CHAPTER 8
General discussion, summary and future perspectives
The general aim of this dissertation was to contribute to various aspects of the management of intermittent claudication (IC). In the following chapter, the findings are summarized and discussed, including methodological considerations, implications for clinical practice, and suggestions for future research.

**PART I: IMPROVING ASSESSMENT OF WALKING PERFORMANCE**

**Walking capacity and treadmill testing**
IC impedes walking ability. Exercise-induced limb symptoms diminish both walking endurance and peak performance. Successful treatment of symptoms may enhance the distance at which symptoms force a patient to stop walking and/or the total distance a patient can walk in a set time. Increasing this ‘walking capacity’ leads to improved (health-related) quality of life in IC patients. Consequently, symptom severity and response to treatment are most commonly expressed through measures of walking capacity. Several validated test protocols exist, providing standardized and reproducible test conditions, allowing for comparisons between time points within one patient or between different individuals. Traditionally, treadmill tests have been most commonly used in peripheral arterial disease (PAD) research, attesting to their reproducibility, accessibility (no need for large test facilities), and extensively studied test characteristics. Several limitations of treadmill walking hamper their use and were thus studied in this thesis.

Treadmill walking has been criticized for being an artificial form of walking. To what extent do the walking limitations as measured on the treadmill correspond to limitations that are experienced in outside, real-world environments? This issue was investigated in Chapter 2 of this thesis. The results show that a treadmill protocol using a gradually increasing inclination during the test optimally reflects outside walking, compared with a non-graded protocol or a patient’s own estimation. However, the overall agreement between treadmill tests and outside walking was just moderate, and there was substantial variation between individual measurements. The findings suggest that treadmill-measured impairment of walking capacity does not necessarily correspond to the impairment patients experience during outside walking. A conclusion that is also supported by another study. To more accurately assess a patient’s daily life impairment (and monitor improvement or deterioration with treatment, perhaps even more relevant to the patient), alternative testing modalities should be explored.

Despite its shortcomings, treadmill testing remains widely used and useful when its limitations are heeded while interpreting their results. Changes in treadmill tests after various treatments in IC are well studied. Comparisons among treatment groups or among various trials and pooling of results in meta-
analyses are thus facilitated. However, what change after treatment do patients consider important? In Chapter 3 the minimally important difference (MID) for walking distance that is measured on a treadmill is investigated to establish a first answer to this question. Changes in treadmill test outcomes were coupled with a clinical ‘anchor’ that is used to define improvement or deterioration as judged by the patient. Using this methodology, the MID of treadmill measured maximum walking distance in IC patients was approximately +300m for improvement and +150m for deterioration. An important takeaway from the study is that small improvements (i.e. <150m) are not satisfactory in the patient’s eyes and may even be considered a deterioration. Of note, MIDs are population and context specific. In this instance, the results of three months of SET in a selected randomized trial population were used. The values that are presented in Chapter 3 should therefore be applied carefully in clinical care and research practice. The MIDs possibly only apply on similar patient populations and treatment circumstances, and should be validated in larger cohorts of patients. Nevertheless, the MIDS as found are helpful in the interpretation of the clinical relevance of numerical changes in walking distances.

Towards physical activity
Walking capacity, such as measured on a treadmill and studied in the first two chapters, provides information on a patient’s (sub)maximal exercise limitations. However, an important part of a patient’s performance is the way they actually use their capacity. In other words, how does improving walking capacity in a PAD patient translate to physical activity in daily life? This is particularly relevant when considering that inactivity is one of the main risk factors and determinants of prognosis for atherosclerosis and thus PAD.4

IC symptoms render patients sedentary.5 Successful treatment of claudication symptoms (i.e. improvement of walking capacity) may facilitate improvement of inactive behaviour by removing the barriers to walking for prolonged distances. However, as shown in Chapter 2, only moderate correlation and substantial variation between measurements of walking capacity on the treadmill and during outside walking exist. Others found only a minimal correlation between walking capacity and physical activity in patients with IC.6 The ability to walk further without claudication pain does not necessarily lead to the behavioural change of becoming more active in daily life. By extension, measuring improved walking capacity on a treadmill after treatment may only provide a proxy for improved physical functioning in daily life.

The benefits of supervised exercise therapy (SET), home-based exercise therapy (HBET), and endovascular revascularization (ER) regarding improving walking capacity have been studied extensively. By contrast, objectively measured
physical activity has only sparsely been used as outcome measure in clinical trials in IC. Some observational studies even reported no significant changes in physical activity after SET or ER. In Chapter 4 all available evidence from randomized trials was aggregated in a network meta-analysis to get an inferred treatment effect. The study showed that SET leads to a moderate short-term improvement of physical activity, translating into some 800 steps/day, compared to control treatments. Mean daily steps at baseline was approximately 3000. This improvement may thus be substantial in the PAD population. HBET showed a similar benefit, but with low quality underlying evidence, thus the confidence in this outcome was less. Furthermore, the paucity of trials on the effect of ER on physical activity barred definite conclusions on this treatment modality.

Future perspectives on assessment of walking performance

One of the main criticisms regarding treadmill testing that was not investigated in this thesis is a possible learning effect associated with SET. As most or all training during therapy is performed on a treadmill, some authors are concerned with a ‘training to the outcome’ phenomenon. Alternatively, the 6-minute walk test (6MWT) is coined as test of walking performance. The 6MWT records the total distance an individual can walk over a total of 6 minutes on a hard, flat surface. Participants traverse back and forth along a marked walkway. They are allowed to self-pace and rest as needed, while timing continues up to 6min. The 6MWT has been validated, shown to be responsive to treatment, and is predictive of mortality and mobility loss in PAD populations. Furthermore, a change in physical activity during daily life was more closely correlated with change in six-minute walk distance compared to change in treadmill walking distance. Including this outcome parameter in future studies on PAD, next to treadmill testing is important, as they likely cover different domains of walking performance. In part 2 of this thesis this was considered as part of the ELECT Registry. Future analyses from this or other studies may shed more light on the relative value of treadmill testing and the 6MWT in the PAD population.

New wearable technology permits ambulatory measurement of walking capacity in the patient’s own environment. Modern smartphones provide internet access, video, audio, social media, and can utilize built-in or wearable measurement devices such as accelerometers or global positioning systems (GPS), aggregating data on a patient’s health behavior, including daily physical activity. Collection and subsequent incorporation of these data permits the provision of interactive interventions, individualized to the specific patient’s individual characteristics and context. Furthermore, with objective information on patients’ daily health behavior, physical therapists can better tailor lifestyle counseling and SET sessions. Future studies in PAD patients using this technology may provide
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researchers and clinicians with novel outcome measures to more accurately reflect the limitations that patients experience in daily life.

**PART II: EFFICIENT MANAGEMENT OF INTERMITTENT CLAUDICATION**

International guidelines recommend SET as primary treatment for IC. Invasive open revascularization (OR) or ER is considered if SET fails to satisfactorily relieve symptoms.10 However, worldwide access to exercise programs remains limited, also in the Western society, partly prompted by lacking reimbursement by insurance plans. This situation was at hand in the Netherlands prior to 2017, as SET was widely available by then, but not reimbursed. In Chapter 5, a study is presented using existing evidence on the effectiveness and costs of PAD treatment that were incorporated into a clinical decision model. With the use of this mathematical model, cost-effectiveness of a SET-first strategy (with ER in the event of SET failure) was compared with an ER-first strategy in a virtual cohort of IC patients. These virtual patients were subjected to a simulated course of disease, changing disease states and undergoing (re-)interventions based on probabilistic chances derived from data from a randomized trial as well as the literature. The accumulated costs and impact on quality of life, secondary interventions, and mortality were calculated. Analyses showed that over the 5 years after start of treatment, a mean of €6500 could be saved per patient if SET would be employed as first treatment as opposed to ER. These savings could be achieved over an extended time horizon and without detrimental effect on quality of life, secondary intervention rate (ER/OR or amputations) or mortality.

The conclusions of Chapter 5 are in line with previous economic evaluations11,12 and cost-effectiveness analyses13-15 that were previously used to inform policymakers in the Dutch government. Consequently, SET was reimbursed for all IC patients per 2017. A decision that has shown great impact on PAD care and outcomes nationally. Guideline compliance (i.e. referral to SET as primary treatment) increased to 87%, with freedom from intervention rates of up to 80% for the first five years after SET.16 Evidently, in a healthcare system where SET is available and reimbursed IC patients can be spared unnecessary interventions. These findings become even more important in light of emerging evidence indicating that early revascularization in IC leads to higher rates of disease progression to chronic limb ischemia and consequent major amputation.17,18

Despite these benefits, some clinicians advocate a more personalized treatment plan where early revascularization is offered to those patients believed to be(come) unresponsive to SET. Their arguments are fueled by studies indicating greater short-term improvements when patients first undergo ER combined with SET
afterwards.\textsuperscript{19,20} In theory, opening up the vessels of these patients provides short term relief of symptoms, with exercise afterwards to sustain results. An evidence-base for selecting these SET non-responders is lacking. One of the main arguments for early revascularization is the location and extent of the atherosclerotic lesion. Aortoiliac lesions are often considered appropriate for an endovascular approach, with more favorable procedural results and patency rates compared to revascularization in distal disease. IC patients with aortoiliac disease are four times more often referred for early revascularization, foregoing an attempt at SET.\textsuperscript{21} However, the influence of arterial disease level on SET outcomes was never investigated. Consequently, the ELECT Registry was designed to study the influence of various potential determinants of outcome - including the location and extent of atherosclerotic disease - on treatment outcomes in IC. The study protocol is outlined in Chapter 6. It is the first study in an IC population that couples relevant anatomical and clinical patient characteristics with diverse outcomes reflecting walking performance, health-related quality of life, and clinical outcomes.

The ELECT Registry was conducted in 10 hospitals (both teaching and non-teaching) throughout the Netherlands, so Dutch vascular surgery practice was properly reflected. In Chapter 7, the short-term results are presented. This prospective observational study demonstrated that patients with IC achieve equal benefits after 3 and 6 months of SET, regardless of arterial disease location. Patients with aortoiliac, femoropopliteal, and multilevel disease showed meaningful improvements in walking performance and health-related quality of life, as well as rates of attainment of the treatment goal. No between-group differences were present. Nonetheless, patients with aortoiliac disease more often underwent a vascular intervention, compared to patients with femoropopliteal disease (26.1% vs. 11.4%). Apart from any functional improvements after SET, the risk-benefit ratio of a possible intervention understandably plays a role in a shared decision to intervene. The lower rates of freedom from interventions in patients with aortoiliac disease are thus probably attesting to the practice of ‘fixing the inflow first’ among vascular professionals. The ELECT Registry showed that all IC patients should receive a trial of exercise therapy before such invasive treatment is considered, regardless of the location or extent of the stenosis.

Future perspectives towards more efficient stepped care management

The studies in this thesis add to an already overwhelming body of evidence favoring SET as primary treatment in IC. Implementation of this strategy nationally reduced the number of patients needing invasive treatment.\textsuperscript{16} Unfortunately, these benefits are withheld from most PAD patients over the Dutch border as worldwide implementation continues to lack. In several developed countries SET costs are still not reimbursed despite the evidence as presented
in this thesis. Even when reimbursement issues are solved, as has been the case in the United States since 2017, referral rates are poor.\textsuperscript{22} One of the important reasons cited from the patient’s perspective is discouragement by the large travel distance to the therapy facilities, as SET is mainly hospital-based in the United States. Efforts should be made to make community-based SET available, as in the Netherlands. Alternatively, HBET alternatives have been propagated as a solution.\textsuperscript{10} However, HBET is possibly less effective than SET when reviewing all available evidence.\textsuperscript{23,24} This is probably due to heterogeneity in the intensity and prescription of exercise in the various included trials. Moreover, some studies lacked elements that appeared successful in others. For instance, some included (remote) monitoring of exercise using wearable devices, goal setting, and regular feedback on performance.\textsuperscript{24} These issues have thus hindered the implementation of efficient home-based alternatives to SET.

Apart from offering symptomatic relief, the main treatment goal in IC is improvement of cardiovascular prognosis. Nonetheless, the effect of IC treatment on cardiovascular outcomes, or even determinants of cardiovascular disease, remains largely unknown. One small prospective study showed a decrease in overall cardiovascular mortality by 52\% and morbidity by 30\% after a 12-week SET program\textsuperscript{25}, but these results have not been confirmed by other authors yet. Our study group conducted a systematic review and meta-analysis on the effect of SET on well-known modifiable risk factors for cardiovascular disease (i.e. hypertension, dyslipidemia, obesity, hyperglycemia, tobacco smoking, and physical inactivity). A total of 29 prospective studies were included. Our analysis provided some evidence that SET contributes to a reduction of systolic and diastolic blood pressure in the short term and a lowering of LDL cholesterol and total cholesterol in the midterm. However, the validity of these conclusions is unclear, as the available studies were of small sample size, moderate quality, and with heterogeneous populations and methodology. Furthermore, the influence of medical treatment of hypertension or dyslipidemia was unclear.\textsuperscript{26} Evidently, cardiovascular mortality and morbidity in PAD patients remains under-reported and under-examined. Future research is needed to evaluate the current cardiovascular health benefit of exercise therapy in IC.

The implementation of eHealth solutions in IC treatment has been advocated to improve cardiovascular health outcomes, as well as support HBET alternatives to SET. As stated in Chapter 4 of this thesis, modern ambulatory devices, such as wearable accelerometers and smartphone apps, make monitoring and adjustment of daily life behavior increasingly accessible. An assessment among PAD patients and therapists showed that a smartphone app aimed at improving health behavior has the potential to reach a substantial proportion of PAD patients.\textsuperscript{27} These devices can function as potentiators of health behavior change, but probably
only when incorporated into larger engagement strategies.\textsuperscript{28,29} Indeed, such technology adjunctive to SET has recently shown promising results\textsuperscript{30}, but failed to improve physical activity in HBET programs with limited in-person guidance\textsuperscript{31,32}. Furthermore, smartphone ownership in the PAD population is associated with younger age and higher attained educational level, both characteristics that carry a relatively favorable cardiovascular risk.\textsuperscript{27} Care must be taken to design a solution that can be incorporated in the current supervised setting. By doing so, results may be optimized whereas patient subgroups who need it most are also included.
REFERENCES

1. Hiatt WR, Rogers RK, Brass EP. The treadmill is a better functional test than the 6-minute walk test in therapeutic trials of patients with peripheral artery disease. Circulation 2014;130:69-78.


