

Extracorporeal shockwave for intermittent claudication and quality of life

CAI, Paris, PYMER, Sean, IBEGGAZENE, Said, RAZA, Ali, HITCHMAN, Louise, CHETTER, Ian and SMITH, George

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1 **Title:**

2 A double-blind, placebo-control, randomized trial of extracorporeal shockwave for
3 claudication

4

5 **Subtitle:**

6 A novel therapy for symptomatic peripheral arterial disease

7

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Key points

Question: Can extracorporeal shockwave therapy improve quality of life and walking distances in patients with lower limb intermittent claudication?

Findings: In this double-blind, placebo-controlled, randomized trial that included 138 patients, patients receiving extracorporeal shockwave therapy had statistically higher measures of quality of life and walking distances when compared to patients receiving placebo.

Meaning: Given the increasing prevalence of peripheral arterial disease, and the low uptake and adherence to supervised exercise programs among patients with intermittent claudication, extracorporeal shockwave therapy is a safe, non-invasive and efficacious alternative with comparable improvements in quality of life and walking distances to supervised exercise.

51 **Abstract**

52 **Importance:** Lower limb intermittent claudication limits function and quality of life.
53 Supervised exercise programs are not readily available, and a non-invasive alternative is
54 required.

55

56 **Objective:** Pilot data in extracorporeal shockwave therapy for claudication showed a likely
57 benefit in walking distances. The aim of this study was to assess extracorporeal corporeal
58 shockwave therapy in improving quality of life in patients with claudication.

59

60 **Design:** Double-blind, placebo-controlled, randomized trial. Patients were randomised at 1:1
61 ratio to extracorporeal shockwave therapy or placebo. Recruitment was between June 2015 and
62 January 2020, with 12 week follow up ending March 2020. Statistical analysis was completed
63 by May 2021.

64

65 **Setting:** Single tertiary centre for vascular surgery. Participants recruited from the outpatient
66 setting.

67

68 **Participants:** A convenience sample of patients with claudication, to be managed
69 conservatively, who refused or were unable to participate in supervised exercise, were eligible.
70 Patients on anticoagulation therapy or with an active cancer were excluded. 522 patients were
71 screened, 389 were eligible and 138 consented to participate and were randomized.

72

73 **Intervention:** 3 times weekly for 3 weeks, the intervention group received 100 impulses of
74 0.1mJ/mm per cm² in an area of the gastrocnemius muscle. The steps for treatment were
75 replicated for the control group, without delivering the treatment.

76

77 **Outcomes:**

78 Primary outcome was the physical functioning domain of SF-36 quality of life questionnaire
79 at 12-week follow-up. Secondary outcomes included walking distances, ankle brachial pressure
80 index, and other quality of life measures.

81

82 **Results:**

83 138 patients recruited and randomized. 67% were male with a mean age of 67 years.

84 The intervention group had a significantly higher physical function score at 12 weeks (Estimate
85 median difference 3.83, 95% CI [0, 7.66], $p=0.033$). However, this significance did not remain
86 when adjusting for covariates ($p=0.07$). At 12-weeks the intervention group had significantly
87 longer pain-free and maximum walking distances (pain-free estimate median difference 34.08,
88 95% CI [11.36, 56.80], $p=0.004$) (maximum estimate median difference 51.37, 95% CI [10.65,
89 86.50], $p=0.013$).

90

91 **Conclusions and Relevance:**

92 This is the first double-blind, placebo-controlled, randomized trial to consider extracorporeal
93 shockwave therapy for the management of intermittent claudication. It has demonstrated
94 efficacy for walking distances, may have a positive effect on quality of life, and can provide a
95 safe, non-invasive alternative.

96

97 **Trial registration**

98 *clinicaltrials.gov*: NCT02652078

99

100

101 **Introduction**

102 An estimated 237 million people worldwide suffer with lower limb peripheral arterial disease
103 (1) with this number expected to rise due to population ageing (2). Intermittent claudication
104 (IC) is the most common symptomatic manifestation of peripheral arterial disease (3) and limits
105 physical function, walking distances and quality of life (4,5)

106

107 The current first-line recommendations for the management of IC consist of smoking cessation,
108 best medical therapy, cardiovascular risk reduction and supervised exercise (6,7). Despite
109 overwhelming evidence for the clinical and cost effectiveness of supervised exercise (8) its
110 utility is limited by suboptimal provision, uptake and adherence rates (9–13). A non-invasive,
111 efficacious, and cost-effective intervention, that is more appealing to patients and easy to
112 implement may be an attractive alternative.

113

114 Extracorporeal shockwave therapy (ESWT) was originally used in urological lithotripsy and
115 has since been utilized in the treatment of musculoskeletal disorders (14), wound healing (15–
116 17) and myocardial ischaemia (18,19). Its use in peripheral arterial disease is less established
117 with small studies reporting heterogenous outcomes (20). Our group has conducted a pilot
118 study on the use of ESWT in patients with IC (21,22), showing it to be safe and well tolerated
119 with a likely benefit on pain free walking distance. However, to date there is no evidence of
120 the effect of ESWT on quality of life in patients with IC. The aim of this study was to address
121 this evidence gap and assess the effects of ESWT on quality of life in patients with IC.

122

123 **Methods**

124 A double-blind, placebo-controlled, randomized trial was conducted at a university teaching
125 hospital that is a tertiary referral center for vascular surgery. The trial was reviewed by a

126 regional research ethics committee and full ethical approval was granted by the UK Health
127 Research Authority (REC reference: 14/EE/1257). It was also compliant with the Declaration
128 of Helsinki (1975)(23) and all participants provided written, informed consent prior to any trial
129 procedures. The trial was prospectively registered on a recognized trial registry
130 (*clinicaltrials.gov*: NCT02652078).

131

132 **Participants**

133 A convenience sample of participants were identified and screened at the outpatient vascular
134 surgery service, where a diagnosis of stable calf IC (Fontaine II with no change in symptoms
135 in a 3-month period prior to recruitment) was made by a vascular surgeon and treated
136 conservatively with best medical therapy, smoking cessation advice and exercise advice. All
137 participants were offered supervised exercise and had either declined participation or had
138 already completed the local 12-week program and remained significantly symptomatic.
139 Participants were deemed eligible if they were over the age of 18 years, were able to provide
140 written, informed consent and adhere to the trial protocol, and had either unilateral lower limb
141 IC or if bilateral, had an index leg that was symptomatically worse. Participants were not
142 eligible if they had contraindications to the use of ESWT including active malignancy, anti-
143 coagulation therapy, known coagulopathies or were pregnant at the time of screening.

144

145 **Randomization**

146 Participants were randomized at a 1:1 ratio using computer-generated numbers in random
147 permuted blocks, with allocation sequence concealment to all investigators, via an online
148 randomization tool (Sealed Envelope Ltd, London, UK, www.sealedenvelope.com) to either
149 ESWT (intervention group) or a placebo treatment (control group). Randomization allocation
150 was concealed from both the participants and the outcome assessors.

151

152 **Intervention**

153 Participants in both groups received a total of 9 treatment sessions over a 3-week period. At
154 each session, participants were positioned prone to expose their calf muscles for treatment and
155 were facing away from the equipment.

156

157 The treatment and placebo protocol have been previously published (24). The intervention
158 group received 100 impulses of 0.1mJ/mm per cm² in an area of 6cm by 5cm per head of
159 gastrocnemius muscle of the index leg, using the PiezoWave 2 shockwave system (Elvation
160 Medical Inc. Duluth, GA, USA). The identical steps for treatment were replicated for the
161 control group, including having the system display on with the correct settings, the application
162 of ultrasound gel and the passage of the transducer over the same area, without delivering the
163 shockwave treatment. Instead, a recording of the sound of the active shockwave treatment was
164 used to simulate the delivery of ESWT, via an MP3 speaker mounted on the device. All
165 participants were followed up at 4 weeks, 8 weeks, and 12 weeks after the first treatment
166 session.

167

168 **Outcomes**

169 All outcome measurements were assessed at all time-points by assessors blinded to group
170 allocation. The primary outcome was Physical Functioning as measured by the Medical
171 Outcomes Survey – Short Form 36 (SF-36) quality of life questionnaire at 12-week follow-up.

172

173 Secondary outcome measures were pre-planned and included pain-free and maximum walking
174 distance assessed via a standardized treadmill test. The treadmill protocol was constant-load
175 and was performed at 1.6 miles per hour and 10% incline for a maximum of 10 minutes.

176 Patients began walking on the treadmill and indicated when their IC pain occurred, which was
177 recorded as the pain-free walking distance. Maximum walking distance was recorded when the
178 patient could no longer continue due to maximal claudication pain or when 10 minutes had
179 elapsed. For patients unable to walk at 1.6 miles per hour, the speed was reduced by the
180 outcome assessor, but remained constant at all follow-up visits to ensure standardization. Ankle
181 brachial pressure index was measured at rest and immediately following the treadmill protocol.
182 Laser doppler flowmetry, used to assess microcirculatory blood flow of the skin on the medial
183 aspect of the calf and the dorsum of the foot, was also undertaken for a period of 5 minutes at
184 rest and immediately following the treadmill protocol using the moorVMS-LDF2 laser doppler
185 monitor (Moor Instruments Ltd, Axminster, UK). Additional quality of life measures were
186 assessed using the EuroQol-5 Dimension 3-Level (EQ-5D-3L), the remainder of SF-36
187 domains, and the disease specific Vascular Quality of Life questionnaire (VascuQoL).

188

189 **Power calculation and sample size**

190 In order to demonstrate at least a 10-point difference in SF-36 physical functioning domain
191 with 80% power and 5% significance, 55 participants were required for each treatment group
192 (25). Based on the completion rates of the local supervised exercise program and the results of
193 the internal pilot study (21), we allowed for a 20% attrition rate resulting in a total sample size
194 of 138 participants required to achieve power.

195

196 **Statistical Analysis**

197 Data was analyzed using SPSS (IBM, Version 28, New York, USA). A *p*-value of <0.05 was
198 considered statistically significant. Outcome measures were analyzed on an intention-to-treat
199 basis, according to the randomization group.

200

201 Baseline characteristics and outcome measures are presented as means and standard deviations
202 for parametric data, medians, and interquartile range (IQR) for non-parametric data. The
203 Shapiro-Wilk test was used to determine the normality of distribution. Mann-Whitney U and
204 Kruskal-Wallis tests were used to estimate the difference in outcomes between groups. Hodges-
205 Lehmann estimator used to provide an estimate of the median differences between groups with
206 95% Confidence Intervals. Secondary analysis by one-way analysis of co-variance (ANCOVA)
207 using rank transformation of non-parametric data was carried out to compare outcomes at
208 follow up, controlling for baseline characteristics.

209

210 This trial is reported in line with the CONSORT guidelines (26).

211

212 **Results**

213 Between June 2015 and January 2020, 522 patients were assessed for eligibility, and 389 (75%)
214 patients were eligible. Of these, 138 (35.5%) consented to participate and were randomized
215 (Figure 1). Table 1 summarizes the participants' baseline characteristics. All patients were
216 White/Caucasian, reflecting the demographics of the local population (27).

217

218 Throughout the study period there were no side effects or serious adverse events recorded that
219 were related to the ESWT. One patient in the intervention group withdrew during the treatment
220 period because they were unable to tolerate lying flat and prone due to dyspnoea.

221

222 **Primary outcome**

223 Normalized medians of the physical functioning domain of the SF-36 questionnaire at 12-week
224 follow up were significantly higher in the intervention group (41.3 [IQR 31.2 – 46.1] when
225 compared to the control group (34.6 [IQR 28.8 – 42.7]; ($p=0.03$); estimate median difference

226 3.83; 95% CI [0.00, 7.66]. There were no statistically significant intragroup differences at any
227 follow up timepoint.

228

229 **Secondary outcomes**

230 *Other Quality of Life Outcomes (Table 2)*

231 Short Form 36 domains

232 No statistically significant intergroup differences in the other SF-36 domain scores were
233 observed at baseline, or at 8 or 12 weeks. At 4-weeks follow up, the intervention group
234 demonstrated significantly better scores in the SF-36 General Health ($p=0.004$) and, Vitality
235 ($p=0.03$) domains, and the Physical Component Summary ($p=0.02$) than the control group
236 (Table 2).

237

238 The intervention group showed statistically significant improvement in multiple domains of
239 SF-36 between baseline and follow up. The Physical Component Summary score had a
240 statistically significant increase between baseline and all follow up time points (4-week $p=0.02$;
241 8-week $p=0.01$; 12-week $p=0.05$). The score for Bodily Pain was significantly increased
242 between baseline and 4-week ($p=0.007$) and baseline and 8-week ($p=0.02$). The score for
243 Vitality was significantly increased between baseline and 4-week ($p=0.009$).

244

245 The control group had a statistically significant improvement in only one component of SF-36,
246 Bodily Pain, between baseline and 4-week ($p=0.02$).

247

248 EuroQol-5 Dimension 3-Level

249 No statistically significant intergroup differences in the EQ-5D-3L VAS scores were observed
250 at baseline, or at 8 or 12 weeks. At 4-weeks the intervention group demonstrated significantly

251 better scores than the control group ($p=0.03$). There were no statistically significant intragroup
252 differences.

253

254 Vascular Quality of Life

255 No statistically significant intergroup or intragroup differences in VascuQoL questionnaire
256 scores were observed at baseline or at any time during follow up.

257

258 ***Pain-free walking distance***

259 No statistically significant intergroup differences in pain-free walking distance were observed
260 at baseline. Thereafter, pain free walking distances were significantly greater in the
261 intervention group at 4, 8 and 12-weeks (Table 3). Statistically significant intragroup
262 improvements in pain free walking distances were observed in both the intervention ($p<0.001$)
263 and the control group ($p<0.001$).

264

265 ***Maximum walking distance***

266 No statistically significant intergroup differences in maximum walking distance were observed
267 at baseline or at 4 weeks. Thereafter, maximum walking distances were significantly greater in
268 the intervention group at 8 and 12-weeks (Table 3). Statistically significant intragroup
269 improvements in maximum walking distances were observed in both the intervention ($p<0.001$)
270 and the control group ($p<0.001$).

271

272 ***Ankle Brachial Pressure Index***

273 No statistically significant intergroup or intragroup differences in ankle brachial pressure index
274 pre or post exercise were observed at baseline or at any time during follow up. (Supplementary
275 Table 1).

276

277 *Laser Doppler Flowmetry*

278 No statistically significant intergroup or intragroup differences in Laser Doppler Flowmetry
279 pre or post exercise were observed at baseline or at any time during follow up. (Supplementary
280 Table 2).

281

282 *Secondary analysis*

283 Secondary ANCOVA analysis, adjusting for baseline values, showed that a history of coronary
284 artery disease appears to have a significant effect on physical functioning domain of the SF-
285 36 questionnaire and there was no statistically significant difference in the physical functioning
286 domain at 12-week follow up $F(1,94)=3.394$, $p=0.07$.

287

288 As above, after adjustment for baseline values, SF-36 General Health and Vitality domains
289 continue to be significantly higher in the intervention group when compared to the control
290 group at 4-week follow up (General Health $F(1,97)=6.321$, $p=0.014$; Vitality $F(1,97)=6.213$,
291 $p=0.014$).

292

293 After adjustment for baseline values, pain-free walking distances continue to be significantly
294 higher in the intervention group when compared to the control group at all follow up points (4-
295 week $F(1,99)=5.562$, $p=0.02$; 8-week $F(1,81)=9.774$, $p=0.002$; 12-week $F(1,78)=10.779$,
296 $p=0.002$).

297

298 After adjustment for baseline values, maximum walking distances continue to be significantly
299 higher in the intervention group when compared to the control group at 12-week follow up
300 ($F(1,92)=9.456$, $p=0.005$).

301

302 **Discussion**

303 In patients with IC who have declined or completed a supervised exercise program, ESWT is
304 safe, well tolerated, and efficacious delivering benefits in walking distances and quality of life.
305 Supervised exercise is the recommended first-line treatment for IC, but suffers from uptake
306 and completion rates as low as 25% and 75% respectively (9–12). Of the 389 patients eligible
307 for this study, 138 (35.5%) agreed to participate, and of these, 110 (80%) completed the
308 intervention and follow up. Additionally, many of these participants had previously declined
309 participation in an exercise program. Therefore, ESWT appears to be a potential alternative to
310 supervised exercise for patients with IC that can improve patient choice and increase access
311 and engagement with non-invasive treatment.

312

313 With regards to the primary outcome, the median improvement in the SF- 36 domain of
314 physical functioning at 12-week follow up was of a magnitude similar to that associated with
315 a 12-week supervised exercise program (8). Post-hoc secondary analysis however, revealed
316 that this difference in physical functioning was no longer significant when accounting for
317 baseline characteristics that can affect outcomes in lower limb peripheral arterial disease in
318 general, though a trend did remain ($p=0.07$). In this cohort, a history of coronary artery
319 disease/ischaemic heart disease, significantly affected the physical functioning score as well
320 as a difference between groups at baseline, likely representing a chance imbalance at
321 randomization.

322

323 Nevertheless, there were statistically significant differences between groups in the General
324 Health and Vitality domains of the SF-36, which were not influenced by baseline differences.
325 This therefore suggests ESWT does have a positive effect on quality of life.

326

327 The remaining SF-36 domains and other measures of quality of life did not show statistically
328 significant improvements. However, the median scores in the intervention group were
329 consistently higher than in the control group. The lack of statistical significance may be due to
330 the trial being powered to detect a significant change in the SF-36 physical functioning domain,
331 therefore lacking the power to detect changes in other quality of life domains. It is also
332 important to note that the aim of the intervention was not to eradicate claudication symptoms,
333 but rather to reduce them to enable patients to mobilize further. This means that there will be
334 a continuing impact of IC on quality of life, which can skew the results obtained from a disease
335 specific quality of life questionnaire such as the VascuQol influencing the lack of a significant
336 change. This will especially apply to patients with bilateral claudication, as the intervention
337 only treated the index leg.

338

339 With regards to other secondary outcomes, walking distances improved at each time point,
340 peaking at 12-week follow-up. The improvements in the intervention group were comparable
341 to those provided by exercise therapy and represented a small to moderate minimal clinically
342 important difference (31,32). Importantly, the control group also had a significant increase in
343 their objective walking distances suggesting adequate blinding, and validating our placebo
344 treatment protocol (20). Another possible explanation for these increases is continuing to check
345 that participants did not discontinue and were appropriately taking their statin and antiplatelet
346 therapy at every follow up point, ensuring strict adherence to best medical therapy. This,
347 coupled with constant smoking cessation and exercise advice and encouragement throughout
348 the trial period is something that patients are unlikely to receive as part of routine clinical
349 practice but has a positive impact on their IC.

350

351 Nevertheless, given that the conservative management approach used within both groups
352 conformed to latest guidance (6,7), the significant increase in walking distances and quality of
353 life measures in the intervention group can be attributed to the effects of ESWT. Future research
354 should perhaps investigate various doses and durations of ESWT, compare ESWT with
355 supervised exercise, investigate the potential additive effects of the two interventions, and
356 consider the potential mechanism of action for ESWT. A previously postulated mechanism of
357 action i.e. upregulation of angiogenic factors (33), does not appear to be evident at a
358 macrovascular level nor is it superficial enough to be adequately detected by laser doppler
359 flowmetry. Other proposed mechanisms of action such as neural stunning, resulting in
360 reduction in ischaemic pain in patients with critical limb threatening ischaemia (34), might
361 have a role in the effects of ESWT seen in this study. However from the current evidence it is
362 unclear whether this reduction in pain is due solely to neural stunning or due to angiogenesis
363 and vasodilation (33).

364

365 A final, but important consideration, is that our findings further the suggestion that quality of
366 life in patients with IC cannot be solely assessed via the functional outcome of walking distance,
367 but requires generic and disease specific quality of life tools. However, our findings also
368 demonstrate the impact that concurrent comorbidities have on such tools. As such, future
369 research in patients with lower limb peripheral arterial disease should adopt patient reported
370 health related quality of life measures as primary endpoint, whilst stratifying for the impact of
371 concurrent comorbidities (4,35,36).

372

373 **Limitations**

374 This study is not without limitations. Firstly, post-hoc secondary analysis revealed that the
375 difference in physical functioning as measured by the SF-36 questionnaire was no longer

376 significant when adjusting for baseline characteristics, in particular a history of coronary artery
377 disease.

378

379 The study is also limited by the use of a constant load treadmill test, for assessing walking
380 distances. Though a reliable test, especially when assessing maximum walking distance in
381 patients with IC (38), it has disadvantages in terms of test, re-test reliability compared to a
382 graded treadmill test and may not be as closely related to every day walking as the 6-minute
383 walking test (39).

384

385 Lastly, this is a single center trial of a modest convenience sample. Future research should aim
386 for a multi-center trial to allow for generalizability of results and will be of great interest for
387 comparison with the current recommendation of supervised exercise therapy.

388

389 **Conclusions**

390 To our knowledge this is the first adequately powered, double-blind, placebo-controlled,
391 randomized trial to consider ESWT for the management of lower limb IC. It has successfully
392 demonstrated efficacy for improving walking distances within a comparable cohort of patients
393 with IC, whilst suggesting a potential positive effect on quality of life. Further trials are
394 required to compare this treatment to the current available treatment, including a supervised
395 exercise program, and identify the potential mechanism of action.

396

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Mr Paris Cai had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors have no conflicts of interest to declare.

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List of Figures and Tables

Figure 1: CONSORT diagram.

Table 1: Baseline characteristics.

Table 2: Median quality of life measures at all time points

Table 3: Median pain free and maximum walking distances at all trial time points.

426 Table 1: Baseline characteristics.

Baseline Demographics	Intervention Group n = 68	Control Group n = 70
Male sex (%)	44 (64.7)	48 (68.6)
Female sex (%)	24 (35.3)	22 (31.4)
Age Mean \pm SD (years)	66 \pm 10.7	67 \pm 8.5
BMI Median (IQR) (kg/m ²)	27.9 (24.3-30.9)	27.8 (24.1-29.9)
Smoking status (%)		
• Current smoker	31 (45.6)	25 (35.7)
• Ex-smoker	33 (48.5)	38 (54.3)
• Never smoker	4 (5.9)	7 (5.6)
Diabetes (%)	16 (23.5)	25 (35.7)
HTN (%)	40 (58.8)	43 (61.4)
Hx CAD/IHD (%)	22 (32.3)	31 (44.3)
Hx CVA (%)	7 (10.3)	6 (8.6)
Hx Resp (%)	16 (23.5)	17 (24.3)
Fontaine Classification		
• Fontaine IIa	5 (7.3)	9 (12.9)
• Fontaine IIb	63 (92.6)	61 (87.1)
Site of claudication		
• Calf (%)	62 (91.2)	66 (94.3)
• Calf and thigh (%)	6 (8.8)	4 (5.7)
Bilateral claudication (%)	7 (10.3)	8 (11.4)

427

428 **KEY**

429 BMI – Body Mass Index

430 HTN – Hypertension

431 CAD – Coronary Artery Disease

432 IHD – Ischaemic Heart Disease

433 CVA – Cerebrovascular Accident

434 Resp – Respiratory Disease

435 Table 2: Median quality of life measures at all time points.

	Intervention Group (n=55)	Control Group (n=55)	p value	Estimate median difference [95% CI]
Baseline				
SF-36 PF	36.5 (30.8 – 44.2)	33.0 (26.9 – 38.9)	0.05	3.82 [0, 5.74]
SF-36 RP	39.1 (31.3 – 48.2)	37.0 (30.2 – 43.1)	0.18	2.25 [0, 6.73]
SF-36 BP	38.2 (30.6 – 43.5)	38.2 (30.6 – 42.2)	0.32	0 [0, 4.03]
SF-36 GH	43.2 (35.2 – 50.8)	38.4 (30.8 – 47.5)	0.07	3.33 [0, 7.13]
SF-36 VT	46.7 (40.7 – 49.6)	43.7 (32.5 – 49.6)	0.16	2.97 [0, 5.94]
SF-36 SF	42.3 (32.3 – 53.6)	42.3 (32.3 – 47.3)	0.06	5.01 [0, 10.02]
SF-36 RE	45.7 (31.8 – 56.2)	42.2 (28.3 – 56.2)	0.33	0 [0, 6.97]
SF-36 MH	50.9 (42.4 – 58.7)	45.6 (37.8 – 56.1)	0.11	2.62 [0, 7.84]
SF-36 PCS	36.1 (31.3 – 41.7)	34.0 (27.6 – 39.8)	0.09	2.46 [-0.46, 5.32]
SF-36 MCS	49.5 (43.1 – 58.3)	45.6 (35.4 – 56.4)	0.16	3.16 [-1.02, 7.49]
EQ-5D VAS	0.66 (0.53 – 0.68)	0.65 (0.38 – 0.66)	0.15	0 [0, 0]
VascuQol	4.4 (3.33 – 5.5)	4.2 (3.2 – 4.8)	0.13	0.36 [-0.12, 0.84]
4-week follow up				
SF-36 PF	39.4 (32.6 – 44.6)	36.5 (28.8 – 44.2)	0.11	2.37 [0, 5.75]
SF-36 RP	40.3 (34.7 – 52.7)	39.2 (32.5 – 48.2)	0.11	2.25 [0, 6.74]
SF-36 BP	42.2 (37.3 – 51.5)	38.2 (34.2 – 46.3)	0.19	3.23 [0, 4.44]
SF-36 GH	43.7 (38.7 – 53.2)	38.0 (33.2 – 46.1)	0.004	5.71 [2.38, 9.51]
SF-36 VT	49.6 (45.9 – 55.6)	46.7 (34.8 – 55.6)	0.03	2.98 [0, 8.91]
SF-36 SF	47.3 (37.3 – 57.3)	42.3 (37.3 – 52.3)	0.37	0 [0, 5.01]
SF-36 RE	49.2 (35.3 – 56.2)	42.2 (31.8 – 56.2)	0.26	0 [0, 6.96]
SF-36 MH	56.1 (42.4 – 58.7)	50.9 (40.4 – 58.7)	0.19	2.62 [0, 5.24]
SF-36 PCS	39.7 (33.9 – 44.5)	35.9 (31.0 – 40.2)	0.02	3.86 [0.78, 6.53]
SF-36 MCS	53.5 (43.5 – 60.0)	49.3 (40.6 – 59.3)	0.27	2.32 [-1.73, 6.61]
EQ-5D VAS	0.66 (0.60 – 0.69)	0.66 (0.36 – 0.69)	0.03	0.03 [0, 0.07]
VascuQol	5.3 (4.2 – 5.9)	4.8 (3.9 – 5.6)	0.14	0.32 [-0.12, 0.80]
8-week follow up				
SF-36 PF	42.2 (31.2 – 46.1)	36.5 (30.3 – 42.7)	0.08	3.83 [0, 7.66]
SF-36 RP	39.2 (32.5 – 52.1)	39.2 (30.2 – 43.7)	0.14	4.49 [0, 8.98]
SF-36 BP	42.2 (34.2 – 49.9)	38.2 (34.2 – 46.3)	0.17	3.63 [0, 4.83]
SF-36 GH	43.7 (36.2 – 50.8)	40.4 (33.2 – 48.4)	0.14	3.32 [-0.95, 7.14]
SF-36 VT	49.6 (38.5 – 55.6)	43.7 (37.7 – 49.6)	0.09	2.98 [0, 8.91]
SF-36 SF	47.3 (37.3 – 57.3)	42.3 (37.3 – 52.3)	0.17	5.01 [0, 10.02]
SF-36 RE	45.7 (31.8 – 56.2)	42.2 (35.3 – 56.2)	0.66	0 [-3.48, 6.96]
SF-36 MH	53.5 (43.0 – 58.7)	48.3 (37.8 – 58.7)	0.37	2.61 [-2.62, 5.24]
SF-36 PCS	41.2 (35.9 – 46.0)	35.9 (30.7 – 40.9)	0.02	4.18 [0.74, 7.38]
SF-36 MCS	52.6 (39.9 – 59.0)	47.2 (39.7 – 57.5)	0.53	1.52 [-2.97, 6.53]
EQ-5D VAS	0.66 (0.60 – 0.69)	0.66 (0.50 – 0.66)	0.10	0.03 [0, 0.09]
VascuQol	5.2 (3.8 – 5.8)	4.6 (3.8 – 5.3)	0.08	0.44 [-0.08, 0.92]
12-week follow up				
SF-36 PF	41.3 (31.2 – 46.1)	34.6 (28.8 – 42.7)	0.03	3.83 [0, 7.66]
SF-36 RP	41.4 (32.5 – 48.2)	39.2 (32.5 – 48.2)	0.39	2.24 [-2.24, 6.73]
SF-36 BP	40.2 (34.2 – 46.7)	38.2 (30.6 – 46.7)	0.48	0 [-0.80, 4.43]
SF-36 GH	44.4 (35.6 – 50.8)	38.0 (33.2 – 46.1)	0.06	4.75 [0, 8.55]

SF-36 VT	49.6 (40.0 – 55.6)	43.7 (37.7 – 52.6)	0.20	2.97 [-2.97, 5.95]
SF-36 SF	47.3 (32.3 – 57.3)	42.3 (37.3 – 47.3)	0.31	0 [0, 10.20]
SF-36 RE	45.7 (35.3 – 56.2)	42.2 (28.3 – 56.2)	0.42	0 [0, 6.96]
SF-36 MH	52.2 (40.4 – 58.7)	48.3 (40.4 – 56.1)	0.28	2.61 [-2.62, 5.24]
SF-36 PCS	40.8 (33.5 – 45.4)	36.6 (31.4 – 43.7)	0.12	2.75 [-0.71, 6.02]
SF-36 MCS	48.7 (39.4 – 58.6)	46.4 (37.7 – 57.4)	0.47	1.71 [-2.88, 6.90]
EQ-5D VAS	0.66 (0.59 – 0.69)	0.66 (0.50 – 0.67)	0.67	0 [-0.03, 0.03]
VascuQol	4.9 (3.9 – 5.9)	4.9 (3.6 – 5.5)	0.48	0.16 [-0.36, 0.64]

436

437 KEY

438 PF – Physical Function

439 RP – Role Physical

440 BP – Bodily Pain

441 GH – General Health

442 VT – Vitality

443 SF – Social Functioning

444 RE – Role Emotional

445 MH – Mental Health

446 PCS – Physical Component Summary

447 MCS – Mental Component Summary

448

449 Table 3: Median pain free and maximum walking distances at all trial time points.

450

Walking distance Meters (IQR)	Intervention Group (n=55)	Control Group (n=55)	p value	Estimate median difference [95% CI]
Baseline Pain Free	49 (32.7 – 82.4)	40 (22.7 – 72.1)	0.10	8.77 [-2.13, 18.99]
Baseline Maximum	85 (55.4 – 132.5)	93 (47.5 – 141.1)	0.93	-1.03 [-22.01, 17.75]
4-weeks Pain Free	87 (58.2 – 127.8)	58 (30.5 – 110.9)	0.03	20.03 [2.14, 38.34]
4-weeks Maximum	142 (90.3 – 176.1)	103 (54.1 – 195.1)	0.12	22.94 [-6.90, 52.54]
8-weeks Pain Free	98 (56.1 – 147.1)	60 (37.1 – 91.2)	0.006	31.95 [10.61, 57.10]
8-weeks Maximum	158 (107.5 – 256.8)	110 (62.4 – 200.6)	0.04	38.34 [1.30, 73.76]
12-weeks Pain Free	106 (67.5 – 157.6)	70 (43.5 – 106)	0.004	34.08 [11.36, 56.80]
12-weeks Maximum	172 (118.6 – 239.3)	114 (68.7 – 200.9)	0.01	51.37 [10.65, 86.50]

451

452 **References**

- 453 1. Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, et al. Global, regional,
454 and national prevalence and risk factors for peripheral artery disease in 2015: an
455 updated systematic review and analysis. *Lancet Glob Heal*. 2019 Aug 1;7(8):e1020–
456 30.
- 457 2. Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al.
458 Comparison of global estimates of prevalence and risk factors for peripheral artery
459 disease in 2000 and 2010: A systematic review and analysis. *Lancet*.
460 2013;382(9901):1329–40.
- 461 3. Harwood AE, Pymer S, Ingle L, Doherty P, Chetter IC, Parmenter B, et al. Exercise
462 training for intermittent claudication: A narrative review and summary of guidelines
463 for practitioners [Internet]. Vol. 6, *BMJ Open Sport and Exercise Medicine*. BMJ
464 Publishing Group; 2020 [cited 2021 Mar 20]. Available from:
465 </pmc/articles/PMC7673109/>
- 466 4. Chetter IC, Spark JI, Dolan P, Scott DJA, Kester RC. Quality of life analysis in
467 patients with lower limb ischaemia: Suggestions for European standardisation. *Eur J*
468 *Vasc Endovasc Surg* [Internet]. 1997 [cited 2021 Mar 22];13(6):597–604. Available
469 from: <https://pubmed.ncbi.nlm.nih.gov/9236714/>
- 470 5. Dumville JC, Lee AJ, Smith FB, Fowkes FGR. The health-related quality of life of
471 people with peripheral arterial disease in the community: The Edinburgh Artery Study.
472 *Br J Gen Pract* [Internet]. 2004 Nov [cited 2021 Mar 20];54(508):826–31. Available
473 from: </pmc/articles/PMC1324915/>
- 474 6. Aboyans V, Ricco J-B, Bartelink M-LEL, Björck M, Brodmann M, Cohnert T, et al.
475 Editor’s Choice – 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral

- 476 Arterial Diseases, in collaboration with the European Society for Vascular Surgery
477 (ESVS). *Eur J Vasc Endovasc Surg* [Internet]. 2018 Mar [cited 2020 Feb
478 2];55(3):305–68. Available from:
479 <https://linkinghub.elsevier.com/retrieve/pii/S1078588417304549>
- 480 7. NICE. Clinical Guideline (CG147) Peripheral arterial disease: diagnosis and
481 management. NICE Guidel [Internet]. 2018;(August 2012). Available from:
482 <https://www.nice.org.uk/guidance/cg147>
- 483 8. Lane R, Harwood A, Watson L, Leng GC. Exercise for intermittent claudication.
484 *Cochrane Database Syst Rev* [Internet]. 2017 Dec 26 [cited 2020 Feb 2]; Available
485 from: <http://doi.wiley.com/10.1002/14651858.CD000990.pub4>
- 486 9. Dua A, Gologorsky R, Savage D, Rens N, Gandhi N, Brooke B, et al. National
487 assessment of availability, awareness, and utilization of supervised exercise therapy for
488 peripheral artery disease patients with intermittent claudication. In: *Journal of Vascular*
489 *Surgery* [Internet]. Mosby Inc.; 2020 [cited 2021 Mar 21]. p. 1702–7. Available from:
490 <https://pubmed.ncbi.nlm.nih.gov/31699514/>
- 491 10. Harwood AE, Smith GE, Cayton T, Broadbent E, Chetter IC. A systematic review of
492 the uptake and adherence rates to supervised exercise programs in patients with
493 intermittent claudication. Vol. 34, *Annals of Vascular Surgery*. Elsevier Inc.; 2016. p.
494 280–9.
- 495 11. Harwood AE, Hitchman LH, Ingle L, Doherty P, Chetter IC. Preferred exercise
496 modalities in patients with intermittent claudication. *J Vasc Nurs* [Internet]. 2018 Jun 1
497 [cited 2021 Mar 20];36(2):81–4. Available from:
498 <https://pubmed.ncbi.nlm.nih.gov/29747787/>
- 499 12. Harwood AE, Pymmer S, Ingle L, Doherty P, Chetter IC, Parmenter B, et al. Exercise

- 500 training for intermittent claudication: a narrative review and summary of guidelines for
501 practitioners. [cited 2021 Mar 21]; Available from: <http://bmjopensem.bmj.com/>
- 502 13. Harwood AE, Pymer S, Ibeggazene S, Ingle L, Caldow E, Birkett ST. Provision of
503 exercise services in patients with peripheral artery disease in the United Kingdom.
504 Vascular [Internet]. 2022 Oct 1 [cited 2022 Oct 15];30(5):874–81. Available from:
505 <https://journals.sagepub.com/doi/10.1177/17085381211035259>
- 506 14. Xu ZH, Jiang Q, Chen DY, Xiong J, Shi DQ, Yuan T, et al. Extracorporeal shock
507 wave treatment in nonunions of long bone fractures. Int Orthop [Internet]. 2009 Jun 25
508 [cited 2021 Mar 21];33(3):789–93. Available from:
509 <https://link.springer.com/article/10.1007/s00264-008-0553-8>
- 510 15. Zissler A, Stoiber W, Pittner S, Sanger AM. Extracorporeal Shock Wave Therapy in
511 Acute Injury Care: A Systematic Review. Rehabil Process Outcome [Internet]. 2018
512 Jan 1 [cited 2021 Mar 21];7:117957271876513. Available from:
513 <http://journals.sagepub.com/doi/10.1177/1179572718765138>
- 514 16. Hitchman LH, Totty JP, Raza A, Cai P, Smith GE, Carradice D, et al. Extracorporeal
515 Shockwave Therapy for Diabetic Foot Ulcers: A Systematic Review and Meta-
516 Analysis. Vol. 56, Annals of Vascular Surgery. Elsevier Inc.; 2019. p. 330–9.
- 517 17. Hitchman LH, Totty JP, Cai P, Smith GE, Carradice D, Chetter IC. Extracorporeal
518 shockwave therapy for diabetic foot ulcers: a feasibility study. J Wound Care
519 [Internet]. 2023 Mar 2 [cited 2023 Apr 11];32(3):182–92. Available from:
520 <https://pubmed.ncbi.nlm.nih.gov/36930191/>
- 521 18. Takakuwa Y, Sarai M, Kawai H, Yamada A, Shiino K, Takada K, et al. Extracorporeal
522 Shock Wave Therapy for Coronary Artery Disease: Relationship of Symptom
523 Amelioration and Ischemia Improvement. Asia Ocean J Nucl Med Biol [Internet].

- 524 2018 [cited 2021 Mar 21];6(1):1–9. Available from: /pmc/articles/PMC5765327/
- 525 19. Čelutkienė J, Burneikaite G, Shkolnik E, Jakutis G, Vajauskas D, Čerlinskaitė K, et al.
526 The effect of cardiac shock wave therapy on myocardial function and perfusion in the
527 randomized, triple-blind, sham-procedure controlled study. *Cardiovasc Ultrasound*
528 [Internet]. 2019 Jul 4 [cited 2021 Mar 21];17(1):13. Available from:
529 [https://cardiovascularultrasound.biomedcentral.com/articles/10.1186/s12947-019-](https://cardiovascularultrasound.biomedcentral.com/articles/10.1186/s12947-019-0163-1)
530 [0163-1](https://cardiovascularultrasound.biomedcentral.com/articles/10.1186/s12947-019-0163-1)
- 531 20. Cayton T, Harwood AE, Smith GE, Totty JP, Carradice D, Chetter IC. Extracorporeal
532 shockwave therapy for the treatment of lower limb intermittent claudication: study
533 protocol for a randomised controlled trial (the SHOCKWAVE 1 trial). *Trials*
534 [Internet]. 2017 Dec 6 [cited 2021 Mar 20];18(1):104. Available from:
535 <http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-1844-4>
- 536 21. Harwood AE, Green J, Cayton T, Raza A, Wallace T, Carradice D, et al. A feasibility
537 double-blind randomized placebo-controlled trial of extracorporeal shockwave therapy
538 as a novel treatment for intermittent claudication. *J Vasc Surg*. 2018 Feb 1;67(2):514-
539 521.e2.
- 540 22. Green JL, Harwood AE, Smith GE, Das T, Raza A, Cayton T, et al. Extracorporeal
541 shockwave therapy for intermittent claudication: Medium-term outcomes from a
542 double-blind randomised placebo-controlled pilot trial.
543 <https://doi.org/10.1177/1708538118773618> [Internet]. 2018 May 3 [cited 2022 Oct
544 25];26(5):531–9. Available from:
545 <https://journals.sagepub.com/doi/abs/10.1177/1708538118773618>
- 546 23. World Medical Association declaration of Helsinki: Ethical principles for medical
547 research involving human subjects. Vol. 310, *JAMA - Journal of the American*

- 548 Medical Association. 2013.
- 549 24. Cayton T, Harwood AE, Smith GE, Totty JP, Carradice D, Chetter IC. Extracorporeal
550 shockwave therapy for the treatment of lower limb intermittent claudication: study
551 protocol for a randomised controlled trial (the SHOCKWAVE 1 trial). *Trials*
552 [Internet]. 2017 Mar 6 [cited 2023 Sep 4];18(1). Available from:
553 <https://pubmed.ncbi.nlm.nih.gov/28264725/>
- 554 25. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey Manual and
555 Interpretation Guide. Bost New Engl Med Cent [Internet]. 1993 [cited 2013 Sep 23];
556 Available from: [http://www.mendeley.com/catalog/sf-36-health-survey-manual-
557 interpretation-guide/](http://www.mendeley.com/catalog/sf-36-health-survey-manual-interpretation-guide/)
- 558 26. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al.
559 CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting
560 parallel group randomised trials. *BMJ* [Internet]. 2010 Mar 24 [cited 2023 Sep
561 2];340:869. Available from: <https://www.bmj.com/content/340/bmj.c869>
- 562 27. How life has changed in Kingston upon Hull: Census 2021 [Internet]. [cited 2023 Sep
563 2]. Available from:
564 <https://www.ons.gov.uk/visualisations/censusareachanges/E06000010/>
- 565 28. Sajobi TT, Wang M, Awosoga O, Santana M, Southern D, Liang Z, et al. Trajectories
566 of health-related quality of life in coronary artery disease. *Circ Cardiovasc Qual
567 Outcomes* [Internet]. 2018 Mar 1 [cited 2021 Mar 21];11(3). Available from:
568 <http://ahajournals.org>
- 569 29. Trikkalinou A, Papazafiropoulou AK, Melidonis A. Type 2 diabetes and quality of life.
570 *World J Diabetes* [Internet]. 2017 [cited 2021 Mar 21];8(4):120. Available from:
571 </pmc/articles/PMC5394731/>

- 572 30. Naito A, Honma T, Sekizawa K. Quality of life in COPD patients. *Respir Circ*. 2002
573 Mar 1;50(3):241–5.
- 574 31. Lane R, Harwood A, Watson L, Leng GC. Exercise for intermittent claudication.
575 *Cochrane Database Syst Rev*. 2017 Dec 26;
- 576 32. Gardner AW, Montgomery PS, Wang M. Minimal clinically important differences in
577 treadmill, 6-minute walk, and patient-based outcomes following supervised and home-
578 based exercise in peripheral artery disease. *Vasc Med (United Kingdom)* [Internet].
579 2018 Aug 1 [cited 2021 Mar 22];23(4):349–57. Available from:
580 [/pmc/articles/PMC6062461/](https://pubmed.ncbi.nlm.nih.gov/36062461/)
- 581 33. Raza A, Harwood A, Totty J, Smith G, Chetter I. Extracorporeal Shockwave Therapy
582 for Peripheral Arterial Disease: A Review of the Potential Mechanisms of Action
583 [Internet]. Vol. 45, *Annals of Vascular Surgery*. Elsevier Inc.; 2017 [cited 2021 Mar
584 21]. p. 294–8. Available from:
585 <http://www.annalsofvascularsurgery.com/article/S0890509617308452/fulltext>
- 586 34. Belcaro G, Cesarone MR, Dugall M, Di Renzo A, Errichi BM, Cacchio M, et al.
587 Effects of Shock Waves on Microcirculation, Perfusion, and Pain Management in
588 Critical Limb Ischemia. <http://dx.doi.org/10.1177/000331970505600407> [Internet].
589 2016 Sep 6 [cited 2022 Oct 16];56(4):403–7. Available from:
590 [https://journals.sagepub.com/doi/10.1177/000331970505600407?url_ver=Z39.88-](https://journals.sagepub.com/doi/10.1177/000331970505600407?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed)
591 [2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed](https://journals.sagepub.com/doi/10.1177/000331970505600407?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed)
- 592 35. Gulati S, Coughlin PA, Hatfield J, Chetter IC. Quality of life in patients with lower
593 limb ischemia; revised suggestions for analysis. *J Vasc Surg* [Internet]. 2009 Jan 1
594 [cited 2022 Oct 23];49(1):122–6. Available from:
595 <http://www.jvascsurg.org/article/S0741521408013608/fulltext>

- 596 36. O'Banion LA, Saadi S, Hasan B, Nayfeh T, Simons JP, Murad MH, et al. Lack of
597 patient-centered evaluation of outcomes in intermittent claudication literature. *J Vasc*
598 *Surg* [Internet]. 2023 Sep 1 [cited 2023 Sep 3];78(3):828–36. Available from:
599 <http://www.jvascsurg.org/article/S0741521423010157/fulltext>
- 600 37. Chetter C, Spark JJ, Dolan P, Scott DJA, Kester RC. ESVS PRIZE WINNER 1996
601 Quality of Life Analysis in Patients with Lower Limb Ischaemia: Suggestions for
602 European Standardisation. *Eur J Vasc Endovasc Surg*. 1997;13:597–604.
- 603 38. Nicolaï SPA, Viechtbauer W, Kruidenier LM, Candel MJJM, Prins MH, Teijink JAW.
604 Reliability of treadmill testing in peripheral arterial disease: a meta-regression
605 analysis. *J Vasc Surg* [Internet]. 2009 Aug [cited 2023 Sep 4];50(2):322–9. Available
606 from: <https://pubmed.ncbi.nlm.nih.gov/19631868/>
- 607 39. McDermott MM, Guralnik JM, Criqui MH, Liu K, Kibbe MR, Ferrucci L. The Six-
608 Minute Walk is a Better Outcome Measure than Treadmill Walking Tests in
609 Therapeutic Trials of Patients with Peripheral Artery Disease. *Circulation* [Internet].
610 2014 Jul 7 [cited 2023 Sep 4];130(1):61. Available from: [/pmc/articles/PMC4154227/](https://pubmed.ncbi.nlm.nih.gov/25111111/)
- 611