Personalized outcomes forecasts in supervised exercise therapy for patients with intermittent claudication

Personalized Outcomes Forecasts in Supervised Exercise Therapy for Patients with Intermittent Claudication

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Navigating Towards Data-Driven, Person-Centered Care

Anneroos Sinnige

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CHAPTER 1

General Introduction

The purpose of this thesis is to investigate a novel person-centered, participatory and evidence-based approach to physical therapy care for patients with intermittent claudication. In the Netherlands, evidence-based guideline recommendations have been widely implemented into daily physical therapy practice for patients with intermittent claudication.[1] On the one hand, this is an impressive accomplishment, as implementation of guidelines in practice is no sinecure. In particular, widespread use of guideline-based care may help in eliminating *unwanted* therapy variation from daily practice. On the other hand, adherence to guidelines may also lead to the elimination of *wanted* therapy variation (i.e. appropriate tailoring of therapy to an individual patient).[2] A shift towards more personalized and participatory care is a logical next step to stimulate wanted therapy variation, on the condition that evidence-based practice is maintained. In the scientific literature, several approaches have been suggested to accomplish this, including: 1) implementing shared decision-making[3], 2) integrating monitoring tools in daily practice[4,5], and 3) employing the principles of a learning health system.[6,7] However, the evidence for successful applications of such approaches in daily physical therapy practice is scarce. In this thesis, we propose personalized outcomes forecasts as a means of combining these different approaches, to support physical therapists in personalizing evidence-based care.

The introduction of this thesis first provides information on the pathogenesis of intermittent claudication and the current state of guideline-based and evidence-based physical therapy for patients with intermittent claudication. Thereafter, we discuss the proposed approaches for shared decision-making, monitoring the course of therapy and utilizing learning health systems. Finally, we introduce the concept of personalized outcomes forecasts as overarching approach to make physical therapy care more personalized and participatory.

INTERMITTENT CLAUDICATION

Intermittent claudication is defined as walking-induced discomfort and pain in the leg or hip muscles, which disappears after a brief rest. Symptoms are caused by atherosclerotic narrowing of the arteries in the lower extremities. This limits the blood supply to the muscles during walking or exercise.[8,9] The mismatch between oxygen demand and oxygen supply causes cramps or pain experienced by patients.[10] Intermittent claudication is associated with limited walking distance and poor health related quality of life.[11]

Intermittent claudication is the most common symptom of peripheral arterial disease. Peripheral arterial disease is a chronic disease mainly caused by atherosclerosis that mostly affects the major arteries of the lower extremities. An important risk factor for atherosclerosis, and thereby peripheral arterial disease, is age.[12] Consequently, prevalence of peripheral arterial disease increases with age. More than 20% of the elder population (>80 years) is affected by peripheral arterial disease.[13] Another major risk factor for peripheral arterial disease is cigarette smoking.[12] It is estimated that 44% of the incidence of peripheral arterial disease is attributed to cigarette smoking.[8] Remaining major risk factors include diabetes, dyslipidemia, hypertension, and hyperhomocysteinemia.[8,12] Symptoms of peripheral arterial disease can be classified according the Fontaine or Rutherfort classification schemes. Both schemes classify symptoms from asymptomatic, to mild, moderate and severe claudication, to resting ischemic pain. The most severe category is minor or major tissue loss.[14]

Prevalence and disease burden of peripheral arterial disease are an increasing problem as the population ages and the presence of risk factors grows. Worldwide, over 200 million patients suffer from peripheral arterial disease.[15,16] In 10-20% of all cases the clinical presentation involves intermittent claudication.[10] Patients with intermittent claudication are at increased risk for (cardiovascular) mortality and morbidity. After 5 years, 20% of the patients presents with a stroke or myocardial infarction and mortality is 10-15%.[17]

CURRENT TREATMENT FOR PATIENTS WITH INTERMITTENT CLAUDICATION

Treatment of patients with intermittent claudication is aimed at reduction of cardiovascular events and symptom relief to improve walking capacity and health related quality of life. To do so, the current evidence-based (inter)national guidelines recommend supervised exercise therapy (SET) in combination with cardiovascular risk management as primary treatment. Cardiovascular risk management consists of antiplatelet and statin therapy, treatment of comorbidities, and lifestyle guidance.[8,9] SET has demonstrated effectiveness in improving disease-related symptoms for patients with intermittent claudication. The supervision component is thought to be important, as supervised exercise programs have been shown to be more effective to improve walking distance than unsupervised exercise programs, such as home-based exercise and walking advice.[18,19]

SET has also shown positive effects on other metrics of health and fitness. SET results in weight loss and improved body composition, reduces hypertension, increases insulin sensitivity, and improves cardioprotective lipid profiles.[20] The precise mechanisms by which exercise therapy exerts these beneficial effects are unclear. Possible mechanisms include:

1) increased and more effective distribution of blood flow to the legs by enlargement of existing collateral vessels and angiogenesis, 2) enhanced nitric oxide endothelium-dependent vasodilatation, 3) improved bioenergetics of skeletal muscles, 4) improved hemorheology, and 5) an altered pain threshold.[21]

THE CHRONIC CARENET MODEL

In the Netherlands, the guideline recommendations for patients with intermittent claudication are implemented through Chronic CareNet. Chronic CareNet is a network of specialized physical therapists that aims to provide evidence-based SET and lifestyle guidance as primary treatment for all patients with non-communicable chronic disease for whom physical therapy is indicated.[22] The guideline recommendations for patients with intermittent claudication are incorporated into a so-called stepped care model; a staged approach where all patients with intermittent claudication are referred for SET as initial treatment. More invasive treatment options (i.e. revascularization) are saved for non-responders to SET.[23,24] Furthermore, in expansion to the (inter)national guidelines, the content of SET is described in Dutch treatment guidelines by the Royal Dutch Society for Physical Therapy (KNGF).[25] All Chronic CareNet therapists are trained to adhere to both the (inter)national and the Dutch treatment guidelines in their daily practice. In the Netherlands, SET is reimbursed for all patients who are referred to specialized Chronic CareNet. This is a results of research that informed the cost efficiency argument.[24]

GUIDELINE-BASED PRACTICE: THE IDEAL IMPLEMENTATION OF EVIDENCE-BASED-PRACTICE?

Due to the work of Chronic CareNet, guideline recommendation for patient with intermittent claudication have been widely implemented. This has resulted in SET as an initial treatment approach for approximately 87% of all Dutch patients with intermittent claudication.[1] The widespread implementation of these consensus recommendations is a success in standardizing care and could be considered as the optimal care. However, this guideline-based practice it is at risk of eliminating patient-centered care. This would be conflicting with the ideals of evidence-based practice, where care decisions are made by the patient, informed by the best available evidence, in the context of available resources.[26] Thus, consensus guidelines are not without limitations; guidelines are mostly informed by research that originates from populations, study samples, or groups, whereas evidence based practice demands decisions at the level of the individual patient.[27] Similarly, SET has demonstrated effectiveness in reducing intermittent claudication specific symptoms at group or population level,[8,9] but translation of these findings into guidelines can result in recommendations that are too general to suit the needs of certain patients. There is a risk in adopting "one-size fits all medicine", while effects from exercise might differ per individual patient.[28,29] Personalization is needed, particularly on relevant criteria like exercise frequency, intensity, timing and type. Additionally, multimorbidity is becoming more and more common and hampers the application of guidelines that are not fully vetted in these more complicated patients.[26] As our population ages, prevalence of non-communicable chronic diseases increases, including intermittent claudication. More than half of the patients over 65 years of age have at least two chronic conditions, due to the overlap in risk factors for most non-communicable chronic diseases overlap which also often coexist in patients.[30] Even if multimorbidity is accounted for in clinical trials, it could affect each patient differently. Thus, a personalized approach is still required.[26] Ideally, evidence-based guideline recommendations should be individualized and applied to the context of the patient. This would be the real implementation of evidence-based medicine: integration of the best available research evidence with clinical expertise and patients' preferences.[31] However, it could be challenging to weight evidence with patient preferences and clinical expertise. Overemphasis on either one can easily result in *demand-based evidence* (only following the wishes of the patient) or *practice-based evidence* (only basing the decision on professional autonomy), respectively.[32]

A MAJOR AIM OF THIS THESIS IS TO ADDRESS THE TENSION BETWEEN GUIDELINE-BASED CARE AND THE IDEALS EVIDENCE-BASED PRACTICE. HOW CAN WE BEST ACHIEVE PERSON-CENTERED CARE WHILE ALSO RETAINING THE "EVIDENCE" IN EVIDENCE-BASED PRACTICE?

Several approaches have been proposed in the literature to make evidence-based care more patient-centered, including: 1) implementing shared decision-making[3], 2) integrating monitoring tools in daily practice[4,5], and 3) employing the principles of a learning health system.[6,7] In the next section, we will discuss how these three options, which in our opinion are underutilized in the field of physical therapy practice, could advance patient-centered care.

Implementing Shared Decision-Making

The ideals of evidence-based practice promote (if not demand) the use of shared decision-making. Shared decision-making is an approach to optimize patient-centered care by supporting clinicians and patients in integrating the best available evidence with the patient's preferences.[3] The theory of shared decision-making has three main components. The first of these is team talk, intended to prepare patients for collaboration. The second is option talk, intended to exchange information between clinicians and patients about treatment options. The final component is decision talk, intended to affirm and implement the decision or plan.[33,34]

To date, the application of shared decision-making in the treatment of patients with intermittent claudication has not been formally described, but the use of shared decision-making in physical therapy in general is (very) limited.[35-37] Although the use of shared decision-making is recommended by the treatment guidelines, they lack guidance on how to achieve this in practice. Guidelines also do not account for specific patient characteristics nor do they provide individualized predictions on what can be expected from the provided therapy.[26,27] Implementation of shared decision-making into daily physical therapy practice might be improved by developing specific decision support tools or approaches. Such tool should identify the key ingredients needed for team talk, option talk and decision talk, for a given patient population or clinical scenario.[38]

Integrating Monitoring Tools

Monitoring the progress of therapy or the course of care is an important element of the treatment of chronic diseases, including intermittent claudication. Monitoring, if done correctly, can help clinicians to better select or adapt treatment based on individual responses.[4] Monitoring can help patients understand the factors influencing their conditions and therapy progress, and can also improve therapy adherence.[5] Within physical therapy, the Hypothesis-Oriented Algorithm for Clinicians II (HOAC II) includes a monitoring component, where the therapist must account for any changes measured or observed. The HOAC II is a practical example of a guide for decision-making. It provides a model to guide therapists in how to determine which intervention is appropriate and how to account for risk factors. To do so, monitoring of response and/or progress is important.[39] However, evidence-based approaches to monitoring are lacking.[40-42]

Monitoring tools should meet some criteria to be valuable for use in daily practice. They should be based on accurate and precise data, have potential to contribute to improved outcomes, be cost effective and easy to use in routine practice.[42] In the course of physical therapy, it may be useful to have a visual representation of the typical progress made on a number of measures, to aid in evaluating patients' progress.[5] However, only visualizing outcomes of therapy over time might not be enough, since criterion on what is reasonable to expected are lacking or population based. [43] Ideally, these visualizations should account for differences in the expected treatment response across individuals, to enable personalized monitoring.

Employing the Principles of a Learning Health System

Learning health systems could be valuable in supporting evidence-based practice and creating personalized care.[44] A learning health system uses health data in cyclical process, aiming to convert data into knowledge, apply this new knowledge into practice and collect new data from the changed practice, thereby informing additional future iterations in care.[7] Large amounts of health data are continuously generated and gathered as part of routine care. A learning health system could use these data to continuously improve population-based and patient-centered care.[45] For example, data could be used to help develop decision support tools, or to set expectations and boundaries for monitoring therapy outcomes. The same applies for physical therapy; large amount of data are collected in the electronic health records as part of daily practice. However, this routinely collected data are often not successfully used, since tools to do so are lacking. Learning health systems could be the link between health data and clinical application.[45] Furthermore, a learning health system might speed up the implementation of research results or innovations into practice for patients to benefit from.[46] This normally can take many years.[47]

The Chronic CareNet Quality system is a practical example of a learning health system within the physical therapy treatment of patients with intermittent claudication. Chronic CareNet initiated the Quality system to continuously improve health care and provide insight into treatment quality specifically for patients with non-communicable diseases, including patients with intermittent claudication. The Chronic CareNet Quality system utilizes an outcomes registry with pseudo-anonymized data, received through the Royal Dutch Society for Physical Therapy (KNGF).[48] Data includes patient, process and outcomes data of patients with intermittent claudication who receive SET though the network. The

Quality system is used to assess quality of care and to provide transparency. Data are used to support continuous learning at therapist, practice, and network level, for example through benchmarking.

OUR ANSWER TO PERSONALIZE EVIDENCE-BASED PHYSICAL THERAPY

The described approaches (shared decision-making, monitoring progress in therapy and utilizing learning health systems) have a certain overlap, as they all have potential to advance evidence-based practice through personalization of care. How to incorporate these approaches in practice remains a work in progress, and concrete examples are lacking. In this thesis, we propose personalized outcomes forecasts as sort of nucleus to support shared decision-making and monitoring as part of a learning health system (figure 1). The central idea is to generate a forecast of important therapy metrics (e.g., walking ability, quality of life) for a patient, which then informs the provider-patient interaction, as therapy is initiated (e.g., setting expectations, shared-decisions on the treatment plan) as well as throughout the course of treatment (e.g., monitoring progress and reassessing the plan).[43,49] These forecasts are generated using specific baseline characteristics that serve as predictors.[49,50] The prediction methodology we have employed utilizes clinical data; forecasts are based on the realized data of previously seen patients.[49] In this way, the approach learns and build on previous experiences. Over time, results from new patients can feed into future predictions as part of a learning health system. Such individual outcome predictions could serve to provide patient-centered care with incorporation of the best available evidence. Moreover, individual outcome predictions provide the opportunity to closely monitor therapy progression and compare actual outcomes to predicted outcomes. They assists therapists to adapt clinical decisions at individual level and optimize clinical reasoning.[51] For example, it creates opportunities to set more realistic treatment goals and adapt the treatment plan to the prognosis.

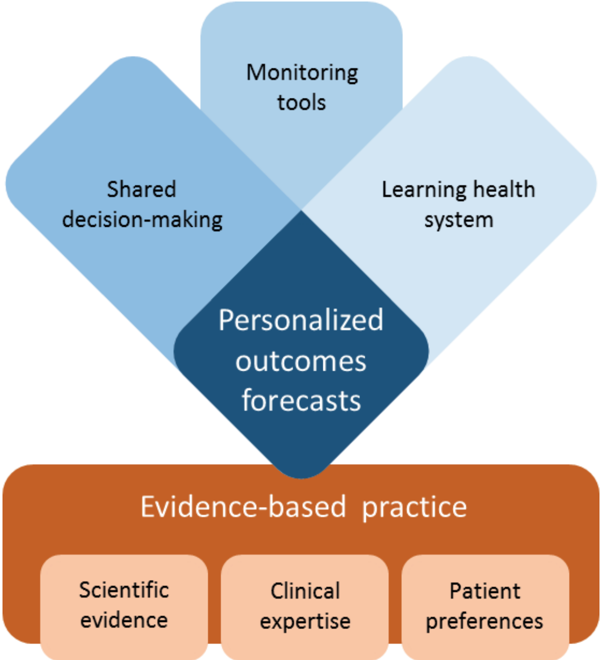

Figure 1. *Schematic view of the interdependence of shared decision-making, monitoring tools and learnings health systems and the added value of individual outcome predictions to achieve evidence-based medicine.*

The concept of personalized outcomes forecasts has been described under different terms in other fields; "expected treatment response" estimates have been promoted in psychotherapy for personalizing care, [43,52] and "curve matching" has been described as a means of individualizing the assessment and monitoring of childhood growth.[49] In physical therapy, related methodologies have been proposed to monitor progress of preoperative inspiratory muscle training[49,53] and to monitor recovery after total knee arthroplasty[40]. We seek to extend this previous methodological and clinical work to personalize evidence-based physical therapy care for patients with intermittent claudication. A first criterion to develop personalized outcomes forecasts is having access to enough data of sufficient quality, which is available through the Chronic CareNet Quality system. Second, the predictions should be clinically meaningful and applicable into daily practice. To do so, several features are important, including: accessibility, usability, interpretability, and salience to both therapists and patients.

OBJECTIVE AND OUTLINE

This thesis aims to create and implement personalized outcomes forecasts to improve physical therapy care for patients with intermittent claudication by advancing the application of evidence-based treatment at the individual level. In the Netherlands, evidence-based guideline recommendations for patients with intermittent claudication are widely implemented through the stepped care model. Successful implementation of the stepped care model, in which SET is provided as an initial treatment approach, has been made possible by the network of Chronic CareNet. This guideline-based medicine seeks to reinforce evidence-based practice, but additional innovations are needed to assist clinicians in adapting and applying group-level evidence with individual patients. We propose personalized outcomes forecasts as mechanism for advancing personalized care, without losing the 'evidence' in evidence-based practice.

Chapter 2 explores whether patient characteristics and functional outcomes of SET are related freedom from revascularization in patients with intermittent claudication. **Chapter 3** describes the use of routinely collected health outcomes to facilitate continuous learning among physical therapists. An example of a learning health system is provided as blueprint for physical therapists to distill meaning from routinely collected clinical data. **Chapter 4** describes the methodological development of personalized outcomes forecasts. **Chapter 5** explores the use of personalized forecasts by physical therapists through a vignette study. This first use provides us with valuable lessons to improve upon the clinical tool and to optimally facilitate implementation and use in daily practice. **Chapter 6** describes the protocol of the methods of implementation and the study design to evaluate process and impact of the implementation of the personalized outcomes forecasts. **Chapter 7** provides a general discussion and conclusion of this thesis.

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CHAPTER 2

Patient Characteristics and Functional Outcomes of Supervised Exercise Therapy for Intermittent Claudication Associated with Freedom from Early Revascularization

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ABSTRACT

Objective

To investigate whether patient characteristics and functional outcomes after three months of Supervised Exercise Therapy (SET) determine freedom from early revascularisation in patients with Intermittent Claudication (IC).

Methods

Participants were recruited between October 2017 and October 2018 in 10 Dutch centers. They received SET as initial treatment followed by invasive therapy if SET was ineffective ('early revascularisation'). Baseline characteristics, vascular laboratory and imaging data were obtained from hospital electronic health records. Walking performance and health-related quality of life were evaluated by the treating physical therapist, three to six months after SET initiation. Primary outcome was freedom from early revascularisation at 12 months. Secondary outcome was change in walking performance after three months. Regression analyses determined possible associations between patient characteristics and outcome parameters.

Results

A total of 252 patients (male 61%, age 68 ± 9) were eligible for analyses, of which 53 (21%) underwent early revascularisation. This group more often had prior revascularisations, more often had aortoiliac disease, had less severe TASC classification, and performed worse on functional tests before and after SET. Former smoking was negatively associated with early revascularisation (HR 0.19 95% CI 0.16 – 0.56, p=0.002). Limited three-month change in Vascular Quality of Life Questionnaire-6 (VascuQol-6) (HR 0.92 95% CI 0.86 – 0.997, p=0.04) and having multilevel disease (HR 2.71 95% CI 1.18 – 6.24, p=0.019) were positively associated with early revascularisation. Predictors for three-month change in walking distance included presence of aortoiliac disease, baseline walking distance, dyslipidemia, TASC score and previous SET treatment.

Conclusion

Patients with IC who undergo early revascularisation after failed SET have different baseline characteristics and walking performance compared to patients who do not. Multilevel disease, VascuQol-6 scores and smoking status are independently associated with the need for revascularisation.

INTRODUCTION

Supervised exercise therapy (SET) is an effective treatment for intermittent claudication (IC) due to peripheral arterial disease (PAD). SET results in improvements in walking performance, quality of life[1] and daily physical activity[2] whereas it positively effects a range of modifiable cardiovascular risk factors[3]. Furthermore, a SET-first-treatment approach is cost effective compared to open or endovascular revascularisation (OR, ER).[4, 5] International guidelines recommend SET as a preferential initial treatment for each patient with IC.[6, 7]

In the Netherlands, SET is reimbursed and made available through a network of specialized physical therapists. In 2017, 87% of all Dutch patients with IC were referred for SET as the initial treatment.[8] Interestingly, only 10% underwent revascularisation after 1 year following SET, and 17% after 5 years.[8, 9] The decision to perform a vascular intervention is likely influenced by a lack of improvement in functional parameters after SET, as well as the risk-benefit ratio of an intervention in these selected cases. The latter is mainly determined by the patient's general health status and characteristics of their atherosclerotic lesion(s).

In Dutch practice, effectiveness of SET is evaluated by physical therapists on the basis of improvements in walking performance and quality of life.[10, 11] Previous studies found that sex, age, and body-mass index predicted treadmill-measured walking performance after SET.[12-14] However, both the need for revascularisation and location of stenosis were not evaluated, nor were functional outcomes other than treadmill walking. Therefore, the association between various measurements of effectiveness of SET and the decision to intervene remains unclear.

The current study aimed to investigate whether patient characteristics and functional outcomes after three months of SET determined freedom from revascularisation for IC within one year ('early revascularisation'). A second aim was to study a possible association between baseline clinical characteristics and changes in walking performance after three months of SET.

METHODS

Study Design and Participants

The ELECT Registry was a multi-center prospective observational study ('Nederlands Trial Register' registration number: NTR732). The primary aim of the ELECT Registry was to determine the effect of stenosis location on outcomes of SET in patients with IC. They were included between October 2017 and October 2018 in ten vascular surgery centers across the Netherlands. Details on methodology and primary results were previously published and are cited below.[15, 16] The ELECT Registry was exempted from formal medical ethical approval by the Medical Research Ethics Committees United 'MEC-U' (reference number W17.071). All participants provided formal written informed consent.

Patients diagnosed with IC (PAD Fontaine II/Rutherford 1-3) who were considered candidates for SET as primary treatment by their vascular surgeon were eligible to participate in this study. Patients were excluded in case of advanced stage of PAD (ischemic rest pain and/or ulcers: Fontaine >II, Rutherford 4-6), if a vascular intervention was their primary treatment, if received prior PAD treatment (SET or revascularisation) <12 months before inclusion, or if they reported co-morbidity limiting proper ambulation. As this study aimed to record the treatment results after at least three months of SET, participants who underwent revascularisation prior to the three-month follow-up evaluation were also excluded.

Treatment and Follow-up

According to the guidelines for patients with IC, SET is the preferred initial treatment.[7, 17] The indication for pursuing invasive treatment instead of SET as an initial treatment step was decided by the vascular surgeon in concert with the patient in a shared-decision environment. SET received by all participants was provided according a standard regimen, which entailed exercise and lifestyle coaching. In the Netherlands, SET is provided by specialized therapists, trained in applying the Dutch treatment guidelines for patients with IC.[18] A typical Dutch SET program is uniform and contains up to 37 individual sessions, which consists of 30 minutes treadmill-based or track-based exercise combined with strength and balance exercises. Ideally, patients complete the entire SET program of 12 months and evaluation of progress takes place every three months.[15, 19] Nonetheless, in daily practice, a SET program lasts anywhere between three and 12 months. However, the walking capacity rapidly improves in the first two months of SET, achieving maximal effectiveness at three months.[19, 20] Dutch guidelines require that the effect of SET is evaluated after three to six months. At this moment, the decision to either continue conservative management or treat invasively (endovascular or open revascularisation) is made at the discretion of the vascular surgeon and patient in a shared-decision making environment. Due to the observational nature of the ELECT Registry, criteria to treat invasively were not standardized between the different vascular surgery centers. Most important reasons were failure to improve walking distance, disease progression and patient dissatisfaction.

Treatment Efficacy

Walking performance and health-related quality of life were evaluated by the treating physical therapist. Walking performance measures included maximal walking distance (MWD), functional walking distance (FWD) and 6-Minute Walking Distance (6MWD). MWD and FWD were measured using a standardized progressive treadmill test (i.e. Gardner_Skinner protocol[22]). The MWD was defined as the distance at which intolerable claudication pain forces a patient to stop. The FWD was defined as the distance a patient prefers to stop walking because of pain. The 6MWD was measured with the six-minute walk test which assesses the walking performance in a setting that resembles daily life more appropriately. The total distance a patient is able to walk during six minutes was recorded as the 6MWD. Health-related quality of life was measured using the Vascular Quality of Life Questionnaire-6 (VascuQol-6). The VascuQol-6 is a shortened version of the VascuQol-25 and contains questions relating to activities, symptoms, pain, and emotional and social well-being. Answers are recorded on a four-point scale and added up resulting in a total score between 6 and 24. Higher scores indicate better health-related quality of life.

Data Collection

Baseline patient characteristics included age, sex, Body Mass Index (BMI), smoking status, comorbidity, prior IC treatment, lesion location and severity, and Ankle-Brachial Index (ABI) were obtained from the participant's hospital electronic health records. Age, sex, BMI and smoking status where gathered through the physical therapist. Smoking status was scored as: participants who never smoked (never), participants who previously smoked but had stopped at the time of the study (former) and participants who smoked at time of inclusion (current). Lesion location was determined using the preferred vascular imaging modality of the treating vascular surgeon. Vascular centers lacking adequate trained duplex ultrasound scanning (DUS) operators chose to use alternative imaging methods including magnetic resonance angiography (MRA) or computed tomography angiography (CTA). Lesion severity was determined using TASC scores. Walking performance parameters were collected by the physical therapist and were extracted from the standardized feedback letter that is sent to the referring vascular surgeon.

Outcome Parameters

The primary outcome was freedom from early vascular intervention, defined as any vascular intervention between three to 12 months after SET initiation. This was considered to be early, since it entails termination of SET before the complete trajectory was finished. A vascular intervention is defined as a PTA (with or without stent), bypass, endarterectomy, or major leg amputation. Freedom from early vascular intervention was extracted from the electronic health records of the hospital, 12 months after SET initiation. The secondary outcome was the change in walking performance (FWD, MWD, 6MWD) after three months of SET. Change in walking distance after three months was chosen since the decision to pursue invasive treatment or not is generally made at this point.[20]

Statistical Analysis

Categorical variables were presented as numbers with percentages and compared using χ^2 or Fisher's Exact test. Continuous variables were reported as means ± standard deviations (SD) or as medians with interquartile range (IQR). They were compared using one-way ANOVA or Man Whitney U Test, as appropriate. Change in walking performance (FWD, MWD, 6MWD) and VascuQol-6 sum scores between baseline and follow-up were analysed using Friedman's test or repeated-measure analysis of variance (ANOVA). Missing continuous outcome and predictor data were imputed using multivariate imputation by chained equation.

Univariable and multivariable regression analysis were used to determine the impact of multiple parameters on three months change in walking performance (MWD, FWD, 6MWD) and freedom from vascular interventions. In univariable analysis, effects with a p-value of less than 0.2 were considered significant and subsequently included in the multivariable model using the enter method. Backwards selection was then used to maintain only factors that significantly affected outcome ($p<0.2$) in the model. Location of disease was deemed of clinical importance and was included in the multivariable model regardless of univariable outcome. All statistical analyses were performed with SPSS version 22 (IBM Corporation, Armonk, NY).

RESULTS

Participants

A total of 439 patients were evaluated for IC during the 1-year inclusion period, and 343 patients were willing to participate in the ELECT Registry. As 46 were excluded for reasons listed in Figure 1, a total of 297 patients participated in the study. Study data were missing or incomplete in 30 patients. Additionally, 15 patients underwent revascularisation within the three-month follow-up period (despite the intention to treat conservatively for at least three months, stated in the inclusion criteria). Baseline characteristics of these excluded patients are shown in Supplemental Table 1 and were not different from the total population. Therefore, 252 patients were eligible for the present study analyses.

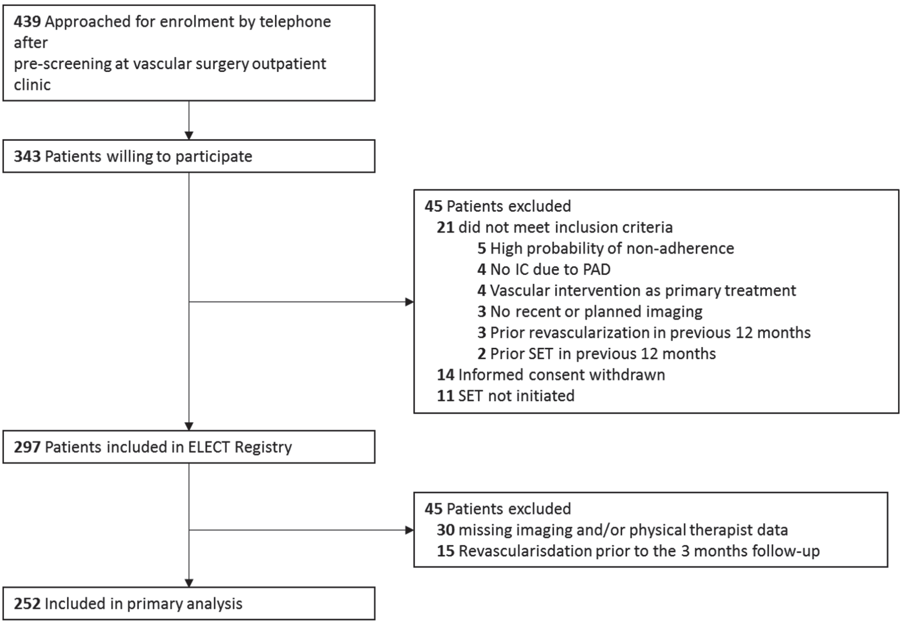

Figure 1. *Flow chart of inclusion process of patients receiving SET for IC*

A total of 53 (21%) patients underwent revascularisation between 3- 12 months after treatment initiation ('early revascularisation', Figure 2). Of these, 29 patients (54,7%) underwent PTA with or without stenting, 14 (26.4%) a combined thromboendarterectomy with PTA, 6 (11.3%) a thromboendarterectomy, 3 (5.7%) arterial bypass surgery, and 1 (1.9%) patient an aortobifemoral bypass procedure.

Baseline characteristics are presented in Table 1. Participants with an early revascularisation had more often undergone a prior revascularisation (>1y before start of SET). Moreover, they also performed worse on functional tests (i.e. treadmill tests and the six-minute walk test), and VascuQol-6 score before SET initiation. In addition, they were also more often suffering from aortoiliac disease (either unilevel, or with concomitant femoropopliteal disease) and had a less severe TASC classification.

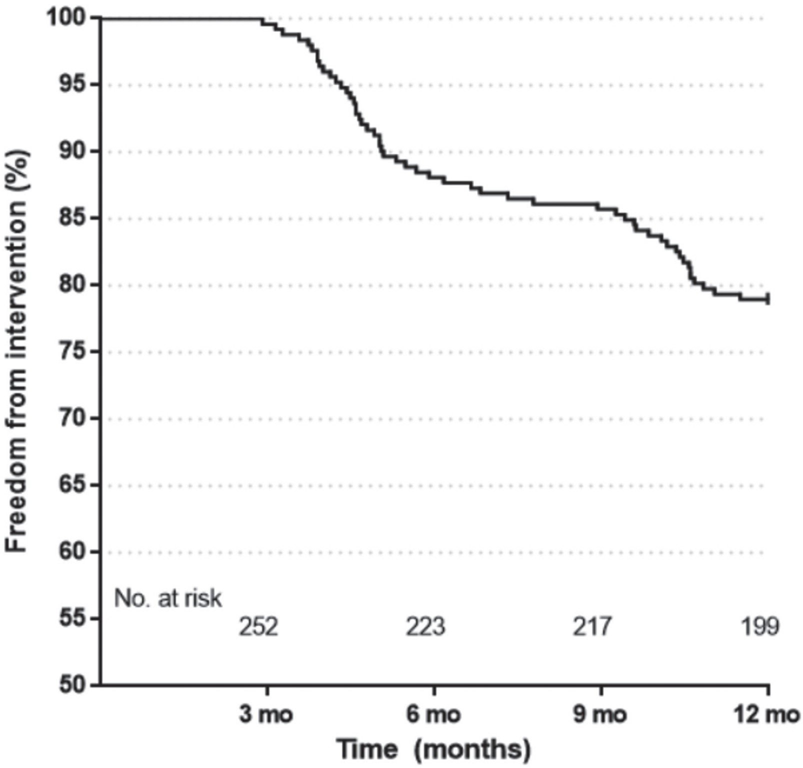

Figure 2. *Freedom from intervention after 12 months of SET for IC*

Table 1. *Baseline study population characteristics. (n=252)*

	Overall population (n=252)	**No intervention (n=199)**	**Early revascularization (n=53)**	***P*****
Age, y	68.3 ± 9.0	68.3 (8.950)	68.5 (9.312)	0.894
Female sex, n (%)	98 (38.9)	74 (37.2)	24 (45.3)	0.342
BMI, kg/m^2	27.2 (4.2) *n=149*	27.14 (4.17) *n=113*	27.34 (4.33) *n=36*	0.701
Smoking, n (%)				0.576
Current	107 (42.5)	81 (40.7)	26 (49.1)	
Former	103 (40.9)	84(42.2)	19 (35.8)	
Never	42 (16.7)	34 (19.6)	8 (15.1)	
Comorbidity, n (%)				
Diabetes	67 (26.6)	53 (26.6)	14 (26.4)	>0.999
Dyslipidemia	134 (53.2)	102 (51.3)	32 (60.4)	0.279
Hypertension	155 (61.5)	119 (59.8)	36 (67.9)	0.341
Kidney disease	28 (11.1)	22 (11.1)	6 (11.3)	>0.999
Cerebrovascular disease	31 (12.3)	22 (11.1)	9 (17.0)	0.346
Ischemic heart disease	56 (22.2)	41 (20.6)	15 (28.3)	0.265
Heart failure	15 (6)	12 (6.0)	3 (5.7)	>0.999
COPD	49 (19.4)	36 (18.1)	13 (24.5)	0.329
Musculoskeletal disease	40 (15.9)	28 (14.1)	12 (22.6)	0.141
Prior CVD intervention, n (%)				
CABG	21 (8.3)	15 (7.5)	6 (11.3)	0.403
PCI	29 (11.5)	21 (10.6)	8 (15.1)	0.467
EVAR	1 (0.4)	0	1 (1.9)	0.210
open AAA repair	5(2.0)	2 (1.0)	3 (5.7)	0.064
Previous IC treatment, n (%)				
Endovascular revascularization	43(17.1)	27 (13.6)	16 (30.2)	**0.007**
Open revascularization	12(4.8)	9 (4.5)	3 (5.7)	>0.999
Supervised exercise therapy	23 (9.2)	16 (8.1)	7 (13.5)	0.280
Symptomatic leg, n (%)				0.279
uni	123 (48.8)	101 (50.8)	22 (41.5)	
Both	129 (51.2)	98 (49.2)	31 (58.5)	
ABI in rest (lowest of legs)	0.64 ± 0.2 *n=243*	0.65 (0.194) *n=191*	0.62 (0.207) *n=52*	0.428
ABI after exercise (lowest of legs)	0.36 ± 0.2 *n=222*	0.37 (0.190) *n=172*	0.34 (0.232) *n=50*	**<0.001**
Functional walking distance, m	321 ± 266 *n=225*	343 (286) *n=179*	235 (140) *n=46*	**<0.001**
Maximal walking distance, m	504 ± 362 *n=226*	546 (383) *n=178*	349 (205) *n=48*	**<0.001**
6-minute walking test, m	376 ± 107 *n=235*	385 (105) *n=184*	341 (110) *n=51*	**0.010**
Vascuqol-6 sumscore	16 ± 4.0 *n=241*	16 (4.0) *n=190*	14 (3.6) *n=51*	**<0.001**
Lesion location, n (%)				**0.001**
Aortoiliac	70 (26.2)	47 (23.6)	17 (32.1)	
Femoropopliteal	115 (43.1)	96 (48.2)	14 (26.4)	
Multilevel	69 (25.8)	43 (21.6)	22 (41.5)	
No aortoiliac or femoral-popliteal	13 (4.9)	13 (6.5)	0	

	Overall population (n=252)	No intervention (n=199)	Early revascularization (n=53)	*P***
TASC Score*, n (%)				**0.011**
TASC A	100 (40.3)	84 (42.9)	16 (30.8)	
TASC B	84 (33.9)	64 (32.7)	20 (38.5)	
TASC C	32 (12.9)	19 (9.7)	13 (25.0)	
TASC D	19 (7.7)	16 (8.2)	3 (5.8)	
No aortoiliac or femoropopliteal	13 (5.2)	13 (6.6)	0	
Unknown	4(1.6)	3 (1.2)	1 (.9)	

No.(%) or Mean±SD or Median (IQR)
*Highest score in case of multilevel disease
** Comparison between no revsc and revasc with statistical test
AAA indicates abdominal aortic aneurysm; ABI, ankle brachial index; BMI, body mass index; AoI, aortoiliac; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ER, endovascular revascularization; EVAR, endovascular aneurysm repair; FP, femoropopliteal; FWD, functional walking distance; IC, intermittent claudication; MWD, maximal walking distance; OR, open revascularization; PCI, percutaneous coronary intervention; SET, supervised exercise therapy.

Outcomes of SET

On average, participants completed 17 ± 5 SET sessions after three months (n=204), and 26 ± 6 after six months(n=171). Functional outcomes of SET for the total population are shown in Supplemental Table 2. Table 2 shows the changes in functional outcomes after three and six months of SET, and the differences between patients receiving early revascularisation and patients who did not. Overall, participants improved in MWD, FWD, 6MWD and VascuQol-6 scores (Supplemental Table 2). Table 2 shows that patients who received early revascularisation had significantly less improvement in MWD, FWD and VascuQol-6 scores compared to patients who did not. The 6MWD did not differ between the two groups.

Table 2. *Walking performance and health-related quality of life outcomes in IC patients after 3 months of SET*

Outcomes	**No intervention (n=199)**	**Early revascularization (n=53)**	***P****
Maximal walking distance, m			
Baseline	546 (383) n=178	349 (205) n=48	0,001
3 months	955 (527) n=160	473 (302) n=43	0,000
Change from baseline	394 (409) n=159	107 (173) n=43	0,001
Functional walking distance, m			
Baseline	343 (286) n=179	235 (140) n=46)	0,015
3 months	746 (523) n=158	335 (184) n=41	0,000
Change from baseline	405 (433) n=158	83 (132) n=41	0,000
6MWD, m			
Baseline	385 (105) n=184	341 (110) n=51	0,008
3 months	432 (104) n=151	376 (134) n=39	0,011
Change from baseline	39 (72) n=146	20 (103) n=39	0,734
Vascuqol-6			
Baseline	16 (4.0) n=190	14 (3.6) n=51	0,000
3 months	19 (3.2) n=160	14 (3.9) n=40	0,000
Change from baseline	3 (3.7) n=156	0 (4.1) n=40	0,017

Values are expressed as mean±SD or median (Q1-Q3), 6MWD indicates 6 minute walk distance
*Between SET-only and Early revascularization group, using Friedman test or repeated-measure ANOVA as appropriate

Predictors of Need for Revascularisation

Univariable regression analysis of factors associated with early revascularisation are summarized in Supplemental Table 3. In the multivariable regression analysis, only former smoking (HR 0.19 95% CI 0.16 – 0.56, p=0.002) was negatively associated with associated with early revascularisation. Limited three-month change in VascuQol-6 sumscores (HR 0.92 95% CI 0.86 – 0.997, p=0.04) and multilevel disease (HR 2.71 95% CI 1.18 – 6.24, p=0.019) were independently associated with early revascularisation (Table 3).

Table 3. *Parameters associated with early vascular intervention in IC*

Variables	***Need for intervention hazard ratio (95% CI)***	***P value***	***Final model hazard ratio (95% CI)***	***P value***
Female sex	1.877 (0.875–4.029)	0.106	1.792 (0.948–3.384)	0.072
Smoking				
Current	0.507 (0.172–1.494)	0.218	0.443 (0.067–1.201)	0.109
Former	0.225 (0.073–0.688)	0.009	0.194 (0.164–0.558)	0.002
Never	Ref		Ref	
Prior CVD intervention				
EVAR or open AAA repair	1.540 (0.311–7.622)	0.597		
Lesion location				
Aortoiliac	1.315(0.485–3.565)	0.591	1.370 (0.570–3.294)	0.482
Femoropopliteal	Ref		Ref	
Multilevel	2.151(0.870–5.318)	0.097	2.710 (1.177–6.241)	0.019
No aortoiliac or femoral-popliteal	No events		No events	
ABI in rest	2.536 (0.127–50.519)	0.542		
<0.5	0.813 (0.233–2.832)	0.744		
ABI after exercise	0.296 (0.039–2.255)	0.240		
3 mo change in FWD, 10 m	1.000 (0.998–1.003)	0.931		
3 mo change in MWD, 10 m	0.998 (0.995–1.001)	0.254	0.998 (0.996–1.001)	0.138
3 mo change in VascuQol-6	0.918 (0.852–0.989)	0.025	0.924 (0.856–0.997)	0.042
TASC Score				
TASC A	2.144 (0.456–10.084)	0.334	2.135 (0.496–9.196)	0.308
TASC B	1.709 (0.444–6.585)	0.436	1.551 (0.420–5.726)	0.510
TASC C	3.393 (0.781–14.732)	0.103	2.792 (0.714–10.924)	0.140
TASC D	ref		Ref	

Number of events is 53. In multivariable model, location of disease (forced variable) and variables with *P* value of <0.2 at univariable analysis were entered into the multivariable XXX model using the backward method.

Predictors of Change in Walking Performance

Supplemental Tables 4-7 show univariable and multivariable regression analyses of predictors of changes in walking performance. In multivariable linear regression analysis (supplemental Table 6), aortoiliac disease and higher baseline FWD were independent predictors of lower three-month change in MWD. Dyslipidemia and TASC C lesions were independent predictors of lower three-month change in FWD. Previous SET treatment was an independent predictor of higher change in 6MWD after three months, higher baseline 6MWD predicted lower change in 6MWD, interestingly. The R2 for the final model of the MWD, FWD and 6MWD was 38.9%, 40.7% and 35.1% respectively.

DISCUSSION

The present study is the first to investigate factors associated with the need for 'early' (<12 months) revascularisation after the initiation of SET for patients with IC. Results show that patients who had early revascularisation performed worse on functional tests at baseline (i.e. treadmill tests, the six-minute walk test), had lower VascuQol-6 scores and showed less improvement after three months in walking performance following SET compared to patients who did not receive early revascularisation. However, after correcting for baseline differences, the functional tests seem of less importance to pursue early revascularisation. Nonetheless, measures of walking performance have proven their value and use to evaluate therapy progress for therapists and patients in previous studies.[21, 22] Following correction for baseline differences, only multilevel disease and three month change in VascuQol-6 were significant associated with the need of an early revascularisation. Previous smoking was negatively associated with the need of an early revascularisation. This finding is not in line with previous literature indicating that smoking increases the risk of disease progression and invasive treatment. Additional analyses determined that this statistically significant finding could not be explained by correlation or interaction with any of the other variables in the model. However, this finding is possibly caused by the low number of patients in the subcategories of smoking (current, former and never) within the early revascularisation group.

Notable baseline differences were found between patients who underwent early revascularisation and patients who did not. First, patients in the early revascularisation group were more often afflicted with aortoiliac disease (either unilevel, or alongside femoropopliteal disease), with generally less severe TASC scores. Naturally, these factors are weighed when considering interventional treatment in PAD patients. One argument is the high success rate of aortoiliac intervention compared to femoropopliteal interventions.[23] Aortoiliac disease was previously found to be an important reason for pursuing invasive treatment instead of SET.[24, 25] However, a previous publication using ELECT Registry data showed that patients with aortoiliac disease showed similar improvements regarding walking performance and quality of life compared to patient with other levels of disease.[16] Second, patients in the early revascularisation group had undergone a prior revascularisation (>1y before SET initiation) more often, although regression analyses found no association between the two. This is in line with previous findings suggesting limited long-term durability of invasive treatment for IC.[26, 27] Revascularisation offers 'local' symptomatic relief, with good short-term effects. However, it likely fails to influence systemic atherosclerosis, which leads to high re-intervention rates and possibly more amputations in the long-term.[27, 28] Thus, all patients with IC should receive SET as initial treatment, which is in line with guideline recommendations.[7, 17] As a consequence, unnecessary interventions (with concomitant re-interventions) are possibly avoided.

Several patient related characteristics were found to be predictive of change in walking performance after three months of SET. These factors include aortoiliac disease, baseline treadmill walking distance, dyslipidemia, TASC score and earlier SET treatment. Previous studies identified other factors influencing walking performance such as sex[12, 14], age[14], BMI[12, 14], cardiac comorbidity[14, 29], diabetes[29] and scores of a baseline walking impairment questionnaire[29]. On the other hand, a more recent study by Patel et al found that baseline walking distance was the only factor affecting responsiveness to SET.[30] In addition to previous research, the current study included a wide array of potentially important clinical parameters such as location and severity of stenosis, and prior vascular surgery. Evidently, literature on predictors for outcome of SET is inconclusive. Moreover, the predictive values in the present study and in previous studies are generally low as evidenced by low reported R^2 in the regression models.[12, 14, 29] These low predictive values are likely explained by a high variance in patient outcome. Outcome prediction in patients with IC is potentially valuable as a standard SET program may be tailored to the needs of the individual patient. However, attempts to identify predictors of outcome after SET or even create prediction rules for this patient population have shown to be of little clinical value. Therefore, individual outcome prediction within physical therapy is possibly more applicable in daily practice.[31] Furthermore, individual outcome prediction has the potential to improve upon patient-centered care and to be able to tailor SET to the individual patient.

Limitations

The present study may have several limitations which will be discussed in the next section. First, the sample size is relatively small. Therefore, the identification of factors predicting outcome of SET may have been hampered. Second, non-responder bias may have influenced results, as approximately 30% of screened patients declined participation. As a result, participants may have been more motivated for treatment compared to a general PAD population. However, non-participants to the study did not necessary decline SET. As mentioned in the introduction, in the Netherlands, 87% of all patients with IC were received SET as the initial treatment.[26] Motivational interviewing is an key component to motivate patient for therapy. Therefore, all physical therapist treating patients with IC in the Netherlands are additionally trained in motivational interviewing. Third, the decision to either continue conservative management or treat invasively, which is made during the standard follow-up at three to six months, is generally made at the discretion of the vascular surgeon together with the patient. There were no standardized criteria among the ten vascular centers. Finally, the VascuQol-6 questionnaire is a disease-specific health-related quality of life instrument and does not measure the generic QoL. This questionnaire measures the perception of the patient regarding the ability to carry out activities, symptom burden, pain, emotion and social consequences of their disease. [32, 33] As a consequence, measuring the experienced limitations with the VascuQol-6 is widely used in research with patients with IC and valuable to detect clinically relevant changes in health related Qol in response to SET.

Future Research

In future studies it would be interesting to include more extensive data to investigate the factors associated with the decision for early revascularisation in patients with IC. For example, distinction in time since quitting smoking or pack years was not available in this current study. Therefore, any differences related to the time since a particpant quit smoking could not be included in the study. Furthermore, data on adherence to prescribed medical treatment would be interesting to gather in future research. In the Netherlands, conservative medical treatment is part of standard clinical practice and adherence of prescribed medicine is controlled by both physical therapist and general practitioner. However, it would still be relevant to measure actual adherence and investigate the association of adherence with early revascularisation. Finally, factors possibly influencing a decision for early revascularisation such as behavioral determinants and pain were not available. Behavioral determinants such as motivation for walking therapy may have influenced SET continuity, or pursue invasive treatment. It is known that patients with lower self-efficacy remain more active after SET, which is in favor of deciding to continue SET.[34]

CONCLUSION

Considering the afore mentioned limitations, data of the present study showed that patients with IC who undergo early revascularisation after SET demonstrate different baseline characteristics and walking performance compared to patients who do not. Furthermore, multilevel disease, smoking status and VascuQol-6 scores are shown to be independently associated with the need for early revascularisation.

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CHAPTER 3

Using a Learning Health System to Improve Physical Therapy Care for Patients with Intermittent Claudication: Lessons Learned From the ClaudicatioNet Quality System

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ABSTRACT

Routinely collected outcomes data can be used to improve physical therapy care through benchmarking, personalization, continued education, and treatment optimization. In this article, we describe how we created a nationwide infrastructure to routinely collect data from daily practice and how we utilized these data through a support system (called the ClaudicatioNet Quality system) to improve physical therapy care for patients with intermittent claudication in the Netherlands. ClaudicatioNet is a nationwide network of 2,100 specialized physical therapists, providing high-quality supervised exercise therapy in combination with lifestyle counseling. The ClaudicatioNet Quality system utilizes a large national registry in which specific relevant health outcomes have been routinely collected since 2015. These data have then been used in turn to assess quality of care and provide transparency to therapists and other stakeholders. The Quality system is intended to serve as a learning health system, to support continuous learning at the therapist, practice, and network level. In our approach, we provide individual patients and physical therapists opportunities to personalize, benchmark, and evaluate (and possibly alter) a treatment plan using routinely collected data from historical patients. In this article, the Quality system is described based on the essential elements of a learning health system. We also describe the challenges and lessons learned in developing the Quality system.

IMPACT STATEMENT

The use of routinely collected health outcomes can, if implemented correctly, facilitate continuous learning among physical therapists and contribute to person-centered care. In this article, we provide an example of a learning health system that might serve as a blueprint for physical therapists on how to optimally implement and distill meaning from routinely collected clinical data.

INTRODUCTION

Routinely collected outcomes data in physical therapy offer opportunities to improve the quality of care. Improvements may be achieved directly, by using these data to aid therapists in personalizing and optimizing their treatment plans with patients, or indirectly, by using these data to help therapists reflect on their practice through benchmarking of performance or by using data to develop new educational courses to stimulate continuous learning cycles.[1-3]

To date, a number of large physical therapy outcomes registries have already been established, for instance: the Physical Therapy Outcomes Registry of the American Physical Therapy Association (APTA),[3] and the National Register for Physical Therapy of the Royal Dutch Society for Physical Therapy (KNGF).[4] However, to fully harness their potential for optimizing care, we believe it is essential to integrate these registries with healthcare networks. Such an integration transforms a regular healthcare network into a learning health system (LHS). An LHS is defined as a system in which (routinely collected) information is used for continuous improvement and innovation. [5 6]

Becoming an LHS can be quite challenging.[7] There are numerous steps involved with creating a data acquisition infrastructure, such as deciding which outcomes to measure, implementing these outcomes in daily practice, dealing with the wide variety of electronic health records (EHRs), and continuously stimulating therapists to collect accurate and complete data alongside their regular duties.[4 8 9] Synthesizing the data from daily practice in a relevant manner is also a substantial task, requiring at least time and analytical expertise. Finally, feeding the results of the data synthesis back to practitioners in a such a way as to stimulate learning and subsequent behavior change is additionally challenging and also benefits from expertise in implementation science and behavioral design, as well as systems-level incentives (e.g., the requirement of practitioners to engage in continuing education). In this article we aim to describe how we transformed the ClaudicatioNet care network into an LHS with the goal of further improving physical therapy care for patients with intermittent claudication in the Netherlands. Furthermore, we aim to share our own insights regarding this transformation process. Through this specific example, we are hoping to help readers appreciate the complexities involved in the transformation into an LHS.

USUAL PHYSICAL THERAPY CARE FOR PATIENTS WITH INTERMITTENT CLAUDICATION

In the Netherlands, progress has been made in routinely gathering outcomes data of patients with intermittent claudication. Intermittent claudication is defined as walking-induced discomfort or pain, which disappears after a brief period of rest. Intermittent claudication is the most common presentation of lower extremity peripheral arterial occlusive disease, a chronic disease caused by atherosclerotic narrowing of the arteries in the lower limbs.[10 11] Supervised exercise therapy combined with lifestyle modification is recommended in international multidisciplinary guidelines as the primary treatment for patients with intermittent claudication.[10 11] In the Netherlands, these guideline recommendations are realized in a so-called stepped-care approach.[12] This approach aims to initially refer patients for supervised exercise therapy and provide invasive treatments only to non-responders.[12 13]

STEPS TOWARDS A LEARNING HEALTH SYSTEM BASED ON ROUTINELY COLLECTED DATA

The ClaudicatioNet Quality system is an export system for collecting patient, process and outcomes data of all patients with intermittent claudication who receive supervised exercise therapy within ClaudicatioNet. Pseudo-anonymized data are gathered based on the National Register for Physical Therapy of the KNGF. The aim of the ClaudicatioNet Quality system is to provide transparency and guarantee quality of care for patients with intermittent claudication using these routinely collected data. The ClaudicatioNet Quality system is part of ClaudicatioNet, a network of specialized physical therapists to provide accessible and evidence-based care for all patients with intermittent claudication in the Netherlands.[13] Nowadays, ClaudicatioNet comprises more than 2,100 specialized therapists who treat over 10,000 patients with intermittent claudication annually. To participate in the network, physical therapists have to meet certain criteria. Criteria are related to their knowledge of exercise and lifestyle interventions and include a baseline training on treating patients with intermittent claudication.

To describe ClaudicatioNet's transformation from a guideline-based physical therapy care network into a transparent, data-driven, personalized physical therapy care network, we use the LHS framework.[5 6 14 15] LHSs go beyond data collection for the purpose of policy making and/or research, because they strive to use data for optimizing the care processes within the healthcare network. To do so, five attributes are essential: (1) collaborating with people who are intrinsically driven to improve healthcare; (2) creating a data infrastructure; (3) gathering data on health outcomes; (4) using knowledge derived from these data; and (5) initiating a continuous process of healthcare improvement.[5 6 14 15] For each attribute, challenges and lessons-learned will be discussed.

1. Collaborating With People Who Are Intrinsically Driven to Improve Healthcare

According to Friedman et al.[6], people with intrinsic motivation to improve healthcare are crucial to successfully operate an LHS. ClaudicatioNet was originally founded by a vascular surgeon motivated to improve healthcare for patients with intermittent claudication. The scope of ClaudicatioNet extended beyond the vascular surgery discipline. The aims of ClaudcationNet actually had potential negative consequences for vascular surgery output, because programmatic success would result in fewer invasive interventions performed. Besides this one intrinsically-driven founder, a dedicated team in collaboration with different stakeholders was necessary to set up ClaudicatioNet as an LHS. Furthermore, knowhow on nationwide collection of relevant health-outcomes was required, as well as expertise in implementation of resulting knowledge for healthcare providers using (for instance) information and communications technology solutions.

ClaudicatioNet is run by a team comprised of a variety of people with a broad range of knowledge, expertise, and education. The team includes project managers who have knowledge of translating research into practice, researchers who provide best practice evidence, and physical therapists with practical experience who know and understand the problems from daily practice (knowledge brokers).

Physical therapists are not only represented on the board and team, but are also deployed as trainers in different courses. The nationwide network of ClaudicatioNet is subdivided in 55 regional networks. Each regional network has at least one senior physical therapist, responsible for the distribution of knowledge and organization of regular meetings to exchange knowledge. Senior physical therapists serve as knowledge brokers and are able to pass on knowledge and new insights from clinical practice to the ClaudicatioNet team and the other way around. Besides the physical therapists with a specific operational function within the network, all therapists affiliated with the network as providers are indispensable to its function as an LHS. Without a sufficient number of therapists, nationwide coverage is not possible and the network would not be able to make supervised exercise therapy available and accessible for all patients with intermittent claudication.

To create a network like ClaudicatioNet, collaboration with different stakeholders is important. In our experience, this has included patients, professional bodies and web-development companies. Patients have been involved in the network for example through their physical therapists, specific patient surveys and focus group meetings to assess the performance of various programmatic initiatives. Also, collaboration with the Dutch patient federation for people with cardiac and vascular disease was important to incorporate the patients' perspective. For example, the collaboration with the KNGF resulted in a collective update of clinical practice guidelines for the treatment of intermittent claudication, sufficient reimbursement of supervised exercise therapy for patients with intermittent claudication, and an adequate and efficient development of the Quality system by use of the KNGF infrastructure to collect data from EHRs. Close collaboration with a web-development company was also important to create and regularly update a website and digital platform, including all specific functionalities like individual online portfolios for therapists to make use of an online referral system and the Quality system.

Intrinsic motivation to improve the care for patients of collaborating stakeholders is important and often self-evident, because patient care is the core business of health professionals and patient associations. To enhance efficient collaboration, ClaudicatioNet learned to define common grounds in early stages of collaboration and discuss the added value of creating an LHS for all stakeholders.

2. Creating a Data Infrastructure

Routinely measured and documented data of sufficient quantity and quality are a prerequisite to successfully build and operate an LHS.[6] Some important lessons were drawn from our experiences with gathering data via spreadsheets, which was the initial practice before the development of the Quality system. Though laudable in the effort, manual data entry into spreadsheets proved cumbersome, error-prone, and distracting to many of the important daily tasks of care providers. With regard to the data infrastructure two points will be discussed: (1) the importance of integrating data collection into daily practice, and (2) the need for uniform data collection.

First, to implement routine data collection, it should be embedded as invisibly as possible in daily practice. Figure 1 is a schematic overview of the LHS, including data collection via the Information and Communications Technology (ICT) infrastructure. ClaudicatioNet receives data from EHRs, which physical therapists use to register patient information and health outcomes. For therapists to adhere to data collection, the administrative workload needs to be as low as possible, because the required documentation burden is already quite high and arguably distracts from the primary goal of providing quality care. A major advantage of data collection via EHRs is the potential for minimal additional workload for the therapist.

Second, data collection via EHRs enables uniform data collection. The set of health outcomes (see "Gathering Data on Health Outcomes" below) is available for all therapists via standardized measures and questionnaires. Limitations in scoring options prevent documentation errors due to variation in interpretations of the measures and questions.

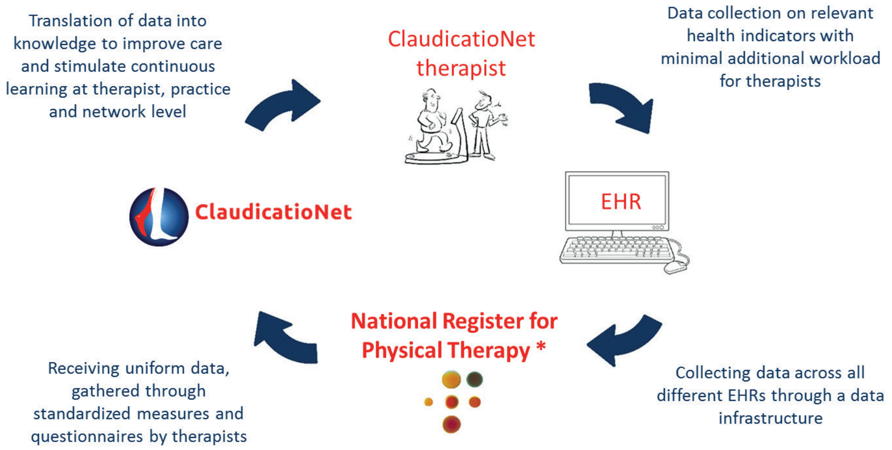

Figure 1. *Data infrastructure of the ClaudicatioNet Quality system. Data are gathered by ClaudicatioNet physical therapists into their Electronic Health Records (EHR). Data from all physical therapy EHRs in the Netherlands are collected by KNGF in the National Register for Physical Therapy. ClaudicatioNet receives this pseudo-anonymized data from KNGF to support continuous learning.*

** The National Registry for Physical Therapy collects data from Electronic Health Records (EHR) of not only ClaudicatioNet therapists. However, ClaudicatioNet receives only data delivered by therapists affiliated with the network.*

ClaudicatioNet has collaborated with KNGF since 2015 to implement uniform measures and questionnaires in all different EHR systems available for therapists. Thereby, ClaudicatioNet is able to access routinely collected health data from different EHRs. In 2015, KNGF started the implementation of an infrastructure to collect data from all physical therapy EHRs in the Netherlands (18 in total), called the National Register for Physical Therapy. This register was initiated to collect data from EHRs to improve patient centered care and effectiveness of physical therapy care.[4] For patients that provide informed consent, pseudo-anonymized data from EHRs are sent to the National Register for Physical Therapy. Therapists enter patient information and outcomes into the EHRs. The variables selected as valuable for the National Register for Physical Therapy are pushed from the EHRs to the register by the therapists. Technical specifications describe how data can uniformly be transferred from the EHRs to the National Register and processed by ClaudicatioNet. Challenges that may arise when collecting data through physical therapists' EHRs have been described by Meerhoff et al[4]; the two most prominent challenges are user-unfriendly EHR systems and lack of integration of outcome measures with patient records.

3. Gathering Data on Health Outcomes

Apart from establishing a data collection and management infrastructure, it is essential to decide on what data are relevant to collect. Over several years, ClaudicatioNet has undertaken a challenging endeavor to select health outcomes that are most relevant to the Quality system's goals. Despite a well-intentioned urge to gather comprehensive data to inform research or policy questions, ClaudicatioNet reduced the number of measures and questionnaires to a bare minimum and aligned the data collection efforts primarily towards the what could be useful to inform real-time clinical decisions (for example: improving clinicians' ability to monitor therapy progress).

Based on expert opinion and in line with current guidelines, relevant health outcomes for the Quality system were selected and refined over time based on user feedback. This resulted in the three major categories of clinical data: patient characteristics, outcome results, and process data. Patient characteristics include sex, age, weight, and height. Outcome results include certain Patient-Reported Outcomes Measurements (PROMs), as well as assessments of smoking behavior, willingness to change lifestyle behavior, walking distance (measured as functional and maximal walking distance using the Gardner Skinner Protocol[16]), quality of life (measured with the Vascular Quality of Life Questionnaire[17]), and patients' perspective on recovery, executing activities of daily living and treatment. PROMs are valuable to improve healthcare by incorporating the patients' perspective and create more personalized healthcare.[18] Process data include duration of treatment, number of treatment sessions, and whether or not the treatment goal has been achieved. Measurements are administered and documented for each patient every three months, beginning at the start of the treatment, up to a maximum of 12 months.

Even though this measurement protocol has been in practice since 2015, it remains challenging to collect data from all ClaudicatioNet therapists (see Figure 2). In 2017, data were only received from approximately half of all associated therapists. Because data collection of at least the minimal set of outcomes is a prerequisite for ClaudicatioNet therapists, several actions were undertaken to increase the completeness of the data. Data collection optimization was initiated using strategies at the group level, followed by strategies at the individual level. Strategies to optimize data collection were mainly driven by knowledge and experience of the network, observations from daily practice, and feedback of therapists. At the group level, data collection was stimulated by:

1. Increasing therapist understanding of the purpose of data gathering. A lack of awareness of the overall purpose of data gathering can contribute to anxiety on the part of therapists.[19] Knowledge on the purpose of data gathering is increased through online training and presentations, provided by the network.

2. Providing information on how therapists can use data in therapy sessions and how healthcare data can be used to improve quality of care. The goal was to increase therapists' intrinsic motivation to gather data.[19-21] We provided information on the usefulness of data gathering through the online portfolios, oral presentations, emails and regular news letters.

3. Making therapists aware of the minimal administrative workload to send the data to the national register. We aim to keep administrative workload as low as possible. However, therapists were generally unaware of the ease with which the requested data could be entered into EHRs. The misconception that multiple onerous steps were needed was a barrier to data entry.[19 21 22] We attempted to increase awareness through emails and regular newsletters, sent by the network.

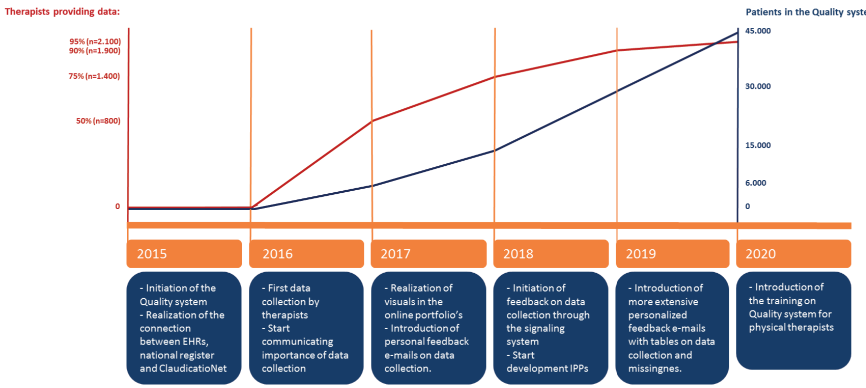

Figure 2. *Timeline of the development of the registry used by the Quality system. The horizontal axis represents the time divided into years, ranging from 2015 to 2020. The left vertical axis represents the number of therapists providing data to the Quality system and right vertical axis represents the number of patients of whom data were available at that time. Important milestones over time are described underneath the graph.*

To reduce missing data at the individual (therapist) level, information on personal data collection was communicated with individual therapists. Such feedback was initially provided via personalized e-mails on whether data was received or not. Thereafter, we provided feedback through a signaling system in their personal account on the ClaudicatioNet website and later we added personalized feedback on the completeness of the received data. The signaling system was designed to automatically send reminders to individual physical therapists who did not transfer any data in the previous two months. Additionally, the system will send a warning in case no data have been collected for a period of 6 months and will temporally suspend therapist participation after 3 warnings. The personalized feedback includes information on whether data has been received or not, as well as information on data completeness and the content of collected data. The feedback is provided via tables as well as in e-mail form. We learned that feedback on data collection could be a drive for therapists to initiate data collection or improve data completeness (see Figure 2).

Besides unawareness of the added value of data collection, missing data may have other causes, including: lack of follow-up of patients, not entering the follow-up data into the EHRs, or lack of adherence to the measurement protocol. The measurement protocol recommends follow-up measurements and data collection at least every three months for a one-year period and describes the relevant measures.[12 23] Substantial efforts have been made to draw attention to these guidelines and to achieve implementation of the recommendations that therapists routinely collect data for the patient, process and outcomes domains. The message conveyed by the network was that performing these measurements and documentation should be part of daily clinical practice and is valuable for the treatment process.

4. Using Knowledge Derived From These Data

A sufficient amount of routinely collected data are necessary to initiate learning cycles consisting of: transformation of data into knowledge, transformation of knowledge into performance, and ultimately the transformation of new performance into new data.[6]

ClaudicatioNet Quality system data are used to initiate learning cycles to answer specific questions from physical therapy practice. Data are used to learn from and improve individual performance, as well as to influence policy making. Data from improved practice are gathered in the Quality system, which completes the initial learning cycle and creates the opportunity to start a new one. There are several examples of how data in the Quality system are used to improve practice:

- Monitor the overall quality at a network level, in terms of therapy outcomes and cost-effectiveness of the treatment.
- Create benchmarks at the national and regional level. This allows for benchmark comparisons, whereby the variations in therapy outcomes over time and among therapists can be readily monitored. The characteristics and circumstances of therapists under- or over-performance may be explored. These national and regional benchmarks contribute to learning at all levels of the system: individual therapist, practice, and network.
- Visualize pseudo-anonymized data on individual therapist treatment results. These so-called visuals can be used to learn at both group and individual therapist level. Therapists may be stimulated to evaluate their own data with respect to the benchmarks and to discuss their evaluations with other ClaudicatioNet therapists. For example, mean outcomes results over time of individual therapists, as well as regional and national averages are shown (see Figure 3). Collaboration with a web-development company has been essential to create these visuals and enable quick, easy, and meaningful benchmark comparisons.

- Provide insight into patients' individual prognosis. Routinely collected data are used to provide insight into patients' individual expected outcome of the supervised exercise therapy using personalized outcome forecasts (see figure 4). Although evidence for optimal treatment content is still derived from guideline recommendations, insight into an individual prognosis may support patients and therapists to align the treatment plan to the needs of the patient. Moreover, these personalized outcome forecasts can elicit shared decision-making and improve clinical reasoning of the therapist, potentially resulting in more realistic and personalized treatment goals and interventions, as well as (importantly) improved monitoring of progression.[24 25] To further improve physical therapy care for people with claudication intermittens, we recently initiated a project aimed to integrate the personalized outcome forecasts with guideline recommendations.[23] Guidelines can have the negative side-effect that they not only reduce the unwanted practice variation, but also the wanted treatment variation in practice.[26] By integrating the personalized outcome forecasts with the guideline recommendations, we aim to facilitate therapists to make their treatment plans more personalized and participatory, whilst still following the guideline recommendations. Not only will this potentially result in better outcomes, it will also set the stage for continuously improving and updating the guideline recommendations themselves. If we succeed, our learning health system will be transformed even further, namely into an evidence ecosystem.[27] This innovative project is only made possible through collaborations with relevant stakeholders.

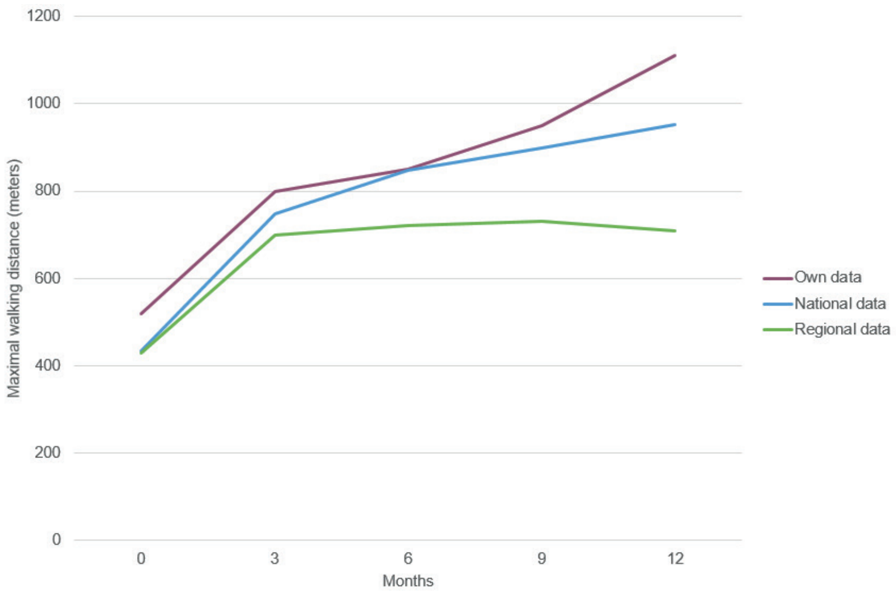

Figure 3. *Example of a visualization of an individual therapist's results (in terms of walking distance) benchmarked to the average regional and national results.*

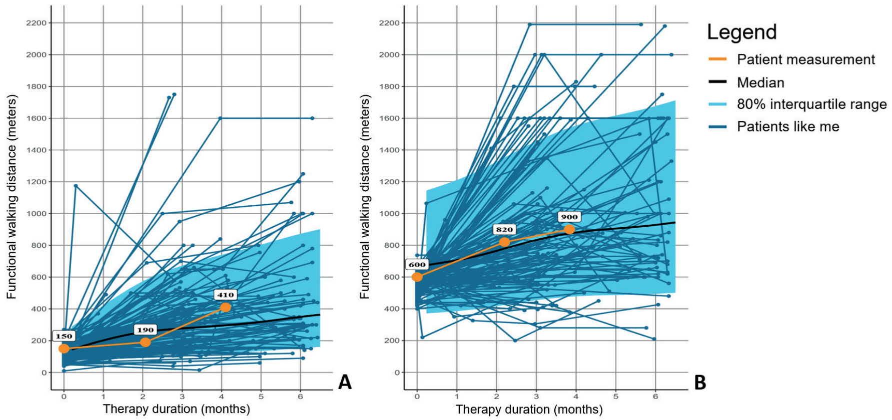

Figure 4. *Two examples of personalized outcome forecasts for two different patients. Personalized outcomes forecasts are individual estimates of a patient's outcome over time, visualized as plots. For people with intermittent claudication, we developed personalized outcomes forecasts which estimate the walking distance during a trajectory of supervised exercise therapy (blue shade and black median line). Outcomes forecasts are based on historic data of patients similar to the index patient (dark blue lines). Actual patient's outcomes are also included in the graphs (orange lines) to enable monitoring therapy progress. In this specific example the left graph (A) represents a personalized outcome forecast for a 75 year old female patient who smokes with a strongly impaired functional walking distance at baseline and the graph on the right (B) represents a 62 year old male who smokes with a moderate impaired walking distance at baseline.*

5. Initiating a Continuous Process of Healthcare Improvement

Routine data collection and use of these data to improve healthcare should be continuous processes. Data on every new patient added to the Quality system should contribute incrementally to improvements in the registry, representation of the experiences of patient population writ large, and enhanced knowledge and perception on data gathering. For example, data on new patients in the Quality system should, over time, result in more accurate personalized outcome forecasts for individual patients.

To continuously improve, new insights and knowledge from data should be made accessible to therapists, patients and relevant stakeholders. Over the past years, ClaudicatioNet has learned that communication on new insights or innovations is important to successfully transfer knowledge and implement change. ClaudicatioNet communicates weekly on the progression of projects to create early awareness through newsletters, websites and social media. Furthermore, ClaudicatioNet uses instructional videos to make information easily accessible, for both patients and therapists. With regard to the personalized outcome forecasts, patient-therapist interaction videos have also been developed based on observations and input from interactions in daily practice. Besides these attempts at good communication, usage of therapists' portfolios, which are known platforms, might enhance the success of implementation. Therefore, personalized outcome forecasts are embedded in the online portfolios of therapists.

The ClaudicatioNet website, social media, newsletters, annual congresses, trainings, and regional meetings are important ways to distributes knowledge. The ClaudicatioNet website contains information on the network: the organizational structure, quality criteria and regular project updates. Additionally, the website provides news on exercise and lifestyle interventions from other resources, which are accessible for therapists, referral sources and other interested people. Regional projects are used to transfer knowledge at a group-level, for example: peer assessment meetings. Peer assessment meetings are organized by ClaudicatioNet and include a small group of physical therapists aiming to exchange experience and knowledge. During these meetings, expertise is developed in assessing physical therapist behavior through self-assessment and peer feedback.[28 29]

To continuously learn, questions and obstacles from (ever-improving) daily practice should be a direct input for new impulses to improve, including training and research. For example, questions or needs from daily practice should create inputs for new scientific research. For example, a historical lack of reimbursement for physical therapy services (resulting in low referral rates of patients with intermittent claudication for supervised exercise therapy)[13] spurred scientific research about the overall cost efficiency of supervised exercise within ClaudiocatioNet.[30] This resulted in increased reimbursement for supervised exercise therapy for all patients in the Netherlands who are referred to specialized ClaudicatioNet physical therapists, since ClaudicatioNet data informed the cost efficiency argument. Besides the input from daily practice for new impulses to improve, all results from collaborating, data gathering, data management, generating and distributing knowledge represent continuous inputs for new learning cycles. For example, recent data have illuminated certain barriers to gathering PROMS in routine practice. Ideally, PROMs should be reported directly by the patients and gathered as part of daily practice. However, misplaced incentives (i.e. an organizational desire to show patient improvement) as well as a lack of time and sufficient technology are barriers to obtaining accurate PROMS data in registries.[18 31] These barriers should be addressed in the future to improve data gathering and the efficacy of the LHS.

FURTHER DEVELOPMENT

The ClaudicatioNet Quality system tries to continuously improve and expand data collection. Data collection could be expanded in several different areas: remote data, other diseases and other disciplines. First, it would be valuable to include remote data, measured by the patient themselves. There is growing interest in remote patient monitoring within physical therapy. Use of activity trackers or smartphone application have great potential in physical therapy in general to remotely monitor patients and support therapists in personalized coaching.[32] However, remote patient monitoring specifically for patients with intermittent claudication is not available yet in the Netherlands. Remote data could be useful to further optimize and personalize treatment for patients with intermittent claudication. Second, data collection could be expanded by collecting data of patients referred for physical therapy with other types of chronic diseases than intermittent claudication. To do so, Chronic CareNet was introduced in March 2020. Chronic CareNet builds on the lessons learned from the ClaudicatioNet network and transfers obtained knowledge to set up new networks for other non-communicable, chronic diseases. The core value of Chronic CareNet is to provide “the right care in the right place”, meaning that all patients with non-communicable chronic disease for whom physical therapy care is indicated should receive evidence-based care.[33 34] This introduction of Chronic CareNet now makes it possible to extend the nationwide data collection to other chronic patient groups. Finally, data collection could be expanded to other allied health professions. Data gathering of other allied health professionals could be valuable and stimulate interdisciplinary treatment.

CONCLUSION

In this article we have discussed how physical therapy care for patients with intermittent claudication in the Netherlands has shifted from generalized guideline-based physical therapy care, towards transparent, personalized evidence-based physical therapy care, using routinely collected data. ClaudicatioNet aims to continuously educate specialized therapists to provide optimal supervised exercise therapy for patients with intermittent claudication in the Netherlands. The initiation of the Quality system has enabled the use of routinely collected data to improve and personalize care. Several lessons can be drawn from initiating ClaudicatioNet and the process of routinely collecting data. An intrinsically motivated team, with a broad range of knowledge and expertise is required. Furthermore, collaboration with intrinsically motivated stakeholders can be beneficial and more efficient to achieve the goals of an LHS, as well as the alignment of the LHS with existing initiatives. To use routinely collected data to continuously learn and improve, data of sufficient quality and quantity are prerequisite. Therefore, data collection should be uniform with minimizing missingness and errors. Finally, data should be transformed into knowledge, leading to new performances in daily practice and new data. To do so, knowledge derived from data should be made applicable for therapists, patients and stakeholders.

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CHAPTER 4

Personalized Outcomes Forecasts of Supervised Exercise Therapy in Intermittent Claudication: an Application of Neighbors-Based Prediction Methods with Routinely Collected Clinical Data

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ABSTRACT

Objective

Insights regarding individual patient prognosis may improve exercise therapy by informing patient expectations, promoting exercise adherence, and facilitating tailored care. Therefore, we aimed to develop and evaluate personalized outcomes forecasts for functional claudication distance over six months of supervised exercise therapy, for patients with intermittent claudication.

Study Design and Setting

Data of 5 940 patients were eligible for analysis. Neighbors-based predictions were generated via an adaptation of predictive mean matching. Data from the nearest 223 matches (a.k.a. neighbors) for an index patient were modeled via Generalized Additive Models for Location Scale and Shape (GAMLSS). The realized outcome measures were then evaluated against the GAMLSS model, and the average bias, coverage and precision were calculated. Model calibration was analyzed via within-sample and out-of-sample analyses.

Results

Neighbors-based predictions demonstrated small average bias (-0.04 standard deviations; ideal=0) and accurate average coverage (48.7% of realized data within 50% prediction interval; ideal=50%). Moreover, neighbors-based predictions improved prediction precision by 24 percent, compared to estimates derived from the whole sample. Both within-sample and out-of-sample testing showed predictions to be well-calibrated.

Conclusion

Neighbors-based prediction is a method for generating accurate personalized outcomes forecasts for patients with intermittent claudication undertaking supervised exercise therapy. Future work should examine the influence of personalized outcomes forecasts on clinical decisions and patient outcomes.

IMPACT STATEMENT

This study describes the development and testing of a neighbors-based prediction method, which yields personalised outcomes forecasts of patients undertaking supervised exercise therapy for intermittent claudication. The neighbors-based prediction method performed well, with small bias, accurate coverage, and improved precision, relative to prognostic models that include the full sample. Personalised outcomes forecasts appear to improve upon previously published prediction models in this patient population. Created personalised outcomes forecasts provide insight into individual prognosis which has the potential to improve and personalise care for this patient population.

INTRODUCTION

Intermittent Claudication (IC) is the most common symptom of peripheral arterial disease, caused by atherosclerotic narrowing in the lower extremity arteries.[1, 2] Patients with IC typically experience discomfort and pain in the legs and buttocks during exercise, which rapidly disappears after a brief rest. The recommended first-choice therapy for patients with IC is supervised exercise therapy.[1, 2]

Although supervised exercise therapy is known to be effective in relieving symptoms, results vary greatly between patients.[3, 4] Several patient-related factors have been associated with the outcome of supervised exercise therapy, including: patient reported function and baseline walking distance.[5-7]

Gaining greater insights into individual prognosis may improve patient-centered care and optimize treatment results by enabling patients and clinicians to better anticipate the course of exercise therapy. Visualizing the prognosis may improve exercise adherence via behavioral science principles such as social norming. Additionally, an individual patient's prognosis can be used to benchmark progress in therapy, thus supporting personalization of an exercise program or other treatment decisions such as discharge from therapy.[8-11] However, prognostic work in this patient population has demonstrated limitations to date. Previous regression analyses have exhibited poor external validity, poor prediction accuracy and limited potential for application in daily practice.[5, 7]

An alternative approach to prognostic modeling is to use a semi-parametric, "neighbors-based" prediction methodology.[8, 12, 13] The central idea is to create individual prognostic profiles using historical outcomes data of patients similar to an index patient (a.k.a. the index patient's neighbors). The realized outcomes data of these similar patients, selected from a large database, are then used to generate the prediction.[8, 12] This approach has potential advantages over commonly used parametric prediction approaches (e.g. mixed effects models); in particular, it enables flexible and realistic estimates, and the display of historical data may improve salience in practice.[14]

This article aims to describe the development and evaluation of personalized outcomes forecasts for functional claudication distance over six months of supervised exercise therapy for patients with IC, using a neighbors-based prediction method. We hypothesized that the outcomes forecasts would demonstrate small average bias (<0.1 standard deviations, on average), with improved precision over prognostic estimates derived from the full sample. Additionally, we hypothesized that forecasts would be well-calibrated via both within-sample and out-of-sample analyses.

METHODS

Study Design

This retrospective cohort study used data from the Chronic CareNet Quality system.[15] Chronic CareNet is a clinical network responsible for the delivery of standardized supervised exercise therapy for all patients with IC in the Netherlands. The Quality system database receives data from the National Register for Physical Therapy; an initiative by the Royal Dutch Society for Physical Therapy.[16] The used pseudo anonymized and non-identifiable data falls out of the remit of the Medical Ethical Committee according the Dutch law. Patients and therapists provided informed consent to use their data for research purposes at initial collection. This study was reported according the standard reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD)-guidelines.[17]

Data Source

Data were gathered in routine clinical practice, extracted from electronic health records of physical therapist practices aligned with Chronic CareNet in the Netherlands. Standardized exercise training and testing is assured through training of all therapists affiliated with Chronic CareNet. Variables included in the database were: patient characteristics (e.g., age, sex, body mass index (BMI)), treatment processes (e.g., treatment duration, number of treatment sessions, achievement of treatment goal), patient reported outcome measures (such as quality of life and activity scores) and walking distances.[15] Patients' measurements were performed and documented by physical therapists every three months of treatment, according to the guideline recommendations.[18] For development and evaluation of the prediction model, data were extracted based on a start date of therapy between 2015 and 2019. To correct for any errors, patients were removed from the database when containing biologically implausible measurements or when lacking either baseline or at least one follow-up measurement for functional claudication distance. The database was split temporally (based on date of evaluation) into a training (75%) and test (25%) dataset. The training dataset was used to tune the procedures for neighbors-based predictions and examine model performance and the test set was used to examine out-of-sample calibration.

Outcome Variable

Personalized outcomes forecasts were developed for functional claudication distance, defined as the distance walked when a patient would elect to stop walking because of IC-induced pain.[5] Functional claudication distance was used as outcome measurement since it is a reliable and valid measurement for determining functional capacity[19] and because it is the primary outcome measure recommended in the Dutch treatment guideline.[18] Functional claudication distance was measured by physical therapists as part of daily clinical practice using standardized treadmill test (i.e. Gardner Skinner protocol)[20], with a speed of 3.2 km/h and increasing incline every 2 minutes by 2%, starting with 0%.

Matching Characteristics

The neighbors-based prediction approach uses patient characteristics to select neighbors (a.k.a. matches) from the existing database. Variables available for use as potential matching characteristics included: 1) age, 2) BMI, 3) functional claudication distance at baseline, 4) maximal walking distance at baseline, 5) motivation score measured as phase of behavior change, 6) pack-years of smoking, 7) quality of life measures using the Vascular Quality of Life Questionnaire-6[21], and 8) walking impairment measured using the Walking Impairment Questionnaire[22]. More detailed description of these variables is available in supplement 1. Of these potential matching characteristics, a subset was selected for use in neighbors-based predictions via procedures described in the following sections. The final set of matching characteristics were selected using backwards selection, which optimized the Akaike Information Criterion (i.e. step AIC function, lm package, R version 3.5.3).

Statistical Analysis

All analyses were conducted using R version 3.5.3 (R Foundation). The steps to generate a neighbors-based prediction by predictive mean matching are described in the following sections and are summarized in table 1.

Table 1. *Neighbors-Based Prediction via Predictive Mean Matching*

1. A Brokenstick model is fit to the training data to estimate functional claudication distance observations at 180 days following the initiation of supervised exercise therapy for all patients in the training set.
2. A multivariable linear model is fit with this 180-day functional claudication distance estimate as the outcome and "matching characteristics" (e.g., age, sex, baseline functional claudication distance measurement) as predictors.
3. Predicted values from the linear model serve as the matching metric. The realized functional claudication distance observations from m=223 matches are modeled with GAMLSS to generate the neighbors-based prediction.
4. Prediction performance is summarized via 3 metrics: Bias, Coverage, and Precision, via a Leave One Out Cross Validation approach.

Model Development: Selection of Matches by Predictive Mean Matching

Because the source dataset contained functional claudication distance measurements at irregularly spaced time intervals, a functional claudication distance measurement was estimated for each patient at 180 days following the initial assessment, using a linear mixed effects model via the Brokenstick package (R statistical computing).[12, 23] This timepoint was chosen since clinical follow-up commonly occurs at six months after the initiation of therapy, and prognostic estimates over this timeframe are therefore likely to carry value for clinical decision-making. The 180-day functional claudication distance estimate was used as the distal anchor for selecting matches by an adaptation of predictive mean matching. Multiple linear regression models were estimated with the 180-day functional claudication distance measurement (Brokenstick estimate) as the outcome variable and potential matching characteristics as explanatory variables. Of the available potential matching characteristics, only variables that contributed significantly ($p<0.05$) to the prediction of 180-day functional claudication distance were retained for subsequent steps.

The predicted values from the linear model were the metric upon which the matches (a.k.a. neighbors) were selected. Briefly, an index patient's matching characteristics would be entered into the multiple linear regression model, and a predicted value would be obtained. The patient records in the database with similar predicted values would be extracted as the neighbors for use in subsequent steps. In preliminary analyses, we determined the number of matches did not substantially influence the performance of the neighbors-based prediction approach when less than 30% (~1,400 patients) of the dataset was used for matching (supplement 2). However, when greater numbers of patients were used as matches, the average precision became substantially worse (i.e. greater uncertainty in prediction). Therefore, we elected to match any given patient to the nearest 5% of patients (matches, m=223).

Flexible Modeling of Outcome Data

For each patient in the training data, the realized functional claudication distance measurements from the patient's matches (m) were used to fit a Generalized Additive Model for Location Scale and Shape (GAMLSS).[24] The GAMLSS approach was chosen for its flexibility in modeling the median (location), variance (scale), and skewness (shape) as smooth function of time (i.e. time since initial evaluation). In particular, since functional claudication distance measurements were positively skewed, we chose to employ a modeling framework that accommodated changes in skewness over time. Cubic splines were fit to each of the parameters; 3 degrees of freedom (df) were used for the location parameter and 1 df was used for each of the scale and shape parameters. Since the degrees of freedom could not be independently optimized for each patient in the training set, this approach was taken to limit the potential for overfitting.[25] This same modeling approach was also used on the full training set to create a prognostic estimate that included the full sample.

Model Evaluation

The training dataset was used to improve the performance of the prediction methodology based on three metrics: 1) bias, 2) coverage, and 3) precision. We chose these metrics to gain insight into multiple relevant aspects of prediction performance. Bias was operationalized as the average difference (on a z-scale) between patients' predicted functional claudication distance measurements and the observed functional claudication distance measurements in the first six months following patients' evaluation appointments. By this approach, an average bias of zero would be ideal and deviations from zero would indicate systematic bias in the prediction approach. Coverage was operationalized as the percentage of observations within the 50% prediction interval (ideal = 50%). Deviations from the expected coverage would indicate limitations in modeling uncertainty. Precision was operationalized as the average width of the 50% prediction interval (narrower is better). These metrics were calculated by a leave-one-out cross validation approach[26], wherein GAMLSS models were fit to existing data from the m=223 closest matches to each of the patients in the training dataset. The realized data from each index patient was compared to the GAMLSS estimate to calculate bias and coverage, and the precision of the GAMLSS model was averaged over the first 180 days of supervised exercise therapy..

Model Calibration

To examine the calibration of the predictions, predicted versus observed functional claudication distance measurements were compared via calibration plots. For both the training and test sets, the predicted functional claudication distance measurements were binned by deciles. Within each decile of predicted functional claudication distance values, the median and the standard error (95%-confidence interval) of the observed functional claudication distance values were calculated. It was determined that the median was a better measure of central tendency given the skewness of functional claudication distance measurements.

RESULTS

Descriptive Statistics

The final dataset for analysis contained 17 926 functional claudication distance measurements of 5 940 patients (Figure 1). In total, 20 073 patient cases were excluded from the analysis, most commonly because of missing data in BMI, pack years and functional claudication distance. Patient characteristics from training and test sets are shown in Table 2. Baseline functional claudication distance was significantly different between the training and test sets, but there were no significant differences in other variables.

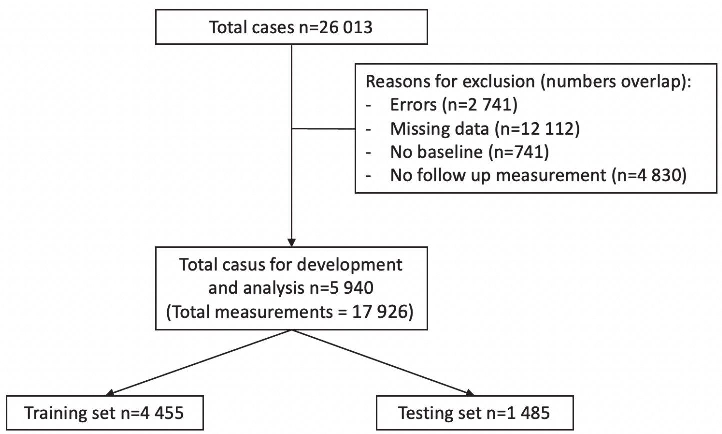

***Figure 1**. Flowchart for patient selection to create datasets to develop and evaluate personalised outcomes forecasts for functional claudication over six months of supervised exercise therapy, for patients with intermittent claudication.*

Table 2*. Baseline characteristics of patients with intermittent claudication treated with supervised exercise therapy and divided in the training and testing dataset to develop and evaluate personalised outcomes forecasts for functional claudication distance*

Characteristics*	Train (n=4 455)	Test (n=1 485)	P
Age in years	69 (9)	69 (9)	0.835
Gender, male (%)	62%	64%	0.168
BMI in kg/m^2	26.7 (4.4)	26.5 (4.4)	0.167
Pack years	34 (23)	34 (22)	0.542
Baseline functional claudication distance, meters	297 (248)	277 (238)	0.004
Motivation	3.11 (1.074)	3.06 (1.053)	0.080

*Mean (sd) unless stated otherwise. Abbreviations: BMI = Body mass index, kg = kilogram, m = meter, n = number of cases, sd = standard deviation.

Model Development: Selection of Matches and Number of Matches

The following characteristics demonstrated a statistically significant relationship with the Brokenstick estimate of 180-day functional claudication distance: age (b = -5.7; p = <0.001), sex (reference = male; female: b = -27.1, p = 0.01), pack years (b = -0.7; p = 0.005), BMI (b = -7.5; p = <0.001), motivation (b=15.5, p=0.002) and baseline functional claudication distance (b = 0.93; p <0.001) (Figure 2). Baseline functional claudication distance was the most important matching characteristic, carrying the most weight in predictive mean matching with a standardized beta coefficient of 0.54 units of standard deviations. (see figure 2) Due to high correlation between functional and maximal walking distance at baseline, maximal walking distance was left out the final model. The predicted values from this multivariable linear regression were used as the matching metric and ranged from 220 meters to 2 522 meters (Figure 2).

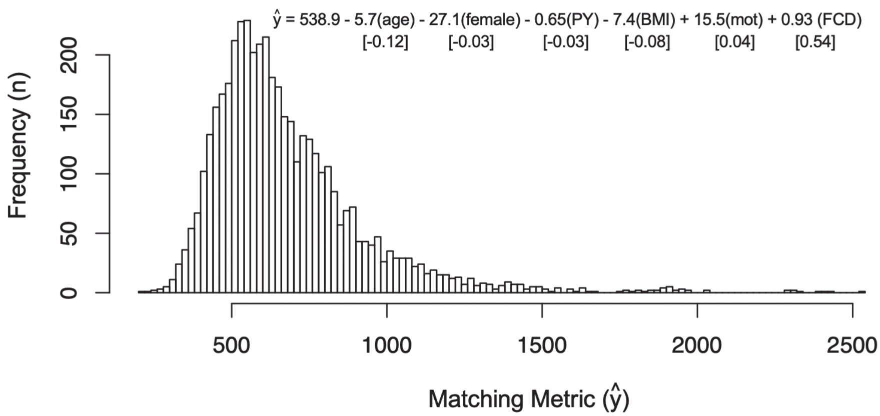

Figure 2. *A histogram of the matching metric (y); the multiple linear regression shown used to calculate the matric metric is inset. PY= Pack Years; FCD= Functional Claudication Distance at baseline; BMI= Body Mass Index; mot= motivation. Standardized beta coefficients are provided in [square brackets].*

Model Evaluation and Calibration

With this approach, the average bias was found to be -0.04 standard deviations, the average coverage (proportion of realized observations within the 50% prediction interval) was found to be 48.7 percent, and the average precision (the average width of the 50% prediction interval) was found to be 313 meters. For comparison, the average precision of the GAMLSS model that including all patients in the training set (i.e. the full-sample prognostic estimate) was 412 meters. Thus, the neighbors-based prediction approach amounted to a 24% improvement in precision relative to a prognostic estimate derived from the full sample (Figure 3). The predictions appeared well-calibrated; the observed values fell within the standard error of the median of predicted values across all deciles, according to both within-sample and out-of-sample analyses (Figure 4).

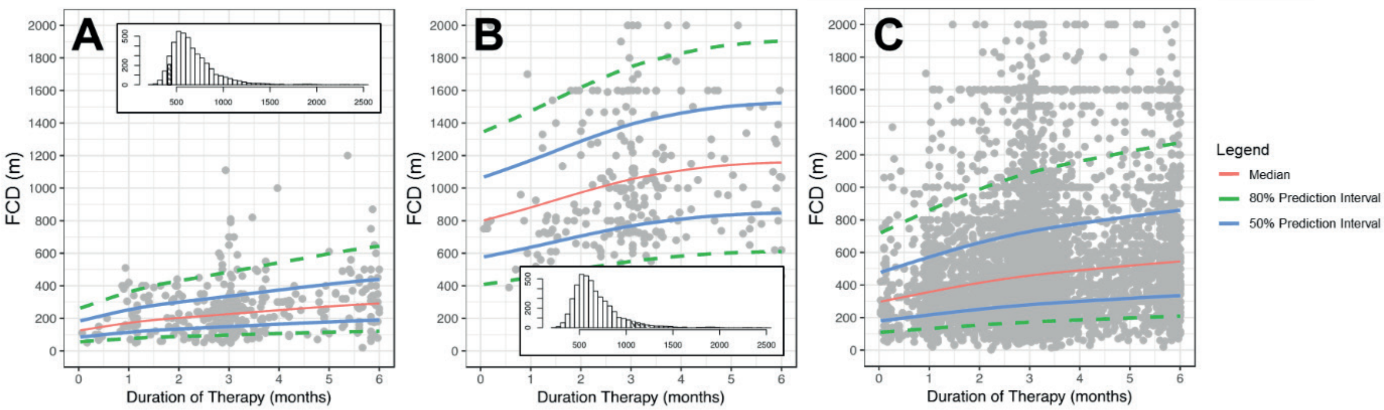

Figure 3. *Neighbors-based predictions for example patients with intermittent claudication with matching metrics A) in the 5th percentile and B) in the 95th percentile. Histograms of the matching metric are shown as insets, with the position of the m=223 used for the neighbors-based prediction indicated. C) The population level GAMLSS model is shown for comparison. FCD: Functional Claudication Distance*

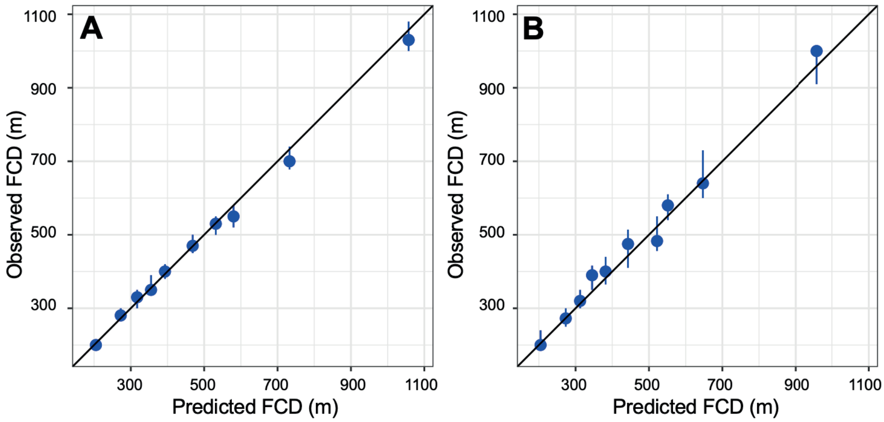

Figure 4. *Calibration plots of neighbors-based predictions for patients with intermittent claudication for A) the training dataset, and B) the test dataset. FCD: Functional Claudication Distance*

DISCUSSION

We developed neighbors-based predictions to forecast functional claudication distance over the course of six months of supervised exercise therapy, for patients with IC. This prediction approach used historical data of selected matches (a.k.a. neighbors) to estimate the functional claudication distance for a new patient, over the course of supervised exercise therapy. Results of the prediction performance were in accordance with our hypotheses; within-sample testing indicated small average bias, accurate average coverage and improved average precision of the individual patient predictions relative to prognostic estimates derived from the full sample. To our knowledge, this is the first use of a neighbors-based prediction method in this patient population.

Several features of this prediction approach may ultimately promote its usefulness in clinical practice. First, the small average bias (-0.04 standard deviations) suggests the predictions are accurate on average, with no evidence of a systematic over or underestimation. Second, we calculated coverage to be 48.7%, meaning 48.7% of realized observations fell within the 50% prediction interval. This suggests the approach accurately models uncertainty in functional claudication distance, which is potentially important for clinical interpretation. If a patient is performing better or worse than expected, it is important to be able to interpret the magnitude of the deviation (i.e. the probability of an observed deviation from the predicted value) as this is an indicator of the degree to which a measurement should be interpreted as good (if it is better than predicted) or bad (if it is worse than predicted). Finally, neighbors-based predictions were 24% more precise, on average, compared to the prediction model derived from the full sample. This suggests the potential for the precision of the neighbors-based predictions to confer clinical utility. For example, with this level of precision, the predictions are distinct between individuals with good versus poor prognosis (Figure 3).

There are at least two major areas where neighbors-based predictions might be useful in clinical practice: 1) setting patient expectations and promoting adherence to exercise therapy, and 2) monitoring progress in therapy to detect treatment success and failure. Neighbors-based predictions may be particularly useful for helping patients and clinicians understand prognosis; the use of historical clinical data enables ensemble visualization (i.e., displaying a group or cluster of data points), which intuitively conveys the prognosis and uncertainty in prognosis. This also creates an opportunity to leverage behavioral science principles such as social norming; by comparing a patient to her or his peers, the patient may be motivated to adhere to the exercise program to match or exceed others' performance. Additionally, the neighbors-based prediction could be used as a template against which to benchmark progress in exercise therapy. If a patient is underperforming expectations, this could stimulate therapists to modify the exercise program or refer the patient for consultation with another provider/discipline (e.g. vascular surgery).

Previous studies have used regression analyses to examine changes in walking distance over the course of supervised exercise therapy.[5-7, 27] These studies have found that factors such as baseline walking distance, BMI, age, sex and comorbidity status are significantly associated with walking distance outcome following supervised exercise therapy. Our results largely align with these previous findings. Of all available matching characteristics, baseline walking distance was the most influential in determining matches (a.k.a. neighbors), carrying roughly five times the weight of the next most influential factor: patient age. Smoking history (measured in pack years), BMI, motivation level, and sex, although statistically significantly associated, were less influential. Although many important clinical factors (e.g. comorbidity status) were not measured in this study (5), a person's baseline walking function may also indirectly capture many important health or functional prognostic factors.[6]

Previous regression analyses in this patient population have reported high levels of uncertainty in predictions. Farah et al reported that less than one third of the predicted walking distance values were within 25% of the realized outcome measurements.[7]

Kruidenier et al reported that between 25 and 34% of patients' realized walking distance outcomes were within a predefined target range of 325 to 400 meters.[5] Direct comparison of these previous findings to our results is difficult due to the different methodologies used; however, there is evidence that the neighbors-based approach may yield improved precision. Briefly, the 50% prediction interval of the neighbors-based approach was 313 meters (on average), and 49% of the realized measurements fell within this interval. This appears to be an improvement on the results of Kruidenier et al., wherein a lesser proportion of the realized data fell within a larger target range.[5] One of the attributes of the neighbors-based approach is its flexibility; both the prognostic trajectory and prediction interval are allowed to vary substantially across individual patients. This may enable improved precision over previously tested approaches.

Limitations

The main limitation of this analysis was our use of clinically collected data. On the one hand, no eligibility criteria were applied to study participants; thus, clinically collected data may be more generalizable to routine practice. On the other hand, because we were reliant on therapists to collect data in the context of routine practice, this contributed to missing data. Additionally, challenges arise when creating and implementing a national data registry like the Chronic CareNet Quality system, including the wide variety of electronic health records from which to extract data.[15] Therefore, many patients were excluded from the database due to incomplete follow-up measurement or no follow-up measurement at all. A valid reason for lacking follow-up measurements might be early termination of supervised exercise therapy or lack of compliance to therapy. This could have caused bias in our prediction approach. For example, if patients who are lost to follow-up tend to have worse clinical outcomes, the predictions would systematically overestimate functional claudication distance. Therefore, prospective testing should be performed to investigate for the presence and extent of any bias in predictions. Nevertheless, our analysis relied upon a relatively large dataset (n=4455), and our temporal validation suggested the predictions performed well in out-of-sample testing.

Finally, our dataset lacked several variables that might be expected to influence patients' prognosis, such as location of stenosis, comorbidity status, and details of the supervised exercise therapy (e.g. adherence, intensity). As mentioned, it is likely that many health factors that affect physical function are captured by the initial walking measurement. Differences in training programs have potential influence on the outcome of supervised exercise therapy, but tend to be very difficult to capture as structured data.[28] Moreover, uniformity in exercise programs might be expected in our source data, as all participating physical therapists are aligned with Chronic CareNet and are educated in the general recommendations stated in the Royal Dutch Society for Physiotherapy guidelines for treatment of peripheral arterial disease.[18]

Future Directions

We foresee two major areas of future work: 1) refining prediction performance and comparing the neighbors-based approach to other prediction approaches, and 2) examining the influence of predictions on clinical decisions and treatment outcomes for patients with IC. Specifically, future research might attempt a direct comparison of the neighbors-based methodology with other prediction approaches, to further probe the strengths and limitations. Additionally, the neighbors-based approach could be extended in future work through the inclusion of additional matching characteristics or with adaptations to the approach (e.g. varying the numbers of matches across individuals). Ultimately, research should focus on translating this or other prediction methodologies to the point-of-care, to explore the effect of real-time prognostic estimates on clinical decision-making and patient outcomes.

CONCLUSION

In this study we developed and tested a neighbors-based prediction approach, to estimate functional claudication distance for patients with intermittent claudication undertaking a supervised exercise therapy program. The neighbors-based prediction approach enabled improved precision over previously described approaches in this patient population. Ultimately, this prediction methodology may inform the clinical use of personalized outcomes forecasts, which have the potential to support patient engagement and clinical decision-making to ultimately improve patient-centered care.

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CHAPTER 5

The Impact of Personalized Outcomes Forecasts on Clinical Reasoning of Physical Therapists in Intermittent Claudication: A Vignette Study

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ABSTRACT

Background

Guidelines recommend supervised exercise therapy and lifestyle counselling by a physical therapist as initial treatment of patients with intermittent claudication (IC). However, guidelines only provide a crude estimate of what outcomes therapists and patients may expect from treatment. We developed a clinical decision support system, which generates personalized outcome forecasts that provide insight in what an individual patient may expect from the treatment.

Aim

Our purpose was to explore the impact of personalized outcomes forecasts (POF) on the decision-making process of physical therapists and to learn lessons on facilitating the use of forecasts in daily practice.

Study design

We utilized a vignette-based, think-aloud interview study design. We included therapists trained in treating patients with IC. Vignettes described fictitious patients diagnosed with IC and included POF. A directed approach was used to code, organize and describe the data. Transcripts were analyzed by a thematic approach.

Results

Sixteen therapists participated in the study. Three themes were identified: 1) setting and contextualizing treatment expectations; 2) setting (shared) goals and (de)motivating the patient, and; 3) establishing and monitoring the treatment plan. Therapists mentioned POF could be useful for setting expectations and realistic treatment goals, contextualizing expected treatment response, stimulating patients to achieve their goals, and deciding on treatment frequency and treatment timing. Therapists thought POF would be of less use for changing treatment goals during follow up visits or for establishing intensity or type of training.

Discussion

This study explores the use of POF by physical therapists for patients with IC. To overcome challenges that may arise when adopting POF in daily practice, adequate training of physical therapists should be conducted. Potential areas to address with training include statistical and data literacy, as well as guidance on integrating outcomes forecasts with existing treatment protocols.

IMPACT STATEMENT

The use of personalized outcomes forecasts (POF) by physical therapists might contribute to a more person-centered care approach. We have provided insights in the first use of POF by physical therapists that might serve as an example and lessons on how to optimally implement such supporting tools into daily practice.

INTRODUCTION

Intermittent Claudication (IC) is caused by atherosclerotic narrowing in the arteries of the lower extremities and is defined as walking-induced discomfort or pain in the leg or hip muscles, which attenuates after a brief rest.[1 2] Recommended treatment for patients with IC is supervised exercise therapy and lifestyle guidance, administered by a trained physical therapist.[1-3] However, recommendations for guidelines are generally very broad and lack support to personalize therapy to the individual patient.[4 5]

To support clinicians in adapting the guidelines to individual patients and making individualized decisions, personalized outcomes forecasts (POF) might be of value.[4 6-9] A personalized outcomes forecast is an estimation of an individual patient's outcome over time based on historic outcome data of patients with similar characteristics to the individual patient.[6] Only a specific subset of previously treated patients are selected from existing records to create the forecasts.[4 6-8] In physical therapy care, outcome forecasts have already been proposed in different sub-fields to support therapists and patients by increasing their insight into the expected treatment course.[7 10 11]

Personalized outcome forecasts might be used in practice to facilitate therapists' clinical reasoning, by supporting the personalization of the care plan. Furthermore, therapists might be able to better inform patients of the expected course and outcome of therapy, thereby supporting patient engagement and shared decision-making. However, the impact of POF on clinical reasoning and shared decision-making potential has yet to be examined.

The goal of this vignette study was to explore how the use of POF might impact the treatment of patients with IC, when used by physical therapists specialized in treating this population. Specifically, the impact of the forecasts on 1) goal-setting, 2) the clinical reasoning process and 3) the willingness of therapists to make shared decisions with patients. Developing and implementing personalized outcome forecasts was considered ideal in the care context of Dutch physical therapists treating patients with IC for two reasons. First, this group of therapists is working evidence- and guideline-based, due to extensive implementation activities in the past[12]. We believe this is a prerequisite for personalizing care. Second, due to the nationwide Chronic Care Network[13], sufficient routinely collected data are available to adequately develop personalized outcome forecasts.[14] A secondary goal was to explore for opportunities to improve the outcomes forecast tool, to facilitate implementation in clinical practice.

METHODS

Study Design and Setting

This study used a vignette-based, think-aloud interview design with a narrative approach to explore the effect of POF on physical therapists' clinical reasoning and willingness to make shared decisions in treating patients with IC. A narrative approach means that individual experiences on the subject are gathered through conversation and used as raw data.[15] The think-aloud method was used to capture participants' thoughts and feelings, as a way of illuminating the underlying reasoning. This method is based on the assumption that an individual's cognitive process is directly accessible as verbal data; it is a well-established method to describe the sequence of clinical reasoning thoughts.[16-18] The study was conducted from June to September 2019 in the Netherlands through Chronic CareNet. Chronic CareNet is a nationwide network of physical therapists specifically trained to treat patients with non-communicable chronic disease (among which IC) according to the most recently published national guideline.[1 2] This study was reported according the Standards for Reporting Qualitative Research (SRQR) guideline.[19] This study was reviewed by the Medical Research Ethics Committees United 'MEC-U' (reference number W19.094) and was determined to be exempt from formal medical ethical approval. Written informed consent was obtained from all participants.

Personalized Outcomes Forecasts

POF are individual estimates of patients' maximal walking distance over a 6-month course of supervised exercise therapy. Maximal walking distance is a commonly used clinical outcome measure in this patient population. Briefly a patient is instructed to walk on a treadmill at a standardized speed until claudication-related pain forces the patient to stop.[20] POF and the underlying methodology were previously developed using a neighbors-based prediction approach.[6 7] By this approach, a prediction for any new patient can be generated using historical data of similar patients. POF are integrated into a web-based application, accessible for therapists to visualize the expected trajectory of maximal walking distance for a patient.

Participants

Participants were recruited by the first author (AS, PhD candidate with Chronic CareNet) through convenience sampling. Physical therapists associated with Chronic CareNet who worked in outpatient clinics close to the interview location were invited by email to participate in this study. All therapists affiliated with Chronic CareNet were naive in using POF, as these forecasts were not implemented in daily practice. Therapists who did not respond to the email were additionally contacted by phone. The final number of participants was based on data saturation. Data saturation was achieved as no new codes emerged during analysis. This was checked by performing one additional interview after coding all the previous interviews. Study participants were compensated with a gift voucher and Chronic CareNet continuing education credits.

Vignettes

Vignettes were designed according to current recommendations, to include a clearly written, concise, narrative and story-like progression. We aimed to include a balance of factors while avoiding misleading details.[21 22] All vignettes were based on real patients with IC referred to a physical therapist for supervised exercise therapy. Each vignette included three different structural elements: 1) experimental aspects, wherein the effect on the outcomes forecasts was assessed by systematically manipulating these aspects across the vignettes, 2) controlled aspects, which were kept consistent across vignettes to limit additional unwanted variance, and 3) contextual aspects, which were used to create some variance across vignettes.[21 23] The complete factorial combination of the experimental aspects resulted in 12 different vignettes of which six case vignettes were selected for the study by a panel of five experts, (three physical therapists (two with experience in treating patients with IC), and two researchers). Experimental effects included: age, walking distance, and therapy outcome over time. Controlled aspects were the diagnostic findings (e.g. diagnosed IC). Contextual aspects included patient sex, symptoms, smoking status, height, and weight.

The vignettes and interview guide (see supplemental material) were developed by the first author (AS) in collaboration with the project group (TJH, AJK, SP and PJW). The development of these vignettes was informed by 1) the framework for clinical reasoning according the Hypothesis Oriented Algorithm for Clinicians II (HOAC II) and 2) the three stages of shared decision-making: a) explanation of treatment options, b) providing information, and c) compiling treatment plan or goals together with the patient.[24 25] Each vignette was divided into five parts: 1) the patient history, 2) treadmill test results, 3) baseline personalized outcome forecasts, 4) three-month follow-up results, and 5) follow-up personalized outcome forecasts. After each part of a vignette, the interviewer asked questions according to the interview guide. The overall structure and content of the vignettes and the interview guide is summarized in Figure 1. In two separate interviews with two physical therapists, the interviewer tested the vignettes and interview guide under the supervision of the project group. No changes were made after testing.

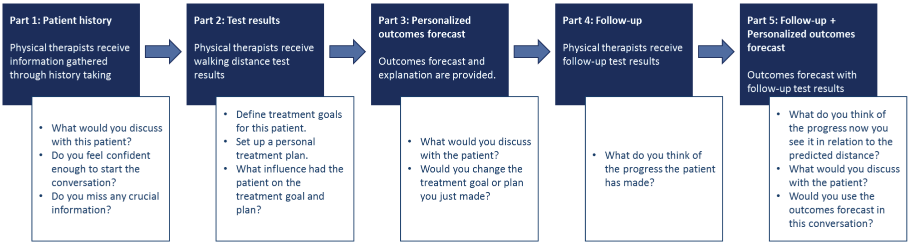

Figure 1. *Overall structure of vignettes.*

Study Procedure and Data Collection

Participants received verbal and written information regarding the aim of the study and the think-aloud method. Interview sessions (~ one hour) were one-on-one. Each participating physical therapist was audio recorded during the session. A directive approach was applied, meaning that the interviewer directed the semi-structured interviews by asking specific questions according to the interview guide and the vignettes.[26] Interviews were performed by a qualified and experienced research assistant (AOB, psychologist, MSc), with 7 years of experience in performing semi-structured interviews. AOB was additionally trained for this study, as she is not a physical therapist. Participants were not familiar with any details of the interviewer. All participants received a brief verbal explanation of the POF and how to interpret them (see supplemental material). Each participant worked through at least one vignette, or two if time allowed. Participants could determine their own tempo on reading and answering the questions.

Data Analysis

Interviews were transcribed by a professional company. Transcriptions were not returned to participants for correction. Transcripts were analyzed by a thematic approach to identify, analyze and report patterns (themes) within the data. Thematic analysis comprised six different phases according to the described outlines of this method: getting to know the data, generating codes, searching for themes, reviewing themes, defining and naming themes and finally producing the report.[27] A directed approach was used to code, organize, and describe the data. Coding and data analyses were performed by two independent researchers (AS and AOB) using coding software (ATLAS.ti 8.4. 20). Description of the coding tree and framework for the themes were provided by the first author. The coding tree and framework were based on the vignette and interview guide. Consensus meetings with the complete research team were used to optimize the coding tree, framework for the themes and final codes. See figure 2 for an example creating codes and themes.

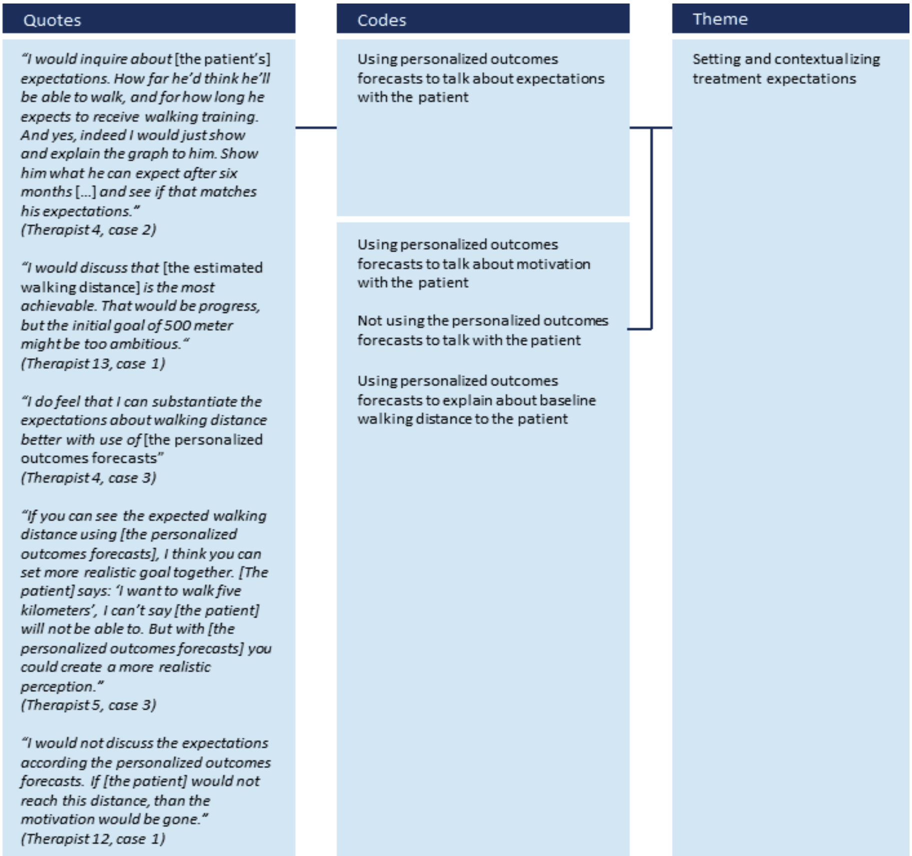

Figure 2. *Example of creating themes from codes from transcripts.*

Trustworthiness

To ensure trustworthiness of the study, different strategies were applied. First, data were coded and analyzed by two independent researchers (AS and AOB). Second, professional coding software was used to enhance confirmability of the outcomes (ATLAS.ti 8.4.

20).[28] Third, detailed context data were gathered to increase transferability, including participant characteristics, description of the vignettes, research group background and interview setting.[29] Fourth, to create a good compatibility between the participants and the interviewer, it was explained that there were no right or wrong answers. Furthermore, since the interviewer was not a physical therapist, which allowed her to easily question every decision that physical therapists made, without being judgmental or normative. Last, member checking was performed continuously during the interview sessions through verbal verifying of information provided by the participants. [29]

RESULTS

A total of 35 physical therapists were approached by phone to participate. Of these potential recruits, 16 therapists agreed to participate. The primary reason for not participating was lack of time. See Table 1 for demographic information participants.

Participant ID	Age	Sex	Degree	Years affiliated Chronic CareNet†	Number of patients with IC	Duration interview (Minutes)
1	43	male	BSc	6	3 / week	40
2	34	female	MSc	3	6 in total *	42
3	48	female	BSc	8-9	5-6 / week	63
4	27	female	BSc	2-3	2-3 / week	57
5	34	female	MSc	8-9	7-8 in total*	51
6	44	female	BSc	3	6 in total*	73
7	41	male	BSc	6	6 -7 / week	73
8	29	male	BSc	3	2 / week	36
9	54	male	BSc	6	6 / week	53
10	60	male	BSc	8-9	6 / week	78
11	28	female	BSc	4	7 / week	78
12	49	female	BSc	4	4 in total*	65
13	59	male	BSc	7-8	1 / week	43
14	30	male	BSc	4-5	6 / week	73
15	30	female	MSc	4 months	2 / week	44
16	31	female	BSc	4 (no longer active)	5 / week	73

Table 1. *Characteristics of participating physical therapists. Abbreviations: MSc = master of science, BSc = bachelor of science, IC = intermittent claudication. *In total means the total number of patients who are treated at the moment, but not necessary visiting every week. †Years affiliated with Chronic CareNet the minimum years of experience in treating specifically patients with intermittent claudication.*

Physical therapists were asked what they would normally discuss with patients during the history taking. Therapists mentioned typically discussing the course of the disease and content (and advantages) of supervised exercise therapy. Moreover, therapists aimed to gain insight into patients' intrinsic motivation, knowledge, and expectations of supervised exercise therapy. Other topics the patient's complaints, symptoms, functional limitations, comorbidity, lifestyle (i.e., smoking habits and diet), social environment, medication use, home situation, and daily activities (including sport activities). Some therapists mentioned using the patient interview to establish a trusting relationship with the patient. In total, three themes were identified related to the potential role of the personalized outcomes forecast in care: 1) setting and contextualizing treatment expectations; 2); setting (shared) goals and (de)motivating the patient, and; 3) establishing and monitoring the treatment plan.

1. Setting and Contextualizing Treatment Expectations

Physical therapists mentioned that they believed POF could be useful for setting expectations of therapy outcome and putting the expected treatment response in context of the patient. Moreover, therapists mentioned POF could be helpful to explain about baseline walking distance in relation to patient-specific characteristics.

> *"I would inquire about* [the patient's] *expectations. How far he'd think he'll be able to walk, and for how long he expects to receive walking training. And yes, indeed I would just show and explain the graph to him. Show him what he can expect after six months […] and see if that matches his expectations."* (Participant 4, case 2)

> [Participant explains what he would discuss with the patient] *"Does* [the patient] *experience any other problems? It is expected that he can walk 380 meters after three months* [of walking therapy]*, but the complete picture is important. Does he suffer from dyspnea afterwards? How is his walking pattern? For example, if he reaches 380m stumbling, he is able to walk that distance, but not pleasantly."* (Participant 12, case 1)
> See figure 3 for the personalized outcomes forecast for case 1.

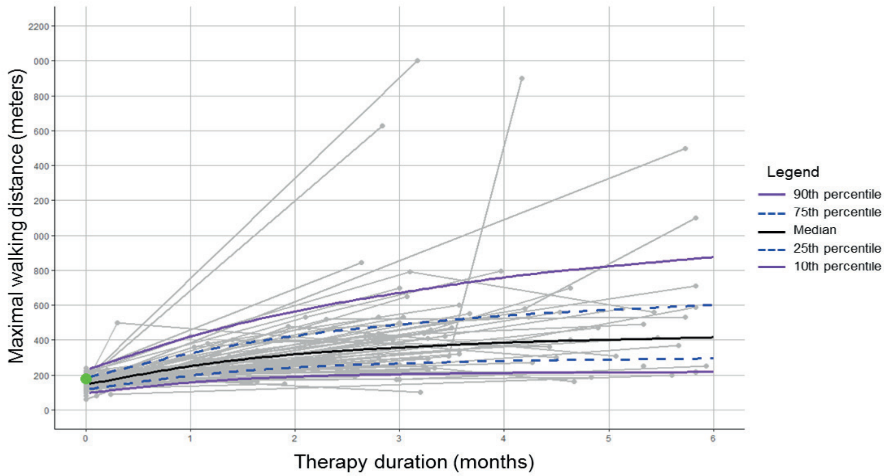

Figure 3. *Personalized outcomes forecast Case 1.*

Conversely, some physical therapists mentioned they would not use the personalized outcomes forecast during the patient interview. These therapists felt confident their personal experience in treating these patients was sufficient to explain the expected prognosis. Others reported that they did not want to compare their patient with results of others, but rather treat them entirely on an individual basis. Also, some therapists believed the graphs to be too complicated for patients and themselves. Finally, some therapists could see themselves using the POF, but did not see it having an impact on the care provided.

> *"I do not need* [the personalized outcomes forecast] *to explain the prognosis to my patients. [...] I can imagine it being useful* [in discussing the therapy] *for the patient though. A patient likes to be displayed the expectations. But I can only speak from my own perspective*" (Participant 3, case 4)

> [A participant who appeared to misinterpret the forecasts said]: "*Most patients will understand the graphs to the same extent as I do and they would think the graphs and questionnaires are pointless, as they come here to walk better. For my patient population it's irrelevant whether they perform better or worse than the national average; they have their own goal."* (Participant 6, case 4)

2. Setting (shared) Goals and (de)Motivating the Patient

Physical therapists explained how they normally set treatment goals together with the patient, based on the initial measured walking distance, as well as the patient preferences. In the case that a patient sets an unrealistic goal, therapists mentioned they would intervene to help set an achievable goal. Physical therapists believed POF could be helpful particularly in setting realistic treatment goals, which would in turn stimulate patients to achieve these goals.

> *"If a patient has a goal to walk 2 kilometers after one year... and the prognosis suggests she will walk 1 kilometer after 6 months... then you can test the feasibility of the walking therapy goal."* (Participant 1, case 6) See figure 4 for the personalized outcomes forecast for case 6.

> *"If you see what the predicted values are, I think you are able to set a realistic goal together. He* [the patient] *says: "I want to walk five kilometers." [...] With the prediction tool you would be able to set a more realistic expectation. You can tell the patient what is the evidence-based prediction and base your goal on that." (Participant 5, case 3)* See figure 5 for the personalized outcomes forecast for case 3.

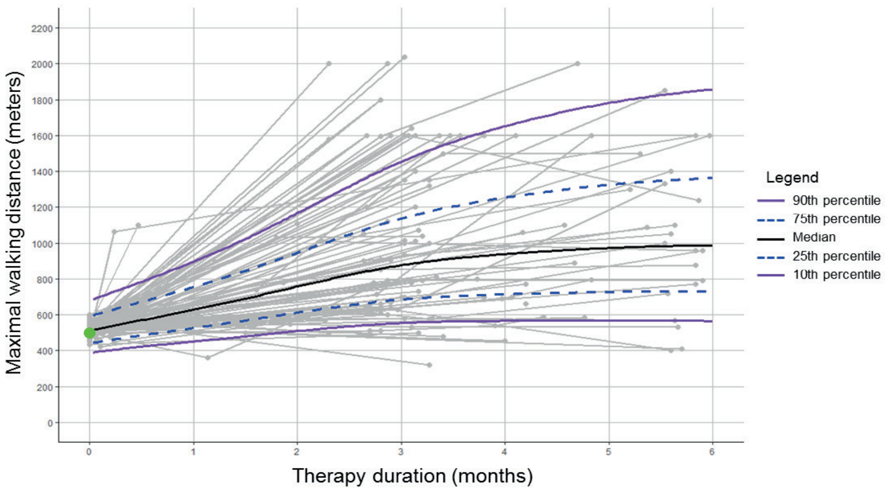

Figure 4. *Personalized outcomes forecast used in Case 6.*

Therapists also believed that POF would be useful for setting secondary therapy goals. Therapists mentioned setting the secondary goals typically by themselves, with less involvement from the patient, based on the patient's needs. Secondary goals could include things like lifestyle modifications, gaining strength, optimizing balance, improving walk pattern quality, increasing daily activity, and enhancing health self-management. The therapists mentioned that POF might provide a springboard for discussing such goals (e.g., patient motivation, physical condition, comorbidity and social factors) with the patient.

> *"Yes, so I would discuss* [setting the primary goals] *with the patients. However, regarding the secondary goals, I think I would actively suggest to the patient what progress would be desirable in my opinion."* (Participant 15, case 2)

Physical therapists pointed out that POF could also stimulate patients to achieve their goals. At the initiation of therapy, therapists mentioned it might be motivating for patients to see what is possible. During therapy, the outcomes forecast would be helpful for starting a conversation about motivation, by showing a patient's progress compared to the original predicted value.

> [Therapist looking at the graphs] *"Well that's just fantastic. I would tell someone: "if you were going to do what is best for you, it is projected that after three months you could already walk 1,160 meters, instead of what you can walk right now." I think that would be a motivation for those people."* (Participant 9, case 3) See figure 5 for the personalized outcomes forecast for case 3.

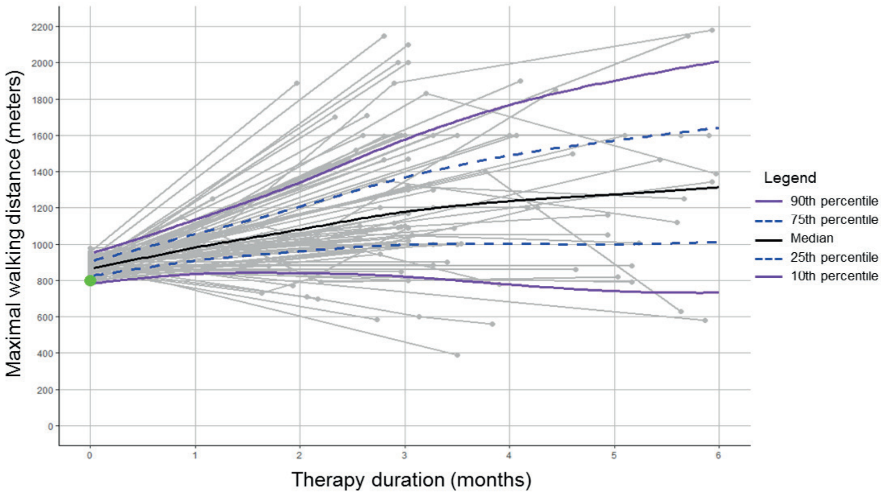

Figure 5. *Personalized outcomes forecast for case 3.*

[Participant is asked whether he/she would change the original treatment goal after seeing the personalized outcomes forecast] *"Yes, I would keep the goal of one kilometer. Well, maybe he will reach 800 meters, or 850m, but I think this will be a good motivation to achieve his own goal."* (Participant 14, case 2)

At the same time, therapists also mentioned how POF could potentially demotivate a subgroup of patients at the start of therapy or during therapy. In particular, therapists believed that patients with a relatively poorer prognosis might be discouraged even before starting therapy. Therapists mentioned they would try to lower the patient's goal before showing the personalized outcomes forecast or only show the personalized outcomes forecast if a patient is performing above the predicted walking distance during follow up measurements. Therapists indicated it could be disappointing for patients to see the personalized outcomes forecast if a patient performs below the predicted walking distance during follow up.

"So, the prognosis is not very favorable. If you follow the line further, the line would flatten. So, at the end there is not much progress anymore. That is absolutely not stimulating." (Participant 1, case 6) See figure 4 for the personalized outcomes forecast for case 6.

"I am not going to compare my patient to other patients. [The patient] *is performing below average. So be it. It is not about how all other patients in the population performed."*

(Participant 12, case 1) See figure 3 for the personalized outcomes forecast for case 1.

Some therapists mentioned they would change their primary and/or secondary treatment goals after receiving the final two sections of the vignette, which included the three-month follow up results combined with the personalized outcomes forecast. Changing treatment goals during follow up was dependent on achieved progress, patients' motivation and needs.

[Participant speaking to the imaginary vignette patient] *"What do you think of this result? Do you still prefer the one kilometer as treatment goal, or could we work towards another goal you are satisfied with?" [...] Looking at the graph, six months equates to roughly 500m. "Shall we see if we can reach 600m?"* (Therapist 14, case 2) See figure 6 for the personalized outcomes forecast for case 2.

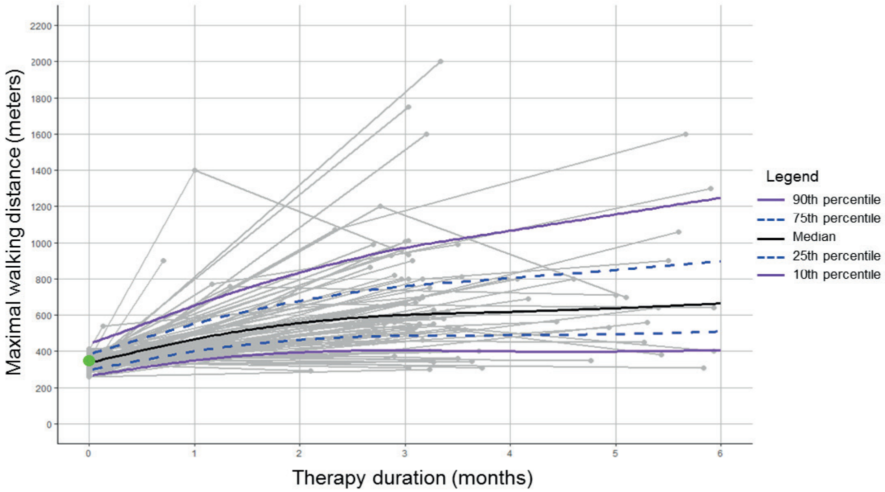

Figure 6. *Personalized outcomes forecast case 2.*

3. Establishing and Monitoring the Treatment Plan

Physical therapists explained that the treatment plan is normally based on the standard treatment protocol as described in the guidelines, but could be influenced by treatment progress, results, motivation and/or self-management. Regarding visitation frequency, they mentioned that they would initially see patients more frequently and decrease frequency after one to three months. Training content included treadmill walking, (outside) walking, cycling, strength training, conditional training, balance exercises and lifestyle coaching. Homework (e.g., outside walking in addition to therapy, or participation in walking groups) was also mentioned as part of the typical care plan. Making shared decisions with the patient about visitation frequency, training content or homework was not mentioned by therapists. Therapists indicated they would use the personalized outcomes forecast to adapt their standard treatment plan to the expected walking distance. For example, they proposed changing visitation frequency, recommending more homework, adding group therapy, or extending the duration of therapy. They suggested that POF would not affect the content of training sessions, which typically included treadmill training.

> [Participant answering whether she would change the treatment plan after seeing the personalized outcomes forecast] *"I would intensify the training. Initially I planned training twice weekly and then reducing the frequency to once per week. However,* [seeing the personalized outcomes forecast] *I would – at the very start – train [the patient]*

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> *maybe even three times per week and then reduce it to twice weekly.*" (Participant 5, case 3) See figure 4 for the personalized outcomes forecast for case 3.

Physical therapists explained they would perform follow-up measurements every three months using treadmill walking tests and standard questionnaires, according to the standard protocol. Additionally, therapists pointed out they would monitor progression through conversations (i.e. asking the patients' experience on therapy progression), observations during training, walking journals, clinical walking tests, and strength tests. Therapists did not mention involving the patient in decisions regarding the monitoring plan. Therapists indicated that POF would not influence the monitoring plan.

> [Interviewer asked whether the participant would change his monitoring plan] *"No, I would measure the first time after 3 months, because at that time* [the patient] *has superseded his initial goal* [as is depicted in the graph of this vignette patient, red]. *That motivates. Then I would leave the monitoring plan like it is, just every 3 months."* (Participant 16, case 2) See figure 6 for the personalized outcomes forecast for case 2.

DISCUSSION

The goal of this study was to understand how the use of POF (displaying the projected walking distance for a patient with IC, over the course of therapy) might impact physical therapists' decision-making. We found that participating physical therapists consider POF useful for setting expectations and contextualizing expected treatment response. Furthermore, therapists believed POF could be helpful for setting realistic primary and secondary treatment goals and to stimulate patients to achieve their goals throughout therapy. A counter-intuitive finding was that therapists thought POF would be of less use for modifying treatment goals during follow-up sessions. Therapists deemed POF helpful in deciding on the treatment frequency and timing, but not for intensity or type of therapy when establishing a treatment plan. The option to alter the treatment program or stop supervised exercise therapy and pursue other treatment options (e.g. medical or surgical options) was also not mentioned. Finally, POF seemed to elicit shared decision-making thoughts on the part of therapists, but many care decisions were still viewed as under the purview of therapist.

Kittelson *et al*, who proposed outcomes forecasts as a practical way of increasing the personalization of physical therapy care, discussed a potential challenge to the adoption of POF in daily practice: a poor prognosis might yield unintended negative consequences.[6]

A number of therapists in our study shared that concern. Some therapists believed that a poor prognosis or poor performance could be discouraging to a patient. However, if patient prognosis or performance is poor, the personalized outcomes forecast is only one route by which patients might come to this realization. Another route could be the failure of patients to achieve personal goals. Thus, it might be best to encounter the understanding of a poor outcome in a setting with a physical therapist to answer questions and provide counseling and treatment options. Nevertheless, a number of therapists in our study mentioned they considered withholding the POF in the case of what they perceived to be a poor prognosis. On the one hand, withholding information is in conflict with the patient's right to know (i.e., autonomy and the right to self-determination), one of the fundamental principles of modern healthcare.[30 31] On the other hand, if POF are viewed as a clinical tool, it could be argued that clinicians often make decisions on the use (or non-use) of various tools or modalities. Such epistemological discussions should continue as these tools are increasingly developed and deployed.

Another challenge for implementing POF is the possible misinterpretation.[9] Problems in understanding the personalized outcomes forecast graphs may arise due to poor numeracy or statistical literacy. A fluent understanding of probabilities and statistical uncertainty would be helpful to fully grasp the prognostic displays. For example, if the prognosis shows the 75th percentile is at 1000 meters, the appropriate interpretation is that 1 out of 4 similar patients achieves a walking distance of at least 1000 meters. This understanding is likely to be important for setting reasonable goals and interpreting successes and failures throughout therapy. Uncertainty of the prognosis is intentionally displayed on the graphs to attempt to facilitate accurate interpretation. In this study, not all therapists seemed to understand the POF correctly after the short explanation they received at the start of the study. Therapists who misunderstood and/or misinterpreted the POF showed more resistance in using the tool. When implementing these forecasts in daily practice, it is essential that therapists are adequately trained in use and interpretation, such that they feel prepared to communicate the information to patients. Furthermore, data science should ideally be included into the courses for physical therapy schooling, if these types of tools are to be effectively employed in practice.

Finally, the current and traditional use of treatment protocols might present a barrier to integration of newer tools like outcomes forecasts. The intention of the forecasts is to inform the dialogue between patient and therapist, to optimize shared decision-making and assist in personalizing care. However, our results suggest that therapists, despite guideline-based recommendations,[32] still retain elements of a more paternalistic approach, which may in turn limit the application of shared decision-making principles. This finding is not novel; others have repeatedly demonstrated the scarce application of shared decision-making in physical therapy practice.[33-35] Our results add to the existing literature to indicate that patient involvement may be limited during the treatment phase; therapists largely stuck with a protocol-driven treatment plan. Developing information on how to adapt a protocol-based approach to accommodate shared decisions may be warranted with future work.[36] To operate as intended, POF should be viewed as a patient-centered and participatory approach that could be applied in combination with the context of the patient's life and patient's preferences.

Limitations

Some limitation should be taken into consideration when interpreting the results of this study. First, concerns may rise about the artificiality of vignettes. It has been questioned whether written descriptions and hypothetical behavior can reflect actual behavior.[21] However, the vignettes were based on real patients to simulate real-world scenarios as accurately as possible. The vignettes also contained intentional differences to elicit possible effects of the experimental elements. During the interviews, therapists were stimulated to read the provided patient cases as if they were real patients. All participating therapists said the vignettes accurately reflected the type of patients they might encounter in daily practice. By creating vignettes based on real patients, results are more likely to be generalizable to real cases and situations. Second, convenience sampling was used, based on the interview location. This choice was made for practical reasons to increase participation rate. Influence of the location on the results was not expected, since only Chronic CareNet therapists were eligible to participate and those are all trained to treat patients with IC. Third, this study lacks the patients' view on the use of POF in therapy. Fourth, it is questionable whether our results are transferrable outside of the Netherlands, as physical therapists are specifically trained to reason from the perspective of the Dutch physical therapy guideline for patients with IC. Finally, member checking was not performed afterwards, but only continuously during the interview sessions through verbal verifying of information provided by the participants.

CONCLUSION

In this vignette-based, qualitative study we explored the use of POF on physical therapists' clinical reasoning process, goal-setting and willingness to make shared decisions with patients with IC. Results showed many opportunities for the use of POF. Therapists thought POF might be used to explain prognosis to the patient, to motivate patients, to set realistic goals, and to inform treatment plans according to the predicted walking distance. There was also substantial variability across therapists within the constructed themes on how outcomes forecasts might be used. Insight in this variability creates important lessons for further improvement of the outcomes forecasts themselves and future implementation strategies. In particular, misinterpretation and misunderstanding are important factors that should be addressed to ensure outcomes forecasts are deployed as intended in daily practice.

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CHAPTER 6

Nationwide Implementation of Personalized Outcomes Forecasts to Support Physical Therapists in Treating Patients with Intermittent Claudication: Protocol for an Interrupted Time Series Study

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ABSTRACT

Introduction

Shared decision-making is the cornerstone of patient-centered care. However, evidence suggests that the application of shared decision-making in physical therapist practice is limited. To elicit shared decision-making and thereby potentially improve patient outcomes for patients with intermittent claudication, we developed a decision support system. This decision support system provides personalized outcomes forecasts that visualize the estimated walking distance of an individual patient in time. We hypothesize that personalized outcomes forecasts can support physical therapists in personalizing care to the needs and priorities of the individual patient to improve therapy outcomes.

Research Objectives

The primary aim is to evaluate the impact of personalized outcomes forecasts for patients with intermittent claudication to optimize personalized treatment. Secondary, this study aims to evaluate the process of implementation.

Methods

This study uses a prospective interrupted time series (ITS) design. Participating physical therapists are divided into four clusters and every month a new cluster will be invited to start using the decision support system. We aim to include data of 11,250 newly referred patients for physical therapy treatment. All therapists associated with a network of specialized therapists (Chronic CareNet) and patients treated by these therapists are eligible to participate. The decision support system, called the *KomPas*, makes use of personalized outcomes forecasts that visualize the estimated outcome of supervised exercise therapy for an individual patient with intermittent claudication. Personalized outcomes forecasts are developed using a neighbors-based approach that selects patients similar to the index patient (a.k.a. neighbors) from a large database. Outcomes to evaluate impact of implementation are functional and maximal walking distance, quality of life and shared decision-making. Process evaluation will be measured in terms of demand, including the outcomes dropout rate and reasons to (not) use the personalized outcomes forecasts. Data will be routinely collected through two online systems: the Chronic CareNet Quality system, and the website logs of the decision support system. Additionally, observations and semi-structured interviews will be conducted with a small subset of the participants.

Ethics

Formal medical ethical approval by the Medical Research Ethics Committees United ‘MEC-U’ was not required for this study under Dutch law (reference number 2020-6250).

INTRODUCTION

Treatment guidelines for patients with peripheral arterial disease encourage to make shared decisions.[1,2] Shared decision-making is an approach for physical therapists to integrate evidence-based knowledge with patients' experiences and preferences.[3,4] The shared decision-making process consists of three stages: 1) team talk, preparing the patients for collaboration; 2) option talk, exchanging information about treatment options; and 3) decision talk, affirming and implementing the decision or plan.[5,6] This patient-centered approach is associated with improved patient outcomes.[5] Although shared decision-making is currently considered the norm, evidence suggests that its application in daily physical therapist practice is very limited.[7-9] A potential explanation for the lack of shared decision-making in daily practice is the lack of available and useful decision aids.[10,11] Therefore, to elicit shared decision-making and thereby improve patient outcomes for patients with intermittent claudication, we developed a decision support system.[12]

Intermittent claudication is the most common symptom of peripheral arterial disease, caused by atherosclerotic narrowing of the arteries in the lower extremity. Intermittent claudication is defined as walking induced discomfort and pain in the hip and leg muscles that typically disappears after a brief rest. Evidence-based first treatment for these patients is supervised exercise therapy (SET) and lifestyle guidance, provided by physical therapists.[1,2] The decision support system that we developed, aims to personalize treatment for this patient population and to elicit shared decision-making by providing therapists and patients insight into an individual's personal prognosis. Insight into an individual's personal prognosis is created by the use of personalized outcomes forecasts that visualize the estimated walking distance over the trajectory of SET. These estimates are based on historical outcome data of patients similar to the index patient, and have been described previously (see methods section).[12-14] Personalized outcomes forecasts can support physical therapists in their clinical reasoning and in shared decision-making processes. Moreover, these forecasts can help therapists in personalizing care to the needs and priorities of the individual and thereby potentially improve patient outcomes.

The use of such a decision support system with personalized outcomes forecasts is a novel approach in the conservative treatment of patients with intermittent claudication. Accordingly, the impact of utilizing personalized outcomes forecasts by physical therapists is unknown. A decision support system is now being implemented within the Chronic CareNet network of specialized therapists in the Netherlands[15], which offers an opportunity to study its potential merits. In this protocol we describe the methods of implementation and the study design for impact and process evaluation.

RESEARCH OBJECTIVES

The primary aim of this study is to evaluate the impact of implementing personalized outcomes forecasts (i.e., KomPas) in the daily practice of physical therapists working with patients with intermittent claudication to optimize personalized treatment on the following outcomes: walking distance, quality of life and shared decision-making, as compared to usual care. In table 1 we have summarized the specific research questions related to the primary aim.

The secondary aim of this study is the process evaluation of the implementation of the personalized outcomes forecasts in terms of demand (Specific research questions are summarized in table 2).

METHODS

Study design and setting

To answer our research questions, we make use of a prospective interrupted time series (ITS) design with a parallel process evaluation ("Netherlands Trial Register" registration

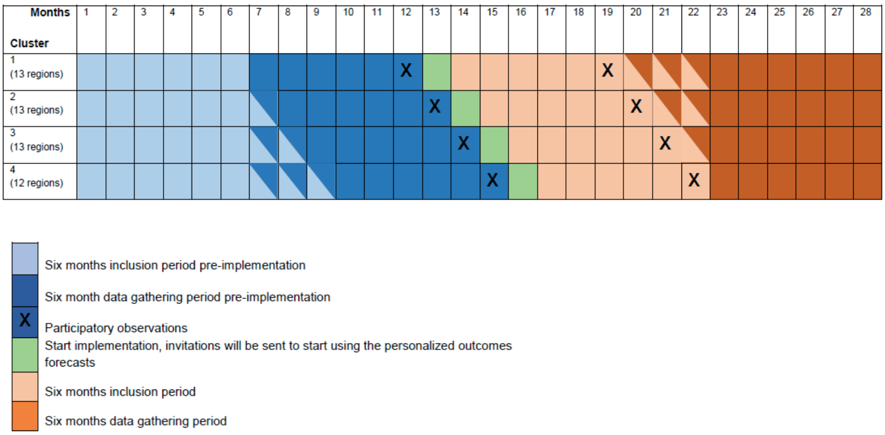

Figure 1. *Timeline*

Participants and Context

The personalized outcomes forecasts have been specifically developed to use in the treatment of patients with intermittent claudication by physical therapists associated with Chronic CareNet. Chronic CareNet is a network of specialized therapists in the treatment of patients with chronic non-communicable diseases, including intermittent claudication.[15] In the Netherlands, SET is only completely reimbursed by basic healthcare insurance if the therapy is provided by Chronic CareNet therapists. Therefore, the network has substantial coverage in this patient population. All patients referred to a Chronic CareNet therapist, specialized in the treatment of intermittent claudication, are eligible to participate. Exclusion criteria are not applicable due to the real world setting of this study.

All participating physical therapists in the Chronic CareNet network participate in routine data collection through the Chronic CareNet Quality system. This Quality system has been set up in collaboration with the National Database Physical Therapy of the Royal Dutch Society for Physical Therapy (KNGF) in which data of all patients with intermittent claudication treated with SET have been gathered since 2015.[15] Data in the Quality system are routinely collected by physical therapists as part of daily practice. According to the SET protocol, a SET trajectory lasts 12 months and includes five measurement time points: at baseline (initiation of treatment) and after every three months. For this study, the six month follow up will be used as end point, since the first six months are considered the most valuable for using the personalized outcomes forecasts.

Decision Support System

The decision support system makes use of personalized outcomes forecasts. These forecasts visualize the estimated outcome of SET, walking distance, for an individual patient with intermittent claudication (see Figure 2).[12-14] A common known example of such forecasts are the reference charts used for monitoring infant growth that plot individual growth against growth of similarly aged infants.[13] Personalized outcomes forecasts are developed using a neighbors-based approach to create the individual forecasts using historical outcome data. This method selects patients similar to the index patient (a.k.a. neighbors) from a large database. The actual outcome data of these similar patients are then used to create an individual forecast.[12-14] Personalized outcomes forecasts are incorporated in an online decision support system, called the *KomPas* (Dutch for ComPass). The *KomPas* plots the estimated therapy outcome in time, thereby making personalized outcomes forecasts easily accessible and interpretable.[12] The decision support system was developed based on feedback from daily practice and the first use was investigated in both a pilot study and an explorative study. Results of these studies were used to optimize the tool and the implementation plan.[18]

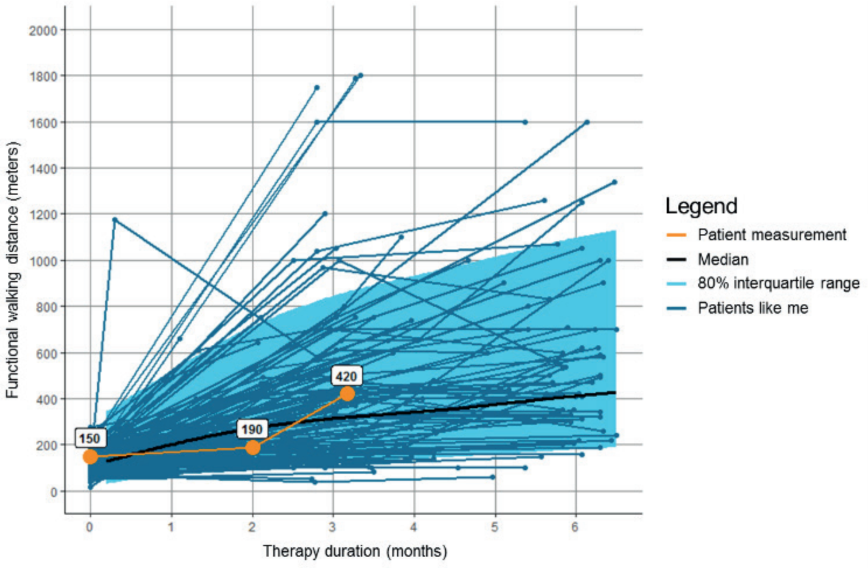

Figure 2. *Personalized outcome forecasts, visualizing a patient's individual prognosis of supervised exercise therapy, based on historic data of patients similar to the index patient.*

Implementation of Personalized Outcomes Forecasts

Personalized outcomes forecasts will be implemented over time in four study clusters at equal intervals of one month. In this study, implementation is defined as making the personalized outcomes forecasts available for therapists to use in daily practice. Chronic CareNet comprises 55 regions (based on ZIP codes) in the Netherlands, four of which already use the personalized outcomes forecasts in the context of the pilot study and explorative study.[18] Each study cluster contains 12 or 13 regions, the number of therapists per region ranges from 25 to 100, resulting in clusters that comprise 400-600 therapists. After implementation, a six-month inclusion period starts (see Figure 1). Use of the personalized outcomes forecasts is not mandatory, but will be promoted during the inclusion period in several ways, including; reminder emails, newsletters and online webinars. Furthermore, during this inclusion period, therapists can gain experience with using the tool. To support therapists in using the personalized outcomes forecasts, three online trainings will be made available: a basic training and two in-depth trainings. The basic training will contain all necessary information to start using the personalized outcomes forecasts in daily practice. For example, how to create a personalized outcomes forecast for an individual patient and how to interpret this forecast. This basic training is mandatory to complete before therapists can start using the personalized outcomes forecasts in daily practice. Two additional in-depth e-learnings will be made available to increase knowledge on personalized outcomes forecasts. These in-depth e-learnings include videos of therapists and patients using the personalized outcomes forecasts during treatment sessions. Videos and associated questions aim to make therapists evaluate and improve the way they use the forecasts in daily practice.

Data Collection

Impact evaluation

The outcomes to determine the impact of the implementation are: 1) functional and maximal walking distance (assessed using a standardized walking test), 2) quality of life (assessed using a questionnaire) and 3) shared decision-making (Table 1).

Specific research question	**Outcome measure**	**Measurement tool:**	**Data routinely collected:**	**Data collection:**	**Sample size:**
1.1 What is the effect of implementing the decision support system in daily practice on the functional walking distance?	Functional walking distance	Treadmill test	Yes	Export from national database and Personalized outcomes forecasts	11,250
1.2 What is the effect of implementing the decision support system in daily practice on the maximal walking distance?	Maximal walking distance	Treadmill test	Yes	Export from national database and Personalized outcomes forecasts	11,250
1.3 What is the effect of implementing the decision support system in daily practice on the Quality of Life?	Quality of life	VascuQoL-6	Yes	Export from national database and Personalized outcomes forecasts	11,250
1.4 What is the effect of the decision support system on shared decision-making during the initial visit?	Shared decision-making	Option 5	No	Participatory observations	30

Table 1. *Specification of research questions and outcome measures.*

Functional and maximal walking distance

Data regarding functional and maximal walking distance will be gathered through the Chronic CareNet Quality system and the personalized outcomes forecasts website. Both are measured by physical therapists as part of clinical daily practice, using a standardized treadmill test (i.e. Gardner Skinner protocol).[19] The test protocol describes a speed of 3.2 km/h with an incline of 0% at start, increasing 2% every 2 minutes. Maximal walking distance is defined as the walking distance where intolerable claudication pain forces a patient to stop. The functional walking distance is defined as the distance at which the patient would prefer to stop walking due to the pain.

Quality of life

Data regarding quality of life will also be gathered through the Chronic CareNet Quality system and the personalized outcomes forecasts website. Quality of life will be assessed using the Vascular Quality of Life Questionnaire-6 (VascuQol-6). This questionnaire is the shortened version of the VascuQol-25 and is used by physical therapists as part of clinical daily practice. Questions are related to a patient's daily activity, current symptoms, experienced pain and social well-being.[20]

Shared decision-making

Shared decision-making will be measured using clinical observations. Observations will be conducted through audio- or video recording. Shared decision-making will be addressed using the OPTION-5. The OPTION-5 is based on a previous 12-item measure, but more specific to the construct of shared decision-making.[21] Assessment of the recordings will be performed by specifically trained physical therapists experienced in using the personalized outcomes forecasts. A random subgroup of physical therapists will be invited by mail and phone to participate in these observations. All therapists who receive a new referral of a patient for SET are eligible to participate.

Process evaluation of implementation

The process evaluation of implementation, the secondary aim of this study, will be measured in terms of demand (Table 2). Demand represents to what extent the personalized outcomes forecasts are likely to be used.[16] This will be measured using dropout rate and reasons to (not) use the personalized outcomes forecasts.

Specific research question	Explanation	Measurement tool?	Data routinely collected?	Data collection?	Sample size
2.1 Did physical therapists use the decision support system during the study period?	Use of the decision support system	Website logs	Yes	Personalized outcomes forecasts export	11,250
2.2 Why did physical therapists (not) use the decision support system during the study period?	Reasons for (not) using it	Qualitative data	No	Semi-structured interviews	15-20
2.3 What is the effect of the decision support system on dropout rate of patients during SET?	Dropout rate	Website logs	Yes	Personalized outcomes forecasts export	11,250

Table 2. *Specification of process measures in terms of demand*

Dropout rate

Dropout rate will be extracted from the website logs. This will be measured as the percentage of patients that terminated therapy before the treatment goal was achieved or when patient terminated therapy on their own initiative. Termination of therapy is indicated by the therapist. Missing values will be measured as percentage of missing measurements at 3 and 6 months.

Reasons to (not) use the personalized outcomes forecasts

Semi-structured interviews with therapists will be used to obtain reasons for (not) using the personalized outcomes forecast. The purpose is to uncover ways to improve the uptake of personalized outcomes forecasts or other electronic decision support systems in this patient population. Semi-structured interviews will be conducted once at 6 months follow-up.

Sample Size

Different samples will be recruited for the different research questions (Table 1 and 2). In the Quality system, data are gathered of approximately 15,000 new patients with intermittent claudication who are referred for SET each year, being 7,500 patients in six months. Since we use the data routinely collected through the Quality system for the pre-implementation period, we expect that data of 7,500 patients will be gathered during the six-month follow-up period. For the post-implementation period, we expect that individual estimates will be made for 3,750 individual patients using the personalized outcomes forecasts within the six months inclusion period. Based on preliminary work (unpublished data), we expect that 50% of all therapists affiliated with Chronic CareNet will start using the personalized outcomes forecasts in daily practice. So, if also routinely collected data of 50% of the patients is received, we expect to include 3,750 patients for the post-implementation period. For the observations to measure shared decision-making, we will aim to obtain 30 observations, according to previous studies who used similar measurements.[22,23] Based on previous pilot testing (unpublished data), we will account for a possible dropout of 20-30%. Therefore, we aim to include 36 to 39 (30*1.20-1.30=36-39) therapists in total. For the semi-structured interviews with therapists to measure reasons for (not) using the tool, data will be sampled until saturation is reached. Data saturation is expected to be reached around 15 to 20 participants in accordance with previous research.[18]

Data Analysis

Statistical analysis will be performed by using IBM SPSS Statistics for Windows, version 25. Baseline participant characteristics will be described using descriptive statistics. Continuous variables will be reported in means and standard deviation (SD) and categorical variables will be reported as frequencies and percentages.

Impact evaluation

Outcomes to evaluate the impact of implementation are maximal and functional walking distance, quality of life and shared decision-making. The impact on walking distance and quality of life will be analyzed after six months of therapy and as change from baseline. To compare pre- and post-implementation, outcomes will be analyzed using segmented regression analysis. Segmented regression analysis is a commonly used method in ITS designs that accounts for possible changes in level and trend as result of implementation of a certain intervention.[24]. Serial autoregressive correlation due to repeated measures will be checked for each outcome measure using the Durbin-Watson test.[25] If no significant autocorrelation is present, a simple time series regression will be used. In case of significant autocorrelation, we will adjust for effects as required. Graphical representation of results will be used to visually inspect change in outcome over time.[26] Individual regression coefficients will be combined in meta-analyses to provided overall estimates.[27]

Shared decision-making will be measured using the OPTION-5 score. OPTION-5 score will be analyzed using a paired t-test to demonstrate a significant difference in the mean overall score between pre and post measurement. Data will be tested for normality using skewness and kurtosis.[28] If the data are not normally distributed, a Wilcoxon matched-pairs test will be used. An alpha level of 0.05 and a 95% confidence interval will be used.

Process evaluation

Outcomes to assess the process evaluation of implementation in terms of demand, include dropout rate and reasons to (not) use the personalized outcomes forecasts. The pre- and post-implementation drop-out rate will be compared using segmented regression analyses, as described for impact evaluation. Qualitative data on reasons to (not) use the personalized outcomes forecasts gathered through semi-structured interviews will be described as result of overall synthesis of the findings.

ETHICS

Formal medical ethical approval by the Medical Research Ethics Committees United 'MEC-U' was not required for this study under Dutch law (reference number 2020-6250). Data will be handled confidentially and in accordance to the General Data Protection Regulation (AVG). Physical therapists who are affiliated with Chronic CareNet agree with the participation conditions of the network. These conditions state, among other things, complying with data delivery procedures. Therefore, for the purposes of this study, therapists already agreed to the necessary use of data when participating in the network. Patients who receive care via a Chronic CareNet therapist provide consent for the use of their clinical data for research and clinical purposes. This enables a number of critical functions within Chronic CareNet; for example: the storage of patient data and recall of treatment results through visuals in the website, the use of aggregated data for quality improvement and research analyses, and the semi-automated generation of standardized documentation (for example, feedback letters for referring physicians regarding patient progress). Informed consent of patients is collected digitally through the Chronic CareNet website with a digital signature. By signing this informed consent, patients agree on the use of their data for research purposes.

Patients and therapists undertaking the shared decision-making observations or semi-structured interviews will be separately consented prior to participation in this part of the project. After formal agreement to participate, therapists receive written information, informed consent forms and self-addressed envelopes by post for both themselves and their patient. For the observations, information is provided to the patient by the therapist. Both therapist and patient will sign two consent forms. All forms will be sent in the self-addressed envelope to the coordinating investigator, who will sign the forms and return one for the patient and one for the therapist.

DISCUSSION

This protocol describes the implementation of personalized outcomes forecasts (KomPas) for physical therapists, specialized in the conservative treatment of patients with intermittent claudication in the Netherlands, using the interrupted times series (ITS) design. The ITS design is a quasi-experimental approach (without randomization) which enables the use of observations to explore possible causal effects.[29] Although Randomized Controlled Trials are often considered to be the optimal design to investigate possible effects, some disadvantages exist. For example, the possible bias created by exclusion criteria and the inability to generalize results to "real world" settings.[29] By choosing the ITS design with no exclusion criteria and use of routinely collected data, we aim to overcome these limitations. Furthermore, the ITS design makes it possible to account for possible effects caused by pre-existing trends independent of the implemented approach.

Limitations

Two limitations should be considered for this study. First, the use of the personalized outcomes forecasts is not mandatory for the physical therapists within the Chronic CareNet network. Therefore, challenges may arise when implementing such an innovative approach. Therapists will have to implement this tool into their practice routine and invest time to do so, based on internal motivation. Time pressure is high within the physical therapy profession and additional administrative workload is a barrier for implementation.[30] Although the use of personalized outcomes forecast may seem to cost additional time initially, we believe it will help therapists in their treatment and thus saves time in the end. To make implementation as successful as possible, good communication on the additional value of using the personalized outcomes forecasts is important. Therapists will also be supported in using the personalized outcomes forecasts. This support includes online training and webinars. Furthermore, therapists are involved in the development as much as possible to make the personalized outcomes forecasts answer their needs from daily practice. The second limitation is the division of participants into only four clusters with only one month in between start dates of the clusters. Ideally, we would have used more clusters with larger time intervals. However, this would be too time consuming and not possible within the timeframe of the project.

CONCLUSION

We expect to improve patient-centered care for patients with intermittent claudication by eliciting more shared decision-making through the implementation of our decision support system that embodies personalized outcomes forecasts.

CHAPTER 7

Summary and General Discussion

The purpose of this thesis was to develop, implement and evaluate a decision support tool which provides additional insight into the expected prognosis of individual patients with intermittent claudication during a trajectory of supervised exercise therapy (SET). We propose personalized outcomes forecasts as a means of advancing the evidence base for clinical decision-making at individual level. In the different chapters of this thesis, we described the steps necessary to develop and implement personalized outcomes forecasts, as well as the importance of routine data collection. This *"General Discussion"* will start with a summary of the general findings of this thesis, followed by reflection on the methodological considerations, the practical applications and the directions for future research.

GENERAL FINDINGS OF THIS THESIS

In the Netherlands, the majority of the patients with intermittent claudication are treated according the guideline recommendations; 87% of all newly diagnosed patients receive SET as initial treatment.[1,2] Implementation of the guideline recommendations are an important step towards optimal clinical care. However, evidence-based recommendations are only one part of the equation for achieving optimal clinical care. When the focus of clinical care is solely on guideline-based practice, this might be at odds with the principles of patient-centered care. Beside the availability of a guideline, therapists should also be supported in applying the recommendations to the context of the individual patient with use of personalized (communication) techniques and shared decision-making.[3-5] Ideally, the guideline recommendations should be integrated with clinical expertise and patients' preferences to accomplish true evidence-based practice.[6,7] In chapter 1 of this thesis, the *"General Introduction"*, we described this limitation of guideline-based practice and advocated for advances in personalized care. To do so, personalized outcome forecasts are suggested in this thesis as the way to achieve personalized evidence-based physical therapy practice.

Personalized outcomes forecasts are incorporated as an online tool, which we termed KomPas (Dutch for compass). KomPas displays an individual patient's estimated trajectory of walking distance throughout a course of SET. This display can then inform patient-clinician collaboration around an individualized plan for SET. The display can also help to inform measurable therapy goals and serve as a benchmark against which to monitor progress during SET. As shown in Chapter 2 of this thesis, it remains challenging to identify patient characteristics that influence the outcome, or to estimate the outcome of SET, due to the high variance in patient outcome. Therefore, individualized approaches such as personalized outcomes forecasts are more suitable.

To develop such outcomes forecasts, data of enough quantity and quality are necessary. Outcome data of patients with intermittent claudication receiving SET in the Netherlands are routinely gathered through the Chronic CareNet Quality system. In chapter 3 of this thesis we described this data gathering system, based on the elements of a learning health system. This chapter includes the lessons learned from initiating ClaudicatioNet, like the relevance of an intrinsically motivated team and collaboration with intrinsically motivated stakeholders. Furthermore, it includes lessons learned on the process of routinely collecting data. For example, the importance of uniform data collection to reduce missingness and errors, but also making data applicable to end users to be able to transform data into knowledge and initiating new performances in practice. In chapter 4 of this thesis we described how the data gathered through the Quality system is used to develop the personalized outcomes forecasts. Results of this chapter demonstrated that the used neighbors-based prediction approach is able to generate accurate personalized outcomes forecasts.

Personalized outcomes forecasts have the potential to optimize physical therapy care for patients with intermittent claudication by making it more patient-centered, participatory and evidence-based. In chapter 5 of this thesis we described the results of initial use of personalized outcomes forecasts by physical therapists treating patients with intermittent claudication. First use demonstrated many opportunities, like supporting physical therapists in explaining about prognosis of the disease with the patient, motivating patients, setting realistic goals and establishing the treatment plan based to the predicted walking distance. Furthermore, the results showed substantial variability across therapists on how outcomes forecasts might be useful, which created important lessons for further improvement as well as the implementation strategy. The personalized outcomes forecasts were implemented as part of a large nationwide interrupted time series study, the protocol for which was described in chapter 6 of this thesis. At the time of writing of this general discussion, more than 1200 therapists have used the personalized outcomes forecasts and almost 5700 individual outcomes estimates have been made. See figure 1 for the time course of implementation over the past two years. Although the actual impact of a nationwide implementation of our personalized outcomes forecasts in daily practice has not been examined yet, we believe that these numbers of implementation into daily practice are a major step forward towards personalized care for patients with intermittent claudication.

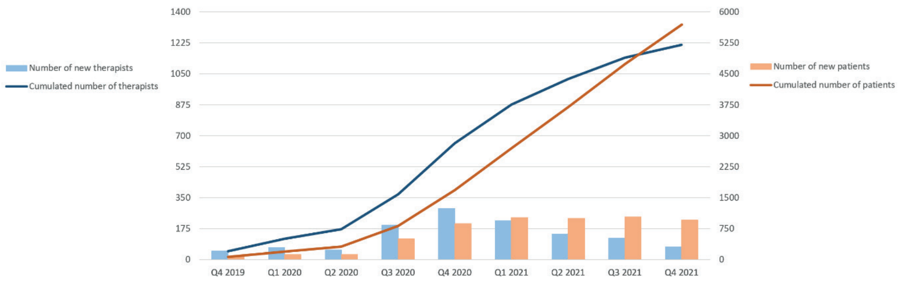

Figure 1. *Numbers of use by therapists and numbers of individual outcome estimates made over the past two years. Lines indicate the cumulative numbers and bars numbers per quartile. Blue indicates therapists, Y-axis on the left, and orange indicated patients, Y-axis on the right.*

METHODOLOGICAL CONSIDERATIONS

Several methodological and statistical decisions were made when developing the personalized outcomes forecasts. Since not all of the decisions could be discussed in the individual chapters of this thesis, we will elaborate on these decisions in the next part of this discussion. The methodological considerations are divided into the following subjects: statistical approach, data source, outcome of the model, the optimal set of neighbors, even more accurate forecasts and evaluating the forecasts' performance.

Considerations Regarding the Statistical Approach

The first decision in the development of the outcomes forecasts was to select the statistical approach. The finally used approach, a neighbors-based prediction, was inspired by the reference charts for monitoring infant growth. Infant growth charts plot the individual growth of a child against growth of similarly aged infants.[8] Van Buuren et al.[8] suggested an approach to make the infant child growth charts more personalized: not only plot against growth of similar aged infants, but select infants who are similar based on different parameters (i.e. length, weight and head circumference). The historic growth data from the matched infants is then added to the chart of the index child to suggest how the index child may grow in the future.[8] We have adapted this idea of neighbors-based prediction to create our personalized outcomes forecasts for patients with intermittent claudication receiving SET.

The neighbors-based prediction approach consists of several steps. First, a walking distance was estimated for each patient at 180 days, since the source dataset contained walking distance measurements at irregularly spaced time intervals. Second, the matches were selected by an adaptation of predictive mean matching. Multiple linear regression models were estimated with the 180-day walking distance measurement as the outcome variable and potential matching characteristics as explanatory variables. Only the matching characteristics that contributed significantly ($p<0.05$) to the prediction were used for the final model (age, body mass index (BMI), walking distance at baseline, motivation score measured as phase of behavior change, pack-years of smoking, and quality of life measures using the Vascular Quality of Life Questionnaire-6). Last, the predicted values from the linear model were used to select the matches of the index patient. The actual outcome data of the selected similar patients are then used to create the individual prediction.[8,9]

There are some advantages of the neighbors-based approach, both statistical as well as practical, that overcome a number of limitations seen in previous attempts to predict the outcome of SET for patients with intermittent claudication. Limitations described by previous studies that used other parametric prediction approaches (e.g. regression analysis) include poor external validity, high levels of uncertainty or poor accuracy of predictions.[10-12] External validity is improved using the neighbors-based prediction approach since a new prediction model is built for each new patient, based on the outcome data of similar patients. This may improve the external validity because each new patient is likely to have at least a few appropriate matches in the source dataset, even if the sample characteristics differ in the aggregate.[13,14] This may explain why the personalized outcomes forecasts appeared well-calibrated via both within-sample and out-of-sample testing.[15] Additionally, the neighbors-based prediction approach, being constrained to realized observations, appeared to consistently produce realistic recovery estimates.[9,15] Furthermore, patients with intermittent claudication have highly heterogeneous outcome results, making predictions in this group challenging. The neighbors-based approach seems to be a good solution here as well, by creating the prediction with data from similar patients matched by selected characteristics.[13]

In addition to the statistical advantages, there are also some potential benefits on clinical usability of the neighbors-based prediction approach. For example, these forecasts estimated the outcome of therapy over the complete six months of SET, instead of only at one endpoint as is commonly done in many analyses. Furthermore, the display itself provides an easy visualization of the patient's prognosis of therapy in relation to other similar patients and is also intended to include an intuitive depiction of the uncertainty in prognosis. This visualization is designed to make the forecasts easy to use and provide information regarding prognosis.[16] The clinical usability of the reference charts will be elaborated on later in this discussion.

Considerations Regarding the Utilized Data

As mentioned previously, to be able to develop personalizes outcomes forecasts, data of sufficient quality and quantity are a prerequisite. In this thesis, we made use of the large database of the Chronic CareNet Quality system. This Quality system is an export system leveraging patient, process and outcomes data of all patients with intermittent claudication who receive SET in the Netherlands. Approximately, data of 9500 patients is added to the Quality system annually. The pseudo-anonymized data are gathered based on the National Register for Physical Therapy of the Royal Dutch Society for Physical Therapy (KNGF).[17] Data in this database are gathered as part of daily clinical practice.

The use of routinely collected data has some disadvantages. First, we had to deal with large amounts of missingness. Approximately 20,000 of 26,000 patient cases available in the database had to be excluded from analyses, due to incomplete follow-up measurements or no follow-up measurements at all. Incomplete follow-up measurements could be caused by the additional administrative workload of data-gathering for therapists. The documentation burden is already quite high and may be perceived as a distraction from the primary goal of providing quality care.[18] Another possibility for lacking follow-up measurements might be early termination of SET. Patients did not explicitly participate in a scientific study and were therefore free to not attend follow-up measurements. This could have potentially caused bias in our data set, patients for whom follow-up data are recorded are systematically different in some way (either poorer or better performing) than patients for whom data are missing. Despite all the missingness, the final dataset used for our personalized outcomes forecasts still contained approximately 18,000 functional walking distance measurements of nearly 6,000 patients. However, we cannot rule out that the predictions generated in our analyses will lack external validity when applied prospectively in routine practice. Future implementation work should inform our understanding of the presence and extent of bias in this regard.

A second disadvantage is that routinely collected data were measured as part of a care quality registry and were not specifically measured with the aim of developing outcomes forecasts. Consequently, the dataset lacked variables that might have been potentially valuable in predicting the outcomes of SET. For example, the dataset did not contain variables like: location of arterial stenosis or occlusion, comorbidity status, and details of the SET (e.g. adherence, intensity), which all potentially influence patients' prognosis.[19] An alternative might be to collect data in a research setting, such as a large prospective cohort study. This provides the opportunity to gather data in a controlled setting, with use of in- and exclusion criteria and specified follow-up visits and measurements. However, data gathered in a controlled research setting also have limitations.[20] Due to specific criteria for data gathering, research data might be less generalizable and applicable to real-world settings than routinely collected data.[21] For example, clinical trials often use in- and exclusion criteria for participants and might even influence regular daily care to comply with the research setting.[22,23] Also, the use of in- and exclusion criteria itself could make data more prone to bias.[24] Another disadvantage of data gathered in a research setting is higher costs, more labor intensive and extra time consuming compared to routinely collected data.[24,25]

Consideration Regarding the Outcome of the Model

To determine which outcome is ideal to predict, different considerations had to be taken into account. Bell et al.[26] described four criteria for tests used for monitoring, that could also be applied to our outcome forecasts: Clinical validity, responsiveness, detectability of long-term change and practicality. Clinical validity is the ability of the test to measure the clinically relevant outcome.[26] The primary goal of any intervention for patients with intermittent claudication is to improve walking distance. A corresponding improvement in quality of life and ultimately the ability to perform daily activities is inferred. Since walking distance could be measured objectively, this seemed to be the ideal outcome to measure and predict. The international guidelines for patients with intermittent claudication advocate measuring the maximal walking distance. Therefore, we initially estimated maximal walking distance as outcome of our forecasts. However, the final model that is implemented estimates functional walking distance, rather than maximal. Functional walking distance is a reliable and valid measurement for determining functional capacity[27] and is the primary outcome measure recommended in the Dutch treatment guidelines.[28] We believe functional walking distance reflects a patient's walking capacity in daily life better and would therefore be better applicable to use in the outcomes forecasts according to the criterion of clinical validity.

Responsiveness is the ability of the test to detect changes over time in response to an intervention.[26] It has been widely described that SET improves the walking distance and that the graded treadmill test is an adequate tool for objective assessment of any changes in walking distance as result of SET.[1,29] Detectability of long-term change is the degree of changes in the test over the long-term. Long-term follow up of patients with intermittent claudication is generally 5 years or more.[30,31] To preserve improvements in walking distance after SET on the long term, an important part of therapy is lifestyle guidance. Additionally, for long-term follow up, walking distance measured using the treadmill test is suitable and commonly used.[32,33] Practicality of the treadmill test includes the ease of use, non-invasiveness, and low cost of the test. Moreover, the protocol for testing has already been implemented nationwide in the Netherlands and all Chronic CareNet therapists are trained in executing the test. So, the test is not only easy to use, but also standardized among therapists in the Netherlands.

Considerations Regarding the Optimal Set of Neighbors

In selecting "neighbors" for an index patient, two considerations are paramount: 1) the matching characteristics and relative weights of those characteristics, and 2) the number of matches or neighbors that are used in the final forecast. First, we consider the matching characteristics. In chapter 2 of this thesis we used freedom from revascularization surgery as outcome of SET. Results showed that multilevel disease, Vascular Quality of Life Questionnaire-6 scores and smoking status were independently associated with the need for revascularization.[34] Other studies who used walking distance as outcome of SET, showed that several patient-related factors, including patient reported function and baseline walking distance, were associated with walking distance.[10-12] However, it remains challenging to identify one set of matching characteristics that significantly influence the outcome of therapy in this patient population. Therefore, we chose to use only variables that contributed significantly to the prediction of future (i.e., 6-month) walking distance via multiple linear regression. The variables used as matching characteristics were weighted according to the beta coefficients in this regression model. This improved the accuracy of the prediction.[13,14] Second, we considered the number of matches needed to create the optimal set of matches. We tried to select the optimal number of matches based on average performance of the predictions according to the following metrics: bias, coverage and precision. However, the number of matches did not substantially influence the performance of the neighbors-based prediction approach when less than 30% (~1,400 patients) of the dataset was used for matching. With greater numbers of matches, the average precision became substantially worse (i.e. greater uncertainty in prediction). For the statistical evaluation of our personalized outcomes forecasts (as described in chapter

3 of this thesis), we decided to match any given patient to the nearest 5% of patients (matches, m=223). For the actual personalized outcomes forecasts used in daily practice we decided to use 160 matches. This provided better visual presentation with negligible changes in prediction performance.

Considerations Regarding the Evaluation of the Forecasts' Performance

To evaluate the performance of our personalized outcomes forecasts, we used the following parameters: bias, coverage and precision. Our personalized outcomes forecasts are able to estimate functional walking distance with small average bias (-0.04 standard deviations), accurate coverage (48.7%, ideal = 50%), and 24% more precise compared to the prediction model derived from the full sample.[15] The small bias suggest that there is no evidence of a systematic over or underestimation. The coverage implies that 48.7% of the actual outcomes will be within the 50% prediction interval. This is an important parameter that indicates accurately modeling of uncertainty and differences between individual patients. Precision of the personalized outcomes forecasts showed an improvement of 24% compared to a prognostic estimate derived from the full sample. These three parameters were selected in an effort to provide complete insight in the prediction performance and to transparently understand the strengths and weaknesses of the approach. Any single summary metric could appear strong overall, but could hide limitations in one specific area.[35] For example, the more commonly used coefficient of determination (R^2) indicates the percentage of the variance in the outcome that has been explained by the used model.[36] If a prediction model is optimized only based on optimizing R-square, one might sacrifice in areas of coverage or precision without realizing it. Bias, as used in this manuscript, is similar to the R^2 in its calculation. So, the addition of coverage and precision provides a more complete view on the prediction performance. Moreover, coverage and precision are relevant for the eventual clinical use, as those are often easier to interpret and understand when explaining about the patient's prognosis. However, the consequence of not using the R^2 is that direct comparison of our findings with findings of previous studies is difficult.

PRACTICAL APPLICATIONS

To ensure that the personalized outcomes forecasts are easy to use in daily practice, we incorporated them into the online tool KomPas. The forecasts are displayed as reference charts in the website of KomPas that plot the estimated outcomes over time. Therapists can easily fill in the factors needed for the forecasts and the website creates the reference charts. Furthermore, therapists can add the follow-up measurements to the chart to visualize progress over time relative to the initial forecast. To supports therapists in using KomPas, we have provided several online trainings to help therapists understand and implement the outcomes forecasts as intended. The practical applications of KomPas aim to support therapists in providing patient-centered care. Furthermore, the visualization of outcome estimates and the possibility to add follow-up measurements to the charts, allows the personalized outcomes forecasts to serve as monitoring tool. Finally, it provides insight into discuss uncertainty and therefore presents opportunities to introduce this variable into clinical-decision making. In the next section we will discuss these different applications of the personalized outcomes forecasts.

Patient-Centered Care

KomPas supports therapists in providing patient-centered care through two different approaches: shared decision-making and motivational interviewing. Shared decision-making within physical therapy care is an approach to make evidence-based care more patient centered.[5] Shared decision-making supports the integration of evidence-based knowledge with patients' experiences and preferences to improve patient outcomes.[37-39] The shared decision-making process consists of three stages: 1) team talk, preparing the patients for collaboration; 2) option talk, exchanging information about treatment options; and 3) decision talk, affirming and implementing the decision or plan.[37,40] As mentioned in the general introduction of this thesis, examples of shared decision-making in the physical therapy literature are generally very limited.[41-43] Implementation of shared decision-making into daily physical therapy practice could be improved by supporting therapists in personalizing the guideline recommendations with decisions-support tools, for which KomPas was developed.[44]

KomPas as decision support system aims to elicit shared decision-making by providing therapists and patients insight into an individual's personal prognosis. The insight into prognosis supports therapists in explaining the expectations of therapy, which is in particularly helpful during the team talk and option talk of shared decision-making. The second approach through which KomPas supports therapists in providing patient-centered care is motivational interviewing. Motivational interviewing is previously described as a patient-centred approach that aims to help patients identify and resolve ambivalence about behaviour change.[45] The motivational interviewing approach supports therapists in examining a patient's interest in or commitment to changing their behaviour.[38] Motivational interviewing consists of four steps: 1) building a working relationship, 2) developing a specific direction about change, 3) eliciting the patient's own motivations for change and 4) developing commitment to change and formulating a concrete plan of action.[38] Within physical therapy for patients with intermittent claudication this approach is especially valuable in achieving healthy lifestyle changes, which optimizes therapy outcome. By providing insight into the expected outcome of therapy, KomPas aims to support therapists in motivating patients for therapy and healthy lifestyle changes. This is based on psychological theories that people will perform behaviors that have expected positive consequences.[46] For patients with intermittent claudication, such behaviors include physical activity and healthy lifestyle. The positive expected consequences could include functional benefits, like an improved walking distance.

Monitoring

Monitoring is "observing and checking a certain process over time".[47] Monitoring within SET for patients with intermittent claudication is already implemented in therapy through the recommended measurements and follow-up moments, described in the treatment guidelines. However, monitoring is more than just measuring progress at follow-up. Monitoring could have impact on therapy by several means: improved adherence, better treatment selection based on individual progress, and improved knowledge about factors influencing progress.[47] KomPas aims to support therapists and patients in adequate monitoring and taking the advantage of monitoring into practice. To do so, actual measured outcomes during follow-up moments can be added to the KomPas. This allows for visual representation of therapy progress and comparison of outcomes to initially estimated progress. Physical therapy treatment of patients with intermittent claudication is particularly suitable for monitoring due to the long treatment trajectory of 12 months, the frequent visits and the possibility of adjusting therapy along the way.

Communicating Uncertainty

The increasing awareness for evidence-based medicine combined with shared decision-making to optimize and personalize care, draws attention to a whole new problem: uncertainty. A working definition for uncertainty has been described as someone's awareness of the lack of knowledge, which could result in uncertain feelings.[48] There are different meanings to uncertainty: incomplete knowledge, absence of awareness of necessary information, incompetence to determine the effect of patient or disease characteristics on the outcome of therapy, and lack of understanding of the patient's preferences.[49] We can split uncertainty into intrinsic uncertainty and informational uncertainty. Intrinsic uncertainty is independent of knowledge and can never be fully eliminated,[50] as it reflects the limited ability of our mind to completely understand all natural phenomena.[49] Informational uncertainty is incomplete or imprecise knowledge and can be dived into three sub-types: 1) technical uncertainty, 2) personal uncertainty and 3 conceptual uncertainty. First, technical uncertainty, which is caused by the lack of available data. Within physical therapy treatment of patients with intermittent claudication, this type of information uncertainty might exist about long term outcomes of therapy. This is caused by decreasing data density with longer follow-up periods. Although our KomPas is not a direct solution for the lack of data on the long term, it might make the therapist aware of the usefulness of data gathering. This could result in more effort of therapists to gather data, also on the long-term. Second, personal uncertainty, which is the result of lack of understanding the patient's wishes by the healthcare professional. The ability of physical therapists to understand the patient's wishes and incorporate these in therapy might vary between individual therapists.[49] KomPas might be useful to talk about expectations, personal goals and therefore wishes of individual patients through visualization of the expected outcome over time. Finally, conceptual uncertainty, which is caused by shortcomings of health care professionals to apply general recommendations into practice.[50] For example, the shortcoming to apply the guideline recommendations to individual patients. KomPas supports therapists in adapting the guideline recommendations to individual patients by facilitating clinical reasoning, such as personalization of the care plan based on individual outcomes forecasts. Another form of uncertainty is the experienced of uncertainty by patients as a consequence of complexity and unpredictability of their illness.[51] Effective communication by the physical therapist about uncertainty is essential to reduce experienced uncertainty by the patient. Our personalized outcomes forecasts have the ability to support therapists in such communication. So, our personalized outcomes forecasts are valuable in addressing the different types of uncertainty.

FUTURE RESEARCH

"Are the forecasts accurate enough to use in daily practice?" is a frequently asked question by critics and therapists. When predicting in medicine, it seems to be the goal to create

the ultimate prediction; to perfectly predict what will happen and when for an individual patient.[52] However, the perfect prediction model will never exist; there will always be a certain level of randomness and uncertainty which cannot be controlled or accounted for.[53] Nevertheless, we should always strive towards creating the optimal estimate. Within our personalized outcomes forecasts, we see a number of potential ways forward to optimizing the performance. However, the goal of our personalized outcomes forecasts is not solely to create a well-performing prediction, but rather to develop a useful decision support tool to support patients and therapists in making care decisions. In the following paragraph we will discuss methods to optimize our personalized outcomes forecasts in the future. At the end of this paragraph, we will also outline new strategies to further optimize our personalized outcomes forecasts as decision support tool.

Optimizing the Performance of the Personalized Outcome Forecasts

Three methods to optimize future performance of our personalized outcomes forecasts will be discussed in the next part: 1) utilizing different forecasting methods, 2) predicting the full trajectory of SET and 3) adding extra data to the model (follow-up data and non-SET data).

Utilizing different forecasting methods would be interesting to optimize future performance. To explore the best method with the most accurate estimates, different methods to estimate the individual outcome of therapy should be compared. A direct comparison of our method to previous attempts to predict the outcome of SET for patients with intermittent claudication is not possible at this moment. Previous studies used different population data, different outcomes to predict and even different evaluation methods. So, to be able to compare different methods, they should be compared directly; applying different methods to the same data base, estimating the same outcome and using the same statistics to evaluate the results. It would be interesting to be able to compare different forecasting or predicting methods to see which fits best and what limitations exist.

Predicting the full trajectory of SET might be of added value to improve the future performance. The current charts are limited to the first six months of therapy, while a complete SET trajectory takes up to 12 months. The current charts are limited to six months due to the large amounts of missingness and lack of follow-up data after the first six months. Consequently, not enough data were available of the last six months of therapy to create accurate estimates. Furthermore, clinical follow-up commonly occurs at six months after the initiation of therapy and the most gain in walking distance is generally achieved in these initial six months. Thus, we feel the expected gain in the first six months is the most relevant to shared decision-making. Nonetheless, it would be interesting to explore the value of predicting the full trajectory of SET in the future when enough data are available to do so.

It could be argued to add extra data to the model to improve upon performance. More detailed knowledge about disease causes and a complete set of data variables could improve a prediction.[52] Two variables can be considered to add to our model: follow-up data and non-SET data. Follow-up data, meaning walking distance at follow-up or change in walking distance over time, would probably have great influence in predicting the final walking distance. However, the addition of the follow-up measurement as matching characteristic would create a "self-fulfilling prophecy". This means that the outcomes forecasts will be adapted at follow-up moments and bend towards the perceived progress. Data of patients who did not receive SET or decided to terminate therapy early, could be considered to include into the model (non-SET data). The current personalized outcomes forecasts only use data of patients with intermittent claudication who received SET for a duration of at least six months. We envision an addition option where you can switch between patient who did and who did not receive SET for six months. This would be useful to visualize the effect of SET to the individual patient.

Optimizing the Personalized Outcomes Forecasts as a Decision Support System

We created a decision support system for physical therapists to use in the treatment of patients with intermittent claudication. However, as described in the introduction of this general discussion, guideline recommendations should be integrated with clinical expertise and patients' preferences to accomplish true evidence-based care. Although we think that KomPas as decision support system is already a major step into the right direction, the guidelines remain limited in their ability to support healthcare providers to personalize the recommendations. So, we envision a guideline-based clinical decision support system: KomPas+. KomPas+ will be an integration of the person-centred approach of KomPas with dynamic integration of the guideline recommendations. The integration of the guideline recommendations will stimulate therapists to discuss preferences of the patient regarding the treatment plan. For example, KomPas+ will stimulate to discuss choices about frequency, intensity, time and type of exercise, the FITT principles. Through KomPas+ we aim to support therapists in incorporating the guideline recommendations with the context of the individual patient. At the time of writing of this general discussion, KomPas+ is already developed and being used in daily practice by a first group of physical therapists.

SO, DID WE SUCCEED IN MAKING PHYSICAL THERAPY CARE FOR PATIENTS WITH INTERMITTENT CLAUDICATION MORE PERSON-CENTERED, PARTICIPATORY AND EVIDENCE-BASED?

This thesis represents a first step to evolve beyond one-size-fits-all guideline recommendations and an important move towards more personalized care. We believe that we have successfully created a decision support tool, based on personalized outcomes forecasts, to support physical therapists in personalizing care for patients with intermittent claudication. The decision support system is evidence-based, supports in making shared decisions and helps to make care more participatory. This thesis represents a first step to move away from the traditional one-size-fits-all guideline recommendations and moves towards more personalized care. Although the actual impact has yet to be evaluated, we believe that this decision support system will supports in making shared decisions and helps to make care more participatory.

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CHAPTER 8

Impact Paragraph

AIM

The purpose of this thesis was to personalize the physical therapy treatment for patients with intermittent claudication. Intermittent claudication is caused by atherosclerotic narrowing of the arteries in the lower extremities, which limits the blood supply to the muscles during movement.[1,2] As a result, patients experience discomfort and pain in the leg or hip muscles during walking, which resolves after a brief period of rest. National guidelines recommend supervised exercise therapy (SET) in combination with lifestyle guidance, provided by a physical therapist, as the primary treatment for this patient population.[1,2] This conservative treatment is aimed at cardiovascular risk reduction and symptom relief.[1]

In the Netherlands, 87% of all patients with intermittent claudication are referred for SET as initial treatment.[3] This successful implementation of the evidence-based guideline recommendations could be considered as optimal care. However, this guideline-based practice it is at risk of eliminating patient-centered care.[4] So, to make SET patient-centered, we developed and implemented a decision support system, named KomPas (Dutch for compass). KomPas utilizes personalized outcomes forecasts to provide insight into the expected outcome of SET for individual patients. The personalized outcomes forecasts were inspired on the well-established 'growth' charts for monitoring infant growth. However, rather than plotting the growth of a child against growth of all similarly aged children in the database, van Buuren et al (2014)[5] suggested to plot the growth of a child against growth of infants who are similar based on multiple parameters (e.g., age, sex, length, weight and head circumference). Van Buuren showed that these personalized growth charts result in a more accurate prediction of a child's growth over time. We have adopted this technique to develop the personalized outcomes forecasts to accommodate physical therapists in their treatment of patients with intermittent claudication. Thus, for every new patient, similar patients are selected from a large database, based on specific patient characteristics. The actual outcome data of these similar patients are then used, anonymously, to create the individual outcomes forecast.

Results of this thesis showed that the personalized outcomes forecasts of KomPas provided an accurate insight into the expected outcome of therapy. Furthermore, the first use of KomPas by physical therapists in real world situations, showcased its different opportunities. KomPas was found to be useful to explain prognosed treatment outcomes, and to inform patients on the treatment plan, based on these outcomes. Furthermore, using KomPas facilitated therapists in motivating patients and setting realistic treatment goals. Both real-world test sessions and scientific studies resulted in the improvement of KomPas. Currently, KomPas has been implemented nationally. As data about its effectiveness are still being gathered, we have not yet been able to examine its definitive impact nationwide. However, based on our experience with participating physical therapists, we believe that the implementation of KomPas in daily practice is a major step forwards towards personalized care for patients with intermittent claudication.

POPULATION

KomPas has been developed specifically to be used by physical therapist treating patients with intermittent claudication. SET for patients with intermittent claudication has already proven to be effective and has been successfully implemented as primary treatment in the Netherlands through the network of ClaudicatioNet.[3] ClaudicatioNet was a nationwide network of specialized physical therapist treating this patient population. This network provided the necessary elements to develop and implement KomPas. The first requirement for the development of KomPas was data of sufficient amount and quality. These data were gathered through the ClaudicatioNet Quality system: a data registry where routinely collected data from daily practice were gathered (e.g. patient characteristics, outcome results). As a result of the KomPas project, the existing ClaudicatioNet data infrastructure evolved into an infrastructure which adheres to the principles of a learning health system. A learning health system uses health data in cyclic processes.[6] These processes aim to convert data into knowledge, apply this knowledge into practice, and collect new data from the changed practice.

In the past decades, we learned that physical therapy is valuable in treating other chronic diseases besides intermittent claudication.[7] Physical activity and a healthy behavioral patterns are found to improve health in general and reduce the risk of morbidity and mortality. In the Netherlands, SET has been made available through the network of Chronic CareNet for all patients with chronic diseases for whom physical therapy is indicated. Chronic CareNet evolved from ClaudicatioNet. This is a network of physical therapists specialized in treating not only patients with intermittent claudication, but also patients with other chronic diseases (e.g. chronic obstructive pulmonary disease (COPD) and heart failure). Personalized physical therapy is relevant to all patients suffering from chronic conditions.[7,8] Therefore, the personalized outcomes forecasts methodology has great potential to be employed in the physical therapy of these other patient populations.

To achieve this, the used methods and lessons learned from the development and implementation of KomPas could serve as blueprint. The first steps – obtaining sufficient quality data – in the development of personalized outcomes forecasts for other chronic conditions, are already being taken. With ClaudicatioNet evolving into Chronic CareNet, the data registry expanded. In the Chronic CareNet Quality system data is gathered on all patients treated by Chronic CareNet physical therapists.

RELEVANCE

Intermittent claudication is the most common symptomatic presentation of peripheral arterial disease (PAD). PAD is a chronic disease caused by atherosclerotic narrowing of the arteries which affects over 200 million people worldwide. This number will increase as the population ages, and the presence of risk factors for PAD (e.g. diabetes mellitus, smoking, chronic kidney disease, hypertension, hyperlipidemia, positive family history) grows.[1,2] PAD, and consequently intermittent claudication, are growing problems worldwide, which warrants continuously optimizing SET.

SET is recommended in treatment guidelines that are based on population research. Population based research provides answers generalizable to the complete patient population. However, these answers are not necessarily applicable to the individual patient.[4] Furthermore, the current guidelines are based on a single condition, while multimorbidity is becoming increasingly common in patients with intermittent claudication. Ideally, guideline recommendations should be individualized and applied to the context of the patient. To make SET more patient-centered, several approaches have been proposed: 1) implementing shared decision-making[9], 2) integrating monitoring tools in daily practice[10,11], and 3) employing the principles of a learning health system.[6,12] We believe that our personalized outcomes forecasts could be valuable to support physical therapist in utilizing these three approaches to personalize physical therapy care. The outcomes forecasts could assist therapists to make individualized clinical decisions by closely monitoring therapy progression and comparing actual outcomes to predicted outcomes.[13]

IMPLEMENTATION/INNOVATION

To make the personalized outcomes forecasts generated by KomPas easily accessible and interpretable, they were embedded in an online tool. The reference charts produced by

KomPas include 1) the estimated outcome of the individual patient, 2) the actual outcome data from similar patients and 3) an uncertainty range. In the Netherlands, KomPas is implemented into daily practice through an interrupted time series study. This means that the KomPas was implemented over time in four clusters at equal intervals of one month. We defined implementation as the availability of KomPas for therapists to use in daily practice. Implementation was accompanied by various online trainings to support physical therapist in understanding and using KomPas. At the time of writing, more than 1200 therapists have used the personalized outcomes forecasts and almost 5700 individual outcomes estimates have been made. The implementation process has provided us with valuable lessons for future initiatives to develop and implement such personalized outcomes forecast for other patient populations.

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CHAPTER 9

Nederlandse Samenvatting

PERIFEER ARTERIEEL VAATLIJDEN

Perifeer arterieel vaatlijden (PAV) is een chronische ziekte die wordt veroorzaakt door slagader verkalking (ook wel atherosclerose), voornamelijk in de slagaders van de benen. Door de slagader verkalking ontstaan er vernauwingen, die de bloedstroom belemmeren. De mate van verkalking en de daarmee gepaard gaande klachten kunnen variëren: van geen klachten tot milde, matige of ernstige klachten, tot het uiteindelijke afsterven van weefsel. Het meest voorkomende symptoom van PAV is claudicatio intermittens. Claudicatio intermittens betekent letterlijk vertaald 'kreupel met tussenpozen'. Patiënten met claudicatio intermittens hebben kramp en pijn in de been- en/of heupspieren tijdens het lopen, die typisch verdwijnt na een korte periode van rust. De pijn tijdens het lopen wordt veroorzaakt door de belemmering van de bloedtoevoer naar de spieren tijdens het lopen. Hierdoor ontstaat een discrepantie tussen de zuurstofbehoefte van de spieren en de zuurstoftoevoer via het bloed. Er ontstaat verzuring van de spieren wat wordt ervaren als kramp en pijn. In de volksmond wordt claudicatio intermittens ook wel etalagebenen genoemd. Dit komt doordat patiënten soms de pijn proberen te verbergen door te doen alsof ze in een winkeletalage aan het kijken zijn tijdens de noodgedwongen rust tijdens het lopen. De klachten kunnen leiden tot beperkingen in het dagelijks leven en hebben daarmee een negatief effect op de kwaliteit van leven.

Wereldwijd lijden meer dan 200 miljoen mensen aan PAV. In 10-20% van alle gevallen is de klinische presentatie claudicatio intermittens. Een belangrijke risicofactor voor perifeer arterieel vaatlijden is leeftijd. Met het toenemen van de leeftijd neemt de kans op PAV, en dus claudicatio intermittens, toe. Een andere belangrijke risicofactor voor het ontstaan van PAV is een ongezonde leefstijl. Geschat wordt dat 44% van de incidentie van PAV wordt veroorzaakt door roken. Andere bijdragende leefstijlfactoren behelzen lichamelijke inactiviteit, diabetes mellitus, een slecht cholesterolprofiel van het bloed en hoge bloeddruk. Naarmate de bevolking vergrijst en ongezond gedrag toeneemt, zal het aantal patiënten met PAV ook toenemen. Slagaderverkalking is een systeemziekte en beperkt zich niet tot alleen de slagaderen van de benen. Hierdoor hebben patiënten met claudicatio intermittens ook een verhoogd risico op andere (cardiovasculaire) aandoeningen. Na 5 jaar heeft ongeveer 20% van de patiënten met claudicatio intermittens een beroerte of hartinfarct doorgemaakt en is 10 tot 15% overleden.

Gesuperviseerde Beweeg- en Leefstijltherapie

De eerste keus behandeling – zoals aanbevolen in de (inter)nationale richtlijnen voor patiënten met claudicatio intermittens – is gesuperviseerde beweeg- en leefstijltherapie. Deze therapie houdt in dat patiënten gaan bewegen onder begeleiding van een fysio- of oefentherapeut met daarbij aandacht voor gezonde leefstijlveranderingen. Het is bewezen dat gesuperviseerde beweeg- en leefstijltherapie net zo effectief is als een invasieve behandelingen (zoals een dotterbehandeling of een omleidingsoperatie) om de loopafstand en kwaliteit van leven te verbeteren. Gesuperviseerde beweeg- en leefstijltherapie heeft een aantal voordelen boven invasieve therapie, zo is het non-invasief en goedkoper en heeft een positief effect op de algehele gezondheid. Het positieve effect op de algehele gezondheid is onder andere een verbetering het cholesterolprofiel, verlaging van de bloeddruk, verbetering van de bloedsuikerwaarde en mensen vallen af. Een invasieve behandeling sorteert daarentegen een sneller effect, maar geeft slechts een lokale oplossing van een systemisch probleem. Tot slot hebben patiënten die een invasieve behandeling ondergaan als eerste behandeling een groter risico op het moeten ondergaan van een tweede invasieve behandeling.

Hoe doen we het in Nederland?

In Nederland is gesuperviseerde beweeg- en leefstijltherapie geïmplementeerd middels het *stepped-care model*. Dit houdt in dat mensen primair worden verwezen voor de minst invasieve behandeling. In dit geval dus beweeg- en leefstijltherapie. Invasieve behandelingen worden bewaard voor patiënten die na drie tot zes maanden geen of onvoldoende baat blijken te hebben bij non-invasieve behandeling.

Gesuperviseerde beweeg- en leefstijltherapie is in Nederland voor iedere patiënt met claudicatio intermittens beschikbaar via Chronisch Zorgnet. Chronisch ZorgNet is een netwerk van gespecialiseerde therapeuten in de behandeling van alle patiënten met niet-overdraagbare chronische aandoeningen. Chronisch ZorgNet is ontstaan uit ClaudicatioNet, dat in 2011 werd opgericht: een landelijk dekkend netwerk voor beweeg- en leefstijl therapie voor patiënten met claudicatio intermittens. Het netwerk beoogde kwaliteit en transparantie te waarborgen middels onder andere (1) de organisatie van scholing en congressen, (2) het vindbaar maken van gespecialiseerde therapeuten via een digitale zorgzoeker, en (3) het inzichtelijk maken van behandelresultaten via een kwaliteitssysteem. In 2020 is ClaudicatioNet overgegaan in Chronisch ZorgNet, met als doel de behaalde successen voor patiënten met claudicatio intermittens ook te realiseren voor patiënten met andere chronische aandoeningen. Binnen Chronisch ZorgNet wordt ook wetenschappelijk onderzoek uitgevoerd om de zorg te kunnen verbeteren. Dit proefschrift is daar een van de resultaten van.

Personaliseren van Zorg

Op dit moment wordt bijna 90% van alle patiënten met claudicatio intermittens behandeld volgens de aanbevelingen uit de richtlijnen: beweeg- en leefstijltherapie als eerste behandeling. Deze aanbevelingen in de richtlijn zijn *evidence-based*, wat wil zeggen dat ze gebaseerd zijn op eerder wetenschappelijk onderzoek. Een adherentiepercentage van 90% aan de richtlijn is een groot succes. Echter, wanneer de praktijk zich volledig zou laten sturen door richtlijnen, ontstaat het risico dat de individuele patiënt uit het oog wordt verloren. Richtlijnen zijn namelijk vaak algemeen, gebaseerd op grote groepen patiënten en gericht op één specifieke aandoening. Terwijl in de praktijk de zorg draait om het individu en de patiënt tegenwoordig vaak meerdere aandoeningen tegelijk heeft. Hoewel er dus al grote successen zijn behaald in de zorg voor patiënten met claudicatio intermittens, is er nog ruimte voor verbetering in het personaliseren van de zorg binnen deze populatie. Het personaliseren van gesuperviseerde beweeg- en leefstijltherapie betekent echter niet dat er geen plaats meer is voor richtlijnen. Idealiter zouden de richtlijnaanbevelingen moeten worden geïndividualiseerd en toegepast binnen de context van de patiënt.

In de literatuur zijn verschillende benaderingen voorgesteld om de zorg patiëntgerichter te maken, waaronder: gezamenlijke besluitvorming, integratie van monitoringtools en het gebruiken van een lerend gezondheidssysteem. Om therapeuten te ondersteunen bij het integreren van (delen van) deze drie methoden in de praktijk, stellen wij individueel voorspelde uitkomsten voor. Hiervoor hebben wij het KomPas ontwikkeld. Het KomPas is een online hulpmiddel waarmee de therapeut op individueel patiëntniveau de uitkomst van therapie kan voorspellen op basis van verschillende persoonseigenschappen. Daarnaast kunnen daadwerkelijk behaalde resultaten worden vergeleken met de gemaakte voorspellingen. Het KomPas kan therapeuten helpen om betere klinische beslissingen te maken voor de individuele patiënt. Het geeft bijvoorbeeld mogelijkheden om realistischere behandeldoelen te stellen en het behandelplan aan te passen aan de prognose.

Het doel van dit proefschrift was het ontwikkelen, implementeren en evalueren van het KomPas. De verschillende stappen die hiervoor nodig zijn geweest staan beschreven in de hoofdstukken van dit proefschrift. De eerste stap was het identificeren van patiëntkenmerken die de uitkomst van therapie beïnvloeden of kunnen voorspellen. Daarnaast zijn de eerste resultaten van gebruik van het KomPas in de praktijk beschreven.

In **hoofdstuk 2** hebben we onderzocht of patiëntkenmerken en uitkomsten van gesuperviseerde beweeg- en leefstijltherapie gerelateerd zijn aan het niet hoeven ondergaan van een invasieve behandeling bij patiënten met claudicatio intermittens. We hebben geconcludeerd dat de groep patiënten die vroegtijdig (dus voor het afronden van de therapie) een invasieve behandeling onderging, andere kenmerken en loopprestaties had dan de patiëntengroep die geen invasieve behandeling onderging. Zo hadden de patiënten die vroegtijdig een dotter of operatie kregen vaker vernauwingen in de slagaders ter hoogte van de heup, waren deze vernauwingen vaker minder ernstig en hadden deze patiënten vaker in het verleden ook al een invasieve behandeling ondergaan. Patiënten die een vroegtijdige invasieve ingreep ondergingen toonden minder verbetering in loopprestatie na drie maanden. Tot slot blijkt dat gelijktijdige vernauwingen op meerdere plaatsen in de beenslagaders, een mindere kwaliteit van leven en rookstatus geassocieerd waren met de noodzaak van een vroegtijdige invasieve behandeling.

In **hoofdstuk 3** beschrijven we de opzet van het Kwaliteitssysteem; een landelijke infrastructuur waarmee routinematig verzamelde zorgdata wordt verzameld uit de dagelijkse praktijk om de fysiotherapeutische zorg te verbeteren. Ten tijden van het schrijven van dit hoofdstuk in 2019 was het Kwaliteitssyteem onderdeel van ClaudicatioNet, een landelijk dekkend netwerk van op dat moment meer dan 2.100 gespecialiseerde fysio- en oefentherapeuten die geschoold zijn in gesuperviseerde beweeg- en leefstijltherapie. ClaudicatioNet en het Kwaliteitssysteem vormen samen een zogenaamd lerend gezondheidssysteem. Een lerend gezondheidssysteem is een systeem waarin ervaringen en/of data worden gebruikt voor continue verbetering en innovatie. Zo wordt de verzamelde data in het Kwaliteitssyteem gebruikt om de fysiotherapeutische zorg te verbeteren door bijvoorbeeld benchmarking, personalisatie van zorg, educatie en optimalisatie van de behandeling. Het KomPas is hier een voorbeeld van. Met behulp van ClaudicatioNet konden we de eerste stappen zetten om de fysiotherapeutische zorg voor patiënten met claudicatio intermittens in Nederland te verschuiven van gegeneraliseerde, op richtlijnen gebaseerde fysiotherapiezorg naar meer transparante, gepersonaliseerde *evidence-based* fysiotherapiezorg.

In **hoofdstuk 4** van dit proefschrift beschrijven we de ontwikkeling en de statistische evaluatie van de zogenaamde persoonlijke uitkomst voorspellingen: Het KomPas. De voorspellingen in het KomPas worden gemaakt met behulp van de *neighbors based* *prediction* methode. Middels deze methode wordt een subgroep patiënten geselecteerd uit de grote ClaudicatioNet database, die het meest lijkt op de patiënt die op dat moment in de spreekkamer zit. De gegevens van deze patiënten worden vervolgens gebruikt om een persoonlijke voorspelling van de therapie uitkomst te maken. Het KomPas is op verschillende manieren statistisch getest en geëvalueerd. Hieruit bleek dat het KomPas een grote nauwkeurigheid heeft en in staat is een preciezere voorspelling te maken dan eerder gebruikte methoden. Hieruit hebben we geconcludeerd dat het *neighbors based prediction* model een geschikt is voor het maken van individueel voorspelde uitkomsten.

In **hoofdstuk 5** hebben we de eerste stap van de implementatie van het KomPas in de praktijk beschreven. In deze studie hebben we aan een groep Chronisch ZorgNet therapeuten geïnterviewd die we fictieve casus hadden voorgelegd, inclusief voorspellingen uit het KomPas. De resultaten van dit onderzoek toonden verschillende mogelijkheden voor het gebruik van het KomPas in de dagelijkse praktijk. Zo zagen de therapeuten mogelijkheden om het KomPas te gebruiken om de prognose aan de patiënt uit te leggen, om patiënten te motiveren, om realistische doelen te stellen en om behandelplannen op te stellen op basis van de voorspelde loopafstand. Daarnaast heeft deze studie belangrijke lessen opgeleverd voor de verdere verbetering en implementatie van het KomPas. Met name misinterpretatie en misverstanden zijn belangrijke factoren om rekening mee te houden zodat het KomPas in de praktijk ook zo wordt gebruikt als het bedoeld is

In **hoofdstuk 6** wordt de uiteindelijke implementatiestrategie van het KomPas besproken. Het KomPas zal stapsgewijs in heel Nederland worden uitgerold onder alle Chronisch ZorgNet therapeuten. Verschillende data worden verzameld om de impact van het KomPas de evalueren, zoals de loopafstand, kwaliteit van leven en de mate van samen beslissen in de praktijk. Daarnaast zal ook het percentage patiënten dat de therapie niet afmaakt en redenen van therapeuten om het KomPas wel of niet te gebruiken worden geregistreerd. Deze gegevens worden zowel voor al na implementatie van het KomPas verzameld, zodat beide situaties met elkaar kunnen worden vergeleken.

CONCLUSIE

Het doel van dit proefschrift was het ontwikkelen, implementeren en evalueren van het KomPas; een beslissingsondersteunend instrument dat aanvullend inzicht geeft in de verwachte prognose van individuele patiënten met claudicatio intermittens tijdens een traject van gesuperviseerde beweeg- en leefstijltherapie. Wij zijn van mening dat we dit met succes hebben gedaan en op deze manier therapeuten kunnen ondersteunen bij het personaliseren van de zorg. Hoewel de daadwerkelijke impact nog moet worden geëvalueerd, lijken de eerste resultaten veel belovend dat het KomPas zal helpen bij het samen beslissen in de praktijk en om de zorg meer participatief te maken. Middels dit proefschrift zetten wij een eerste stap om de traditionele *one-size-fits-all* richtlijnaanbevelingen te verlaten en streven wij naar geïndividualiseerde aanbevelingen voor patiënt en therapeut.

APPENDICES

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SUPPLEMENTAL CONTENT CHAPTER 2

Supplemental Table 1. *Baseline characteristics of patients excluded due to revascularization <3 months after SET initiation.*

	Overall population (n=252)	Excluded (n=15)	*P**
Age, y	68.3 ± 9.0		0.360
Female sex, n (%)	98 (38.9)	5 (33.3)	0.789
BMI, kg/m^2	27.2 (4.2) *n=149*		0.271
Smoking, n (%)			0.596
Current	107 (42.5)	8(53.3)	
Former	103 (40.9)	6 (40.0)	
Never	42 (16.7)	1 (6.7)	
Comorbidity, n (%)			
Diabetes	67 (26.6)	2 (13.3)	0.367
Dyslipidemia	134 (53.2)	8 (53.3)	>0.999
Hypertension	155 (61.5)	8 (53.3)	0.612
Kidney disease	28 (11.1)	1 (6.7)	0.713
Cerebrovascular disease	31 (12.3)	1 (6.7)	0.704
Ischemic heart disease	56 (22.2)	3 (20)	>0.999
Heart failure	15 (6)	0	0.410
COPD	49 (19.4)	1 (6.7)	0.317
Musculoskeletal disease	40 (15.9)	0	0.721
Prior CVD intervention, n (%)			
CABG	21 (8.3)	1 (6.7)	0.645
PCI	29 (11.5)	2 (13.3)	>0.999
EVAR	1 (0.4)	0	>0.999
open AAA repair	5(2.0)	0	>0.999
Previous IC treatment, n (%)			
Endovascular revascularization	43(17.1)	4 (26.7)	0.482
Open revascularization	12(4.8)	1 (6.7)	>0.999
Supervised exercise therapy	23 (9.2)	3 (20.0)	0.085
Symptomatic leg, n (%)			0.437
uni	123 (48.8)	9 (60.0)	
Both	129 (51.2)	6 (40.0)	
ABI in rest (lowest of legs)	0.64 ± 0.2 *n=243*	0.55 ± 0.2 *n=15*	0.551
ABI after exercise (lowest of legs)	0.36 ± 0.2 *n=222*	0.31 ± 0.2 *n=14*	0.234$^+$
Functional walking distance, m	321 ± 266 *n=225*	288 ± 208 *n=14*	0.803$^+$
Maximal walking distance, m	504 ± 362 *n=226*	377 ± 242 *n=14*	0.176$^+$
6-minute walking test, m	376 ± 107 *n=235*	330 ± 108 *n=15*	0.736
Vascuqol-6 sumscore	16 ± 4.0 *n=241*	13 ± 4 *n=15*	0.342
Lesion location, n (%)			0.531
Aortoiliac	70 (26.2)	6 (40.0)	
Femoropopliteal	115 (43.1)	5 (33.3)	

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	Overall population (n=252)	Excluded (n=15)	*P**
Multilevel	69 (25.8)	4 (26.7)	
No aortoiliac or femoral-popliteal	13 (4.9)	0 (0)	
TASC Score*, n (%)			0.721
TASC A	100 (40.3)	6 (40)	
TASC B	84 (33.9)	6 (40)	
TASC C	32 (12.9)	1 (6.7)	
TASC D	19 (7.7)	2 (13.3)	
No aortoiliac or femoropopliteal	13 (5.2)	0	
Unknown	4(1.6)	0	

Supplemental Table 2. *Walking performance and health-related quality of life after 3 and 6 months of SET.*

Outcomes	*Baseline*	*3 months*	*6 months*	*P**
Maximal walking distance, m	504 ± 362 n=226	853±526 n=203	967 ±526 n=170	<0.001
Change from baseline, m	-	332(-250 – 1590) n=202	444 (-160 –2066) n=169	
Functional walking distance, m	321 ± 266 n=225	661 ± 501 n=199	781 ± 524 n=167	<0.001
Change from baseline, m	-	228(-130 – 2074) n=199	449 (-190 – 2099) n=167	
6MWD, m	376 ±107 n=235	420 ±112 n=190	434 ±147 n=160	<0.001
Change from baseline, m	-	35 (-200 – 538) n=185	52 (-165 – 1138) n=159	
Vascuqol-6	16±4 n=241	18 ±4 n=200	19 ±4 n=169	<0.001
Change from baseline	-	2 (-12 – 13) n=196	3 (-5 – 14) n=168	

*Between baseline, 3 months and 6 months, using Friedman test or repeated-measure ANOVA as appropriate.

Supplemental Table 3. *Univariable analysis of factors associated with early revascularization at 12-months clinical follow-up.*

Variables	***Hazard Ratio***	***95% CI***	***P***
Age, y			
per 1	0.992	0.963–1.022	0.598
>80	1.178	0.502–2.763	0.706
Female sex	**1.566**	**0.910–2.695**	**0.105**
BMI, kg/m2			
per 10	0.878	0.871– 0.885	0.158
>30	1.193	0.594–2.396	0.619
Smoking			
Current	**0.574**	**0.259–1.272**	**0.172**
Former	**0.281**	**0.122–0.945**	**0.003**
Never	Ref	Ref	-
Comorbidity			
Diabetes	0.811	0.440–1.494	0.501
Dyslipidemia	1.109	0.639–1.925	0.714
Hypertension	0.843	0.473–1.502	0.563
Kidney disease	1.163	0.496–2.723	0.729
Cerebrovascular disease	0.887	0.433–1.817	0.742
Ischemic heart disease	1.116	0.612–2.034	0.720
Heart failure	0.797	0.248–2.557	0.703
COPD	0.913	0.488–1.707	0.775
Musculoskeletal disease legs	1.335	0.700–2.547	0.380
Prior CVD intervention			
CABG	0.948	0.405–2.221	0.903
PCI	1.104	0.520–2.343	0.798
EVAR or open AAA repair	**3.335**	**0.991–11.225**	**0.052**
Previous IC treatment			
ER or OR			
ER	0.876	0.486–1.577	0.659
OR	1.019	0.318–3.271	0.974
SET	0.952	0.440–2.166	0.952
Symptomatic leg			
Unilateral	0.945	0.546–1.636	0.840
Bilateral	1.058	0.611–1.831	0.840
Lesion location			
Aortoiliac	1.182	0.582–2.402	0.644
Femoropopliteal	Ref		
Multilevel	1.439	0.735–2.817	0.288
No aortoiliac or femoral-popliteal	No events		
ABI in rest	**0.833**	**0.721–0.975**	**0.023**
ABI in rest <0.5	**0.458**	**0.337–0.623**	**0.011**
ABI after exercise	**0.895**	**0.779–1.028**	**0.117**

Variables	*Hazard Ratio*	*95% CI*	*P*
ABI decrease after exercise	1.039	0.912–1.183	0.570
Baseline FWD, 10 m	1.010	0.987–1.034	0.403
Baseline MWD, 10 m	1.004	0.992-1.016	0.523
Baseline 6-minute walking test, 10 m	0.979	0.948- 1.012	0.216
Baseline Vascuqol-6 sumscore	0.972	0.904–1.047	0.456
3-month change FWD, 10 m	**0.985**	**0.970- 1.000**	**0.051**
3-month change FWD, >250m	0.724	0.381–1.376	0.323
3-month change MWD, 10 m	**0.984**	**0.972- 0.997**	**0.016**
3-month change MWD, >305m	0.405	0.164–0.998	0.049
3-month change 6-minute walking test, 10m	1.011	0.965- 1.059	0.639
3-month change Vascuqol-6 sumscore	**0.923**	**0.859–0.993**	**0.031**
3-month change Vascuqol-6 sumscore >2	**0.647**	**0.350–1.198**	**0.116**
TASC Score, n (%)			
TASC A	2.204	0.641–7.580	0.210
TASC B	**2.489**	**0.739–8.389**	**0.141**
TASC C	3.447	0.977–12.161	0.054
TASC D			

*Controlling for xxx, xxx, xxx, xxxx, and other independently predictive variables (<0.2 P value).

* In most symptomatic leg, most severe trajectory.

Supplemental Table 4. *Univariable predictive value of patient characteristics for change in maximal walking distance at 3-months clinical follow-up.*

Variables	*Beta per unit*	*95% CI*	*P-Value*
Age, y			
per y	3.891	-2.647– 10.428	0.240
>80y	124.356	-114.887– 363.599	0.299
Female sex	33.132	-78.131– 144.395	0.558
BMI			
per 10 kg/m2	-95.390	-269.438– 78.658	0.294
>30	-36.899	-178.338–104.539	0.605
Smoking			
Current	-15.244	-162.337–131.848	0.839
Former	-74.073	-227.728– 79.582	0.344
Never	Ref		
Comorbidity, n (%)			
Diabetes	-17.536	-151.698– 116.625	0.796
Dyslipidemia	**-129.886**	**-234.450– -25.321**	**0.015**
Hypertension	**-98.258**	**-205.494– 8.978**	**0.072**
Kidney disease	**-109.838**	**-269.866– 50.189**	**0.178**

Variables	*Beta per unit*	*95% CI*	*P-Value*
Cerebrovascular disease	-67.116	-225.282– 91.051	0.405
Ischemic heart disease	**-135.958**	**-280.304– 8.388**	**0.064**
Heart failure	-104.130	-344.941– 136.682	0.394
COPD	**-105.857**	**-245.386– 33.672**	**0.136**
Musculoskeletal disease legs	**-108.253**	**-255.760– 39.253**	**0.150**
Prior CVD intervention, n (%)			
CABG	-125.694	-321.206– 69.819	0.206
PCI	-93.133	-264.808– 78.451	0.286
EVAR or open AAA repair	-237.976	-605.256– 129.295	0.204
Previous IC treatment, n (%)			
ER or OR			
ER	-90.524	-230.782– 49.735	0.205
OR	3.718	-230.734– 238.170	0.975
SET	**-132.587**	**-329.397– 64.223**	**0.185**
Symptomatic leg, n (%)			
Unilateral	-23.263	-127.897– 81.371	0.662
Bilateral	23.263	-81.371– 127.897	0.662
Lesion location, n (%)			
Aortoiliac	**-161.229**	**-289.217--33.241**	**0.014**
Femoropopliteal	Ref		
Multilevel	**-167.198**	**-300.919--33.477**	**0.015**
No aortoiliac or femoral-popliteal	-3.899	-241.882–234.084	0.974
ABI in rest	-0.344	-26.856– 26.167	0.980
<0.5	-3.922	-137.077– 139.232	0.954
ABI after exercise	3.941	-22.277– 30.160	0.768
ABI decrease after exercise	4.258	-23.789– 32.305	0.766
Baseline FWD, 10 m	**-1.463**	**-3.502 – 0.575**	**0.163**
Baseline MWD, 10 m	-0.712	-2.182– 0.758	0.343
Baseline 6-minute walking test, 10 m	**4.488**	**-0.647– 9.623**	**0.088**
Baseline Vascuqol-6 sumscore	1.374	-13.784–16.533	0.857
TASC Score, n (%)			
TASC A	-24.071	-251.952– 203.918	0.835
TASC B	-68.776	-284.247–146.695	0.430
TASC C	**-200.644**	**-474.998–73.709**	**0.149**
TASC D			

Supplemental Table 5. *Univariable predictive value of patient characteristics for change in functional walking distance at 3-months clinical follow-up.*

Variables	*Beta per unit*	*95% CI*	*P-Value*
Age, y			
per y	0.342	-6.585–7.269	0.922
>80y	54.133	-183.801– 292.066	0.649
Female sex	36.512	-81.120–154.144	0.541
BMI			
per 10 kg/m2	**-132.142**	**-279.744– 15.461**	**0.086**
>30	**-98.853**	**-230.623–32.918**	**0.141**
Smoking			
Current	**-108.475**	**-267.199– 50.249**	**0.180**
Former	-53.330	-206.494–99.833	0.495
Never	ref		
Comorbidity, n (%)			
Diabetes	-33.139	-176.454– 110.176	0.646
Dyslipidemia	**-182.900**	**-298.198– -67.602**	**0.002**
Hypertension	**-121.868**	**-231.659–-12.077**	**0.030**
Kidney disease	-76.963	-242.510– 88.584	0.362
Cerebrovascular disease	-2.495	-171.794– 166.804	0.977
Ischemic heart disease	**-148.964**	**-293.558– -4.369**	**0.044**
Heart failure	-178.126	-468.544– 122.293	0.223
COPD	**-107.107**	**-257.197– 42.984**	**0.160**
Musculoskeletal disease legs	-74.934	-225.594– 75.726	0.329
Prior CVD intervention, n (%)			
CABG	**-167.406**	**-356.104– 21.292**	**0.082**
PCI	-95.618	-272.060– 80.825	0.287
EVAR or open AAA repair	-199.464	-582.006– 183.078	0.306
Previous IC treatment, n (%)			
ER or OR			
ER	**-126.802**	**-265.868– 12.264**	**0.074**
OR	-18.578	-268.734– 231.578	0.884
SET	-90.168	-287.608– 107.272	0.369
Symptomatic leg, n (%)			
Unilateral	-0.421	-113.452– 112.611	0.994
Bilateral	0.421	-112.611–113.452	0.994
Lesion location, n (%)			
Aortoiliac	**-106.067**	**-239.923–27.789**	**0.120**
Femoropopliteal	Ref		
Multilevel	**-157.376**	**-283.857–-30.896**	**0.015**
No aortoiliac or femoral-popliteal	23.789	-232.218–279.796	0.855
ABI in rest	9.045	-19.848– 37.939	0.540
<0.5	5.275	-128.937– 139.486	0.938
ABI after exercise	14.755	-16.296– 45.806	0.355

Variables	*Beta per unit*	*95% CI*	*P-Value*
ABI decrease after exercise	6.242	-23.505– 35.990	0.682
Baseline FWD, 10 m	0.214	-1.893–2.321	0.842
Baseline MWD, 10 m	**2.131**	**0.631–3.632**	**0.006**
Baseline 6-minute walking test, 10 m	**5.547**	**-0.034–11.128**	**0.054**
Baseline Vascuqol-6 sumscore	4.148	-13.126–21.423	0.631
TASC Score, n (%)			
TASC A	-49.624	-280.289– 181.042	0.671
TASC B	**-160.674**	**-400.103–78.756**	**0.186**
TASC C	**-234.284**	**-489.246–20.677**	**0.0.71**
TASC D			

Supplemental Table 6. *Univariable predictive value of patient characteristics for change in 6-minute walking distance at 3-months clinical follow-up.*

Variables	*Beta per unit*	*95% CI*	*P-Value*
Age, y			
per y	-0.190	-1.222– 1.603	0.790
>80y	5.414	-34.982– 45.810	0.792
Female sex	**20.750**	**-7.733– 49.233**	**0.150**
BMI			
per 10 kg/m2	-7.055	-41.820– 27.710	0.694
>30	-6.399	-45.302–32.503	0.739
Smoking			
Current	18.313	-51.808–15.181	0.591
Former	-9.198	-42.890– 24.494	0.591
Never	ref		
Comorbidity, n (%)			
Diabetes	-4-949	-38.951– 29.053	0.777
Dyslipidemia	3.396	-18.841– 25.634	0.764
Hypertension	-0.068	-25.320– 25.184	0.996
Kidney disease	**23.091**	**-11.751– 57.932**	**0.194**
Cerebrovascular disease	11.374	-28.167– 50.915	0.569
Ischemic heart disease	-24.429	-63.881– 15.023	0.215
Heart failure	2.319	-57.767– 62.406	0.938
COPD	-12.172	-41.804– 17.460	0.416
Musculoskeletal disease legs	6.584	-24.971– 38.140	0.682
Prior CVD intervention, n (%)			
CABG	-17.410	-62.712– 27.892	0.488
PCI	-14.576	-64.329– 35.178	0.555
EVAR or open AAA repair	**57.310**	**-26.982– 141.602**	**0.182**
Previous IC treatment, n (%)			
ER or OR			

Variables	*Beta per unit*	*95% CI*	*P-Value*
ER	-12.172	-42.376– 18.033	0.429
OR	-17.267	-71.609– 37.076	0.532
SET	**50.706**	**12.145– 89.267**	**0.010**
Symptomatic leg, n (%)			
Unilateral	9.045	-13.757–31.847	0.436
Bilateral	-9.045	-31.847 –13.757	0.436
Lesion location, n (%)			
Aortoiliac	**6.999**	**-26.723–40.722**	**0.680**
Femoropopliteal	Ref		
Multilevel	12.291	-16.921–41.502	0.408
No aortoiliac or femoral-popliteal	**-40.968**	**-96.139–14.204**	**0.145**
ABI in rest	-0.854	-7.401– 5.693	0.799
<0.5	0.199	-33.247– 33.645	0.991
ABI after exercise	-0.805	-7.082– 5.471	0.802
ABI decrease after exercise	-0.014	-6.387– 6.359	0.997
Baseline FWD, 10 m	0.106	-0.404–0.616	0.684
Baseline MWD, 10 m	0.169	-0.207–0.455	0.382
Baseline 6-minute walking test, 10 m	**-2.291**	**-3.461–-1.122**	**0.000**
Baseline Vascuqol-6 sumscore	-0.488	-3.709–2.732	0.764
TASC Score, n (%)			
TASC A	-6.559	-56.344– 43.226	0.794
TASC B	-7.700	-59.158–43.758	0.767
TASC C	-36.324	-107.377–34.730	0.306
TASC D			

Supplemental Table 7. *Multivariable linear regression of factors independently correlated with change in walking performance or quality of life after 3 months of treatment.*

Variables	*Multivariable regression*[a]		*Final model*[b]	
	P value	*Beta per unit*	*P value*	*Beta per unit*
Change in maximal walking distance				
Dyslipidemia	0,087	-90,176	0,082	-91,412
Hypertension	0,230	-68,357	0,129	-84,174
Kidney disease	0,644	-38,325		
Ischemic heart disease	0,329	-72,903		
COPD	0,226	-87,387	0,173	-97,001
Musculoskeletal disease legs	0,375	-67,551		
Previous SET treatment	0,291	-99,749		
Lesion location, n (%)				
Aortoiliac	0,001	-211,008	0,001	-214,893
Femoropopliteal	ref		ref	
Multilevel	0,098	-112,380	0,100	-110,821
No aortoiliac or femoral-popliteal	0,707	-58,566	0,672	-62,221
Baseline FWD, 10 m	0,007	-3.245	0,007	-3.219
Baseline 6-minute walking test, 10 m	0,194	4.157	0,105	4.926

Variables	*Multivariable regression*[a]		*Final model*[b]	
	P value	*Beta per unit*	*P value*	*Beta per unit*
TASC Score, n (%)				
TASC A	0,715	-37,642	0,820	-22,484
TASC B	0,396	-85,040	0,375	-84,720
TASC C	0,095	-211,855	0,065	-224,212
TASC D	ref		ref	
Change in functional walking distance				
BMI per 10 kg/m2	0,070	-128,292	0,507	-13,924
Smoking				
Current	0,090	-134,951	0,115	-126,480
Former	0,810	-18,041	0,741	-24,573
Never	ref		ref	
Dyslipidemia	0,072	-104,501	0,040	-118,842
Hypertension	0,136	-90,176	0,110	-95,700
Ischemic heart disease	0,393	-69,329		
COPD	0,525	-48,380		
Prior CABG intervention	0,540	-66,875		
Previous ER treatment,	0,488	-50,905		
Lesion location, n (%)				
Aortoiliac	0,084	-120,200	0,062	-129,955
Femoropopliteal	ref			
Multilevel	0,299	-70,151	0,191	-84,943
No aortoiliac or femoral-popliteal	0,771	-45,744	0,825	-34,458
Baseline MWD, 10 m	0,344	0,806	1,061	0,121
Baseline 6-minute walking test, 10 m	0,686	1,398		
TASC Score, n (%)				
TASC A	0,410	-88,600	0,428	-84,535
TASC B	0,062	-202,598	0,067	-195,478
TASC C	0,029	-262,563	0,022	-274,590
TASC D	ref		ref	
Change in 6-minute walking test				
Female sex	0,558	8,229		
Kidney disease	0,662	8,484		
EVAR or open AAA repair	0,540	29,147		
Previous SET treatment	0,010	48,031	0,012	47,173
Lesion location, n (%)				
Aortoiliac	0,531	10,143	0,483	11,320
Femoropopliteal	ref			
Multilevel	0,963	-0,692	0,998	0,030
No aortoiliac or femoral-popliteal	0,128	-43,125	0,118	-44,367
Baseline 6-minute walking test, 10 m	0,002	-2,106	0,001	-2,290

[a] R^2 = 41.3% (maximal walking distance), 42.5% (functional walking distance), 36.0%(6-minute walking test)
[b] R^2 = 38.9% (maximal walking distance), 40.7% (functional walking distance), 35.1% (6-minute walking test)

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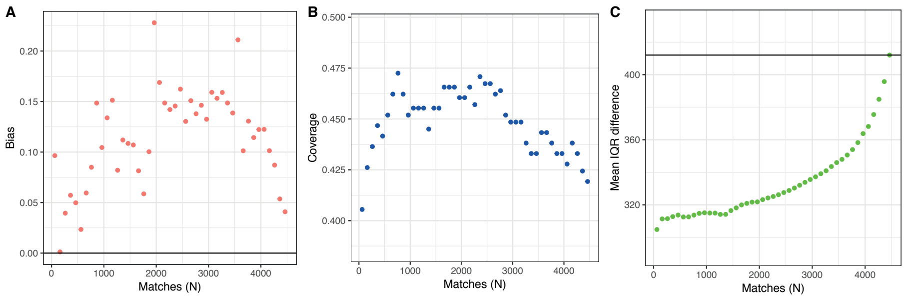
SUPPLEMENTAL CONTENT CHAPTER 4

Supplemental figure 1. *Variation in bias, coverage and mean IQR difference with varying number of matches.*



SUPPLEMENTAL CONTENT CHAPTER 5

Supplement 1

Introductie voor de fysiotherapeut

Momenteel zijn we bij ClaudicatioNet bezig met het ontwikkelen van een tool die inzicht kan geven in de individuele prognose van patiënten met claudicatio intermittens na een traject gesuperviseerde looptherapie (GLT). Deze tool maakt een voorspelling van de te verwachten toename in loopafstand van de patiënt tijdens een GLT-traject. De voorspelling zal worden weergegeven in de vorm van een grafiek en begeleidende tekst en uitleg.

De voorspelling wordt gemaakt aan de hand van het patiënten zoals ik -principe. Dat werkt als volgt. Op basis van een aantal specifieke patiënt karakteristieken (geslacht, leeftijd, BMI, pakjaren*, en loopafstand) wordt een nieuwe patiënt gematched met patiënten uit een database die vergelijkbaar zijn op basis van deze karakteristieken. De resultaten van deze historische patiënten worden gebruikt om een individuele voorspelling te maken voor de nieuwe patiënt.

** Pakjaren is een maat voor hoeveel de patiënt in zijn leven heeft gerookt. 1 pak jaar staat voor 1 jaar lang een pakje per dag. 30 pakjaren is dus 30 jaar een pakje per dag of 15 jaar 2 pakjes per dag, enzovoort.*

Het doel van deze studie is het bekijken wat het effect zou zijn van het gebruik van onze tool in de praktijk. Dit gaan we doen met behulp van de vignettemethode, waarin we de praktijk nabootsen met behulp van papieren casussen. In een vignettestudie krijgen de deelnemers namelijk casussen te lezen waarna met behulp van vragen de mening ten aanzien van verschillende situaties gevraagd wordt.

Je krijgt straks 6 fictieve vignette/casussen te lezen. Deze beschrijven allemaal een patiënten met claudicatio intermittens die door de vaatchirurg is verwezen voor gesuperviseerde looptherapie. De casussen bestaan uit 4 delen en zijn als volgt opgebouwd:

1. Informatie verkregen vanuit de verwijzing en anamnese;
2. Objectieve informatie vanuit de uitgevoerde testen en metingen;
3. Extra informatie betreft de te verwachten vooruitgang tijdens het behandel traject vanuit de tool;
4. Informatie uit de follow-up afspraak na een aantal maanden.

Tussen de verschillende delen in krijg je steeds een aantal vragen. Het is de bedoeling dat je hardop nadenkt over deze vragen zodat wij kunnen horen hoe je redeneert en denkt.

Uitleg bij de grafiek

De volgende grafiek laat een voorspelling zien van de te verwachte maximale loopafstand na 6 maanden gesuperviseerde looptherapie. De zwarte middelste lijn is het gemiddelde van de voorspelling, de blauwe stippellijnen het 25ste en 75ste percentiel, en de paarse onderste en bovenste lijn het 10de en 90ste percentielen. Het 90ste percentiel betekend dat 90% van de patiënten onder deze lijn zal uitkomen, en het 10de betekend dat 10% onder deze zal uitkomen. Het merendeel (80%) van de patiënten zal dus uiteindelijk ergens uitkomen binnen deze twee lijnen. De grijze lijnen op de achtergrond zijn de resultaten van de historische patiënten waarop de voorspelling is gebaseerd.

Supplement 2

Vragenlijst baseline patiënt

Deel 1 – Je hebt nu de informatie verkregen uit de anamnese

- Herken je je in de patiënt zoals beschreven in de casus?
- Wat zou je, na afronden van de anamnese, met de patiënt gaan bespreken? Hoe ga je dit doen?

- Heb je het idee dat je, na het afnemen van een anamnese, voldoende in staat bent om dit gesprek te voeren met deze patiënt? Waarom wel/niet?
- Welke informatie ontbreekt nog voor jouw gevoel?

Deel 2 – Naast de anamnese heb je nu ook objectieve informatie over de loopafstand

- Welke doelen zou je opstellen? (Formuleer een concreet hoofd en subdoel)
- Welke factoren neem je mee in het opstellen van het doel? Waarom deze?
- Hoe heeft de patiënt invloed op het opstellen van de doelen?
- Beslist je samen? Waarom wel/niet?
- Hoe gaat het behandeltraject eruit zien? Kan je dit beschrijven? (Hoeveel sessies, welke inhoud gaan de sessies hebben, wanneer ga je afbouwen en wat zijn de huiswerkopdrachten?)
- Hoe kom je dit behandeltraject? En hoe ga je dit behandeltraject monitoren?
- Op welke manier is de patiënt betrokken bij het opstellen van het behandeltraject?
- Beslis je samen? Waarom wel/waarom niet?

Deel 3 – Je hebt nu de individuele voorspelling uit het voorspel model gekregen

- Vertel eens, wat valt je op?
- Wat zou je nu bespreken met deze patiënt? Waarom? Hoe gaat u dit doen?
- Zou je de doelen die je zojuist hebt beschreven aanpassen? Waarom wel/niet en hoe? (indien wordt gekozen voor aanpassen van het doel, een concreet nieuw doel laten formuleren)
- Zou je het behandelplan dat je zojuist hebt beschreven aanpassen? Waarom wel/niet en hoe?
- Voel je je beter in staat het gesprek met de patiënt te voeren (waar we aan het een het begin over hebben gehad) nu je deze informatie hebt? Waarom wel/niet?

Deel 4 – Het 3 maanden controle moment is aangebroken

- Vind je dat de therapie de goede kant op gaan? Waarom wel of niet?
- Wat kan volgens jou dit therapieresultaat verklaren? Welke factoren hebben volgens jou gewoonlijk invloed op het resultaat van de therapie.
- Zou je het doel van de behandeling nog aan willen passen? Waarom wel/niet en hoe?
- Zou je de inhoud van de behandeling nog aan willen passen? Waarom wel/niet en hoe?
- Hoe zou je de laatste maanden van de therapie nog inrichten?
- Zou je de informatie uit de grafiek gebruiken bij het invullen van de rest van het behandeltraject? Waarom wel/niet?
- Ziet u in uw dagelijkse praktijk de ruimte om de tool te passen zoals we zojuist hebben besproken?

Supplement 3 – Casussen

Casus 1

Deel 1

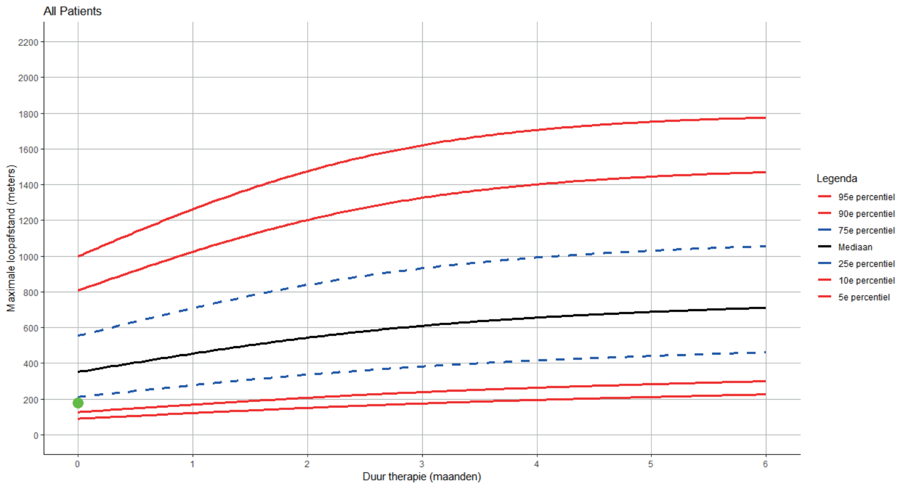
Meneer Peters is 81 jaar en naar u doorverwezen voor gesuperviseerde looptherapie. Hij is doorverwezen door de vaatchirurg met de diagnose claudicatio intermittens. Hij heeft een BMI van 29 en is bekend met hypertensie, hypercholesterolemie en diabetes. Hij heeft nog nooit gerookt en zijn vasco-cardiale voorgeschiedenis is blanco. Meneer Peters is met pensioen en komt niet zo veel meer buiten door zijn klachten. Hij zou graag naar de supermarkt kunnen lopen (500meter) zonder pijn in zijn benen. Hij ziet er tegenop om zo vaak naar de praktijk te komen voor de therapie, maar is gemotiveerd om van start te gaan.

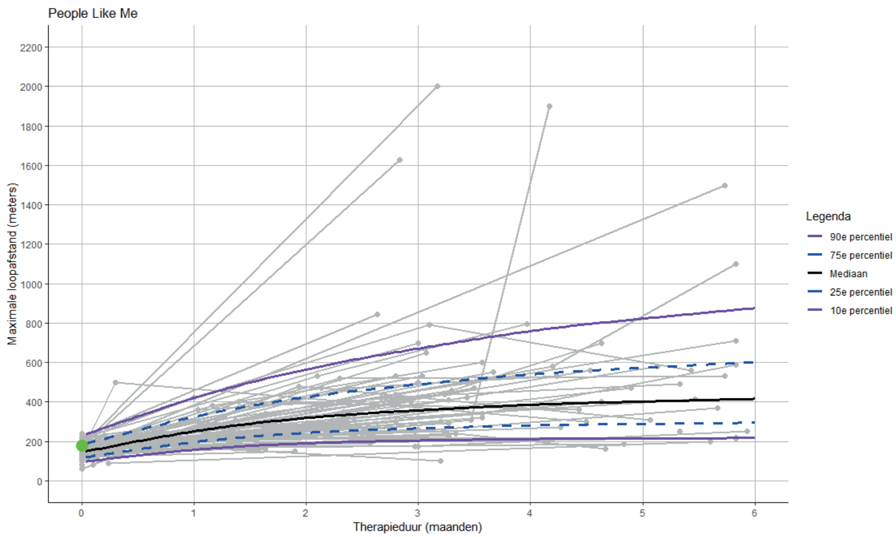
Deel 2

Bij de loopbandtest meet je een functionele loopafstand van 100 meter en een maximale loopafstand van 180 meter.

Deel 3

De ClaudicatioNet tool laat zien dat dhr. laag scoort ten opzichte van het gemiddelde van de gehele populatie, namelijk onder het 25^e percentiel. Dit wil zeggen dat hij bij de 25% van de populatie met een korte loopafstand hoort. De ClaudicatioNet tool voorspelt een MWD van 380 meter na 3 maanden GLT (de zwarte lijn). Dit is een absolute voorruitgang van 200 meter en een relatieve vooruitgang van 110%. De blauwe stippellijnen geven het 25^e en 75^e percentiel, in dit geval 220 en 500 meter. Dit houdt in dat in 50% van de gevallen de loopafstand van de patiënt hiertussen zal vallen.





Deel 4

Na 3 maanden is het eerste controle moment. Het kost dhr. veel moeite ieder week weer naar de therapie te komen, maar hij is wel erg benieuwd naar zijn resultaat. Je meet nu een FWD van 420 meter en een MWD van 550 meter.

Casus 2

Deel 1

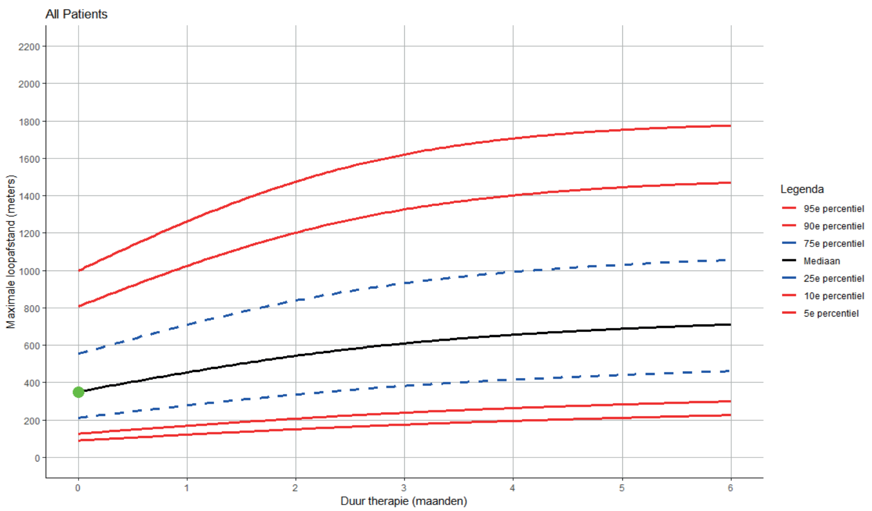
Meneer de Vries is 66 jaar en naar u doorverwezen voor gesuperviseerde looptherapie. Hij is doorverwezen door de vaatchirurg met de diagnose claudicatio intermittens. Hij heeft een BMI van 30, is bekend met hypertensie en rookt al 40 jaar een pakje per dag (40 pakjaren). Meneer de Vries is vervroegd met pensioen gegaan en was tot die tijd vrachtwagenchauffeur. Zijn vrouw wandelt veel en hij zou graag met haar mee kunnen wandelen zonder steeds te hoeven stoppen (1km). Hij zit hier omdat het moet, maar begrijpt niet waarom hij niet gewoon gedotterd kon worden.

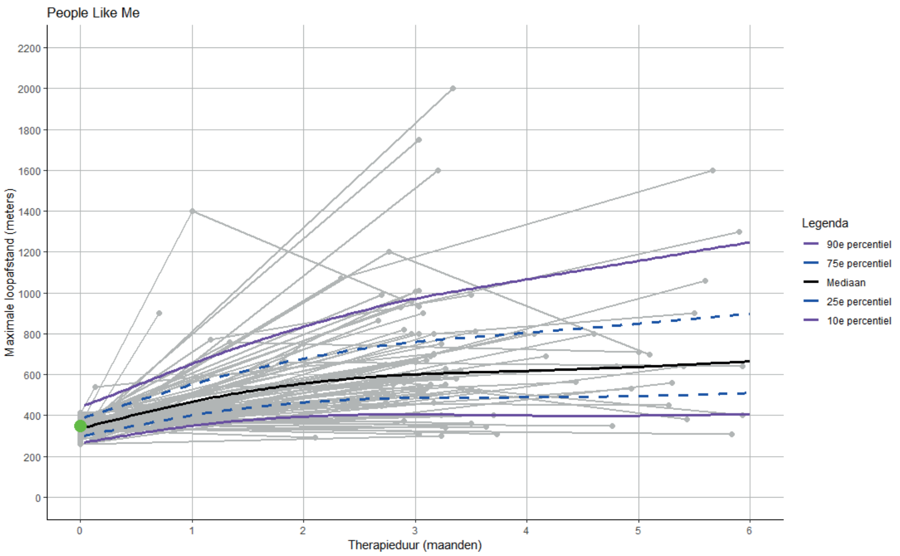
Deel 2

Bij de loopbandtest meet je een functionele loopafstand van 200 meter en een maximale loopafstand van 350 meter.

Deel 3

De ClaudicatioNet tool laat zien dat dhr. ten opzichte van de gehele populatie gemiddeld scoort, precies op de mediaan. De ClaudicatioNet tool voorspelt een MWD van 600 meter na 3 maanden GLT (de zwarte lijn). Dit is een absolute voorruitgang van 250 meter en een relatieve vooruitgang van 71%. De blauwe stippellijnen geven het 25e en 75e percentiel, in dit geval 480 en 760 meter. Dit houdt in dat in 50% van de gevallen de loopafstand van de patiënt hiertussen zal vallen.





Deel 4

Na 3 maanden is vindt het eerste controle moment plaats. dhr. is zelf niet zo positief over de therapie en het behaalde resultaat. Je meet nu een FWD van 380 meter en een MWD van 500 meter.

Casus 3

Deel 1

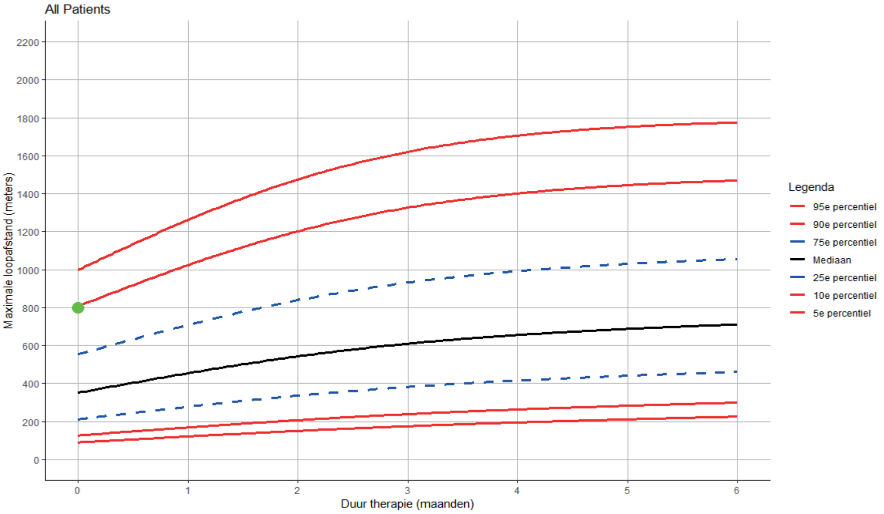
Meneer Janssen is 48 jaar en naar u doorverwezen voor gesuperviseerde looptherapie. Hij is doorverwezen door de vaatchirurg met de diagnose claudicatio intermittens. Hij heeft een blanco voorgeschiedenis, zijn BMI is 24 en hij is 10 jaar geleden gestopt met roken. Tot die tijd heeft hij 30 jaar lang een half pakje per dag gerookt (15 pakjaren). Meneer Janssen werkt parttime als administratief medewerker en woont samen mijn zijn vrouw. Hij zou graag weer met de hond kunnen wandelen zonder pijn in zijn benen (5km) en is gemotiveerd om iedere week bij u, maar ook thuis aan de slag te gaan.

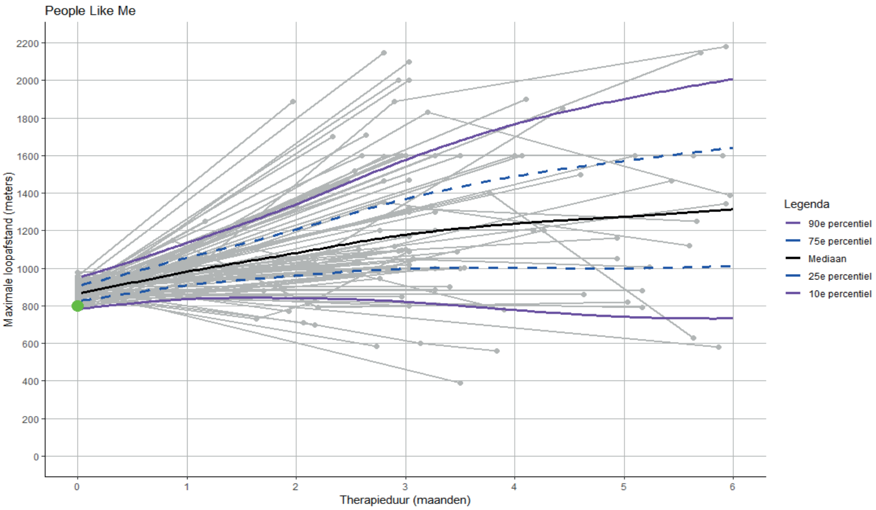
Deel 2

Bij de loopbandtest meet je een functionele loopafstand van 700 meter en een maximale loopafstand van 800 meter.

Deel 3

De ClaudicatioNet tool laat zien dat dhr. ten opzichte van het gemiddelde van de gehele populatie hoog scoort, namelijk in het 90^{e} percentiel. Dit wil zeggen dit hij een betere loopafstand heeft dan 90% van de populatie. De ClaudicatioNet tool voorspelt een MWD van 1160 meter na 3 maanden GLT (de zwarte lijn). Dit is een absolute vooruitgang van 360 meter en een relatieve voorruitgang van 45% ten opzichte van de baseline. De blauwe stippellijnen geven het 25^{e} en 75^{e} percentiel, in dit geval 1000 en 1350 meter. Dit houdt in dat in 50% van de gevallen de loopafstand van de patiënt hiertussen zal vallen.





Deel 4

Na 3 maanden is vindt het eerste controle moment plaats. dhr. had als doel om weer 2km pijnvrij te kunnen lopen en is ontevreden dat dit niet lukt. Je meet een FDW van 1050 meter en een MWD van 1400 meter.

Casus 4

Deel 1

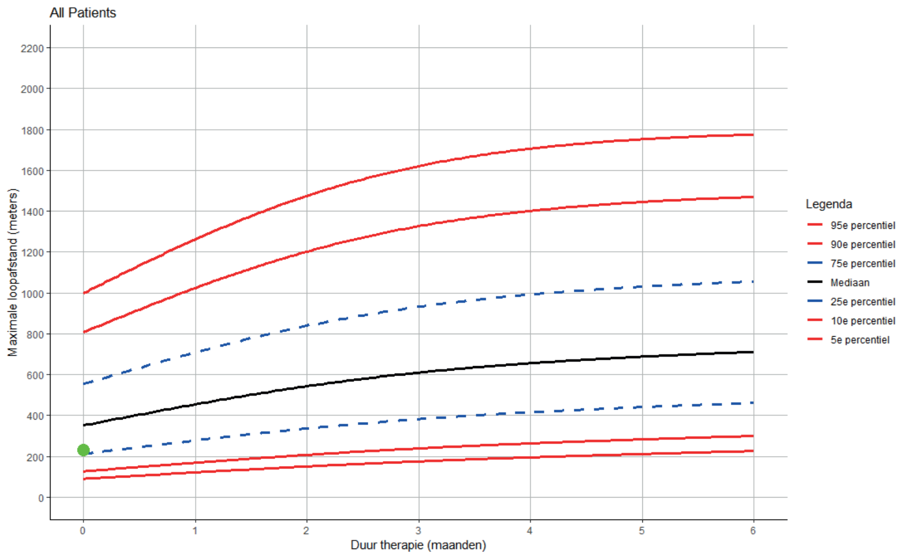
Mevrouw Smith is 84 jaar en naar u doorverwezen voor gesuperviseerde looptherapie. Ze is doorverwezen door de vaatchirurg met de diagnose claudicatio intermittens. Ze is bekend met hypertensie, hypercholesterolemie en artrose. Haar BMI is 23 en ze heeft nog nooit gerookt. Mevrouw Smith heeft een groot sociaal netwerk en doet graag mee aan activiteiten in het buurthuis, zoals kienen en de bingo. Ze zou graag weer naar het buurthuis toe kunnen lopen zonder te hoeven stoppen vanwege pijn in haar benen (1km). Ze zal haar best gaan doen bij de therapie, maar vind het wel erg spannend allemaal.

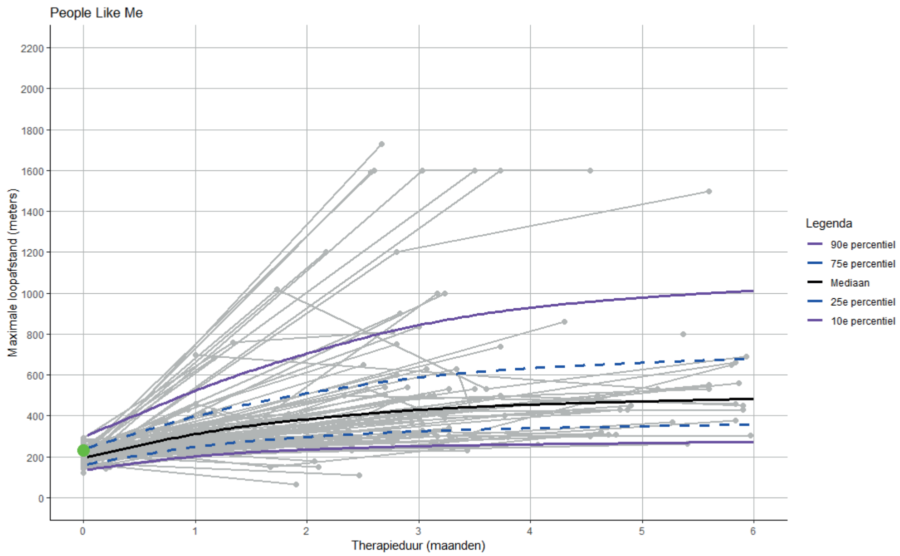
Deel 2

Mevr. komt moeizaam binnen lopen en bij de loopbandtest meet je een functionele loopafstand van 180 meter en een maximale loopafstand van 230 meter.

Deel 3

De ClaudicatioNet tool laat zien dat mevr. laag scoort ten opzichte van het gemiddelde van de gehele populatie, namelijk onder het 25^{e} percentiel. Dit wil zeggen dit zij bij de 25% van de populatie met een korte loopafstand hoort. De ClaudicatioNet tool voorspelt een MWD van 440 meter na 3 maanden GLT (de zwarte lijn). Dit is een absolute voorruitgang van 210 meter en een relatieve vooruitgang van 91%. De blauwe stippellijnen geven het 25^{e} en 75^{e} percentiel, in dit geval 300 en 600 meter. Dit houdt in dat in 50% van de gevallen de loopafstand van de patiënt hiertussen zal vallen.





Deel 4

Na 3 maanden is vindt het eerste controle moment plaats. Mevr. heeft het idee dat de therapie erg goed helpt. Je meet een FDW van 250 meter en een MWD van 300 meter.

Casus 5

Deel 1

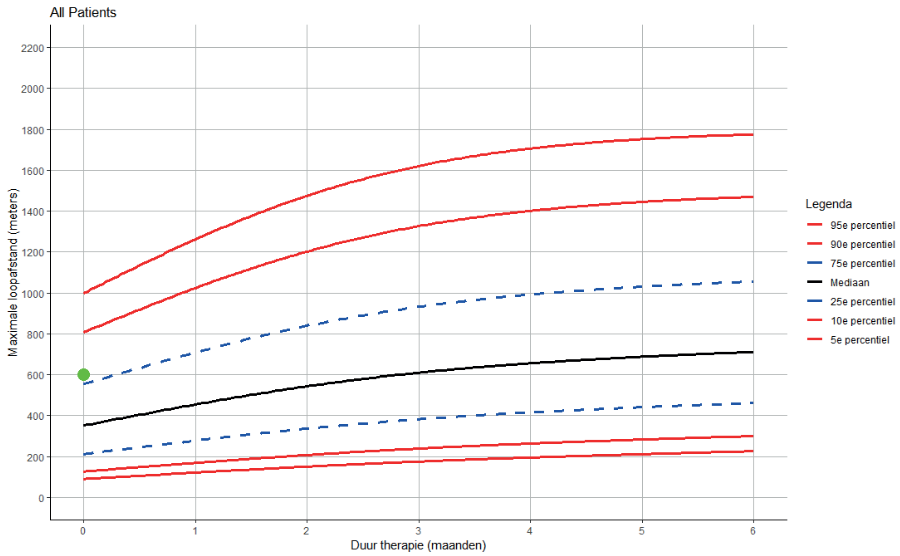
Mevrouw Peters is 70 jaar en naar u doorverwezen voor gesuperviseerde looptherapie. Ze is doorverwezen door de vaatchirurg met de diagnose claudicatio intermittens. Mevrouw Klaassen is bekend met hypertensie, hypercholesterolemie en COPD. Ze heeft een BMI van 28 en ze rookt al 40 jaar ongeveer een pakje per week (6 pakjaren). Mevrouw Klaassen is met pensioen en past regelmatig op de kleinkinderen. De pijn in de benen belemmert haar om eropuit te gaan met de kleinkinderen. Ze zou bijvoorbeeld graag naar de grote speeltuin wandelen met de kleinkinderen zonder te hoeven stoppen (1km). Ze is gemotiveerd om bij u aan de slag te gaan.

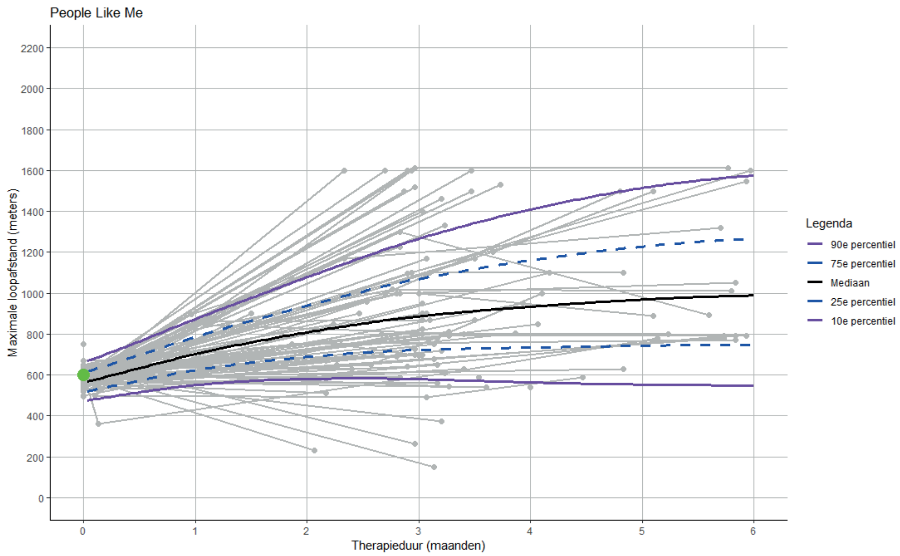
Deel 2

Bij de loopbandtest meet je een functionele loopafstand van 400 meter en een maximale loopafstand van 600 meter.

Deel 3

De ClaudicatioNet tool laat zien dat mevr. hoger scoort ten opzichte van het gemiddelde van de gehele populatie, namelijk net boven het 75^{e} percentiel. Dit wil zeggen dit zij bij de 25% van de populatie met een lange loopafstand hoort. De ClaudicatioNet tool voorspelt een MWD van 880 meter na 3 maanden GLT (de zwarte lijn). Dit is een absolute voorruitgang van 280 meter en een relatieve vooruitgang van 47%. De blauwe stippellijnen geven het 25^{e} en 75^{e} percentiel, in dit geval 680 en 1060 meter. Dit houdt in dat in 50% van de gevallen de loopafstand van de patiënt hiertussen zal vallen.





Deel 4

Na 3 maanden is vindt het eerste controle moment plaats. Mevr. is een beetje zenuwachtig en hoop dat ze het goed zal doen bij de controle. Je meet een FDW van 780 meter en een MWD van 1000 meter.

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Casus 6

Deel 1

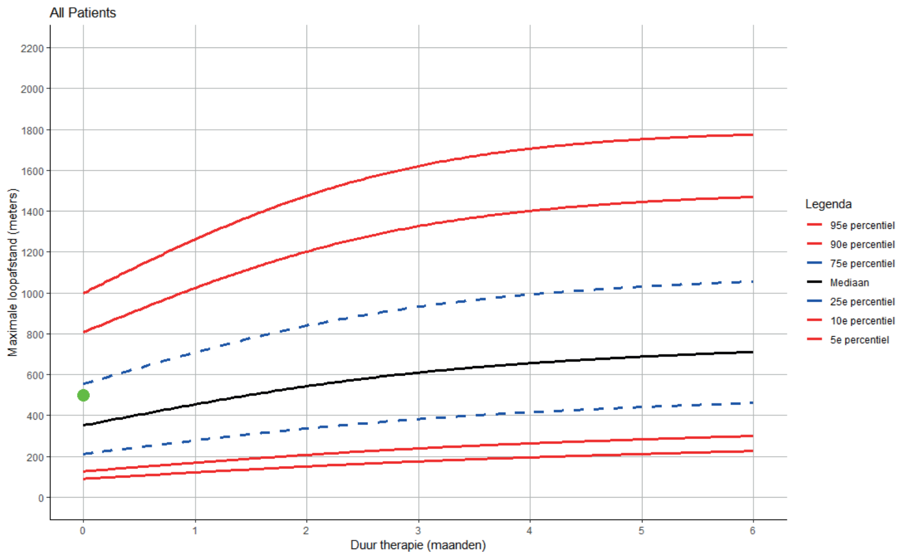
Mevrouw Pieters is 55 jaar en naar u doorverwezen voor gesuperviseerde looptherapie. Ze is doorverwezen door de vaatchirurg met de diagnose claudicatio intermittens. Ze heeft een blanco voorgeschiedenis, haar BMI is 28 en ze rookt al 30 jaar een pakje per dag (30 pakjaren). Mevrouw Pieters heeft een gezin met 3 volwassen kinderen en werkt parttime als doktersassistente. De pijn in haar benen belemmert haar in het dagelijks leven en ze zou graag weer echte stukken kunnen wandelen zonder pijn (10km). Ze is zich bewust van de ernst van haar aandoening en daardoor gemotiveerd om aan de slag te gaan.

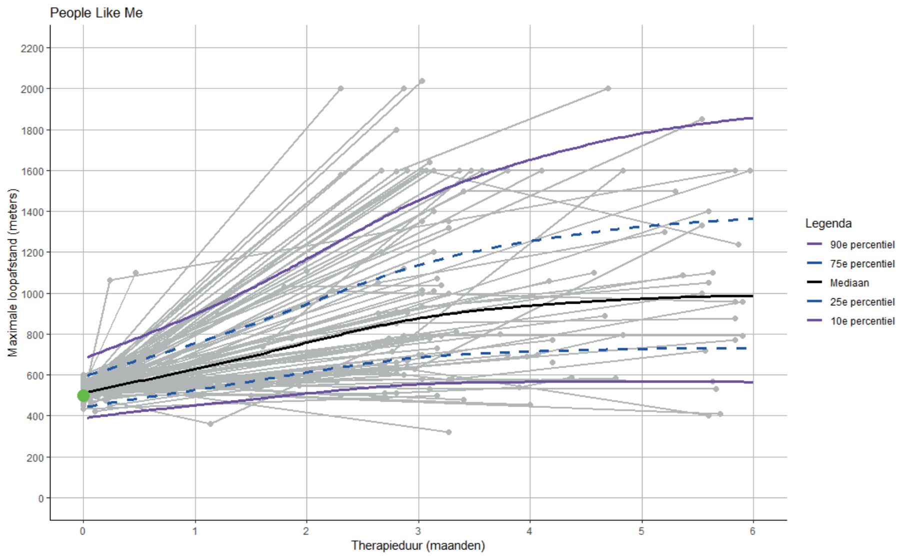
Deel 2

Bij de loopbandtest meet je een functionele loopafstand van 350 meter en een maximale loopafstand van 500 meter.

Deel 3

De ClaudicatioNet tool laat zien dat mevr. iets hoger scoort ten opzichte van het gemiddelde van de gehele populatie, namelijk net onder het 75e percentiel. Dit wil zeggen dit zij beter loopt dan 50% van de populatie. De ClaudicatioNet tool voorspelt een MWD van 880 meter na 3 maanden GLT (de zwarte lijn). Dit is een absolute voorruitgang van 380 meter en een relatieve vooruitgang van 76%. De blauwe stippellijnen geven het 25e en 75e percentiel, in dit geval 680 en 1120 meter. Dit houdt in dat in 50% van de gevallen de loopafstand van de patiënt hiertussen zal vallen.





10

Deel 4

Na 3 maanden is vindt het eerste controle moment plaats. Mevr. is benieuwd of ze al in de buurt is van haar doel, 1km lopen. Je meet een FDW van 480 meter en een MWD van 650 meter.

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Sinnige A, Sliepen M, van Rooijen S, Teijink J. In beweging tegen niet overdraagbare chronische aandoeningen. *Magazine Leefstijl is. 2021*

CURRICULUM VITEA

Anneroos Sinnige was born on May 2nd, 1993 in Nijmegen, the Netherlands. She grew up in Beuningen and graduated from her high school "Stedelijke Scholengemeenschap Nijmegen" in 2011.

In the same year, she enrolled in the bachelor of Biomedical Sciences, at Maastricht University and obtained her degree in 2014. In order to realize her childhood dream – becoming a medical doctor – she continued her studies with the master program *Art-Klinisch Onderzoeker* at Maastricht University. She successfully graduated in 2018.

After her study she started her PhD under supervision of Prof. J.A.W. Teijink at the Catharina Hospital, Eindhoven. During her PhD time she worked as project leader on the "KomPas-project", which resulted in this thesis. Beside the scientific activities carried out in the context of her PhD, she actively participated in the Chronic CareNet network. She did this by providing educational courses to therapists, co-developing online trainings and assisting with various projects within the network.

After a fulltime PhD of 2.5 years, she started working as medical doctor at the Intensive Care Unit of the Catharina Hospital, Eindhoven (2021). During this period she finished her PhD. In 2022 she continued her career as surgical resident not in training at the Catharina Hospital, Eindhoven.

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you will be able to visit The Netherlands once again to attend my PhD defense or else to just have a beer and a real life chat.

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