Functional status and quality of life after treatment of peripheral arterial disease
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INTRODUCTION AND OUTLINE of the thesis

‘Quod scripsi, scripsi’
Patient Reported Outcome Measures

Knowledge of a patient’s well-being and insight how this is influenced by treatment, is an unquestionable need for daily clinical practice. The primary goal of a doctor is to improve the patient’s well-being, and not only an attempt to control his disease.

In 1947 the World Health Organisation (WHO) defined health as “a state of complete physical, mental and social well-being and not merely the absence of disease and infirmity”. In the following years, the daily functioning and well being of people was more and more conceptualised by the term ‘quality of life (QoL)’. Nowadays, the WHO defines QoL as “an individual’s perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectations, standards, and concerns. It is a broad ranging concept incorporating in a complex way the individual’s physical health, psychological state, level of independence, social relationships, personal beliefs, and relationships to salient features in the environment.”

Over the past two decades the development, validation and translation of instruments measuring this “individuals’ perception” has been of increasing influence in patient care and in clinical research. These so called patient reported outcome measures (PROMS) are grouped under the broad headings of not only physical, psychological and social health, but also functioning in daily life and patient happiness, spiritual aspects and satisfaction with health care can be included.

Patient reported outcome measures (PROMs) with regard to specific assessment of QoL are multidimensional involving a number of relatively independent domains that at least include physical, functional and psychosocial aspects, and social well-being.

Furthermore, in order to structure and describe disease outcomes and distinguish impairment, disability and handicap, the WHO developed the International Classification of Functioning, Disability and Health. Disability refers to the consequences of impairments in terms of the patient’s functional status (FS) and defines a patient’s level of independence and mobility. Therefore, in addition to QoL, assessment of the level of performing activities in daily life (measuring FS) is another very important PROM.
Patient Reported Outcome Measures in Peripheral Arterial Disease

Treatment
Peripheral Arterial Disease (PAD), a manifestation of atherosclerosis, is a chronic disease that remains asymptomatic for a very long time. Nevertheless, when the chronically expanding atherosclerotic lesion causes lumen stenosis or occlusion this can result in intermittent claudication (IC) and critical limb ischemia (CLI). Although drugs and surgery are effective treatments for IC, the most frequently applied therapies for IC are exercise programmes and percutaneous transluminal angioplasty (PTA). At the start of the research described in this thesis two reviews already attempted to identify the most optimal treatment for IC (PTA or exercise therapy (ET)), but were unable to demonstrate the superiority of one therapy over another. For patients with CLI, multiple treatment options are available. Treatment decisions are often thoroughly discussed in multidisciplinary teams and tailored to the individual patient. Nowadays, whenever technically possible, endovascular revascularisation (with or without stent placement) will be persuaded.

Clinical trials regarding PAD are generally designed to evaluate the effectiveness of a therapy, for example in trials where new developed stents are investigated, or to optimise different therapeutic approaches. Particularly randomized controlled trials play a key role as they provide the scientific evidence needed to adopt the best treatment. Furthermore, the provision of quality care depends on the ability to make choices from robust scientific data. Historically, the main purpose of studies in PAD has been to avoid major amputation, improve ankle brachial index (ABI) and increase patency rates and walking distance. Although these are still common endpoints to evaluate the effectiveness of treatment, they do not fully address the broad range of concerns in the patients with PAD and therefore the necessity to go beyond these traditional outcomes has been increasingly recognized. The main reason is that more attention should be given to overall health conditions and how the patient is affected by his chronic illness. Assessment of QoL and FS may be more relevant to assess the impact of PAD.

Quality of Life
Before starting treatment in patients with PAD, patients’ opinion and goals should be considered, since their expectations and values might differ from their physician. For example, a walking distance of 100 meters could be regarded as disabling by one patient,
while another patient might be very satisfied with walking 100 meters without pain. Since Qol expresses the perception of disease and expectations and values by the patient on mental, social and physical functioning, Qol instruments could aid to daily practice and clinical decision making, thereby providing patients the best options available. Whilst the importance of assessing Qol has been widely proven to be of use when evaluating the whole treatment effectiveness of a given trial, the choice of a Qol instrument should be related to the trial structure and the questions to be answered. Other important factors in instrument choice are the patient population, the treatment and, concerning the logistics, the resources of the investigators and the participating investigators. In addition the Qol questionnaires should be available in the appropriate languages in relation to potential participants in the study concerned. When these issues are addressed, valid and robust PROMs could support clinical decision-making.

Qol questionnaires are divided in ‘generic’ and ‘disease-specific’ questionnaires. Generic instruments measure general characteristics and consequences of illness, and have the advantage of being broadly applicable to people with different disorders. They allow comparisons between individuals or groups with different illnesses, or comparisons between patients and healthy controls. However, they may not touch on the most relevant topics of a specific illness. Disease-specific instruments on the other hand, have the advantage of addressing problems which are specific to a given population, and may permit cross-study comparison.

In patients with PAD disease-specific instruments to measure Qol have been developed, such as the Vascular Quality of Life questionnaire (VascuQol). This disease-specific instrument detects small changes in Qol more precisely than generic instruments such as the Short Form-36 or EuroQol-5D. The VascuQol was developed and validated in English speaking patients with IC and CLI, and has been translated into other languages.

Functional status
Although the domains of Qol also aim to measure physical and functional aspects, which could refer to impairments and disabilities, the main difference between measuring FS and Qol is that Qol takes into account the patients’ perception of this functional impairment. Previous studies have shown there is a large variability in the way of measuring FS in PAD. Although the Walking Impairment Questionnaire (WIQ) is a well-validated instrument for expressing perceived walking impairment in patients with IC, this questionnaire does
not consider performance on other activities.\textsuperscript{20} Furthermore, in patients with CLI, the few available data on functional outcome after treatment are mainly confined to gross measures such as ambulation and residential status and short instruments covering a small range of functional levels.\textsuperscript{21-24} More comprehensive multi-item instruments are available, however the problem with these multi-item instruments is that responses to all items on a scale are required to calculate a sum score, which are often difficult to interpret on a patients’ individual level. These instruments do not consider patients’ preferences and variability in performance on particular activities. For example, patients with IC are not likely to have problems with bathing and the ability to climb stairs will not be relevant to a patient with CLI who always takes the elevator.

Patient-specific instruments on FS could identify relevant issues on an individual level and allow the evaluation to focus on what is important to each patient. Therefore, a more sophisticated instrument to measure FS has been developed, the Academic Medical Center Linear Disability score (ALDS). This ALDS expresses FS more precise, since it measures FS in terms of activities of daily life.\textsuperscript{25-29}

The ALDS is a generic item bank that is able to measure the disability status of patients with a broad range of diseases. It has been developed within the framework of item response theory (IRT). Hence, its hierarchical properties are well suited to assess the effect of treatment over time, compare different treatment modalities and difference in effects of treatment between hospitals. Scores range between 0 and 100 on a linear scale, with higher scores corresponding with the ability to perform more difficult activities. Construct and clinical validity of the ALDS has been proven in patients with PAD.\textsuperscript{30} Nevertheless the ALDS has not yet been used to measure the effect of treatment on FS in patients with PAD.

**OUTLINE**

This thesis focuses on the treatment and outcome of patients with IC and CLI and especially the role and interpretation of PROMs in these patients.

**Part I: Intermittent Claudication (IC)**

In chapter 2, the reliability and validity of the Dutch version of two PROMs for QoL and FS in patients with stable IC were assessed (VascuQol and ALDS respectively). Despite the increasing application of PROMs in research settings, in daily practice the ABI and limited walking distance are still considered important outcome measures with regard to decision
making for (invasive) treatment of IC. A standardized treadmill test can assist in detecting the presence of PAD in case of a normal resting ABI, and is regarded as an objective and reproducible assessment of the walking distance. However, treadmill testing is an artificial condition which does not represent daily life in which patients experience pain during walking on a flat surface at their own pace. The WIQ is a well-validated instrument for expressing perceived walking impairment in patients with IC and has been suggested as an alternative to treadmill testing because of its correlation with changes in claudication distances on a treadmill. If the WIQ were to be used as an alternative to assess walking distances, it would be desirable to have information on the relation between the WIQ and daily life walking distances on the floor. For that reason, chapter 3 describes correlations between walking distances estimated by the patient, on the corridor and on a treadmill, and their correlation with the WIQ in patients with IC.

Currently, the most frequently applied therapies for IC are exercise programmes and PTA. Although both supervised exercise therapy (SET) and PTA already had proven to be effective in increasing maximum and pain-free walking distance in IC, there was no strong evidence of the superiority of one treatment over another. In chapter 4, we have described the results of a systematic review of studies comparing SET with PTA in patients with IC.

Consequently, in chapter 5 we present the design and rationale of a multicenter randomized controlled trial in which patients with IC due to iliac artery stenosis or occlusion will be randomly assigned to PTA (with additional stent placement on indication) or SET to determine the optimal treatment strategy (SUPER study). The aim of the SUPER study is to compare the clinical effectiveness and cost-effectiveness of SET and PTA as treatment for IC due to an iliac artery obstruction to determine the optimal treatment strategy. We hypothesised that first-line treatment with PTA is more effective than SET with regard to maximum walking distance, QoL and costs after 1 year.

Part II: Critical Limb Ischemia (CLI)
In accordance with patients suffering from IC, patient-reported outcomes such as QoL and FS are as important and increasingly recognized in patients with CLI. So far, no longitudinal studies were performed to evaluate changes in FS with the ALDS in patients who were treated for CLI.
In **chapter 6**, we have evaluated changes in FS measured with the ALDS and Qol measured with the VascuQol in patients who were treated for CLI and explored whether the ALDS and VascuQol could help identify subgroups of patients that might benefit from primary amputation instead of revascularization. Although PROMs are frequently recorded in patients with PAD to determine change in Qol as measure of effectiveness of treatment, the interpretation of such outcomes may be difficult. The interpretation of scores on these questionnaires is hampered by the lack of a definition as to what amount of change or difference in scores constitutes a clinically meaningful change or difference. For example, is a statistically significant mean difference of 0.44 from the baseline score, relevant for an individual patient? For that reason we introduce the minimally important difference (MID) to express clinically important benefit or deterioration rather than statistically significant differences or changes in PRO scores in **chapter 7**. We used Qol outcomes of patients treated for CLI and applied two different MID approaches (anchor-based and distribution-based).

Finally, in **chapter 8** we provide a summary, general discussion and recommendations for future research and the translation in Dutch.
REFERENCES


