, ankle brachial index; BMI, body mass index; AoI, aortoiliac; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ER, endovascular revascularization; EVAR, endovascular aneurysm repair; FP, femoropopliteal; FWD, functional walking distance; IC, intermittent claudication; MWD, maximal walking distance; OR, open revascularization; PCI, percutaneous coronary intervention; SET, supervised exercise therapy; TASC, TransAtlantic Inter-Society Consensus.

Freedom From Revascularization

After 6 months follow-up, 73.9% (51/69) of patients in the aortoiliac group remained free from intervention, compared to 88.6% (101/114) of femoropopliteal disease patients, 75.4% (52/69) of multilevel disease patients and all (100%) participants in the no disease group. Kaplan-Meier survival curves (Fig. 2) show that between-group differences start to seem after 3 months of follow-up (log rank test for overall comparison: $\chi^2 = 10.92$, $P = 0.012$; for aortoiliac versus femoropopliteal disease $\chi^2 = 6.559$, $P = 0.0104$). Subsequently, the association between aortoiliac disease versus femoropopliteal disease and freedom from revascularization was assessed while adjusting for potential confounding variables that were distributed differently between disease level groups at baseline, using Cox proportional hazard analysis (Table 4). Aortoiliac disease was associated with a statistically significant higher risk for early revascularization in the adjusted, but not the unadjusted, analysis. For the overall population, only resting ABI was identified as additional significant predictor of early revascularization (Supplemental Table 7, Supplemental Digital Content, http://links.lww.com/SLA/C255).

Attainment of the Treatment Goal

Data accrual for attainment of the main treatment goal was poor with 87/267 (32.6%) missing cases at 3 months, and 111/267 (41.6%) at 6 months. Nonetheless, of the participants with complete data sets, 7/46 (15.9%) patients with aortoiliac disease, 25/79 (31.6%) femoropopliteal disease patients, 11/45 (24.4%) of the multilevel group, and 1/10 (10%) of the no disease group had attained their treatment goal at the 3 months follow-up visit ($P = 0.14$). After 6 months of therapy these percentages were 20/40 (50%), 33/70 (47.1%), 15/38 (39.5%), and 3/8 (37.5%), respectively ($P = 0.79$).

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TABLE 2. Unadjusted Mean Changes From Baseline After 3 and 6 mo of SET in Patients With IC, According to Disease Level

	Aortoiliac (n = 70)		Femoropopliteal (n = 115)		Multilevel (n = 69)		No Disease (n = 13)		*P*-value Overall		*P*-value AoI Versus FP	
Outcome Measures	**3 mo Change**	**6 mo Change**	**3 mo Change**	**6 mo Change**	**3 mo Change**	**6 mo Change**	**3 mo Change**	**6 mo Change**	**3 mo Change**	**6 mo Change**	**3 mo Change**	**6 mo Change**
MWD, m												
Mean	270	437	405	498	250	328	408	381	0.056	0.20	0.039	0.43
99% CI	151–388	289–586	300–509	381–614	155–344	221–435	80–737	86–675				
FWD, m												
Mean	312	512	397	503	248	341	427	325	0.097	0.081	0.26	0.50
99% CI	190–434	364–660	287–508	382–624	154–343	231–451	76–779	50–599				
6MWT, m												
Mean	44	78	36	38	50	54	−6	24	0.11	0.33	0.62	0.15
99% CI	13–76	24–131	17–55	12–64	25–76	11–96	−52 to 40	−60 to 108				
Vascuqol-6												
Mean	1.3	3.4	2.6	3.9	2.3	3.1	3.4	4.1	0.31	0.45	0.081	0.52
99% CI	0–2.7	2.0–4.9	1.7–3.5	2.9–4.9	0.8–3.7	1.6–4.5	−0.6 to 7.5	0.7–7.6				

P-values are added for overall comparison between groups using Kruskal-Wallis rank sum test, and between aortoiliac and femoropopliteal disease using Mann-Whitney *U*.
6MWT indicates, 6-min walking test; AoI, aortoiliac; CI, confidence interval; FP, femoral-popliteal; FWD, functional walking distance; MWD, maximal walking distance.

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DISCUSSION

This prospective observational study demonstrates that patients with IC achieve equal benefits after 3 and 6 months of SET, regardless of arterial disease location. Disease level groups showed similar improvements in walking performance and health-related quality of life, and rates of attainment of the treatment goal. Nonetheless, patients with aortoiliac disease appeared more likely to undergo a vascular intervention compared to femoropopliteal disease, especially after adjustment for baseline differences.

The results of the ELECT registry justify guideline recommendations advocating exercise therapy first, before considering more invasive treatment options.[1] IC patients with aortoiliac, femoropopliteal, and multilevel stenoses showed meaningful improvements on all outcomes beyond previously established minimally important differences.[25–27] No between-group differences were present. These results are consistent with previous randomized trials on the effectiveness of SET,[2,28] and the presumed working mechanisms of exercise therapy in PAD. With SET, improvement of claudication symptoms is established due to a combination of (cardiovascular) systemic mechanisms and adaptations in pain tolerance, rather than improving measures of limb vascular resistance such as the ABI.[29] Moreover, alternative modes of exercise such as upper-extremity training seem to have similar effects on walking performance compared with walking exercise.[30] This study confirms that the distribution of atherosclerotic disease does not determine any functional outcomes of SET. As a consequence, it is not necessary to obtain imaging (CTA, MRA, or duplex) of the lower extremity arteries before referral to a physical therapist contributing to the cost-effectiveness of SET. Although this is already recommended in current guidelines,[1] it is not widespread standard practice.

In this study, single-level aortoiliac disease appeared associated with a higher probability of undergoing vascular interventions. Likewise, multilevel disease patients showed similar intervention rates probably attesting to the practice of ‘‘fixing the inflow first’’ among vascular professionals. An earlier study identified proximal

TABLE 3. Adjusted Mean Changes From Baseline After 3 and 6 mo of SET in Patients With IC, According to Disease Level

	Aortoiliac (n = 69)		Femoropopliteal (n = 113)		Multilevel (n = 68)		No Disease (n = 13)		*P*-value Overall		*P*-value AoI Versus FP	
Outcome Measures	**3 mo Change**	**6 mo Change**	**3 mo Change**	**6 mo Change**	**3 mo Change**	**6 mo Change**	**3 mo Change**	**6 mo Change**	**3 mo**	**6 mo**	**3 mo**	**6 mo**
MWD, m												
Mean	273	439	385	466	274	353	370	403	0.20	0.40	0.093	0.63
99% CI	148–398	297–581	291–479	359–574	148–399	210–496	66–673	58–749				
FWD, m												
Mean	308	479	381	491	269	364	421	388	0.26	0.28	0.28	0.60
99% CI	178–437	334–623	283–479	381–600	139–399	219–510	106–736	37–740				
6MWT, m												
Mean	44	69	34	40	56	58	−12	16	0.11	0.40	0.52	0.23
99% CI	16–72	25–113	13–55	7–74	27–84	14–102	−81 to 56	−92 to 123				
Vascuqol-6												
Mean	1.3	3.3	2.6	3.9	2.2	2.8	3.8	5.8	0.16	0.18	0.072	0.46
99% CI	−0.1 to 2.7	1.9–4.8	1.6–3.7	2.8–5.0	0.8–3.6	1.4–4.2	0.4–7.2	2.3–9.2				

Covariates used for adjustment include age, sex, body-mass index, comorbid chronic obstructive pulmonary disease, prior endovascular revascularization, and TASC score (4 patients excluded due to missing TASC score).
P-values are added for overall comparison between all 4 groups and between aortoiliac and femoropopliteal disease using 1-way MANCOVA *F*-test.
6MWT indicates 6-min walking test; AoI, aortoiliac; CI, confidence interval; FP, femoral-popliteal; FWD, functional walking distance; MWD, maximal walking distance.

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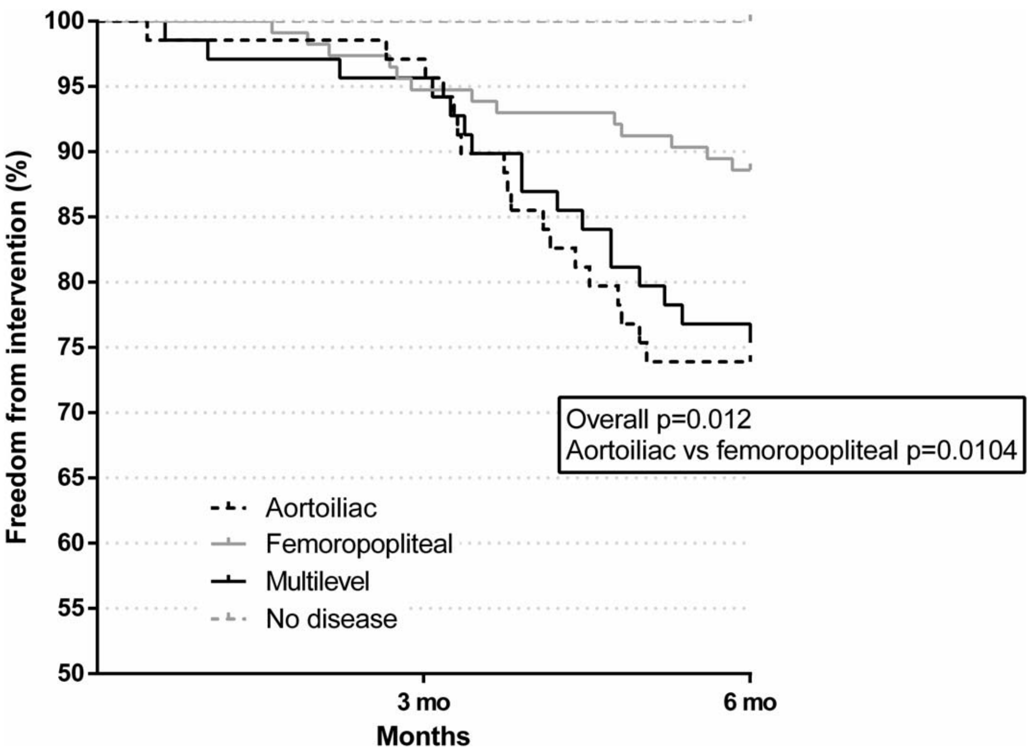

FIGURE 2. Freedom from intervention after 6 mo of treatment.

disease as the strongest predictor of primary revascularization as opposed to conservative management.[10] Apart from any functional improvements after SET, the risk-benefit ratio of a possible intervention understandably plays a role in a shared decision to intervene. In aortoiliac disease, risks are less and benefits more durable, compared to ER in more distal lesions.[1] Moreover, in the current study, patients with aortoiliac disease had overall less severe TASC scores and were younger than femoropopliteal disease patients, factors possibly playing a role in the trend towards more interventions. When correcting for these and other factors, statistical certainty for the difference in freedom from revascularization increased.

In general, the need for revascularization in this study cohort (23%) was higher than reported in other Dutch population-based series with longer follow-up (6%–19%).[5,31] This may be partly explained by bias introduced by the study design and setting. First, as dictated by the inclusion criteria, the location of disease was known for all patients in the analysis. This knowledge may have lowered the threshold to intervene. Second, all participants were recruited from outpatient vascular surgery clinics. Over the past years, a growing sample of patients in the Netherlands is referred to SET by a first-line general practitioner. As only the presence of symptoms of IC and a valid ABI reading suffice for an appropriate referral, a consultation of a vascular surgeon is generally not needed unless more invasive treatment is possibly indicated. In addition, a hospital patient population may be more inclined to a vascular intervention by default. Furthermore, the proportion of patients with prior vascular interventions was relatively high, as was having TASC A lesions. Interestingly; however, only aortoiliac disease and resting ABI appeared significant predictors for early revascularization. More research is needed to elucidate the determinants of the need for intervention relative to location of disease and functional outcomes. The longer-term results from the ELECT registry will be used in this regard.

TABLE 4. Cox Proportional Hazard Analysis of Association of Aortoiliac Disease Versus Femoropopliteal Disease With Need for Revascularization After 6 mo Follow-up

	Hazard Ratio (99% CI)	P
Unadjusted	2.46 (0.96 – 6.30)	0.013
Model 1 (adjusted)*	2.99 (1.09 – 8.05)	0.005
Model 2 (adjusted)*	3.82 (1.11 – 13.11)	0.005
Model 3 (adjusted)*	3.68 (1.04 – 13.05)	0.008

*Models adjusted for: Model 1 = TASC score (5 patients excluded because of missing data); Model 2 = Model 1 + age, smoking status, diabetes, ankle brachial index in rest and after exercise; Model 3 = Model 2 + sex, cerebrovascular accident, and chronic obstructive pulmonary disease.

CI indicates confidence interval; HR, hazard ratio.

The ELECT registry is the first study to couple the extent and location of atherosclerotic disease in IC patients treated with SET to a wide range of functional and clinical outcome measures. However, several limitations should be taken in consideration when interpreting the results. First, a relatively large number of patients declined participation, possibly introducing bias where only patients most motivated for the treatment are reflected in the results. Second, more participants were having multilevel disease than projected causing a smaller sample size in the aortoiliac group. Therefore, the current study lacked power for detecting small differences in outcomes between groups, especially with the stringent $P < 0.01$ significance level. However, the sample size was sufficient to detect clinically relevant differences, especially in the inflow versus outflow disease

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sensitivity analysis. Moreover, the reported *P*-values exceed more conservative significance levels, especially after correction for confounders. Third, although a wide range of baseline characteristics were measured and accounted for in the analyses, unmeasured confounding may possibly have influenced the results. For instance, the intensity of exercise during SET sessions is not recorded, nor daily life physical activity levels. Fourth, DUS is a noninvasive and accurate tool to assess location and extent of stenosis in PAD, but has its limitations. For instance, visualization of the iliac vessels can be limited due to body habitus and/or bowel gas, possibly introducing bias in the study design. Finally, the current report shows short-term results but not any long-term data.

In conclusion, the efficacy of SET with regards to improving walking performance and health-related quality of life in IC patients in the short term is not influenced by arterial disease level. Despite equal improvements in functional measures, aortoiliac disease patients were prone to early revascularization compared with patients with femoropopliteal stenoses. This study confirms that all IC patients should receive a trial of exercise therapy before invasive treatment is considered, regardless of the location or extent of the stenosis.

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