

# Patients With Intermittent Claudication and Chronic Widespread Pain Improves in Health-Related Quality of Life After Invasive but Not After Noninvasive Treatment

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## ABSTRACT

**BACKGROUND:** Intermittent claudication (IC) is traditionally managed with risk factor modification, best medical treatment (BMT), and exercise training. Comorbidities such as diabetes and ischemic heart disease affect both results of invasive treatment and health-related quality of life (HRQoL) negatively. It is unknown how chronic widespread pain (CWP) influences the results of invasive treatment. We evaluated the influence of CWP on HRQoL in patients undergoing invasive (open surgery or endovascular treatment) and noninvasive BMT of IC.

**METHODS:** A total of 242 patients with IC treated with invasive or noninvasive methods responded to the validated HRQoL questionnaires Short Form 36 Health Survey, EuroQoL 5-dimensions, and distribution of pain with the Epipain questionnaire at baseline and after 12 months.

**RESULTS:** Invasively treated patients without CWP improved in all primary outcome measures. Patients with CWP reported significant improvements in most of the HRQoL-related outcome measures after invasive treatment, but patients with CWP in the noninvasive treatment group did not improve in any HRQoL-related outcome measure.

**CONCLUSIONS:** The presence of CWP not should be a cause to withhold invasive treatment in patients with IC.

**KEYWORDS:** Intermittent Claudication, invasive treatment, chronic pain, HRQoL

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## Introduction

Intermittent claudication (IC) is a common disorder, with a prevalence of 6.5% in women and 7.2% in men aged 60 to 90 years in Sweden<sup>1</sup> and affecting 20 to 40 million individuals worldwide.<sup>2</sup> First-line management of IC traditionally consists of risk factor modification, best medical treatment (BMT), and exercise training.<sup>3</sup> Results of invasive IC treatment are better in patients with suprainguinal lesions than in those with infrainguinal.<sup>4</sup>

Chronic pain (defined as pain with duration of 3 months or more) has a prevalence of 30% to 50% in the general population.<sup>5</sup> Regarding distribution of musculoskeletal pain in the body, a distinction is often made between chronic regional pain (CRP) and chronic widespread pain (CWP). Chronic regional pain is more common with a prevalence of 24%, whereas CWP occurs with a prevalence of 11%.<sup>5</sup>

Among patients with peripheral arterial disease (PAD), the prevalence of CWP is almost 2 times higher than in the general population.<sup>6</sup> Invasive treatments of patients with PAD, IC,

and critical limb ischemia lead to significant improvement in HRQoL.<sup>7</sup>

Patients with IC caused by lesions in the superficial femoral artery (SFA) experience significant improvement in HRQoL, ankle-brachial index (ABI), and walking distance (WD) 12 months after primary endovascular stenting compared with patients treated conservatively with BMT.<sup>6</sup>

It is unknown to what extent the presence of CWP influences the results of invasive treatment in patients with IC in terms of HRQoL, and how noninvasive treatment influences HRQoL in IC patients with and without CWP. At present, we do not know whether comorbidity such as CWP should be regarded as a reason to avoid or to recommend invasive treatment.

The aim of this study was to evaluate the impact of CWP on HRQoL in patients with IC subjected to conservative or invasive treatment, to improve patient selection for invasive treatment of IC.



## Methods

### *Ethics*

Informed consent was obtained in accordance with the ethical standards of the Helsinki Declaration of 1975, and the study was approved by the Ethics Committee at Lund University (ref. nos 2010/549 and 2016/827).

### *Patient characteristics*

This was a 12-month retrospective follow-up study of 242 patients from 2 prospectively collected study cohorts.<sup>6,7</sup> In total, 100 patients with infrainguinal IC prospectively randomized to either invasive treatment (stent treatment of lesions in the SFA; n=48) or noninvasive treatment (BMT alone; n=52)<sup>6</sup> were analyzed together with 142 IC patients from another prospective study originally consisting of 240 consecutive patients with symptomatic PAD planned for invasive treatment (open surgery or endovascular treatment).<sup>7</sup> Study designs have been reported in detail.<sup>6,7</sup>

### *Data collection/questionnaires*

All study subjects, from both initial trials, responded to the same below described HRQoL questionnaires, and distribution of pain was assessed with the Epipain questionnaire concerning musculoskeletal pain at baseline and after 12 months.<sup>5</sup> Based on a key question on pain for 3 months or more, and a pain drawing with predefined body regions, patients with CWP were identified as those reporting pain in 2 contralateral body quadrants (right or left and above or below the waist) and the axial skeleton (spine or anterior chest) for 3 months or more. Those reporting pain for at least 3 months but not fulfilling CWP criteria were designated as having CRP. Those with no pain or pain duration less than 3 months were regarded as having no chronic pain (NCP).<sup>7</sup> Main outcome measure was HRQoL assessed with the generic instruments Short Form 36 Health Survey (SF-36)<sup>8</sup> and EuroQoL 5-dimensions (EQ5D),<sup>9</sup> and the PAD-specific Walking Impairment Questionnaire (WIQ).<sup>10</sup> The SF-36 rates HRQoL 0 to 100 (worst to best) in 8 domains; WIQ rates 0 to 100 (worst to best).<sup>10</sup> The HRQoL in patients fulfilling criteria for CWP was compared with NCP and CRP (together classified as non-CWP).

Secondary outcome measures were ABI and WD.

### *Statistics*

The sample size was determined to study a clinically relevant difference between the groups regarding the primary outcome variable, HRQoL. With a significance level of 5%, a difference of 10 points in SF-36 could be detected with a power of at least 80%.

Patient characteristics including pain group category and results from the HRQoL questionnaires (commonly analyzed with parametric methods) were analyzed, using SPSS 20.0

(SPSS Inc., Chicago, IL, USA). The HRQoL data are reported as mean (SD). Student *t* test and paired *t* tests were used to evaluate differences in continuous variables, and the  $\chi^2$  test was used to evaluate group differences in nominal variables, between baseline and follow-up regarding treatment modality and pain group affiliation.

Comparisons were performed at the 5% significance level based on 2-sided tests. Results are presented with 95% confidence intervals and *P* values.

## Results

### *Baseline*

A total of 242 patients with IC (78 due to suprainguinal lesions and 164 due to infrainguinal lesions) entered the study. At baseline, 75 patients (31%) reported CWP, 167 patients (69%) reported non-CWP (CRP: 132, NCP: 35). Characteristics and baseline demographics of all 242 patients are presented in Table 1.

In all, 185 patients were treated invasively, and 57 patients were treated conservatively with BMT alone (Table 2).

Among invasively treated patients, those with CWP reported significantly lower baseline values of SF-36; BP, GH, VT, SF, RE, and MH scores than patients without CWP, and corresponding differences were seen among noninvasively treated patients concerning baseline SF-36; PF, RP, BP, GH, VT, SF, and MH (Table 2), whereas no such differences were seen for EQ5D or WIQ.

### *12 months*

After 12 months, patients in the invasively treated group without CWP at baseline improved in all outcome measures and those with CWP at baseline improved in all outcome measures except SF-36 domains GH and MH. Noninvasively treated patients without CWP at baseline improved in SF-36 domains PF, EQ5D, WIQ, ABI, and WD, whereas those with CWP at baseline showed unchanged scores in all outcome measures (Figure 1).

After 12 months, patients without CWP reported significantly higher values than those with CWP concerning all outcome measures except ABI and WD in both treatment groups (Table 3). Lesion characteristics in terms of supra- or infrainguinal localization did not influence the primary outcomes.

## Discussion

This study evaluated the impact of CWP on treatment results in patients with IC. Patients with CWP showed significant lower values of HRQoL before treatment. Invasive treatment of IC resulted in significant improvement in both primary and secondary outcome measures after 12 months irrespectively of presence of CWP at baseline or not. After intervention, patients with CWP still scored significantly lower in almost all outcome measures compared with patients without CWP. Noninvasively treated patients without CWP improved

**Table 1.** Characteristics of 242 patients with intermittent claudication (IC) with or without chronic widespread pain (CWP).

	ALL PATIENTS	NON-CWP (N = 167)	CWP (N = 75)	P VALUE
Age, y	70.7 (6.6)	70.7 (8.8)	70.1 (6.5)	.929
Gender				
Male	115 (47.5)	86 (51)	29 (39)	.479
Female	127 (52.5)	81 (49)	46 (61)	
Diabetes mellitus	78 (28.2)	45 (26)	23 (29.5)	.610
Smoking				
Yes	60 (25)	43 (26)	17 (23)	.189
No	151 (63)	103 (62)	48 (64)	
No data	31 (12)	21 (12)	10 (13)	
Previous myocardial infarction	63 (26)	39 (23)	19 (25)	.945
Previous stroke	12 (5)	6 (4)	3 (4)	.904
Body mass index	26.2 (4.7)	26.3 (4.2)	27.6 (4.9)	
Systolic blood pressure, mmHg	155 (22)	155 (22)	154 (23)	.984
Ankle-brachial index	0.58 (0.20)	0.56 (0.20)	0.60 (0.18)	.178
Self-reported walking distance, m	165 (148)	163 (149)	177 (148)	.523
B-hemoglobin, g/L	137 (24)	136 (14)	136 (38)	.888
S-creatinine, $\mu$ mol/L	86 (30)	85 (30)	87 (30)	.792
P-C-reactive protein, mg/L	10 (25)	8.9 (25)	11.1 (26)	.599
P-total cholesterol, mmol/L	5.0 (8.3)	5.4 (10.1)	4.2 (1.0)	.238
P-triglycerides, mmol/L	1.8 (0.9)	1.7 (0.9)	1.8 (1.2)	.585
P-HDL cholesterol, mmol/L	1.6 (1.7)	1.7 (2.6)	1.4 (0.6)	.161
P-LDL cholesterol, mmol/L	2.4 (0.9)	2.5 (0.9)	2.4 (0.8)	.596
P-glucose, mmol/L	6.9 (2.3)	6.9 (2.4)	6.8 (2.5)	.673
Antiplatelet or anticoagulant treatment	230 (95)	159 (95)	71 (95)	.910
Statin treatment	227 (94)	155 (93)	72 (96)	.184
Antihypertensive treatment	196 (81)	132 (79)	64 (86)	.967

Abbreviations: B, blood; HDL, high-density lipoprotein; LDL, low-density lipoprotein; P, plasma; S, serum. Mean (SD) or No. (%).

significantly in several outcome measures (SF 36 domain PF, EQ5D, WIIQ, ABI, and WD), whereas noninvasively treatment in patients with CWP had a less successful outcome, without improvement in any outcome measure.

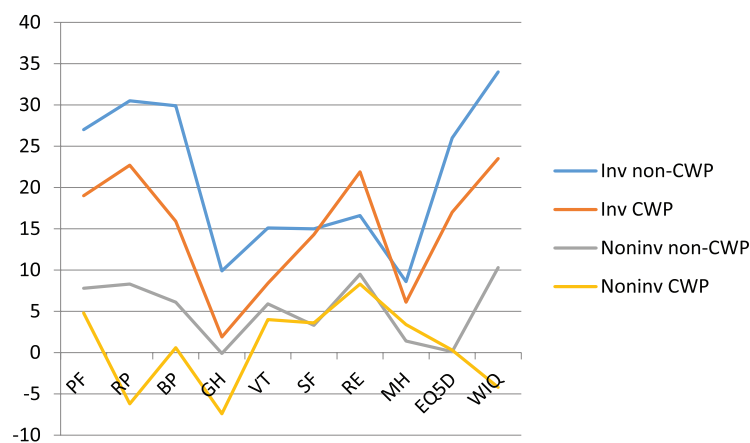
Invasive treatment improved HRQoL in patients with IC and concomitant CWP but to a lower level compared with those without CWP. This is consistent with results previously

reported in patients with PAD of all severities.<sup>7</sup> The present finding of lack of impact on HRQoL in noninvasively treated patients with IC and concomitant CWP has previously not been demonstrated. Other comorbid conditions such as diabetes, ischemic heart disease, and chronic obstructive pulmonary disease are known to affect both results of invasive treatment and HRQoL negatively in patients with PAD<sup>11</sup>

**Table 2.** Baseline values of primary and secondary outcome measures in patients with intermittent claudication (IC) treated invasively (invasive group, n=185) or with best medical treatment alone (noninvasive group, n=57) regarding presence of chronic widespread pain (CWP) or not (non-CWP).

	INVASIVE GROUP NON-CWP		INVASIVE GROUP CWP		P	NONINVASIVE GROUP NON-CWP		NONINVASIVE GROUP CWP		P
	MEAN VALUE	SD	MEAN VALUE	SD		MEAN VALUE	SD	MEAN VALUE	SD	
PF	37.5	19.6	32.4	20.7	.140	43.6	15.1	30.1	15.7	.006
RP	30.7	38.2	24.1	35.9	.261	41.2	40.8	18.3	31.9	.034
BP	36.5	19.9	30.1	18.2	.035	38.5	17.3	22.0	15.0	.001
GH	55.9	19.9	46.6	20.0	.004	55.7	17.9	41.6	23.6	.041
VT	45.6	22.8	37.5	24.0	.030	51.3	19.2	32.8	23.9	.010
SF	69.8	26.2	58.2	25.3	.004	74.1	27.0	46.0	31.8	.005
RE	50.1	45.7	28.6	39.3	.001	60.3	44.3	35.5	42.7	.067
MH	71.2	22.4	59.1	22.6	.001	76.7	18.2	54.7	25.4	.005
EQ5D	0.47	0.29	0.43	0.30	.366	0.47	0.29	0.29	0.33	.062
WIQ	31.3	20.4	30.6	23.8	.827	34.1	18.7	27.9	16.9	.264
ABI	0.54	0.20	0.59	0.18	.164	0.60	0.19	0.64	0.16	.462
WD	154	153	166	155	.612	189	133	212	116	.509

Abbreviations: ABI, ankle-brachial index; Short Form 36 Health Survey (SF-36, rating HRQoL 0-100 from worst to best in 8 domains—Physical Function [PF], Role Physical [RP], Bodily Pain [BP], General Health [GH], Vitality [VT], Social Function [SF], Role Emotional [RE], and Mental Health [MH]) (9), EuroQoL 5-dimensions (EQ5D, rating health-related quality of life states 0-1 from worst to best) (10); WD, walking distance; Walking Impairment Questionnaire (WIQ, rating 0-100 from worst to best) (11).



**Figure 1.** Changes between baseline and 12 months in primary outcome measures in patients with intermittent claudication (IC) treated invasively (invasive group, n=185) or with best medical treatment alone (noninvasive group, n=57) regarding presence of chronic widespread pain (CWP) or not (non-CWP) at baseline.

Short Form 36 Health Survey (SF-36, rating HRQoL 0-100 from worst to best in 8 domains—Physical Function [PF], Role Physical [RP], Bodily Pain [BP], General Health [GH], Vitality [VT], Social Function [SF], Role Emotional [RE], and Mental Health [MH]) (9), EuroQoL 5-dimensions (EQ5D, rating health-related quality of life states 0-1 from worst to best) (10) shown as % of 1, and Walking Impairment Questionnaire (WIQ, rating 0-100 from worst to best) (11).

and might therefore be considered as contraindications for intervention in some cases. The risk of bias caused by the fact that our results are based on patients from 2 originally separated small study cohorts merged together constitutes a limitation of our study. However, categorization of pain groups and evaluations of HRQoL were performed identically in all patients reported. The high number of comparisons made in the study increases the risk of rejecting a true null hypothesis,

and caution is necessary when interpreting the actual significance of *P* values.

The prevalence of CWP in patients with IC was high (28%) compared with 11% in the general population.<sup>5</sup> A high proportion of CWP has also been seen in other chronic painful conditions such as rheumatoid arthritis, osteoarthritis, endometriosis, and ulcerative colitis.<sup>12</sup> It is not known whether this is due to a sensitization of the nervous system

**Table 3.** The 12-month values of primary and secondary outcome measures in patients with intermittent claudication (IC) treated invasively (invasive group, n=185) or with best medical treatment alone (noninvasive group, n=57) regarding presence of chronic widespread pain (CWP) or not (non-CWP) at baseline.

	INVASIVE GROUP NON-CWP		INVASIVE GROUP CWP		P	NONINVASIVE GROUP NON-CWP		NONINVASIVE GROUP CWP		P
	MEAN VALUE	SD	MEAN VALUE	SD		MEAN VALUE	SD	MEAN VALUE	SD	
PF	66.0	23.7	52.7	26.4	.002	51.3	20.1	35.2	18.5	.012
RP	51.4	41.5	47.3	43.5	.047	51.3	42.1	16.6	28.7	.003
BP	65.8	41.5	46.7	24.7	<.001	43.5	21.9	23.5	14.5	.001
GH	64.9	22.9	49.4	21.4	<.001	56.2	19.6	38.4	18.9	.009
VT	60.7	25.1	47.4	24.2	.001	57.1	23.2	37.1	20.2	.005
SF	84.4	22.3	73.2	23.5	.004	76.6	25.0	52.7	36.1	.034
RE	67.3	39.9	50.0	44.5	.016	68.5	41.5	36.1	48.1	.052
MH	80.5	18.9	64.7	22.5	<.001	77.6	19.4	58.0	23.5	.011
EQ5D	0.75	0.23	0.60	0.27	.002	0.58	0.27	0.29	0.37	.019
WIQ	66.1	25.4	55.3	28.4	.018	44.3	23.2	30.2	12.5	.009
ABI	0.85	0.19	0.86	0.15	.496	0.70	0.23	0.63	0.16	.193
WD	833	399	693	473	.088	369	339	251	262	.254

Abbreviations: ABI, ankle-brachial index; Short Form 36 Health Survey (SF-36, rating HRQoL 0-100 from worst to best in 8 domains—Physical Function [PF], Role Physical [RP], Bodily Pain [BP], General Health [GH], Vitality [VT], Social Function [SF], Role Emotional [RE], and Mental Health [MH]) (9), EuroQoL 5-dimensions (EQ5D, rating health-related quality of life states 0-1 from worst to best) (10); WD, walking distance; Walking Impairment Questionnaire (WIQ, rating 0-100 from worst to best) (11).

due to chronic nociceptive pain or if there is another common background or vulnerability explaining the coexistence of CWP with these disorders. As in this study, CWP adds to the burden of the disease with a lower self-reported HRQoL.<sup>13</sup> Interestingly, also patients with CWP improved in the invasively treated group but not in the noninvasively treated group, indicating that the presence of CWP not should be a cause to withhold invasive treatment.

## Conclusions

Invasively treated patients without CWP improved in all outcome measures and invasively treated patients with CWP reported significant improvements in most of the HRQoL-related outcome measures, whereas patients with CWP in the noninvasive treatment group did not improve in any HRQoL-related outcome measure at all. In conclusion, the presence of CWP should not be a cause to withhold invasive treatment in patients with IC.

## Author Contributions

HL performed conception and research design, data analysis and data interpretation, wrote manuscript and acted as corresponding author.

SB supervised concept and helped in data interpretation. SB, AG, HP performed critical manuscript evaluation. All the authors reviewed and approved the final manuscript.

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