

# A Comparison of Quality of Life in Elderly Patients with Intermittent Claudication and Chronic Limb-Threatening Ischemia

Citation for published version (APA):

Roijers, J. P., van den Houten, M. M., Hopmans, N. J., Vriens, P. W. H. E., Willigendael, E. M., Lodder, P., de Vries, J., Tejjink, J. A., & van der Laan, L. (2020). A Comparison of Quality of Life in Elderly Patients with Intermittent Claudication and Chronic Limb-Threatening Ischemia. *Annals of Vascular Surgery*, 69, 285-291. <https://doi.org/10.1016/j.avsg.2020.05.048>

## Document status and date:

Published: 01/11/2020

## DOI:

[10.1016/j.avsg.2020.05.048](https://doi.org/10.1016/j.avsg.2020.05.048)

## Document Version:

Publisher's PDF, also known as Version of record

## Document license:

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# A Comparison of Quality of Life in Elderly Patients with Intermittent Claudication and Chronic Limb-Threatening Ischemia

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**Background:** Intermittent claudication (IC) and chronic limb-threatening ischemia (CLTI) are both associated with a decreased health status and possibly quality of life (QOL). A better understanding of the differences in QOL between patients with IC and CLTI could be of additional value in shared decision-making. The aim of this study was to compare the QOL at baseline between patients with IC and patients with CLTI.

**Methods:** The study population was based on 2 study cohorts, 1 cohort consisted of patients with IC (ELECT registry) and the other cohort of patients with CLTI (KOP-study). Patients with an age of  $\geq 70$  years were included. QOL at baseline was measured by the WHOQOL-BREF questionnaire. Nonresponders were excluded from data analyses. Student's *t*-tests and analysis of covariance (ANCOVA) analyses were used to compare QOL between the 2 groups. Outcomes of the ANCOVA analyses were expressed as estimated marginal means.

**Results:** In total, 308 patients were included, 115 patients with IC and 193 patients with CLTI. Patients with CLTI were older (median age 80 years vs. 75 years,  $P < 0.001$ ) and had more comorbidities. Patients with IC had a statistically significant higher QOL regarding physical health (mean 13.7 [standard deviation (SD) 2.3] vs. 10.8 [SD 2.8],  $P < 0.001$ ), psychological health (mean 15.3 [SD 2.1] vs. 14.1 [SD 2.4],  $P < 0.001$ ), environment (mean 16.3 [SD 2.4] vs. 15.5 [SD 2.0],  $P < 0.002$ ), and the overall domain (mean 3.5 [SD 0.7] vs. 3.1 [SD 0.9],  $P < 0.001$ ). After correcting for the confounding effect of age and sex, patients with IC still had a statistically significant higher QOL in the physical, psychological, environment, and overall domain.

**Conclusions:** Patients with IC had a significantly higher QOL in the physical, psychological, environment, and overall domains of the WHOQOL-BREF questionnaire compared with patients with CLTI. This underlines the importance of strategies that reduce disease progression as disease progression is associated with a decrease in QOL.

*Conflict of interest:* The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

*Funding:* This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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*Ann Vasc Surg* 2020; 69: 285–291

<https://doi.org/10.1016/j.avsg.2020.05.048>

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Manuscript received: April 11, 2020; manuscript accepted: May 14, 2020; published online: 3 June 2020

## INTRODUCTION

The World Health Organization (WHO) defines quality of life (QOL) as “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad ranging concept affected in a complex way by the person’s physical health, psychological state, personal beliefs, social relationships, and their relationship to salient features of their environment.”<sup>1</sup> Health status (HS) or health-related QOL, on the other hand, uses a strictly functional approach to measure physical, psychological, and social functioning.

HS in patients with peripheral arterial disease (PAD) is mainly affected because of a decreased physical capacity.<sup>2</sup> Classically, there are 2 distinct forms of PAD: intermittent claudication (IC) and chronic limb-threatening ischemia (CLTI). Treatment strategies in patients with IC and CLTI may differ from one another. For example, supervised exercise therapy that results in an improved walking distance results in improved HS for a patient with IC.<sup>3–5</sup> Whereas, adequate pain management may improve HS for a patient with CLTI.<sup>6</sup>

Rather than outcomes that assess the success of treatment by its effect on technical measures or symptomatology (e.g., walking distance, patency, or limb salvage), the perception of a patient’s treatment experience is becoming increasingly important. Nowadays, the incorporation of patient-reported outcomes as a clinical outcome measure is therefore strongly recommended by the recently published guideline for CLTI.<sup>7</sup>

In contrast to HS, the WHOQOL-BREF questionnaire measures QOL. It assesses a patient’s subjective appraisal of their satisfaction with various domains of health.<sup>8</sup> To do so, this questionnaire assesses a range of domains of health: physical health, psychological health, social relationships, environment, and overall health. HS uses a functional approach to measure functioning (‘Are you able to climb the stairs?’). On the other hand in QOL, the emphasis is laid on evaluating the patients feelings about functioning (‘How satisfied are you about your ability to climb the stairs?’). Several studies have described QOL-related outcomes in separate IC and CLTI cohorts.<sup>9–13</sup> One study compared HS between CLTI and milder forms of PAD by using the Short Form 36 and the EuroQol-5D questionnaires.<sup>11</sup> A diminished HS was observed for patients with CLTI. Thus, while a diminished general QOL for CLTI patients as compared with IC patients may be expected, it has not been confirmed.

Furthermore, insight in which of the various domains of health are affected in CLTI and CI may be of particular interest.

A better understanding of the differences in QOL between patients with IC and CLTI could be of additional value in the shared decision making process. The aim of this study was to compare the QOL at baseline between patients with IC and patients with CLTI using the WHOQOL-BREF questionnaire.

## MATERIAL AND METHODS

### Patient Population

The study population was based on 2 individual study cohorts, 1 cohort consisted of patients with IC and the other cohort of patients with CLTI.

Patients with IC were part of the ELECT registry, and the study protocol of this registry has been previously published.<sup>14</sup> In summary, one goal of this registry was to obtain data on QOL at different time intervals in patients with IC that underwent supervised exercise therapy (SET). Inclusion criteria were patients with IC that were candidate for SET as a primary treatment. Exclusion criteria were patients with CLTI, a vascular intervention as primary treatment, prior SET or revascularization less than 12 months ago and patients with neurogenic/venous/orthopedic claudication. Patients from the ELECT registry with an age  $\geq 70$  years were eligible for inclusion.

Patients with CLTI were part of the KOP-study. The methods have been previously published.<sup>10</sup> The KOP-study served to assess QOL at different time intervals in patients with CLTI that underwent surgical, endovascular, or conservative treatment. Inclusion criteria were patients with a diagnosis of CLTI with an age  $\geq 70$  years. Exclusion criteria were patients with cognitive impairment, a recent diagnosis of a malignancy, and a prior major lower limb amputation.

Informed consent was obtained and signed for each individual patient in both study cohorts. A formal written waiver for ethical approval was not required as was confirmed by the institutional review board (AMOA).

### Data Collection

Data on age, gender, smoking status, medical history, and prior vascular surgery were obtained from the medical charts. Medical history was put into the following categories: history of cardiac disease (myocardial infarction, atrial fibrillation, history of heart failure, valvular disease, coronary

**Table I.** Baseline characteristics of both cohorts

Variable	IC (n = 115)	Missing	CLTI (n = 193)	Missing	P-value
Age, years (range)	75 (70–93)	4	80 (70–94)	0	<0.001
Gender, male (%)	66 (57.4)	1	108 (56)	0	0.812
Active smoking (%)	30 (26.1)	15	45 (23.3)	4	0.449
Diabetes mellitus (%)	36 (31.3)	0	91 (47.2)	0	0.008
Hypertension (%)	84 (73)	0	161 (83.4)	0	0.040
Hypercholesterolemia (%)	74 (64.3)	0	137 (71)	0	0.254
Renal impairment (%)	18 (15.7)	2	108 (56)	0	<0.001
Cardiac History (%)	37 (32.2)	0	133 (68.9)	0	<0.001
Pulmonary History (%)	28 (24.3)	0	109 (56.5)	3	<0.001
Cerebrovascular History (%)	16 (13.9)	0	62 (32.1)	0	<0.001
History of PTA/stent (%)	23 (20)	0	51 (26.4)	0	0.217
History of Thromboendarterectomy (%)	2 (1.7)	0	12 (6.2)	0	0.090
History of Bypass Surgery (%)	5 (4.3)	0	31 (16.1)	0	0.002

PTA, percutaneous transluminal angioplasty.

artery bypass graft, or percutaneous coronary intervention), history of pulmonary disease (chronic obstructive pulmonary disease, asthma, obstructive sleep apnea syndrome), history of renal impairment (eGFR < 60 ml/min/1.73 m<sup>2</sup>), history of cerebrovascular disease (cerebrovascular incident or transient ischemic attack), and a history of diabetes mellitus, hypercholesterolemia, and hypertension.

### Quality of Life

The WHOQOL-BREF questionnaire was used to measure QOL at baseline. This questionnaire consists of 26 items with a 5-point Likert type response scale. The questions are divided into 4 individual domains: physical health, psychological health, social relationships, and environment. Additionally, answers to 2 questions are summed to retrieve an overall QOL score.<sup>8</sup>

### Outcome Measures

The primary end point was QOL at baseline as measured with the WHOQOL-BREF questionnaire. Secondarily, the various subdomains of the WHOQOL-BREF were compared between both cohorts.

### Statistical Analysis

Categorical variables were presented as numbers with percentages, continuous variables as medians with range, normally distributed continuous variables as means with standard deviation (SD). Baseline characteristics were compared using a Pearson's chi-squared test or Fisher's exact test for categorical variables and the Mann-Whitney *U*-test for continuous variables. The Student's *t*-test was used to calculate differences in QOL between the

IC and CLTI group. In a subgroup analysis of patients with CLTI, the QOL of patients with rest pain (Fontaine III) was compared with patients with ulcers/gangrene (Fontaine IV).

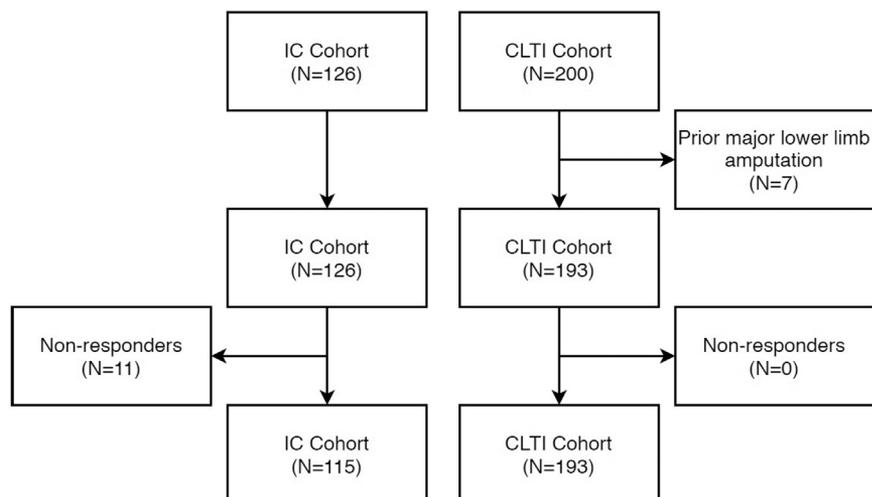
To calculate the QOL domains, patients had to have at least 5 answers in the physical domain, 4 answers in the psychological domain, 2 answers in the social relationships domain, 6 answers in the environment domain, and 2 answers in the overall domain. Mean imputation was used in case of missing answers. Nonresponders were excluded from data analysis.

Differences in QOL between the 2 groups were also analyzed by means of analysis of covariance (ANCOVA) analyses. The covariates age and sex were added to the model as possible confounders. In a secondary ANCOVA analysis, age, sex, diabetes, hypertension, renal impairment, cardiac history, pulmonary history, cerebrovascular history, and history of bypass surgery were added as possible confounders based on the results of Table I. Outcomes of the ANCOVA analyses were expressed as estimated marginal means with associated 95% confidence intervals (CIs). The estimated marginal mean displays the mean difference in QOL between the IC and CLTI group given a similar age and sex in both groups. Cohen's *d* values with corresponding 95% CIs were calculated to assess the effect sizes of the differences in QOL between the 2 groups.

A *p* value <0.05 was considered statistically significant in all analyses. Statistical analyses were performed using SPSS, version 25.

## RESULTS

In total, 308 patients were included in the study population. Of these, 115 patients had IC and 193



**Fig. 1.** Flowchart of the intermittent claudication (IC) and chronic limb-threatening ischemia (CLTI) cohorts.

patients had CLTI. In [Figure 1](#), a flowchart is presented, and 11 nonresponders from the IC arm of the study were excluded from data analyses. In [Table I](#), an overview of baseline characteristics and a comparison between the IC and CLTI groups is presented. In general, patients with CLTI were older and had more comorbidities than patients with IC.

A comparison of QOL between the IC and CLTI group is presented in [Table II](#). Patients with IC had a higher QOL in the physical health (mean difference 2.9), psychological health (mean difference 1.2), environment (mean difference 0.8), and the overall domain (mean difference 0.4). Patients with CLTI had a slightly higher QOL in the social relationships domain (mean difference 0.2), but this difference was not statistically significant.

After correcting for the confounding effect of age and sex, IC patients still had a statistically significant higher QOL in the physical, psychological, environment, and overall domain (see [Table III](#)). The QOL in the social relationships domain was nonsignificantly higher in the CLTI group.

In [Table IV](#), the results of the analyses corrected for age, sex, diabetes, hypertension, renal impairment, cardiac history, pulmonary history, cerebrovascular history, and history of bypass surgery are presented. The psychological and environment domains were no longer statistically significantly different between the 2 groups. The other 4 domains remained statistically significantly different.

The largest differences in QOL between the IC and CLTI group were observed in the physical and psychological domains of QOL (Cohen's *d* values in [Tables III and IV](#)).

The QOL between Fontaine III and Fontaine IV patients did not differ in any domain. This remained after both correcting for age and sex and for comorbidities.

## DISCUSSION

This study compared QOL between patients with IC and patients with CLTI using WHOQOL-BREF questionnaire. After adjustments for age and sex, patients with IC had a significantly higher QOL in the physical, psychological, environment, and overall domains than patients with CLTI.

A prior study observed a diminished HS in patients with CLTI in comparison to patients with less severe forms of PAD.<sup>11</sup> It should be noticed, however, that Sprengers et al. looked at HS. Our study compared the different subdomains of QOL and showed similar results. This is indicating that both objective functioning (HS) and the subjective appraisal of well-being (QOL) is diminished in patients with CLTI compared with patients with IC.

The largest difference in QOL between the 2 patient groups occurred in the physical and the psychological domain. This implicates that physicians should not only be focused on treatments that improve physical health. Instead, they should simultaneously consider treatments that may improve psychological health. As expected, patients with CLTI experience more pain than patients with IC.<sup>15</sup> Consequently, treatment strategies such as adequate pain management may be effective to increase QOL.

**Table II.** WHOQOL-BREF values of both cohorts at baseline

Quality of life domains	IC ( <i>n</i> = 115)	Missing	CLTI ( <i>n</i> = 193)	Missing	<i>P</i> value <sup>a</sup>
Physical health (SD)	13.7 (2.3)	0	10.8 (2.8)	3	<0.001
Psychological health (SD)	15.3 (2.1)	0	14.1 (2.4)	0	<0.001
Social relationships (SD)	15.3 (2.7)	0	15.5 (2.6)	4	0.488
Environment (SD)	16.3 (2.4)	0	15.5 (2.0)	7	0.002
Overall (SD)	3.5 (0.7)	0	3.1 (0.9)	2	<0.001

<sup>a</sup>An independent samples *t*-test was used.

**Table III.** Analysis of variance analyses of QOL between the IC and CLTI group

Quality of life domains <sup>a</sup>	IC ( <i>n</i> = 115)	CLTI ( <i>n</i> = 193)	<i>P</i> value	Cohen's <i>d</i>
Physical health (95% CI) <sup>b</sup>	13.5 (12.9–14)	10.7 (10.3–11)	<0.001	1.01 (0.76–1.26)
Psychological health (95% CI) <sup>b</sup>	15.5 (15–15.9)	14 (13.7–14.4)	<0.001	0.64 (0.40–0.88)
Social relationships (95% CI) <sup>b</sup>	15 (14.4–15.6)	15.4 (15–15.8)	0.002	–0.15 (–0.38 to –0.09)
Environment (95% CI) <sup>b</sup>	16.3 (15.9–16.8)	15.6 (15.2–15.9)	0.005	0.32 (0.08–0.55)
Overall (95% CI) <sup>b</sup>	3.4 (3.3–3.6)	3.0 (2.9–3.2)	0.004	0.48 (0.24–0.72)

<sup>a</sup>Covariates age and sex were added to the model as possible confounders.

<sup>b</sup>Outcomes are expressed as estimated marginal means.

The results may also indicate that QOL deteriorates when patients progress from IC to CLTI. With the study outcomes, patients may now be educated on the decrease in QOL that is associated with the progression of IC to CLTI. This may increase, a patients' awareness and intrinsic motivation to initiate lifestyle modifications.

Simultaneously, it underlines the importance of a SET program for patients with IC. In the Netherlands, patients are accompanied by a therapist trained in motivational interviewing during the program. The multicomponent program is not only aimed to increase the maximal walking distance but also focusses on intrinsic motivation and initiating lifestyle modifications. These lifestyle modifications, such as smoking cessation and exercise therapy, have been shown to be beneficial for patients with IC.<sup>16–18</sup> Another effect such as the use of statins effectively reduces disease progression and enhances walking distance and may enhance QOL.<sup>19</sup> Nevertheless, studies about the effect of lifestyle modifications and pharmacotherapy on QOL in patients with PAD are scarce. Future research should investigate the effect of lifestyle interventions on QOL as they may have a beneficial effect.

It should be noted that no statistically significant difference between the IC and CLTI group in the psychological and environment domain remained after several covariates were added to the model (Table IV). Hence, the differences in the psychological and environment QOL domains between the 2 groups that were observed in this study are largely

explained by differences in preexistent comorbidities. Simultaneously, this reveals a negative effect of comorbidities on psychological QOL in both the IC and CLTI cohort. Physicians should be aware of this as psychological interventions may enhance QOL-related outcomes.<sup>20</sup> The physical, social relationships, and overall domain were not altered by adding comorbidities as confounders to the model. Apparently, the differences in the other QOL domains are explained by other factors than comorbidities alone.

The social relationships QOL domain was the only QOL domain that was in favor of the CLTI group, after correcting for age, sex, and comorbidities. In contrast to the other QOL domains, it seems that social relationships are not negatively affected by disease progression. Hypothetically, the increased need for personal care enables patients with CLTI to interact with different individuals. Thus, social relationships may be more easily maintained in patients with CLTI.

The minimal clinically important difference (MCID) for the WHOQOL-BREF in patients with PAD has not been studied. In a study cohort that consisted of patients with lung cancer, the MCID ranged from 0.88 to 1.55, and the MCID for the WHOQOL-100 was 1 in a cohort of patients with early stage breast cancer.<sup>21,22</sup> By extrapolating the MCID of 1 to our study results, the differences in QOL between the IC and CLTI group may be considered clinically relevant. Further research on the MCID of the WHOQOL-BREF in patients with PAD is warranted to add further value to these study results.

**Table IV.** Analysis of variance analyses of QOL between the IC and CLTI group

Quality of life domains <sup>a</sup>	IC (n = 115)	CLTI (n = 193)	P value	Cohen's d
Physical health (95% CI) <sup>b</sup>	13.2 (12.6–13.8)	10.8 (10.4–11.2)	<0.001	0.83 (0.58–1.08)
Psychological health (95% CI) <sup>b</sup>	15 (14.5–15.5)	14.1 (13.8–14.5)	0.066	0.35 (0.11–0.59)
Social relationships (95% CI) <sup>b</sup>	14.9 (14.3–15.5)	15.4 (15–15.8)	0.004	–0.17 (–0.41 to –0.06)
Environment (95% CI) <sup>b</sup>	16.1 (15.6–16.6)	15.6 (15.3–15.9)	0.16	0.21 (–0.03 to 0.45)
Overall (95% CI) <sup>b</sup>	3.4 (3.2–3.5)	3.1 (3–3.2)	0.009	0.34 (0.10–0.58)

<sup>a</sup>Covariates age, sex, diabetes, hypertension, renal impairment, cardiac history, pulmonary history, cerebrovascular history, and history of bypass surgery were added to the model as possible confounders.

<sup>b</sup>Outcomes are expressed as estimated marginal means.

PROMs are gaining popularity in contemporary literature. Most PROMs merely focus on asking patients about objective outcomes (HS) and do not take the patient's evaluation (satisfaction) of QOL into account.<sup>23,24</sup> The WHOQOL-BREF measures a patient's QOL and is represented in 5 domains. In essence, it enables physicians to specifically target the domains of QOL that are most susceptible for improvement. We, therefore, argue that the WHOQOL-BREF is the most suitable PROM to be used to determine treatment strategies. Future studies examining QOL should include the WHOQOL-BREF as the main outcome measure if one wants to assess QOL and not, for example, HS.<sup>23,24</sup>

## LIMITATIONS

Because this study cohort consisted of 2 separate cohorts, no direct statements about the causative effect of IC or CLTI on QOL can be made based on this study. Nevertheless, this study provided insight into the differences in QOL at baseline between the 2 groups. Furthermore, both cohorts contain patient populations from similar regional hospitals in the Netherlands, in similar time-periods (with similar treatment options).

## CONCLUSION

Patients with IC have a significantly higher QOL in the physical, psychological, environment, and overall domains compared with patients with CLTI, even after correcting for age and sex. This underlines the importance of strategies that reduce disease progression as disease progression is associated with a decrease in QOL.

None.

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