Supervised exercise therapy for intermittent claudication : subgroups, gait and physical activity

Citation for published version (APA):

Gommans, L. N. M. (2015). *Supervised exercise therapy for intermittent claudication : subgroups, gait and physical activity*. [Doctoral Thesis, Maastricht University]. Maastricht University.
<https://doi.org/10.26481/dis.20151222lg>

Document status and date:

Published: 01/01/2015

DOI:

[10.26481/dis.20151222lg](https://doi.org/10.26481/dis.20151222lg)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Download date: 26 Apr. 2023

Supervised Exercise Therapy for Intermittent Claudication

subgroups, gait and physical activity

Lindy Nicolaas Maria Gommans

Supervised Exercise Therapy for Intermittent Claudication

subgroups, gait and physical activity

Lindy Nicolaas Maria Gommans

Printing of this thesis was financially supported by:

ClaudicationNet - Catharina Ziekenhuis - Maxima Medisch Centrum - Lode / Procare - McRoberts -
The Scientific College Physical Therapy (WCF) of the Royal Dutch Society for Physical Therapy (KNGF) -
Rabobank - Samcon - Stichting Fonds voor het Hart

máxima
medisch centrum

ProCare
Be take intensive Care

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged

Colofon

Author:	Lindy Nicolaas Maria Gommans
Cover design en lay-out:	Miranda Dood, Mirakels Ontwerp
Printing:	Gildeprint - The Netherlands
ISBN:	978-90-9029455-1

© L.N.M. Gommans, 2015

All rights reserved. No part of this publication may be reproduced or transmitted in any form by any means, without permission of the author.

Supervised Exercise Therapy for Intermittent Claudication

subgroups, gait and physical activity

Proefschrift

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, prof. dr. L.L.G. Soete
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op dinsdag 22 december 2015 om 12:00 uur

door

Lindy Nicolaas Maria Gommans

Geboren op 18 september 1985
te Venlo

Promotor

Prof. dr. J.A.W. Teijink

Copromotoren

Dr. M.R.M. Scheltinga (Máxima Medisch Centrum, Veldhoven)

Dr. K. Meijer

Beoordelingscommissie

Prof. dr. M.H. Prins (voorzitter)

Prof. dr. H. ten Cate

Prof. dr. I.C. Heyligers

Prof. dr. ir. N. Verdonschot (Radboud Universitair Medisch Centrum, Nijmegen)

TABLE OF CONTENTS

Chapter 1	General introduction and outline of thesis. <i>Adapted from “Attitudes to supervised exercise therapy”, Br J Surg. 2015 Sep;102(10):1153-5.</i>	p.12
Chapter 2	The effect of supervision on walking distance in patients with intermittent claudication: a meta-analysis. <i>Eur J Vasc Endovasc Surg. 2014 Aug;48(2):169-84.</i>	p.26
Chapter 3	Safety of supervised exercise therapy in patients with intermittent claudication. <i>J Vasc Surg. 2015 Feb;61(2):512-518.</i>	p.60
Chapter 4	Gender differences following supervised exercise therapy in patients with intermittent claudication. <i>J Vasc Surg. 2015 Sep;62(3):681-8.</i>	p.88
Chapter 5	Effect of diabetes on outcomes of supervised exercise therapy for intermittent claudication. <i>Submitted to J Vasc Surg.</i>	p.110
Chapter 6	The minimally important difference of absolute and functional claudication distance in patients with intermittent claudication. <i>Accepted in Eur J Vasc Endovasc Surg.</i>	p.128
Chapter 7	Minimal correlation between physical exercise capacity and daily activity in patients with intermittent claudication. <i>Accepted in J Vasc Surg.</i>	p.144

Chapter 8	Intermittent claudication prolongs stance phase during walking. <i>Submitted to Eur J Vasc Endovasc Surg.</i>	p.164
Chapter 9	Altered joint kinematics and increased electromyographic muscle activity during walking in patients with intermittent claudication. <i>Accepted in J Vasc Surg.</i>	p.184
Chapter 10	Summary & general discussion	p.206
Chapter 11	Samenvatting & algemene discussie Valorisatie	p.232 p.256
Chapter 12	Dankwoord List of publications Curriculum vitae	p.266 p.272 p.275

CHAPTER 1

General introduction and outline of the thesis

Adapted from "Attitudes to supervised exercise therapy", Br J Surg. 2015 Sep;102(10):1153-5.

PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease (PAD) is a chronic atherosclerotic disease resulting in obstruction or occlusion of the large peripheral arteries.¹ Symptoms of lower extremity PAD are classified according to Rutherford and range from mild, moderate and severe claudication (stage 1-3) respectively, to pain at rest and/or at night (stage 4) or ulceration or necrosis (stage 5-6).¹ Major amputation of the affected limb is required in less than 1% of the patients per year.² Conversely, the majority of patients with PAD are asymptomatic (stage 0).

Risk factors associated with PAD are similar to those classically identified for coronary and cerebrovascular diseases.³ However, the relative importance of these factors may be different in PAD. Numerous reports have now confirmed that advanced age, tobacco use and diabetes mellitus are the most important risk factors for developing PAD.⁴

The prevalence of PAD is approximately 15% among people aged >69 years.⁴ A conservative estimate revealed that worldwide some 202 million individuals are having PAD.⁵ In high-income countries, PAD prevalence is equal between men and women. In aging populations where cigarette smoking persists and the incidences of diabetes mellitus, hypertension and obesity continue to grow, PAD prevalence is expected to increase in the upcoming years.⁵ As a result, growing numbers of PAD patients will increasingly drain (inter)national health care resources.

INTERMITTENT CLAUDICATION

Intermittent claudication (IC) is the most common clinical manifestation of PAD. It was found that up to 40% of PAD population suffers from IC.¹ IC can be defined as muscle pain/discomfort in the lower limbs during exercise that is relieved after a short period of rest.¹ Obstruction of the arterial blood supply to the leg muscles limits augmented blood flow when required during exercise. As a consequence, a mismatch between oxygen and muscle metabolic demand leads to cramps and pain in calf, thigh, and/or buttock.

The range of symptom severity and consequent effects on daily function and quality of life may vary widely among IC patients.⁶ Moreover, concomitant conditions such as

cardiopulmonary disease, arthritis and obesity can markedly limit exercise capacity. The presence of IC is associated with serious health risks as an approximately 20% five-year mortality rate is reported, most commonly due to cardiovascular causes.¹

TREATMENT FOR INTERMITTENT CLAUDICATION

IC treatment should consist of two modules, cardiovascular risk management including lifestyle modification and symptomatic therapy. The first aims to prevent the onset of cardiovascular events (i.e. myocardial infarction, stroke) and related comorbidity and mortality in this high risk patient group. Cardiovascular risk management consists of antiplatelet and statin therapy and optimal treatment of hypertension and diabetes. Lifestyle modification ideally focusses on smoking cessation, weight reduction, a balanced diet and increased daily physical activity level. Many of these recommendations for risk-factor modification in PAD/IC were extrapolated from literature on secondary prevention in coronary artery disease. Evidence specific to PAD regarding these measures is largely lacking. Similarly, high-quality trials on the effect of health-behavior changes techniques in IC patients are required.⁷

The first-line symptomatic treatment of IC is conservative. According to contemporary international guidelines, supervised exercise therapy (SET) should be provided to all patients with IC.^{4, 8} SET comprises of regular training under supervision of a physical therapist (in the Dutch situation), or any other exercise specialist. Although the optimal content and frequency of SET are unclear⁹, most frequently described programs consist of interval-based (treadmill) walking to a near-maximum pain level. A combination with both cardiopulmonary endurance and strength training at a minimum of three times per week (30-60 minutes per session) for at least 12 weeks is advised.¹⁰

SET for IC is a refinement of a basic exercise therapy as originally described in 1898 by a German neurologist Wilhelm Erb.¹¹ In 1966, a randomized clinical trial by Larsen et al. demonstrated a significantly improved maximum walking distance in the intervention group (instructed to take an extra daily walk of at least one hour) versus controls (receiving a placebo medical treatment of lactose tablets).¹² Nowadays, SET has repeatedly proven to be the most effective among conservative therapies with respect to

decreasing IC symptoms, increasing walking capacity and improving quality of life.^{13, 14} Moreover, a 12-week SET program showed to reduce the overall cardiovascular mortality by 52% and morbidity by 30%.¹⁵ SET is in essence an ‘athletic’ training, albeit on a much more limited scale than generally practiced by elite athletes. However, the potential biomechanical mechanisms underlying the effect of SET are largely exercise-related and include enlargement of existing collateral vessels, exercise-induced angiogenesis, enhanced nitric oxide endothelium-dependent microcirculation vasodilatation, improved skeletal muscles bioenergetics and better hemorheology.^{4, 16}

If SET fails to achieve satisfying results, invasive techniques may be considered such as a percutaneous transluminal angioplasty (PTA) or vascular surgery (i.e. bypass).⁸ A stent may for instance be inserted to ensure the vessel’s patency. Good results of these invasive interventions for IC are reported.¹⁷ However, effects on walking capacity and quality of life are similar for either SET or invasive revascularization after long-term follow-up.^{18, 19} These results are not unexpected as restoration of the peripheral circulation itself does not provide the necessarily behavioral change.²⁰ Moreover, the irrevocable risks associated with invasive procedures (i.e. bleeding, infection, thrombo-embolic events) and associated substantial costs need to be considered when deciding to perform an intervention.

ATTITUDES TO SUPERVISED EXERCISE THERAPY

Despite the substantial evidence on the (cost-)effectiveness of SET²¹⁻²⁵ and the contemporary guideline recommendations, SET is largely underused²⁶ and most IC patients still do not receive SET.²⁶ A recent analysis of invoice data from a Dutch health insurance company found that only 14% of the patients with IC were initially referred for SET.²⁷ Interestingly, in January 2015 *The New York Times* highlighted the inappropriate use of invasive interventions for patients with IC.²⁸ This article questioned conflicts of interest and motives of doctors performing these interventions in view of the potential harm for patients and unnecessary costs for the healthcare system.

There seem to be three categories of reasons why this cost-effective treatment is not widely adopted yet.^{29, 30} First, there is resistance among patients as effort and

responsibility are required rather than undergoing a ‘fast fix’ for their discomfort. However, decisions regarding therapy are nowadays a shared responsibility (‘shared decision making’). Second, resistance in clinicians themselves. Self-interest of doctors performing interventions that involve fee-for-service is undoubtedly a contributor. Next to the powerful influence of the medical devices industry who repeatedly underscore the argument of an immediate effect, underline ever-increasing long-term patencies, and continue to lobby and sponsor scientific meetings. Moreover, outdated arguments for performing an invasive intervention, instead of prescribing SET, are still prevailing among clinicians. However, it must be appreciated that the CLEVER study (Claudication: Exercise Versus Endoluminal Revascularization) in symptomatic aortoiliac stenosis provided clear evidence that improvement in functional status and quality of life following PTA and stenting or SET were comparable after a 18 months follow-up.¹⁸ Results of the SUPERvised Exercise Therapy or Endovascular Revascularization for Intermittent Claudication due to an Iliac Artery obstruction (SUPER) trial have to be awaited to provide further insight on this subgroup of IC patients. Third and foremost important category, is the ongoing resistance of politicians, health policy makers and insurers who persist to ignore SET and fail to stimulate measures for SET access and reimbursement. In most countries of the world, as the Netherlands is a rare exemption, SET programs are not readily available.^{26, 31} As a result, even clinicians who fully endorse SET as initial treatment for IC may end up performing invasive interventions if their patients cannot find a qualified SET practitioner or SET appears to be not reimbursed by their health care insurer. Surprisingly, for a tenfold expensive invasive intervention no budgetary restrictions exist. In addition, incipient SET initiatives, in the UK for example, are prevented from coming to fruition by a lack of funding.³²

GENERAL AIM OF THE THESIS

This thesis aims to enhance knowledge on various aspects of SET in patients with IC. In the first part, current barriers and misconceptions regarding the indications for SET in certain subgroups are elucidated. In the second part, various aspects of gait pattern in IC and correlations between physical exercise capacity outcomes and daily activity are

studied. This thesis strives to contribute in minimizing barriers for SET referral. Moreover, results of this thesis may facilitate the development of new rehabilitation strategies, may promote the initiation of studies quantifying the effects of specified supervised exercise regimens and may introduce potential new outcome parameters in IC.

Specific aims of the thesis

1. To evaluate the safety of supervised exercise therapy in patients with IC.
2. To summarize the evidence on the effect of exercise therapy with various levels of supervision on walking distance in IC.
3. To assess gender-specific outcomes of supervised exercise therapy in IC.
4. To study the literature on the effect of diabetes on walking distance after supervised exercise therapy in IC.
5. To define the minimally important difference of treadmill-based walking distances in IC.
6. To determine correlations between physical exercise capacity and daily activity of patients with IC.
7. To describe spatio-temporal parameters, kinematics and electromyographic muscle profiles of the gait pattern in IC.

OUTLINE OF THE THESIS

It has been suggested that some patients with IC may be unsuitable for SET as they also suffer from co-morbidities leading to increased safety risks.²⁹ There is no evidence to support such claims, but literature addressing the safety issue in IC is lacking. **Chapter 2** describes the results of a systematic review evaluating the safety of SET by determining the number of (cardiovascular) adverse events during SET in patients with IC.

Recent studies reported on the value of home-based exercise programs for patients with IC.^{34, 35} These programs might be an attractive alternative to SET, considering the limited availability of SET in countries other than the Netherlands. However, there is only ‘low-level’ evidence that home-based programs improve walking capacity and quality of life in patients with IC.³⁶ Therefore, a meta-analysis is provided in **chapter 3** to study the

value of home-based programs by comparing results of a control group, a 'go home, and walk' advice group and a group receiving the conventional SET program.

Prevalence of IC is equal among men and women.⁴ Surprisingly, no study has addressed the possible gender-specific response to SET in terms of absolute walking distances or perceived walking (dis)ability yet. This paucity of data is likely due to a consistent female underrepresentation in randomized controlled trials. However, the idea of gender-specific responses to SET in patients with IC is sensible considering data from cardiac rehabilitation where gender-specific programs are readily discussed.³⁷ In line with a recent scientific statement of the American Heart Association releasing a 'call to action' for more research into gender-based differences of patients with PAD³⁸, **chapter 4** describes an analysis on the response of men and women with IC to SET.

Diabetes mellitus (DM) is a strong risk factor for the development of PAD.³⁹ DM is known to affect almost each vascular bed and it is associated with an impaired microvascular function in patients with IC. Moreover, IC patients with DM demonstrate reduced physical function as compared to IC patients without DM.⁴⁰ It has previously been suggested that IC patients with comorbidities might benefit less from SET.²⁹ However, the available evidence is not yet overviewed yet. In **chapter 5** a review is provided aimed at studying the current literature on the effect of DM regarding the response of patients with IC to SET.

Effects of SET are usually evaluated in term of (improved) walking capacity by using a treadmill test. Walking distance however is an outcome parameter with limitations. Nonetheless, it is widely used in clinical trials and daily practice, as its value in assessing treatment effect has been well established.^{41, 42} Minimally important differences (MID) of commonly used outcome measures can aid clinicians and researchers in determining what numerical change indicates a clinically meaningful change from a patient's perception. For treadmill-based walking distances in patients with IC, MIDs have not been determined yet. Therefore, MIDs for maximal and functional walking distance are assessed in an IC population in **chapter 6**.

Recent insight suggested that improved exercise (i.e. walking) capacity does not automatically imply an increase in daily physical activity (PA).⁴³ In addition, it has increasingly been recognized that PA is a strong predictor of morbidity and mortality in patients with IC.⁴⁴ Whether exercise capacity outcomes could serve as a surrogate marker

for PA is currently unknown, as the relationship between exercise capacity and daily PA is still unclear. In **chapter 7** the association between exercise capacity and daily PA is studied in patients with IC.

It is known that patients with IC consume about 40% more oxygen during normal walking at a speed similar to healthy controls, possibly due to biomechanical changes.⁴⁵ A limited number of suboptimal studies included gait analysis in patients with IC.^{42, 43} In **chapter 8**, spatio-temporal parameters of gait in patients with IC are described. Subsequent electromyographic and kinematic analyses aimed at responding to a priori generated hypotheses are described in **chapter 9**. Results of these studies may lead to new targets in the development of SET programs for IC.

In **chapter 10**, the main findings of this thesis are discussed including methodological aspects of the different studies, implications for clinical practice and suggestions for future research. A Dutch summary, discussion and valorization are provided in **chapter 11**.

Finally, **chapter 12** includes the acknowledgements, list of publications and curriculum vitae of the author.

REFERENCES

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg.* 2007;45 Suppl S:S5-67.
2. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med.* 1992;326(6):381-6.
3. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation.* 2004;110(6):738-43.
4. Society for Vascular Surgery Lower Extremity Guidelines Writing G, Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JE, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg.* 2015;61(3 Suppl):2S-41S.
5. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet.* 2013;382(9901):1329-40.
6. Regensteiner JG, Hiatt WR, Coll JR, Criqui MH, Treat-Jacobson D, McDermott MM, et al. The impact of peripheral arterial disease on health-related quality of life in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) Program. *Vasc Med.* 2008;13(1):15-24.
7. Galea MN, Weinman JA, White C, Bearne LM. Do behaviour-change techniques contribute to the effectiveness of exercise therapy in patients with intermittent claudication? A systematic review. *Eur J Vasc Endovasc Surg.* 2013;46(1):132-41.
8. Layden J, Michaels J, Bermingham S, Higgins B, Guideline Development G. Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance. *BMJ.* 2012;345:e4947.
9. Fakhry F, van de Luijngaarden KM, Bax L, den Hoed PT, Hunink MG, Rouwet EV, et al. Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg.* 2012;56(4):1132-42.

10. Gardner AW, Montgomery PS, Parker DE. Optimal exercise program length for patients with claudication. *J Vasc Surg.* 2012;55(5):1346-54.
11. Erb W. About intermittent walking and nerve disturbances due to vascular disease. *Deutsch Z Nervenheilk.* 1898;13:1-76.
12. Larsen OA, Lassen NA. Effect of daily muscular exercise in patients with intermittent claudication. *Lancet.* 1966;2(7473):1093-6.
13. Fokkenrood HJ, Bendermacher BL, Lauret GJ, Willigendael EM, Prins MH, Teijink JA. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev.* 2013;8:CD005263.
14. Gommans LN, Saarloos R, Scheltinga MR, Houterman S, de Bie RA, Fokkenrood HJ, et al. Editor's choice--The effect of supervision on walking distance in patients with intermittent claudication: a meta-analysis. *Eur J Vasc Endovasc Surg.* 2014;48(2):169-84.
15. Sakamoto S, Yokoyama N, Tamori Y, Akutsu K, Hashimoto H, Takeshita S. Patients with peripheral artery disease who complete 12-week supervised exercise training program show reduced cardiovascular mortality and morbidity. *Circ J.* 2009;73(1):167-73.
16. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. *N Engl J Med.* 2002;347(24):1941-51.
17. Wilson SE. Trials of endovascular treatment for superficial femoral artery occlusive lesions: a call for medically managed control patients. *Ann Vasc Surg.* 2010;24(4):498-502.
18. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, 3rd, Cohen DJ, Reynolds MR, et al. Supervised Exercise, Stent Revascularization, or Medical Therapy for Claudication Due to Aortoiliac Peripheral Artery Disease: The CLEVER Study. *J Am Coll Cardiol.* 2015;65(10):999-1009.
19. Perkins JM, Collin J, Creasy TS, Fletcher EW, Morris PJ. Reprinted article "Exercise training versus angioplasty for stable claudication. Long and medium term results of a prospective, randomised trial". *Eur J Vasc Endovasc Surg.* 2011;42 Suppl 1:S41-5.
20. Cunningham MA, Swanson V, Pappas E, O'Carroll RE, Holdsworth RJ. Illness beliefs and walking behavior after revascularization for intermittent claudication: a qualitative study. *J Cardiopulm Rehabil Prev.* 2014;34(3):195-201.
21. Bermingham SL, Sparrow K, Mullis R, Fox M, Shearman C, Bradbury A, et al. The cost-effectiveness of supervised exercise for the treatment of intermittent claudication. *Eur J Vasc Endovasc Surg.* 2013;46(6):707-14.

22. Mazari FA, Khan JA, Carradice D, Samuel N, Gohil R, McCollum PT, et al. Economic analysis of a randomized trial of percutaneous angioplasty, supervised exercise or combined treatment for intermittent claudication due to femoropopliteal arterial disease. *Br J Surg.* 2013;100(9):1172-9.
23. O'Brien-Irr MS, Harris LM, Dosluoglu HH, Dryjski ML. Endovascular intervention for treatment of claudication: is it cost-effective? *Ann Vasc Surg.* 2010;24(6):833-40.
24. Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Cost-effectiveness of endovascular revascularization compared to supervised hospital-based exercise training in patients with intermittent claudication: a randomized controlled trial. *J Vasc Surg.* 2008;48(6):1472-80.
25. van Asselt AD, Nicolai SP, Joore MA, Prins MH, Teijink JA, Exercise Therapy in Peripheral Arterial Disease Study G. Cost-effectiveness of exercise therapy in patients with intermittent claudication: supervised exercise therapy versus a 'go home and walk' advice. *Eur J Vasc Endovasc Surg.* 2011;41(1):97-103.
26. Shalhoub J, Hamish M, Davies AH. Supervised exercise for intermittent claudication - an under-utilised tool. *Ann R Coll Surg Engl.* 2009;91(6):473-6.
27. Fokkenrood HJ, Scheltinga MR, Koelemay MJ, Breek JC, Hasaart F, Vahl AC, et al. Significant savings with a stepped care model for treatment of patients with intermittent claudication. *Eur J Vasc Endovasc Surg.* 2014;48(4):423-9.
28. Creswell J, Abelson R. Medicare Payments Surge for Stents to Unblock Blood Vessels in Limbs. *The New York Times.* 2015.
29. Popplewell MA, Bradbury AW. Why do health systems not fund supervised exercise programmes for intermittent claudication? *Eur J Vasc Endovasc Surg.* 2014;48(6):608-10.
30. Gommans LN, Teijink JA. Attitudes to supervised exercise therapy. *Br J Surg.* 2015.
31. Makris GC, Lattimer CR, Lavid A, Geroulakos G. Availability of supervised exercise programs and the role of structured home-based exercise in peripheral arterial disease. *Eur J Vasc Endovasc Surg.* 2012;44(6):569-75; discussion 76.
32. Evans T, Roberts M, Lewis M. Re: 'why do health systems not fund supervised exercise programmes for intermittent claudication?'. *Eur J Vasc Endovasc Surg.* 2015;49(4):487.
33. Lauret GJ, van Dalen HC, Hendriks HJ, van Sterkenburg SM, Koelemay MJ, Zeebregts CJ, et al. When is supervised exercise therapy considered useful in peripheral arterial occlusive disease? A nationwide survey among vascular surgeons. *Eur J Vasc Endovasc Surg.* 2012;43(3):308-12.

34. Al-Jundi W, Madbak K, Beard JD, Nawaz S, Tew GA. Systematic Review of Home-based Exercise Programmes for Individuals with Intermittent Claudication. *Eur J Vasc Endovasc Surg.* 2013.
35. McDermott MM, Liu K, Guralnik JM, Criqui MH, Spring B, Tian L, et al. Home-based walking exercise intervention in peripheral artery disease: a randomized clinical trial. *JAMA.* 2013;310(1):57-65.
36. Al-Jundi W, Madbak K, Beard JD, Nawaz S, Tew GA. Systematic review of home-based exercise programmes for individuals with intermittent claudication. *Eur J Vasc Endovasc Surg.* 2013;46(6):690-706.
37. Bjarnason-Wehrens B, Grande G, Loewel H, Voller H, Mittag O. Gender-specific issues in cardiac rehabilitation: do women with ischaemic heart disease need specially tailored programmes? *Eur J Cardiovasc Prev Rehabil.* 2007;14(2):163-71.
38. Hirsch AT, Allison MA, Gomes AS, Corriere MA, Duval S, Ershow AG, et al. A call to action: women and peripheral artery disease: a scientific statement from the American Heart Association. *Circulation.* 2012;125(11):1449-72.
39. Cimminiello C. PAD. Epidemiology and pathophysiology. *Thromb Res.* 2002;106(6):V295-301.
40. Dolan NC, Liu K, Criqui MH, Greenland P, Guralnik JM, Chan C, et al. Peripheral artery disease, diabetes, and reduced lower extremity functioning. *Diabetes Care.* 2002;25(1):113-20.
41. Nicolai SP, Leffers P, Kruidenier LM, De Bie RA, Prins MH, Teijink JA. Extending the range of treadmill testing for patients with intermittent claudication. *Med Sci Sports Exerc.* 2010;42(4):640-5.
42. Nicolai SP, Viechtbauer W, Kruidenier LM, Candel MJ, Prins MH, Teijink JA. Reliability of treadmill testing in peripheral arterial disease: a meta-regression analysis. *J Vasc Surg.* 2009;50(2):322-9.
43. Larson JL. Functional performance and physical activity in chronic obstructive pulmonary disease: theoretical perspectives. *COPD.* 2007;4(3):237-42.
44. Garg PK, Tian L, Criqui MH, Liu K, Ferrucci L, Guralnik JM, et al. Physical activity during daily life and mortality in patients with peripheral arterial disease. *Circulation.* 2006;114(3):242-8.

45. Marconi C, Ferretti G, Anchisi S, Catalano M, Scandale G, Antico A, et al. Energetics of walking in patients with peripheral arterial disease: a proposed functional evaluation protocol. *Clin Sci (Lond)*. 2003;105(1):105-11.

CHAPTER 2

The effect of supervision on walking distance in patients with intermittent claudication: a meta-analysis

L.N.M. Gommans
R. Saarloos
M.R.M. Scheltinga
S. Houterman
R.A. de Bie
H.J.P. Fokkenrood
J.A.W. Teijink

ABSTRACT

Background: A number of reviews reported on the influence of exercise therapy (ET) for treatment of intermittent claudication (IC). However, a complete overview of different types of ET is lacking. The aim of this meta-analysis is to study the effect of supervision on walking capacity in IC. We hypothesized the presence of a positive treatment effect in relation to intensity of supervision and improvement of walking capacity ('dose – response' hypothesis).

Methods: A systematic search in CENTRAL, MEDLINE and EMBASE was performed (January 1966 to March 2013). Only randomized controlled trials (RCTs) evaluating the efficacy of an ET in IC were included. Type of supervision, treadmill protocol, length of ET, total training volume and change in walking distance were extracted. RCTs were categorized according to type of support: no exercise (NO-ET), walking advice (WA), home-based exercise (HB-ET) and supervised exercise therapy (SET). A standardized mean difference (SMD) between pre- and post-training maximal walking distance (MWD) and pain-free walking distance (PFWD) was calculated for all subgroups at six weeks, three and six months of follow up (FU).

Results: A total of 30 studies involving 1406 IC patients were included. The overall quality was moderate to good although number of included patients varied widely (20 to 304). Intensity of supervision was directly related to MWD and PFWD. SET was superior compared to other conservative treatment regimens with respect to improvement in walking distances at all FU moments. However, the difference between HB-ET and SET at six months of follow up was not significant.

Conclusion: Supervised exercise therapy for intermittent claudication is superior compared to all other forms of exercise therapy. Intensity of supervision is related to improved walking distances.

INTRODUCTION

Worldwide, 202 million people were coping with peripheral arterial obstructive disease (PAOD) in the year of 2010.¹ During the preceding decade, the number of affected individuals increased by 13.1% and 28.7% in high and low-middle income countries, respectively.¹ These huge numbers illustrate that PAOD has become a global health problem affecting vast quantities of individuals. Some 50% to 80% of PAOD patients are symptomatic and suffer from intermittent claudication (IC), the mildest manifestation of symptomatic arterial obstructive disease.²

International guidelines indicate that the treatment of IC should consist of cardiovascular risk management to protect patients from cardiovascular events and related morbidity and mortality. Moreover, supervised exercise therapy (SET) is advised to reduce symptoms and restore physical function.²⁻³ However, widespread implementation of SET is restricted by the combination of insufficient number of available facilities and issues on reimbursement, awareness and motivation.^{2, 4-6} To overcome some of these problems, a community based network for SET was implemented in the Netherlands.⁵ Community based SET solves the problem of transportation time and costs for individual patients as well as the restricted capacity of hospital based SET.⁷⁻⁸ Others suggested to initiate exercise programs in a home-based environment and thereby diminishing the amount of labour-intensive supervision.⁹⁻¹⁰ A recent published trial revealed promising results regarding the effect of such an approach.¹¹

Several reviews are currently available regarding the value of different conservative treatment options in IC.¹²⁻¹⁶ However, no meta-analysis compared SET with home-based exercise, non-supervised regimens and a control group yet. A recently updated Cochrane review compared unsupervised exercise with supervised exercise concerning walking improvement.¹⁶ A second review that was aimed to identify components of SET contributing to maximal improvement of walking capacity only compared supervised exercise with no exercise at all.¹³ Despite the use of strict inclusion criteria in both reviews, some overlap in included trials was inevitable. Moreover, the latter reported that neither intensity nor duration or program content were independently associated with improvement of maximal or pain-free walking distance, but the role of support was not addressed.

2

The present effort was aimed to evaluate the effect of various grades of supervision on walking capacity by providing a meta-analysis of existing literature concerning exercise programs for IC. It was hypothesized that a dose-response relationship was present between supervision and improvement on walking capacity.

METHODS

Eligibility criteria

Only randomized controlled trials (RCT) on patients with IC (Fontaine II/Rutherford 1-3) were eligible for inclusion in this meta-analysis. A RCT was included if each intervention group received at least one type of exercise, if type of supervision was different between study groups, if supervision and duration of exercise therapy (ET) exceeded six consecutive weeks, and if >50% of the exercise time included lower limb training. Outcomes had to be reported as maximal walking distance/time (MWD/T) or pain free walking distance/time (PFWD/T), or both. Only English or Dutch studies were included. Trials with a control group undergoing invasive therapy or specific drug treatment were excluded.

Trial selection strategy

The electronic search was conducted in MEDLINE (1966 to March 2013), EMBASE (1974 to March 2013) and the Cochrane Central Register of Controlled Trials (CENTRAL) database (1966 to September 2012). The search strategy contained the following MeSH terms: Arteriosclerosis, Arterial Occlusive Diseases, Intermittent Claudication, Peripheral Vascular Diseases, Exercise, Exercise Therapy, Physical Exertion, Sports, Exercise Movement Techniques, Locomotion, Leisure Activities, Fitness Centers, and Physical Exertion. In addition, reference lists of papers identified from these searches were hand searched for additional trials. Three authors (LG, RS and HF) independently selected trials on the basis of title and abstract. A definite selection was based on a full-text evaluation of the report. Disagreement between the reviewers was discussed and resolved by consensus.

Risk of bias assessment

The included articles were assessed with the Cochrane scale by two authors (LG and RS) to determine methodological quality and to assess the risk of bias. Blinding of staff and patients during exercise programs is not possible and was therefore not taken into account. Study quality was determined using a table of risk of bias on the basis of a checklist of design components including random sequence generation, allocation concealment, incomplete outcome data and selective reporting (*appendix I*). Adequacy of each category was assessed as 'low', 'unclear', or 'high' risk, as suggested in the Cochrane Collaboration Handbook.¹⁷

Data collection and processing

Trial data were extracted by three authors (LG, HF and RS) using a standardized data extraction form that was checked by a fourth author (SH). Study characteristics, year of publication, study location and type of supervision were collected as well as patient group characteristics including mean age and sex, number of patients in each group and walking distances (maximal walking distance (MWD) and pain free walking distance (PFWD), pre- and post-training). Authors were contacted for additional information in case of ambiguity or missing data.

When maximal or pain-free walking time were reported, conversion into distances (meters) was performed by multiplying the time spent on the treadmill with the given walking speed (m/s). If standard errors (SE) were available (and authors did not reply or declined our request to send unpublished data), we converted these values into standard deviations (SD). In articles reporting non-parametric data, the SD was calculated by dividing the interquartile range (IQR) by 1.35 as suggested by the Cochrane Handbook.¹⁷

Labeling of supervision

Two authors (RS and LG) independently categorized treatment arms per study by classifying the type of supervision given per arm. The following groups were defined:

Control group - No Exercise Therapy (NO-ET): Participants were mainly advised to consolidate current levels of activities, while some additionally received best medical treatment (BMT). Supervised walking exercise or a walking advice was not provided during the treatment period.

Walking Advice (WA): Participants were actively advised by a physician, nurse or physical therapist to increase activity levels by walking, defined as a “go home and walk” advice. However, supervision or monitoring was absent.

Home-based Exercise Therapy (HB-ET): Participants were advised to increase physical activity that was monitored by keeping a walking diary, by pedometers or by using physical activity monitors. They were stimulated by regular telephone calls or were visited at home. Active monitoring by a physician, nurse or physiotherapist was limited to a maximum of two moments per week.

Supervised Exercise Therapy (SET): Participants were treated with a SET regimen with or without an additional walking advice. The training was hospital- or community-based under supervision of a physical therapist or other trained medical personnel. The program consisted of a least two supervised sessions per week.

Statistical analysis

The main outcome was difference in walking distances (MWD and PFWD) after treatment (i.e. NO-ET, WA, HB-ET and SET) compared to baseline measures. Results are presented as standardized mean difference (SMD) with 95% confidence intervals (CIs), at 6 weeks, 3 and 6 months follow-up. SMD expresses the size of the intervention effect in each study relative to the variability observed in that study. It is used as a summary statistic when studies assess the same outcome but measure it in a variety of ways¹⁷, as in our meta-analysis by the use of different treadmill protocols. We used a DerSimonian and Laird random-effects model to pool continuous data of each group.¹⁸ We examined statistical heterogeneity with Cochran's test and I^2 statistic measured. Studies with an initial supervised period followed by an unsupervised follow-up period were analyzed separately in a sensitivity analysis.

Differences in SMD between the subgroups were investigated as a means to evaluate the presence of a dose-response relation. Testing for subgroup differences based on random-effects models are preferable to those based on fixed-effects, due to the high risk of false-positive results in a fixed-effect model.¹⁹ Therefore, we only applied a random-

effects model as previously described. A test for subgroup differences as described by Borenstein was used.²⁰

Review Manager Software of the Cochrane Collaboration (version 5.2, Cochrane Collaboration) was used for SMD calculation, pooled effect estimation, test for heterogeneity and determination of differences between SMDs of the subgroups. A two-sided p-value <0.05 was considered statistically significant. Graphs were created with Graphpad Prism 6 (GraphPad Software Inc, La Jolla, USA).

RESULTS

Study selection

In the MEDLINE and EMBASE search, 2544 studies were identified. Another 240 potentially relevant studies were found by a search using the CENTRAL library whereas the hand search yielded another 8 eligible studies. After removing duplicates and selection based on title and abstract, a total of 108 studies underwent full text reviewing. A total of 78 studies was excluded by failing to meet predefined criteria. Eventually, 28 RCTs met all inclusion criteria. A flow chart of the trial selection is depicted in figure 1.

Figure 1. Flow chart of trial selection

Study characteristics

A total of 1406 participants (68% males, mean age 68 years) were studied (*table 1*). All trials were conducted between 1974 and 2012 in eight different countries. The NO-ET group was formed on the basis of data derived from sixteen trials containing a total of 262 participants (*table 1*). The WA group was formed on the basis of ten trials with a total of 302 participants (*table 1*). Walking instructions were generally provided at baseline. Patients were mostly advised to continue to walk to near maximal pain. One study provided patients with an additional brochure²⁶, while patients were educated using video material in another.¹⁰ Two studies stipulated that patients did not receive any life-style coaching or risk factor management.^{11, 31} The HB-ET group consisted of 140 participants obtained from six trials (*table 1*). Subjects received similar walking advice as the WA group, although regimens were supplemented with weekly (telephone) contact.^{9-11, 21-23} In two studies, participants had to log their exercise^{9, 11}, while in a third study participants received SET once a week.¹⁰

All trials used a SET regimen as comparator (n=702) except for one study which compared a home-based exercise regimen with a group receiving a walking advice.¹⁰ In seven trials, subjects were treated twice a week with SET^{26, 28-29, 34-35, 45, 47}, while in the remaining trials SET was given three times a week (*table 2*). The length of the ET programs varied between 6 and 52 weeks with nine, twenty and sixteen trials lasting 6 weeks, 3 and 6 months, respectively (*table 2*). One trial consisted of a WA group, a HB-ET group and a SET group; all three arms were included.¹¹ A graded treadmill protocol was used in 23 trials, while the remaining 7 trials used a fixed protocol (*table 1*). Outcome was based on a conversion from a time to distance format in eight studies.

Risk of bias assessment

The risk of bias is presented in appendix II. Of the included trials, 83% reported random sequence generation whereas a mere 27% used allocation concealment. The outcome assessor was blinded for intervention in 23% of the trials. In 57% correct handling of incomplete outcome measures was reported, while description of all outcome measures was provided in 93% of the trials. The overall quality of included trials was rated as moderate to good.

Effect of interventions

Six weeks

Sixteen studies reported data on MWD and 13 on PFWD at 6 weeks of follow up. No studies were found that investigated the effect of home-based exercise on walking distances at 6 weeks of follow up. A non-significant effect on MWD was present for both the NO-ET and WA programs, while on PFWD both programs groups showed a significant increase in SMD. The SET regimen demonstrated a significant increase in SMD of 0.90 (95% CI: 0.67 – 1.13) and 0.94 (95% CI: 0.64 – 1.24) for MWD and PFWD, respectively (*figure 2*). Significant differences between groups were only found when comparing with the SET group (*figure 2*). Heterogeneity was absent for all groups on MWD and PFWD (All: $I^2 < 15\%$; $P > .32$).

Three months

Results of MWD were reported in 8, 6, 5 and 20 trials for NO-ET, WA, HB-ET and SET groups, respectively. PFWD was described in 6, 3, 5 and 13 trials for the subsequent groups. A significant increase in MWD was found for the WA, HB-ET and SET programs, whereas only the SET program revealed a significant effect for PFWD too (*figure 3*). The SET program showed a significant difference compared to all other groups. MWD was also significantly higher in the HB-ET compared to the NO-ET group. There was no heterogeneity for all groups on MWD and PFWD (All: $I^2 < 18\%$; $P > .29$) except for the SET group (MWD: $I^2 = 83\%$; $P < .001$, PFWD: $I^2 = 87\%$; $P < .001$).

Six months

Results of MWD were reported in 6, 5, 1 and 9 trials for NO-ET, WA, HB-ET and SET groups, respectively. PFWD was described in 2, 3, 1 and 4 trials, respectively. A non-significant increase in MWD and PFWD compared to baseline measurements was found for the NO-ET. For the WA and SET group however, the increase in MWD and PFWD was significant. Between groups analysis showed a significant differences in MWD and PFWD in the SET and WA group (*figure 4*).

In six trials the follow up period was longer than the actual exercise program.^{9, 21-22, 29, 34-35} Results of these trials were added to the 6-month results and were used in the sensitivity analysis (*figure 5*). In this analysis, MWD was described in 8, 6, 4

and 15 trials for NO-ET, WA, HB-ET and SET groups, while PFWD was found in 4, 4, 4 and 10 trials, respectively (*figure 5*). SET results were superior with a SMD of 0.96 (95% CI: 0.76 – 1.16) and 0.89 (95% CI: 0.65 – 1.14) for MWD and PFWD, respectively. SET results were also significantly better compared to the NO-ET and WA group, regarding both outcomes. Homogeneity was observed for all groups on both outcomes (All: $0\% < I^2 < 62\%$; $P > .07$).

Table 1. Study characteristics

Author	Year	Country	Treatment (1)	Control (2)	Subjects analysed		Mean age ± SD	% male	6 wk FU	3 mo FU	6 mo FU	6 mo FU	Mean pain free walking distance (meter)		Mean maxi- mum walking distance (meter)		Graded treadmill protocol
					1	2							Start	FU	Start	FU	
Patterson ²³	1997	USA	SET	HB-ET	19	19	69.3 ± 8.1	53	x	x	x^	SET HB	88 88	385 203	145 145	445 247	Yes
Treat-Jacobson ²⁵	2009	USA	SET	HB-ET	9	8	67.7 ± 10.5	71	x	x	x^	SET HB	200 119	356 130	483 361	778 434	Yes
Gardner ¹¹	2011	USA	SET	HB-ET	33	29	66.0 ± 12	48	x			SET HB	196 225	361* 209*	288 357	480 468	Yes
Regensteiner ¹⁰	1997	USA	SET	HB-ET	10	10	64.5 ± 7	NR	x			SET HB	109 125	272 158	250 337	529 353	Yes
Savage ²⁴	2001	USA	SET	HB-ET	11	10	66.3 ± 8.8	71	x	x	x^	SET HB	241 183	484 484	522 532	742 715	Yes
Cheetham ³²	2004	UK	SET	WA	27	28	67 (45 - 86)	73	x	x		SET WA	NR NR	NR NR	132 103	302 174	No
Kakkos ³³	2005	UK	SET	WA	4	9	66.5 ± 8.0	79	x		x	SET WA	60 70	70 70	145 135	220 140	No
Gardner ¹¹	2011	USA	SET	WA	0	30	66.0 ± 12	48	x			SET WA	196 200	361* 185*	288 505	480* 494*	Yes
Nicolai ²¹	2010	NL	SET	WA	169	83	66.2 ± 9.4	61	x	x		SET WA	NR NR	NR NR	260 260	617 400	Yes
Sanderson ²⁵	2006	Australia	SET	WA	13	14	63.0 ± 9.0	57	x			SET WA	309 294	455 [§] 335 [§]	686 305	905 [§] 310 [§]	Yes
Hodges ²⁸	2008	UK	SET	WA	14	14	68.0 ± 8.0	NR	x	x		SET WA	NR NR	NR NR	347 362	622* 405*	Yes
Stewart ²⁷	2008	UK	SET	WA	27	24	68 ± 9	70	x	x	x^	SET WA	56 47	113 62	109 73	217 104	No
Parr ²⁸	2009	SA	SET	WA	8	8	60 ± 13	64	x			SET WA	125 175	255 [§] 175 [§]	290 460	485 430	Yes
Gardner ⁷	2012	USA	SET	WA	80	27	68 ± 8	85	x*	x**	x	SET WA	176 130	365 194	383 164	663 218	Yes

Hiatt ³⁶	1990	USA	SET	NO-ET	10	9	60.0±12	100	x	x	SET	NR	NR	NR	341	741 [#]	Yes
															320	379 [#]	
Hiatt ³⁷	1994	USA	SET	NO-ET	10	8	67.0±6	100	x		SET	176	357 [#]	512	784 [#]	Yes	
													165 [#]	394	390 [#]		
Hobbs ²⁷	2007	UK	SET	NO-ET	9	9	67 (63-74)	78	x	x [^]	SET	60	127	99	206	No	
												59	64	94	120		
Hobbs ²⁶	2006	UK	SET	NO-ET	6	7	72±NR	71		x [^]	SET	59	92	111	124	Yes	
												47	56	84	145		
Dahlöf ⁸	1976	Sweden	SET	NO-ET	10	8	61.4±1.0	79		x	SET	91	230	296	620	No	
												55	55	340	340		
Gardner ³⁹	2001	USA	SET	NO-ET	28	24	72±1	NR		x	SET	172	402	396	702	Yes	
												163	203	379	425		
Tsai ⁴⁰	2002	Taiwan	SET	NO-ET	27	20	76±4	83	x		SET	176	331 [#]	395	667 [#]	Yes	
												155	171 [#]	384	405 [#]		
Langbein ⁴¹	2002	USA	SET	NO-ET	27	25	67±9	98	x	x	SET	NR	NR	NR	626	921	Yes
												NO	NR	664	620		
Mika ⁴²	2005	Poland	SET	NO-ET	41	39	61±6	83	x		SET	87	192	NR	NR	No	
												87	102	NR	NR		
Mika ⁴³	2006	Poland	SET	NO-ET	27	28	59±8	87	x	x	SET	191	386 [#]	438	656 [#]	Yes	
												204	210 [#]	430	451 [#]		
Wood ⁴⁴	2006	Australia	SET	NO-ET	7	6	60±8	69	x		SET	284	456 [§]	761	905 [§]	Yes	
												55	55 [§]	966	1019 [§]		
Schlager ²⁹	2011	Austria	SET	NO-ET	20	19	69±10	60		x	SET	NR	NR	102	154	Yes	
												NR	NR	85	100		
Mika ⁴⁵	2011	Poland	SET	NO-ET	30	31	63±7	88	x	x	SET	292	610 [#]	551	848 [#]	Yes	
												258	258 [#]	551	515 [#]		
Schlager ³⁰	2012	Austria	SET	NO-ET	26	25	70±9	62	x	x	SET	NR	NR	102	132	No	
												NO	NR	85	100		
Collins ⁹	2011	USA	HB-ET	WA	64	65	66.5±10.1	69		x	HB	149	216	422	447	Yes	
												166	218	473	511		

SD: standard deviation; FU: follow-up; SET: supervised exercise therapy; HB-ET: home-based exercise therapy; WA: walk advice; NO-ET: no exercise therapy; NR: not reported; m: meters; min: minutes, NL: Netherlands SA: South Africa, * = outcome at 2 months instead of 3 months, ** = outcome at 4 months instead of 6 months; ^ = studies included in the sensitivity analysis; # = follow up data at 3 months, § = follow up data at 6 weeks.

Table 2. Specification of patient population and exercise protocols

Author	Patient population	Inclusion criteria	Exclusion criteria	Length program (weeks)	Training freq*	Type of exercises	Type of supervision	Adherence (%)
Patterson ²³	NR	50-75 years, claudication >3 month, ABI <0.9, no cardiac ischemia during exercise test	Ischemic leg pain*, major comorbidities	12	3	Mixed exercise	SET: 180 min per week. In case of missed sessions contact by study nurse	74
				12	3	Walking	HB-ET: exercise logbook. Weekly lecture and contact with study nurse for 90 min	74
Treat-Jacobson ²⁵	Outpatient clinics and advertisements. Additional screening by telephone	>18 years, ABI <0.9, able for treadmill walking	Major comorbidities, ischemic leg pain, recent MI, recent revascularisation procedure <3 month	12	3	Treadmill and arm ergometry	SET: 210 min per week	73
				12	3	Walking	HB-ET: walking instructions, daily exercise record, weekly visit at exercise laboratory	75
Gardner ¹¹	Outpatient clinics, referral to vascular clinics and by newspaper advertisement.	History of leg pain, walking test limited my leg symptoms, ABI <0.9	Asymptomatic PAOD, exercise intolerance by other diseases	12	3	Treadmill	SET: 120 min per week	77
				12	3	Walking	HB-ET: step activity monitor and exercise logbook. 7 visits of 15 min with exercise physiologist to get feedback	80
Regensteiner ¹⁰	Recruitment from vascular centre	Claudication with restriction during daily life, stable symptoms for 3 month, ABI <0.94	Ischemic leg pain*, inability to treadmill walking, major comorbidity, vascular surgery <6 month	12	3	Treadmill	SET: up to 165 min per week	100
				12	3	Walking	HB-ET: walking description from study nurse. Weekly call from study nurse	100

Savage ²⁴	Recruitment by three vascular surgeons	>50 years, clinically diagnosed with IC, grade I, II, III on IC questionnaire of the society of vascular surgery	12	3	Treadmill	SET: up to 120 min per week	NR
Cheetham ²²	Patients visiting an outpatient vascular centre with symptoms of claudication	ABI <0.9, PAOD duplex confirmed, positive score on Edinburgh questionnaire, stable symptoms >6 months, >300 meter on 6MWT	12	3	Walking	HB-ET: monthly call from study nurse	NR
Kakko ²³	Recruitment from vascular outpatient clinic	Stable IC symptoms >6 months, SFA occlusion >6 cm	25	2	Circuit training in group sessions	Training supervision for 30 min per week. Weekly talk of 10 min on benefits of walking	97
Nicolai ⁸	Recruitment from vascular outpatient clinic	ABI <0.9, walking distance <500 meter	25	3	Treadmill: individual or group session	Training supervision for 180 min per week.	50
Sanderson ²⁵	Patients with reduced ABI were invited by post mail	ABI <0.9, IC symptoms >12 months	52	2.5	Treadmill	Training supervision for 75 min per week and use of accelerometers during training	90
Hodges ²⁸	Recruitment of vascular patients from inpatient department	ABI <0.9, positive score on Edinburgh questionnaire	6	3	Treadmill	Training supervision	NR
Stewart ²⁷	Patients visiting an outpatient vascular centre with symptoms of claudication	Symptoms of IC, ABI <0.9	12	2	Treadmill	Training supervision for 90 min per week	100
			12	2	Circuit training	Training supervision for 120 min per week	99

Parr ²⁸	History of PAOD	IC diagnosed by duplex	Ischemic leg pain ^a , exercise intolerance by comorbidity, COPD	6	3	Strenght training	Training supervision for 135 min per week	100
Gardner ⁷	Recruitment from outpatient vascular clinics and by newspaper en radio	History of PAOD, able to perform walking tests, ABI <0.9,	Asymptomatic PAOD, Ischemic leg pain, IC symptoms reducing medication, vascular procedure, exercise intolerance by other comorbidities, non-compliance	25	3	Treadmill	Training supervision for 82.5 min per week	83
Hiatt ³⁶	NR	ABI <0.95	Ischemic leg pain ^a , RR ankle <50 mmHg, inability to walk on a treadmill, exercise intolerance by other comorbidity	12	3	Treadmill	Training supervision for 180 min per week	79
Hiatt ³⁷	NR	IC symptoms >3 months, restrictions in daily life, ABI <0.9,	Ischemic leg pain, vascular procedure <12 months, inability to walk on a treadmill, exercise intolerance by other comorbidity	12	3	Treadmill	Training supervision for 180 min per week	90
Hobbs ²⁷	Patients referred from primary care to a vascular outpatient clinic	ABI <0.9, positive score on Edinburgh questionnaire, maximal walking distance of 50-500 meter	Significant aortoiliac disease, unable to complete treadmill test, MI, CVA, TIA, PTCA <3 months, congestive heart failure, known predisposition for bleeding	12	2	Circuit training	Training supervision for 120 min per week	91
Hobbs ²⁶	Patients referred from primary care to a vascular outpatient clinic	Maximal walking distance of 50-500 meter due to IC symptoms as exercise limiting factor	No IC, significant aortoiliac disease, walking distance <50 meter	12	2	Circuit training	Training supervision for 120 min per week	NR
Dahlöf ³⁸	Patients from outpatient vascular clinics with IC symptoms >1 year	IC confirmed with oscillometry, leg symptoms after 400 meter of walking	Ischemic leg pain ^a , severe varices	26	3	Dynamic leg exercises	Training supervision for 90 min per week	NR
Gardner ³⁹	Patients were originally recruited from another study on IC	ABI <0.97, positive score on Rose questionnaire, >60 years, severe restrictions due to IC	Exercise intolerance by other comorbidities	26	3	Treadmill	Training supervision up to 120 min per week	61

Tsai ⁴⁰	NR	ABI <0.95, positive score on Rose questionnaire, stable symptoms >3 months	Ischemic leg pain ^a , history of AP, exercise intolerance by non-vascular origin, PAOD surgery or MI <3 months	12	3	Treadmill	Training supervision for 90 min per week	82
Langbein ⁴¹	Recruitment of patients with history/IC from hospital records	ABI <0.95, exercise limiting symptoms of IC	PAOD surgery <6 months, comorbidity which coincides with ET	20	3	Treadmill or outside walking	Training supervision at least 90 min per week	85
Mika ⁴²	Recruitment from outpatient vascular clinics	50-70 years, IC Fontaine II, symptoms >3 months, ABI <0.9	MI, PAOD surgery <12 months, relevant comorbidity, enable to walking speed of 3.2 km/h, medication	12	3	Treadmill	Training supervision for 120 min per week	84
Mika ⁴³	Recruitment from outpatient vascular clinics	50-70 years, IC Fontaine II, symptoms >3 months, ABI <0.9	MI, PAOD surgery <12 months, relevant comorbidity, enable to walking speed of 3.2 km/h, medication	12	3	Treadmill	Training supervision for 120 min per week	83
Wood ⁴⁴	NR	IC Fontaine II	Instable AP, relevant comorbidities, vascular procedure <12 months, cardiac ischemia on ECG	6	3	Treadmill	Training supervision for 120 min per week	100
Schlager ⁴⁹	Patients referred to vascular clinic were screened for recruitment	ABI <0.9, symptoms >2 weeks	Ischemic leg pain ^a , exercise intolerance by other comorbidities	26	2	Treadmill	Training supervision for 110 min per week	100
Mika ⁴⁵	Recruitment by records from vascular clinic	Fontaine II, ABI <0.9, 50-70 years, <150 meter walking without pain	History op AP, MI <12 months, relevant comorbidity, enable to perform walking test	12	3	Treadmill	Training supervision up to 165 min per week	88
Schlager ⁵⁰	Patients referred to vascular clinic were screened for recruitment	ABI <0.9, symptoms >2 weeks	Ischemic leg pain ^a , exercise intolerance by other comorbidities	26	2	Treadmill	Training supervision for 110 min per week	100
Collins ⁹	Recruitment by telephone	>40 years, ABI <0.9, previous vascular procedures, DM, leg symptoms	Amputations, critical ischemia, coronary ischemia during exercise testing, exercise intolerance by other comorbidity	25	3	Walking	HB-ET: weekly supervised walking during group session. Two times a month contact by telephone	83

* = per week, # = ischemic pain in rest, ABI: ankle-brachial index, DM: diabetes mellitus, ET: exercise training, ECG: electrocardiography, HB-ET: home-based exercise therapy, IC: intermittent claudication, min: minutes, MI: myocardial infarction, NR: not reported, PAOD: peripheral arterial occlusive disease, SET: supervised exercise therapy, SFA: superficial femoral artery, 6MWT: six minutes walking test.

Figure 2. Maximal (MWD) and pain-free walking distances (PFWD) for the different support types at 6 weeks of follow up

Figure 3. Maximal (MWD) and pain-free walking distances (PFWD) for the different support types at 3 month of follow up

Figure 4. Maximal (MWD) and pain-free walking distances (PFWD) for the different support types at 6 month of follow up

Figure 5. Maximal (MWD) and pain-free walking distances (PFWD) for the different support types at 6 month of follow up: sensitivity analysis

DISCUSSION

2

The aim of this meta-analysis was to study the effect of supervision on improvement of walking distance in patients with intermittent claudication (IC). Our findings demonstrated a superior role of supervised exercised therapy (SET) as significant effect sizes >0.8 for all the follow up periods were found. These effects are generally considered as 'large'.⁴⁸ Moreover, the results of SET were significantly better compared to the three other types of ET. Although we failed to demonstrate significant differences between all groups mutually, a dose-response trend as present with increasing supervision resulting in larger walking distances, most evident for the PFWD, at six month of follow up. The results as found in our study indicate that exercise programs supplemented with supervision have significant beneficial effects on walking capacity, which is in line with existing data.^{13, 16}

One may question the additional value of just another meta-analysis as various other reviews were published in the previous decade.¹²⁻¹⁶ For instance, Fakhry et al.¹³ described the effectiveness of SET on walking distances although they failed to include the factor supervision in their overview. By extending the number of included trials we were confident that the results were genuine. By doing so, the total number of participants was increased by 50%. Moreover, the present study is the first to include three conservative treatment arms including a control group facilitating a more extensive comparison. Secondly, it was judged that evaluation of the factor support was required. Thirdly, the alternative method of calculation used in our review allowed for evaluating the four individual groups as well as comparing them. Since calculation of SMDs was based on group pre- en post-training values, significant differences reflect the actual effect of any treatment. In addition, significant differences in SMDs between groups represent the difference in effect between groups.

One would intuitively think that a dose response relationship would be present between intensity of support and increased walking performance, since a comparison between SET and non-supervised regimens already demonstrated the additional value of supervision.¹⁶ Obvious or not, a dose response relation was never identified. We demonstrated a clear dose response trend in our review, but since not all differences between groups were statistically significant we failed in revealing a genuine relationship.

Conversely, failing to identify such a relation does not necessarily mean that there is none. Moreover, comparing statistical significance levels of the results is misleading, given the low power and variation in number of participants per subgroup. However, we included the largest number of participants so far¹⁷, and as such, this finding may have profound consequences on structure of these and future programs.

Despite the overwhelming evidence supporting the use of supervised exercise programs for IC^{12-13, 16}, and the class I recommendation by three leading international guidelines^{2-3, 49}, uncertainty surrounds the relative contribution of all components of an optimal SET program.¹³ Moreover, the most optimal length of a SET program is a matter of debate. Gardner et al. described a tendency of middle-term length programs (12-26 weeks) leading to greater improvement in MWD and PFWD compared to shorter (<12 weeks) or longer (>26 weeks) programs.³¹ They also concluded that walking distances increased rapidly within the first 2 months of exercise rehabilitation.³¹ With respect to the support component, our meta-analysis confirms these findings, as the effect after 3 months of SET (SMD 1.28; 95% CI 0.94-1.62) was larger compared to the effect after 6 months of training (SMD 0.96; 95% CI 0.76-1.16). Moreover, the SET results after 6 months of follow-up were not significantly different from the HB-ET group suggesting that extra supervision does not result in better outcomes after a long period of training and demonstrating the potential value of HB-ET.

Consequently, a 3 months SET program appears most preferable, but given the limited utilization of SET in daily practice⁵⁰⁻⁵¹ and lessons learned in the worldwide available cardiac rehabilitation programmes, ongoing program modifications could possibly lead to a more viable supervised exercise schedule for patients with IC. After 3 months of training, SET may be replaced by a home-based program as our extensive meta-analysis demonstrated a equivalent effect of SET and HB-ET after six months. HB-ET may be more cost-effective by limiting expensive supervision and reducing issues regarding to training facilities. Interestingly, monitor options for HB-ET could be extended by incorporating eHealth and mHealth technologies.^{4, 50} Such technologies may increase adherence and consequent effectiveness. Future research should therefore focus on cost-effectiveness of home-based programs revealing the optimal mixture of home-based and supervised training.

Some limitations of this meta-analysis should be addressed. First, the methodological quality of original RCTs is not always optimal, in particular the questionable allocation concealment and lack of blind outcome assessment. As a consequence, the effect of SET may have been overestimated in individual studies. However, knowledge about appropriateness of patients for SET is not available yet, making favorable allocation unlikely. Moreover, the use of standardized exercise testing procedures and quantitative outcome measures may compensate for the lack of blind outcome assessment. Second, sample size of some studies was limited (<10 participants per treatment arm) which may have resulted in imprecise effect estimates. Thirdly, we chose to calculate SMDs in order to be able to compare more than two groups. Therefore, interpretation of the overall intervention effect can be difficult as it is reported in units of standard deviation rather than in meters. However, in reality the intervention effect is a difference in means and not a mean of differences.¹⁷ On the other hand, conversion to SMDs allowed us to compare walking distances which were assessed with different treadmill tests. Fourthly, a large diversity has been observed in the HB-ET group regarding the supervision strategy (e.g. diary, pedometers or physical activity monitors), frequency and length of the programs. The sample size of this group was also considerably smaller compared to the other three groups. These effects may potentially have contributed to an inaccurate effect assessment and may also explain the absence of a significant difference between the WA and HB-ET group. Fifthly, outcomes were measured by using a treadmill test. Patients in the SET group may have been favored as they were accustomed to train on a treadmill leading to a potential overestimation of the results of SET. Last, results of the present meta-analysis may also be explained in part by a difference in extend of support or a difference in training regimen (e.g. outdoor walking in the WA group compared to mainly indoor walking in the SET group). However, this potential bias is inherent to the retrospective methodology as groups were not identical in terms of training program. An interesting contribution to this discussion is provided by a recent study that found no difference in walking performance when comparing to different training regimens.⁵² Therefore, the exact effect of training type on walking distance is not identified yet.

CONCLUSION

SET is superior compared to other forms of ET in patients with IC. Increased supervision tends to lead to a larger improvement on walking distance. At six months of follow-up however, efficacy of home-based programs may be equal to SET. Future research should focus on identifying an optimal mixture of supervised and home-based programs.

REFERENCES

1. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013 Oct 19;382(9901):1329-40.
2. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg*. 2007 Jan;45 Suppl S:S5-67.
3. Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *J Am Coll Cardiol*. 2006 Mar 21;47(6):1239-312.
4. Fokkenrood HJ, Lauret GJ, Scheltinga MR, Spreuuenberg C, de Bie RA, Teijink JA. Multidisciplinary treatment for peripheral arterial occlusive disease and the role of eHealth and mHealth. *J Multidiscip Healthc*. 2012;5:257-63.
5. Lauret GJ, Gijssbers HJ, Hendriks EJ, Bartelink ML, de Bie RA, Teijink JA. The ClaudicationNet concept: design of a national integrated care network providing active and healthy aging for patients with intermittent claudication. *Vasc Health Risk Manag*. 2012;8:495-503.
6. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. *N Engl J Med*. 2002 Dec 12;347(24):1941-51.
7. Kruidenier LM, Nicolai SP, Hendriks EJ, Bollen EC, Prins MH, Teijink JA. Supervised exercise therapy for intermittent claudication in daily practice. *J Vasc Surg*. 2009 Feb;49(2):363-70.
8. Bendermacher BL, Willigendael EM, Nicolai SP, Kruidenier LM, Welten RJ, Hendriks E, et al. Supervised exercise therapy for intermittent claudication in a community-based setting is as effective as clinic-based. *J Vasc Surg*. 2007 Jun;45(6):1192-6.

9. Collins TC, Lunos S, Carlson T, Henderson K, Lightbourne M, Nelson B, et al. Effects of a home-based walking intervention on mobility and quality of life in people with diabetes and peripheral arterial disease: a randomized controlled trial. *Diabetes Care*. 2011 Oct;34(10):2174-9.
10. Regensteiner JG, Meyer TJ, Krupski WC, Cranford LS, Hiatt WR. Hospital vs home-based exercise rehabilitation for patients with peripheral arterial occlusive disease. *Angiology*. 1997 Apr;48(4):291-300.
11. Gardner AW, Parker DE, Montgomery PS, Scott KJ, Blevins SM. Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication: a randomized controlled trial. *Circulation*. 2011 Feb 8;123(5):491-8.
12. Bendermacher BL, Willigendael EM, Teijink JA, Prins MH. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev*. 2006(2):CD005263.
13. Fakhry F, van de Luijngaarden KM, Bax L, den Hoed PT, Hunink MG, Rouwet EV, et al. Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg*. 2012 Oct;56(4):1132-42.
14. Watson L, Ellis B, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2008(4):CD000990.
15. Wind J, Koelemay MJ. Exercise therapy and the additional effect of supervision on exercise therapy in patients with intermittent claudication. Systematic review of randomised controlled trials. *Eur J Vasc Endovasc Surg*. 2007 Jul;34(1):1-9.
16. Fokkenrood HJ, Bendermacher BL, Lauret GJ, Willigendael EM, Prins MH, Teijink JA. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev*. 2013 Aug 23;8:CD005263.
17. Higgins JPT, S. *Cochrane handbook for systematic reviews of interventions*. collaboration Tc, editor, 2011.
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986 Sep;7(3):177-88.
19. Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. *Stat Med*. 2004 Jun 15;23(11):1663-82.
20. Borenstein M HL, Higgins JPT, Rothstein HR, . *Introduction to meta-analysis*. Chichester: John Wiley and Sons Ltd; 2008.

21. Nicolai SP, Teijink JA, Prins MH. Multicenter randomized clinical trial of supervised exercise therapy with or without feedback versus walking advice for intermittent claudication. *J Vasc Surg.* 2010 Aug;52(2):348-55.
22. Gardner AW, Montgomery PS, Parker DE. Optimal exercise program length for patients with claudication. *J Vasc Surg.* 2012 May;55(5):1346-54.
23. Patterson RB, Pinto B, Marcus B, Colucci A, Braun T, Roberts M. Value of a supervised exercise program for the therapy of arterial claudication. *J Vasc Surg.* 1997 Feb;25(2):312-8; discussion 8-9.
24. Savage P, Ricci MA, Lynn M, Gardner A, Knight S, Brochu M, et al. Effects of home versus supervised exercise for patients with intermittent claudication. *J Cardiopulm Rehabil.* 2001 May-Jun;21(3):152-7.
25. Treat-Jacobson D, Bronas UG, Leon AS. Efficacy of arm-ergometry versus treadmill exercise training to improve walking distance in patients with claudication. *Vasc Med.* 2009 Aug;14(3):203-13.
26. Hobbs SD, Marshall T, Fegan C, Adam DJ, Bradbury AW. The constitutive procoagulant and hypofibrinolytic state in patients with intermittent claudication due to infrainguinal disease significantly improves with percutaneous transluminal balloon angioplasty. *J Vasc Surg.* 2006 Jan;43(1):40-6.
27. Hobbs SD, Marshall T, Fegan C, Adam DJ, Bradbury AW. The effect of supervised exercise and cilostazol on coagulation and fibrinolysis in intermittent claudication: a randomized controlled trial. *J Vasc Surg.* 2007 Jan;45(1):65-70; discussion.
28. Hodges LD, Sandercock GR, Das SK, Brodie DA. Randomized controlled trial of supervised exercise to evaluate changes in cardiac function in patients with peripheral atherosclerotic disease. *Clin Physiol Funct Imaging.* 2008 Jan;28(1):32-7.
29. Schlager O, Giurgea A, Schuhfried O, Seidinger D, Hammer A, Groger M, et al. Exercise training increases endothelial progenitor cells and decreases asymmetric dimethylarginine in peripheral arterial disease: a randomized controlled trial. *Atherosclerosis.* 2011 Jul;217(1):240-8.
30. Schlager O, Hammer A, Giurgea A, Schuhfried O, Fialka-Moser V, Gschwandtner M, et al. Impact of exercise training on inflammation and platelet activation in patients with intermittent claudication. *Swiss Med Wkly.* 2012;142:w13623.

31. Stewart AH, Smith FC, Baird RN, Lamont PM. Local versus systemic mechanisms underlying supervised exercise training for intermittent claudication. *Vasc Endovascular Surg.* 2008 Aug-Sep;42(4):314-20.
32. Cheetham DR, Burgess L, Ellis M, Williams A, Greenhalgh RM, Davies AH. Does supervised exercise offer adjuvant benefit over exercise advice alone for the treatment of intermittent claudication? A randomised trial. *Eur J Vasc Endovasc Surg.* 2004 Jan;27(1):17-23.
33. Kakkos SK, Geroulakos G, Nicolaides AN. Improvement of the walking ability in intermittent claudication due to superficial femoral artery occlusion with supervised exercise and pneumatic foot and calf compression: a randomised controlled trial. *Eur J Vasc Endovasc Surg.* 2005 Aug;30(2):164-75.
34. Sanderson B, Askew C, Stewart I, Walker P, Gibbs H, Green S. Short-term effects of cycle and treadmill training on exercise tolerance in peripheral arterial disease. *J Vasc Surg.* 2006 Jul;44(1):119-27.
35. Parr BM, Noakes TD, Derman EW. Peripheral arterial disease and intermittent claudication: efficacy of short-term upper body strength training, dynamic exercise training, and advice to exercise at home. *S Afr Med J.* 2009 Nov;99(11):800-4.
36. Hiatt WR, Regensteiner JG, Hargarten ME, Wolfel EE, Brass EP. Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation.* 1990 Feb;81(2):602-9.
37. Hiatt WR, Wolfel EE, Meier RH, Regensteiner JG. Superiority of treadmill walking exercise versus strength training for patients with peripheral arterial disease. Implications for the mechanism of the training response. *Circulation.* 1994 Oct;90(4):1866-74.
38. Dahllof AG, Holm J, Schersten T, Sivertsson R. Peripheral arterial insufficiency, effect of physical training on walking tolerance, calf blood flow, and blood flow resistance. *Scand J Rehabil Med.* 1976;8(1).
39. Gardner AW, Katzel LI, Sorkin JD, Bradham DD, Hochberg MC, Flinn WR, et al. Exercise rehabilitation improves functional outcomes and peripheral circulation in patients with intermittent claudication: a randomized controlled trial. *J Am Geriatr Soc.* 2001 Jun;49(6):755-62.
40. Tsai JC, Chan P, Wang CH, Jeng C, Hsieh MH, Kao PF, et al. The effects of exercise training on walking function and perception of health status in elderly patients with peripheral arterial occlusive disease. *J Intern Med.* 2002 Nov;252(5):448-55.
41. Langbein WE, Collins EG, Orebaugh C, Maloney C, Williams KJ, Littooy FN, et al. Increasing exercise tolerance of persons limited by claudication pain using polestriding. *J Vasc Surg.* 2002 May;35(5):887-93.

42. Mika P, Spodaryk K, Cencora A, Unnithan VB, Mika A. Experimental model of pain-free treadmill training in patients with claudication. *Am J Phys Med Rehabil.* 2005 Oct;84(10):756-62.
43. Mika P, Spodaryk K, Cencora A, Mika A. Red blood cell deformability in patients with claudication after pain-free treadmill training. *Clin J Sport Med.* 2006 Jul;16(4):335-40.
44. Wood RE, Sanderson BE, Askew CD, Walker PJ, Green S, Stewart IB. Effect of training on the response of plasma vascular endothelial growth factor to exercise in patients with peripheral arterial disease. *Clin Sci (Lond).* 2006 Dec;111(6):401-9.
45. Mika P, Wilk B, Mika A, Marchewka A, Nizankowski R. The effect of pain-free treadmill training on fibrinogen, haematocrit, and lipid profile in patients with claudication. *Eur J Cardiovasc Prev Rehabil.* 2011 Oct;18(5):754-60.
46. Gelin J, Jivegard L, Taft C, Karlsson J, Sullivan M, Dahllof AG, et al. Treatment efficacy of intermittent claudication by surgical intervention, supervised physical exercise training compared to no treatment in unselected randomised patients I: one year results of functional and physiological improvements. *Eur J Vasc Endovasc Surg.* 2001 Aug;22(2):107-13.
47. Crowther RG, Leicht AS, Spinks WL, Sangla K, Quigley F, Golledge J. Effects of a 6-month exercise program pilot study on walking economy, peak physiological characteristics, and walking performance in patients with peripheral arterial disease. *Vasc Health Risk Manag.* 2012;8:225-32.
48. Cohen J. *Statistical Power Analysis in the Behavioral Sciences.* 2 ed. Hillsdale: Lawrence Erlbaum Associates Inc.; 1988.
49. Layden J, Michaels J, Bermingham S, Higgins B. Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance. *BMJ.* 2012;345:e4947.
50. Makris GC, Lattimer CR, Lavida A, Geroulakos G. Availability of supervised exercise programs and the role of structured home-based exercise in peripheral arterial disease. *Eur J Vasc Endovasc Surg.* 2012 Dec;44(6):569-75; discussion 76.
51. Shalhoub J, Hamish M, Davies AH. Supervised exercise for intermittent claudication - an under-utilised tool. *Ann R Coll Surg Engl.* 2009 Sep;91(6):473-6.
52. Delaney CL, Miller MD, Chataway TK, Spark JL. A randomised controlled trial of supervised exercise regimens and their impact on walking performance, skeletal muscle mass and calpain activity in patients with intermittent claudication. *Eur J Vasc Endovasc Surg.* 2014 Mar;47(3):304-10.

APPENDIX I Methodological quality of trials included in meta-analysis

Author and year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome assessment	Selective reporting	Other bias
Cheetham ⁴⁰	+	?	-	+	+	-	+
Collins ⁹	+	?	-	?	+	+	?
Dahlöf ⁴⁵	?	?	-	?	+	+	?
Gardner ¹¹	+	?	-	?	+	+	+
Gardner ³⁴	+	+	-	?	+	?	?
Gardner ²⁴	+	+	-	?	+	+	?
Hiatt ⁴²	+	-	-	?	?	+	+
Hiatt ⁴³	+	-	-	?	+	+	+
Hobbs ²¹	+	?	-	?	?	+	?
Hobbs ⁴⁴	+	?	-	?	+	+	+
Hodges ²⁶	+	?	-	?	-	+	+
Kakkos ⁴¹	+	?	-	?	+	+	?
Langbein ⁴⁷	+	?	-	?	?	+	+
Mika ⁴⁸	+	?	-	+	?	+	+
Mika ⁴⁹	+	?	-	+	?	+	+
Mika ³⁰	+	?	-	?	?	+	+
Nicolai ²³	+	+	-	+	+	+	?
Parr ²⁹	+	?	-	?	?	+	+
Patterson ²⁵	?	?	-	?	?	+	?
Regensteiner ¹⁰	?	?	-	?	+	+	+
Sanderson ²⁸	+	+	-	?	+	+	+
Savage ³⁹	?	?	-	?	+	+	+
Schlager ²⁷	+	+	-	+	?	+	+
Schlager ⁵¹	+	?	-	+	+	+	+
Stewart ⁶	+	+	-	?	+	+	?
Treat-Jacobson ³⁸	?	?	-	-	+	+	+
Tsai ⁴⁶	+	?	-	+	?	+	+
Wood ⁵⁰	+	?	-	?	?	+	?

APPENDIX II Overview of excluded studies after full-text review

Author and year	Journal	Reasons for exclusion
Degischer, 2002	Vasc Med. 2002;7(2):109-15	No RCT
Nielsen, 1977	Ugeskr Laeger. 1977;139(46):2733-6	Language
Arosio, 2001	Life Sci. 2001;69(4):421-33	Research with drug treatment
Collins, 2003	Med Sci Sports Exerc. 2003;35(3):384-93	Less than 50% walking
Gardner, 2002	J Cardiopulm Rehabil. 2002;22(3):192-8	Data already used in other publication
Gibellini, 2000	Int Angiol. 2000;19(1):8-13	Less than 6 weeks of training
Lepantalo, 1991	Clin Rehabil. 1991;5:65-9	No difference in supervision between groups
McDermott, 2004	J Cardiopulm Rehabil. 2004;24(3):187-96	Different patient population
Nawaz, 2001	J Vasc Surg. 2001;33(2):392-9	Only cycling
Taft, 2001	Eur J Vasc Endovasc Surg. 2001;22(2):114-23	No outcome measures on walking
Taft, 2004	Eur J Vasc Endovasc Surg. 2004;27(1):24-32	No outcome measures on walking
Tisi, 1997	Eur J Vasc Endovasc Surg. 1997;14(5):344-50	Less than 6 weeks training
Bronas, 2011	J Vasc Surg. 2011;53(6):1557-64	Data already used in other publication
Ciuffeti, 1994	Int Angiol. 1994 Mar;13(1):33-9	Research with drug treatment
Collins, 2005	J Cardiovasc Nurs. 2005;20(3):177-85	Data already used in other publication
Fahkry, 2011	Arch Phys Med Rehabil. 2011;92:1066-73	Data already used in other publication
Fowler, 2002	Aust J Physiother. 2002;48(4):269-75	No outcome measures on walking
Gardner, 2005	J Vasc Surg. 2005;42(4):702-9	No difference in supervision between groups
Greenhalgh, 2008	Eur J Vasc Endovasc Surg. 2008;36(6):680-8	No difference in supervision between groups
Grizzo, 2011	Vasa. 2011;40(5):390-7	No difference in supervision between groups
Krause, 1974	Munch Med Wochenschr. 1974;116(8):385-8.	Different research scope
Kruidenier, 2011	J Vasc Interv Radiol. 2011;22(7):961-8	Patients underwent invasive therapy
Leon, 2005	Clin J Sport Med. 2005;15:285-6	No outcome measures on walking
Manfredini, 2008	Circ J. 2008;72(6):946-52	No difference in supervision between groups
Meneses, 2011	J. Vasc. Nurs. 2011;29, 81-86	Different research scope
Murphy, 2012	Circ. 2012;125(1):130-9	Research with invasive therapy
Pinto, 1997	J Aging Phys Act. 1997;5:311	Data already used in other publication

>>

Ritti-Dias, 2010	J Vasc Surg. 2010;51(1):89-95	No difference in supervision between groups
Spronk, 2009	Radiol. 2009;250(2):586-95	Research with invasive therapy
Steiner, 2009	Eur Heart J. 2009;30(984):985	Data already used in other publication
Tebbutt, 2011	Phys Ther. 2011;97:244-249	Less than 50% walking
Tew, 2009	Clin Sci. 2009;117(12):405-13	Less than 50% walking
Van Asselt, 2011	Eur J Vasc Endovasc Surg. 2011; 41, 97-103	No outcome measures on walking
Walker, 2000	J Vasc Surg. 2000;31(4):662-9	Less than 50% walking
Wood, 2006	Clin Sci. 2006;111(6):401-9	No outcome measures on walking
Zwierska, 2005	J Vasc Surg. 2005;42(6):1122-30	Less than 50% walking
Mazari, 2012	Br J Surg. 2012;99(1):39-48	Research with invasive therapy
Mohler, 2011	Vasc Med. 2011;16(5):346-53	No exercise intervention
Cousin, 2011	Ann Phys Rehabil Med. 2011;54(7):429-42	No RCT
Duscha, 2011	Arterioscler Thromb Vasc Biol. 2011;31(11):2742-8	No outcome measures on walking
Szymańska, 2011	Ortop Traumatol Rehabil. 2011;13(3):279-92	No difference in supervision between groups
Malagoni, 2011	Circ J. 2011;75(9):2128-34	No outcome measures on walking
Villemur, 2011	Ann Phys Rehabil Med. 2011;54(5):275-81	Language
Nordanstig, 2011	Eur J Vasc Endovasc Surg. 2011;42(2):220-7	Research with invasive therapy
Vitale, 2011	Pharmacol Res. 2011;63(4):278-83	Different research scope
Franz, 2010	Vascular. 2010;18(6):325-35	No RCT
Hiatt, 2011	J Cardiopulm Rehabil Prev. 2011;31(2):125-32	Research with drug treatment
Allen, 2010	Free Radic Biol Med. 2010;49(6):1138-44	Different research scope
Casto-Sanchez, 2010	Med Clin (Barc). 2010;134(3):107-10	Language
Martinez, 2009	J Vasc Nurs. 2009;27(1):2-7	Different research scope
Andreozzi, 2008	Int Angiol. 2008;27(5):401-7	No RCT
Spronk, 2008	J Vasc Surg. 2008;48(6):1472-80	Data already used in other publication
Carlön, 2008	Monaldi Arch Chest Dis. 2008;70(2):76-83	Language
Gardner, 2008	J Cardiopulm Rehabil Prev. 2008;28(4):258-65	Research with drug treatment
Saxton, 2008	Eur J Vasc Endovasc Surg. 2008;35(5):607-13	No outcome measures on walking
Wang 2007	Clin Rehabil. 2007;21(7):579-86	Research with drug treatment

Nyłaende, 2007	Vasc Med. 2007;12(4):275-83	Research with invasive therapy
Bendermacher, 2007	J Vasc Surg. 2007;45(6):1192-6	No RCT
Andreozzi, 2007	Int Angiol. 2007;26(1):12-7	No outcome measures on walking
Slørdahl, 2005	Scand Cardiovasc J. 2005;39(4):244-9	No difference in supervision between groups
McGuigan, 2001	J Gerontol A Biol Sci Med Sci. 2001;56(7):B302-10	No difference in supervision between groups
Cachovan, 2001	Angiology. 2001;52(6):381-91	Research with drug treatment
Belcaro, 2000	Angiology. 2000;51(8 Pt 2):S15-26	Research with drug treatment
Ubel, 1999	Diabetes Care. 1999;22(2):198-201	Different patient population
Perkins, 1996	Eur J Vasc Endovasc Surg. 1996;11(4):409-13	Different patient population
Regensteiner, 1996	J Vasc Surg. 1996;23(1):104-15	Data already used in other publication
Hiatt, 1996	J Appl Physiol. 1996;81(2):780-8	No outcome measures on walking
Streminski, 1992	Vasa. 1992;21(4):392-402	Language
Scheffler, 1991	Vasa Suppl. 1991;33:350-2	Language
Lundgren, 1989	Clin Sci (Lond). 1989;77(5):485-93	No outcome measures on walking
Mannario, 1989	Angiology. 1989;40(1):5-10	No outcome measures on walking
Diehm, 1989	Vasa Suppl. 1989;28:26-30	No data on effect of exercise intervention
Kiesewetter, 1987	Dtsch Med Wochenschr. 1987;112(22):873-8	Language
Lepantalo, 1984	Scand J Rehabil Med. 1984;16(4):159-62	Data already used in other publication
White, 1984	JAMA. 1983 Jun 24;249(24):3355-6	No actual research data
Sandri, 2005	Circ. 2005;111:3391-9	Less than 6 weeks training
Gelin, 2001	Eur J Vasc Endovasc Surg. 2001;22(2):107-13	Different follow up time
Crowther, 2008	Vasc Surg. 2008;47(2):303-9	Different follow up time

RCT = randomized controlled trial.

CHAPTER 3

Safety of supervised exercise therapy in patients with intermittent claudication

L.N.M. Gommans
H.J.P. Fokkenrood
H.C.W. van Dalen
M.R.M. Scheltinga
J.A.W. Teijink
R.J.G. Peters

ABSTRACT

Background: Supervised exercise therapy (SET) is recommended as primary treatment for patients with intermittent claudication (IC). However, there is concern regarding the safety of SET, as IC patients are at risk for untoward cardiovascular events. The Dutch physical therapy guideline advocates cardiac exercise testing prior to SET if indicated. Perceived uncertainties concerning safety may contribute to the underutilization of SET in daily practice. The objective of this review is to analyze the safety of supervised exercise training in patients with IC.

Methods: Two authors independently studied clinical trials investigating SET. Data was obtained from Medline, EMBASE and CENTRAL libraries. Complication rates were calculated and expressed as number of events per number of patient-hours. A subanalysis was executed to evaluate the usefulness of cardiac screening prior to SET.

Results: Our search strategy revealed 2,703 abstracts. A total of 121 articles was selected of which 74 met inclusion criteria. Studies represent 82,725 hours of training in 2,876 IC patients. Eight adverse events were reported, six of cardiac and two of non-cardiac origin, resulting in an all-cause complication rate of 1 per 10,340 patient-hours.

Conclusion: SET can safely be prescribed in patients with IC as an exceedingly low all-cause complication rate was found. Routine cardiac screening prior to commencing SET is not required. Our results may diminish perceived uncertainties regarding safety and will possibly increase the use of SET in daily practice.

INTRODUCTION

Some 50 to 80% of patients with peripheral arterial disease (PAD) are symptomatic and suffer from intermittent claudication (IC).¹ IC is defined as muscle discomfort in the lower limb(s) elicited by exercise that resolves following a short period of rest.¹ IC is associated with significant disability, reduced quality of life²⁻³ and an increased risk of death.⁴ A recent study found a significant difference in survival when patients with and without PAD were compared. For instance, the all-cause and cardiovascular mortality rates were 24% and 7.7% in PAD patients versus 9.5% and 2.4% in patients without, respectively.⁵

The unfavorable prognosis associated with PAD is dominated by the concomitant presence of cerebral and coronary artery disease (CAD) due to generally accepted risk factors (smoking, hypertension, diabetes mellitus, hyperlipidemia).⁶⁻⁸ The estimated overall prevalence of atherosclerotic CAD in PAD is 72%, with an obstructive nature in 61 to 98% in certain subgroups.^{9, 10} The Quebec Cardiovascular Study reported that the risk on fatal and nonfatal cardiovascular events in men with IC was twice as high compared to men without known cardiovascular disease (CVD).¹¹

International guidelines state that treatment of IC should consist of a multimodal approach including cardiovascular risk reduction in combination with symptomatic treatment.^{1, 7} First choice symptomatic treatment, demonstrated by level I evidence, is daily exercise with supervision (i.e. supervised exercise therapy: SET).¹²⁻¹⁷ Apart from symptomatic improvement, a 12-week SET program also reduced overall cardiovascular mortality and morbidity by 52% and 30%, respectively.¹⁸ Although it is generally accepted that SET should be part of the initial treatment for each patient with IC, this therapeutic tool is seriously underused in clinical practice.¹⁹⁻²¹ A study among surgeons in the United Kingdom revealed that only 24% of IC patients had access to SET.²¹ Moreover, a large variation in the proportion of eligible patients referred to such an exercise program was found. Lack of knowledge on referral criteria was also observed in a recent nationwide survey among Dutch vascular surgeons. Approximately 70% of the interviewed surgeons were convinced that coexisting cardiopulmonary comorbidity and/or aortoiliac stenosis or occlusion were relative contra-indications for participation in a SET program.²⁰ These doubts are strengthened by a worry among physical therapists providing SET as they fear the onset of cardiovascular events that may possibly occur during exercise. Moreover,

physical therapists guidelines advocate cardiac screening prior to SET²², although evidence to support such a strategy is currently lacking. On the contrary, SET is often described as well tolerated whereas cardiovascular complications were rarely found in two studies.²³⁻²⁴ The aim of the present study is to analyze the safety of SET in patients suffering from IC in terms of onset of untoward (cardiovascular) events.

METHODS

Participants

We included studies that investigated the role of SET in patients diagnosed with IC (Fontaine II/Rutherford 1-3).

Types of studies

Eligible studies examined SET alone, or in a comparison model with other treatment modalities (e.g. endovascular treatment, vaso-active medication or non-supervised exercise therapy). Both randomized and non-randomized studies were included. Although treadmill walking is considered an important component of a SET program, uncertainty remains regarding the most effective content of such a program.²⁵ All types of SET programs were therefore included (e.g. pole-striding and strength training). The search was limited to studies in human and articles written in Dutch, German or English. No limitation to date of publication was considered.

Search strategy

We performed a search in MEDLINE (1966 to June 2013) using the following (MeSH) terms: 'peripheral arterial diseases', 'peripheral vascular diseases', 'intermittent claudication', 'peripheral arter* occlus*', 'claudica*', 'isch* limb*', 'exercise', 'exercise therapy', 'exercise movement techniques', 'walk*', 'runni*', 'exerc*', 'train*', 'treadmill'. Additional articles were found by matching a previous search of CENTRAL (1966 to September 2012) and EMBASE (1974 to June 2013) and removing duplicates. Additionally, we searched bibliographies of included articles. After screening titles and abstracts, two reviewers (LG and HF) independently selected articles, based on a full-text evaluation. Disagreement between reviewers was discussed and resolved by consensus.

Data extraction and management

The following data were extracted by two authors (LG and HF) using a standardized data extraction form: details of study population, country, research setting, number of participants, number of drop-outs/lost to follow up, reasons for drop-out, age, gender, in- and exclusion criteria, description of the supervised exercise protocol, frequency, duration, content, all types of reported complications related to SET and the use of cardiopulmonary exercise testing. In order to exclude the potential influence of medication, only results obtained from participants in the placebo control group of RCTs were included. If studies did not explicitly report possible occurrence of adverse events, we used information on the number of drop-outs and reasons for drop-out. Studies which contained drop-outs due to medical causes were excluded. An email was sent to authors reporting unclear data regarding SET related complications or reasons for drop-out, in order to obtain details on the occurrence of untoward events. Studies of authors who did not respond to this mail were also excluded.

Statistical analysis and data synthesis

Data were analyzed using SPSS for Windows 18.0 (SPSS Inc., Chicago, Illinois). The total number of patient-hours was calculated as the number of patients multiplied with number of training sessions corrected for mean duration of each session. When information on exact duration of training sessions was lacking, an approximation of 30 minutes was assumed. Adverse events were characterized as cardiac or non-cardiac, and as fatal or nonfatal. The role of cardiac screening was studied by performing a subanalysis. We calculated separated event rates based on the use of cardiopulmonary exercise testing (CPET) prior to SET.

RESULTS

Study selection

A total of 2,703 records was identified resulting in the study of 121 relevant articles. Overall, 74 studies (*appendix 1*) with a total number of 2,876 IC patients met inclusion criteria (*figure 1*). Patients represented 82,725 patient-hours of SET.

Figure 1. Flow chart of study selection

Study characteristics

The majority of SET studies were performed in Western Europe and North America. Mean age ranged from 54 to 76 years, whereas more males than females were participating (*table 1*). Frequently reported patient exclusion criteria were IC presenting with pain at rest or critical ischemia, exercise capacity limited by symptoms of angina, congestive heart failure, chronic obstructive pulmonary disease or arthritis and poorly controlled

hypertension. Exercise programs consisted of treadmill training (n=49), mixed exercise therapy (n=8), circuit training (n=11), strength training (n=2), arm ergometry (n=2) or pole-striding (n=2). Duration of the exercise programs ranged from 2 weeks to 12 months. Training frequencies varied from one to seven times a week, 30-120 minutes per day (*table 2*).

Table 1. Demographic characteristics (n=2,876)

	Mean (range)
Age, years	64 (54-76)
Men, %	71 (30-100)
Country ^a (n)	
Europe	44
Asia	2
North-America	18
South-America	4
Oceania	5
Africa	1

a = number of studies performed in listed continents

Main outcome measurement

Some 35 of the 74 studies explicitly reported on potential adverse events. Another 32 studies reported either no drop-outs or drop-outs without medical cause. The remaining 7 studies were included after positive e-mail conformation. Eight adverse events of cardiac (n=6) and non-cardiac (n=2) origin were reported (*table 3*). The total all-cause event rate was 1 per 10,340 patient-hours. Total cardiac and non-cardiac event rates were 1 per 13,788 and 1 per 41,363 patient-hours, respectively (*table 4*).

Table 2. Characteristics of included studies

Author and year of publication		Country	N	Mean age	% male	Supervised exercise program			Adverse events
						Duration (weeks)	Frequency ^a (per week)	Content (main component)	
Andreozzi	2008	Italy	74	65	91	6	3	Treadmill	None
Andreozzi	2007	Italy	22	67	100	6	3	Treadmill	None
Arosio	2001	Italy	12	65	NR	2	7	Treadmill	None
Badger	2007	Ireland	8	70	NR	6	2	Treadmill	None
Beckitt	2012	UK	27	68	98	12	2	Circuit training	None
Beckitt	2012	UK	42	66	69	12	2	Circuit training	None
Bendermacher	2007	Netherlands	93	64	63	24	2.5	Treadmill	None
Cachovan	1994	Germany	21	62	NR	4	5	Treadmill	None
Carlön	2008	Italy	41	NR	NR	12	3	Treadmill	None
Cheetham	2004	UK	30	65	NR	24	1	Circuit training	None
Ciuffeti	1994	Italy	15	56	>99	12	2	Mixed exercises	None
Collins	2005	USA	27	70	98	24	3	Pole striding	None
Collins	2012	USA	103	66	93	24	3	Treadmill/pole striding	None
Collins	2011	USA	72	66	75	24	1	Walking	None
Cousin	2011	France	31	56 ^b	97	4	5	Treadmill	None
Crowther	2008	USA	11	71	50	52	3	Treadmill	None
Degischer	2002	Switzerland	46	68	NR	12	1	Treadmill	None
Franz	2010	USA	101	72	46	12	3	Treadmill	None
Gardner	2005	USA	77	NR	88	24	3	Treadmill	None
Gardner	2011	USA	40	66	45	12	3	Treadmill	None
Gardner	2002	USA	31	68	NR	24	3	Treadmill	None
Gardner	2012	USA	106	67	86	24	3	Treadmill	None
Gibelline	2000	Italy	20	65	99	4	5	Treadmill	None
Greenhalgh	2008	UK	127	65	63	24	1	Treadmill	None
Grizzo Cucato	2011	Brazil	34	67	60	12	2	Circuit training	None

>>

Hiatt	1996	USA	29	61	NR	20	3	Treadmill	None
Hiatt	1990	USA	25	67	100	12	3	Treadmill	None
Hiatt	2011	USA	30	66	83	24	0.29	Treadmill	None
Hobbs	2007	UK	9	NR	78	12	2	Circuit training	None
Hodges	2008	UK	14	67	NR	12	2	Treadmill	None
Jones	2012	USA	30	69	60	12	3	Treadmill	None
Kakkos	2005	UK	12	61	92	6	3	Treadmill	None
Kiesewetter	1987	Germany	15	64	70	6	5	Treadmill	None
Krause	1978	Germany	63	66	77	6	5	Mixed exercise	None
Krause	1976	Germany	55	65	74	6	5	Mixed exercise	1 myocardial infarction
Kruidenier	2011	Netherlands	35	67	63	24	2.5	Treadmill	None
Lee	2007	UK	33	68	67	12	3	Circuit training	None
Leicht	2011	Australia	12	64	50	52	3	Treadmill	None
Lundgren	1989	Sweden	25	61	79	24	2	Mixed exercise	None
Mannarino	1991	Italy	10	63	67	24	2	Treadmill	None
Mannarino	1989	Italy	8	69	75	24	2	Treadmill	None
Martinez	2009	Israel	84	69	66	37	2	Treadmill	None
Mazari	2012	UK	60	69	62	12	3	Circuit training	None
McDermott	2009	USA	103	NR	52	24	3	Treadmill	1 cardiac arrest; 1 chest pain
McDermott	2004	USA	24	70	50	12	3	Treadmill	1 heart arrhythmias; 1 chest pain
McGuigan	2001	Australia	11	61	36	24	3	Circuit training	None
Mika	2011	Poland	34	64	90	12	3	Treadmill	None
Mika	2005	Poland	49	64	85	12	3	Treadmill	None
Murphy	2012	USA/Canada	43	69	49	26	3	Treadmill	None
Nawaz	2001	UK	52	69	83	6	2	Treadmill	None
Ng	2005	UK	16	NR	63	8	3	Walking	None
Nicolai	2010	Netherlands	202	62	67	52	2.5	Treadmill	None
Parr	2009	South-Africa	17	68	30	6	3	Strength training	None

>>

Patterson	1997	USA	27	NR	53	12	3	Mixed exercise	None
Perkins	1996	UK	26	65	NR	24	2	Mixed exercise	None
Regensteiner	1997	USA	10	NR	NR	12	3	Treadmill	None
Ritti Dias	2010	Brazil	34	62	67	12	2	Strength training	None
Sanderson	2006	Australia	28	66	39	6	3	Treadmill	None
Savage	2001	USA	11	68	68	12	3	Treadmill	None
Saxton	2011	UK	71	60	79	24	2	Treadmill	None
Scheffler	1994	Germany	15	69	70	4	5	Treadmill/ walking	None
Schlager	2011	Austria	20	66	65	24	2	Treadmill	None
Slørdahl	2005	Norway	18	66	NR	8	3	Treadmill	None
Spronk	2009	Netherlands	75	68	52	24	2	Treadmill	None
Stewart	2008	UK	30	62	67	12	2	Circuit training	None
Streminski	1992	Germany	30	69	67	4	5	Treadmill	1 increased heart rate/ dyspnea; 1 worsening arthritis; 1 ischialgia
Tew	2009	UK	27	69	NR	12	2	Arm ergo- metry	None
Tisi	1997	UK	22	67	69	4	1	Mixed exercise	None
Treat-Jacobson	2009	USA	37	76	33	12	3	Treadmill/arm ergometry	None
Tsai	2002	Taiwan	27	68	81	12	3	Treadmill	None
Villemur	2011	France	11	72	NR	2	5	Treadmill	None
Wang	2007	Australia	22	54	100	12	3	Treadmill	None
Winterfeld	1983	Germany	17	64	NR	12	2	Circuit training	None
Wood	2006	Australia	7	65	72	6	3	Treadmill	None

NR = not reported, a= recalculated to frequency per week, b= median age

Table 3. Overview of adverse events occurred during SET (n=8)

	Number of events
Heart arrhythmias	1
Angina pectoris	2
Cardiac arrest ^a	1
Myocardial infarction ^b	1
Increased heart rate and dyspnea	1
Worsening of osteoarthritis ^c	1
Ischialgia ^c	1

a = successfully resuscitated, b = fatal outcome, c = no treatment needed

Table 4. Complication rates during SET

	Number of events	Complication rates ^a
All cause	8	1:10,340
Cardiac	6	1:13,788
Non-cardiac	2	1:41,363

a = expressed as 1 event per number of patient-training hours

Subanalysis on cardiac screening

Some 28 studies (26,790 patient-hours of SET; 32%) included cardiac screening before initiating SET, of which 23 studies used electrocardiography registration. Four of the eight adverse events were reported in these 28 studies. The remaining four, including a fatal myocardial infarction, were found in the 46 remaining studies not including cardiac screening (55,935 patient-hours of SET; 68%). Six studies reported results of 1,703 CPETs prior to SET inclusion. A total of 59 patients (3.5%) were excluded from SET participation based on abnormal CPET findings.

DISCUSSION

3 The aim of this review was to identify SET related complications in patients with IC as a means to determine its safety. To our knowledge, this is the first study addressing the safety issue of SET. Eight complications were described during more than 80,000 patient-hours of SET, resulting in an all-cause complication rate of 1 to 10,340 patient-hours. Therefore, the risk of complications during SET is considered exceedingly low. Focusing on major cardiac complications (n=2), an even lower event rate of 1 to 41,362 patient-hours was calculated. These results are in line with a prospective registry on complications during exercise for cardiac rehabilitation reporting an almost similar 1 per 49,565 patient-hours event rate.²⁶ Moreover, these rates may even be considered relatively high as events that were reported in studies from more than three decades ago were also included. Medical treatment has greatly improved the overall prognosis, potentially resulting in even lower current event rates.

Although cardiopulmonary exercise testing (CPET) has been used over 60 years for risk stratification in patients with heart diseases²⁷, this technique is no longer recommended as a screening tool for myocardial ischemia in people without known coronary artery disease (CAD) as suggested by a recent guideline of The National Institute for Health and Clinical Excellence (NICE).²⁸ Prediction of a future severe cardiac event during exercise is very difficult, if not impossible.²⁶ In the present review, one third of the studies (n=28; 32% of total patient-hours) included cardiac screening. But as an equal number of adverse events (n=4) was found in studies with or without cardiac screening, the results may indicate that cardiac screening in IC patients is indeed not useful. However, by the observational and retrospective design of our study firm conclusions cannot be drawn. Yet, given the very low complication rate, cardiac screening as a tool for a safe execution of SET seems clinically irrelevant.

There is also a downside using CPET as a screening technique. As all screening tests do, CPET also inherently carries a risk of false positive testing. For instance, a 15% false positive rate is observed in patients with chest pain²⁹, while in asymptomatic patients this percentage is even higher.³⁰ A false positive test will incorrectly and unnecessarily exclude IC patients from a first choice treatment.^{1,7} In addition, false positive tests may lead to unneeded (invasive) interventions (e.g. coronary angiography) with accompanied

morbidity, mortality and costs. On the other hand, the risk of false negative testing following CPET is also present as illustrated by one study.³¹ A cardiac arrest was reported during exercise although no obstructive coronary disease was found during prior testing. Cardiac screening may therefore create a false sense of safety. Moreover, CPET itself also harbors a risk of cardiac complications. About 1 to 5 complications per 10,000 tests were reported^{27, 32}, a percentage that clearly exceeds any risk caused by SET.

Some suggested that CPET is useful in detecting silent ischemia.³³ As the majority of patients with IC will experience myocardial ischemia as anginal pain during exertion, some 17-47% will be asymptomatic, i.e. silent ischemia type I.³⁴ Extensive research is executed in patients with diabetes mellitus, a condition associated with an even higher prevalence of silent ischemia.³⁵ A difference between silent and symptomatic CAD with respect to prognosis was never found.^{34, 36, 37} Although, patients with IC may potentially benefit from routine CAD screening through detection of silent ischemia. However, considering the high prevalence of silent ischemia and assuming that these patients were also present in our review, a larger number of incidents would have been expected. The value of CPET is therefore also questionable from this perspective.

Lastly, CPET is potentially useful as a tool allowing for training optimization. A recent review attempted to identify the most important exercise components resulting in an optimal training protocol for patients with IC. It was concluded that neither intensity nor duration or program content were independently associated with improvement of maximal or pain-free walking distance.²⁵ Therefore, selection of SET components based on CPET does not seem to be a useful strategy.

Our study has limitations associated with its retrospective methodology and the possibility of publication bias. Only 35 of 74 studies explicitly reported the possible occurrence of adverse events whereas a detailed description was sometimes lacking. It remains therefore uncertain whether all reported events were indeed related to SET and occurred during supervision. While other complications may have been missed. However, these are most likely minor events preventing the patient from stopping any activity. By our strategy of using information on drop-outs, the number of patient-hours was increased as was the chance on some extra uncertainty.

Included studies were very heterogenic in terms of content of the SET program, and an exact description of intensity was often lacking. Therefore it was not possible

to identify any potential association between intensity of SET and complication risk. Moreover, subgroup analyses were impossible due to the small number of adverse events. An additional disadvantage of the present study is the fact that the vast majority of participants were men. Consequently, safety of SET is not demonstrated in female IC patients, although gender differences regarding the response to SET were never reported.

3 A major methodological concern is the fact that patients with limited exercise capacity due to angina, heart failure, chronic obstructive pulmonary disease, arthritis, poorly controlled hypertension or recent myocardial infarction were excluded in some studies. Exclusion of these vulnerable cardiac patients may have resulted in an underestimation of the number of adverse events. Therefore, generalizing these results to IC patients with major comorbidities is hazardous. On the other hand, it must be appreciated that exercise training also reduces the all-cause mortality in patients with congestive heart failure by 11%.⁴¹ Others demonstrated in patients with stable coronary artery disease that a 12-month program of regular physical exercise resulted in superior event-free survival and exercise capacity compared to percutaneous coronary angioplasty (88% vs. 70%, $P=.023$).⁴² As a consequence, patients with (cardiac) comorbidity should not routinely be excluded from SET in daily practice. However, each patient obviously requires careful monitoring.

In conclusion, the present review demonstrates that SET can safely be prescribed in IC patients as (cardiovascular) complication rates associated with this type of therapy are extremely low. However, caution should be taken when applying these results on patients with major comorbidity.

REFERENCES

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg.* 2007 Jan;45 Suppl S:S5-67.
2. Spronk S, Bosch JL, Veen HF, den Hoed PT, Hunink MG. Intermittent claudication: functional capacity and quality of life after exercise training or percutaneous transluminal angioplasty--systematic review. *Radiology.* 2005 Jun;235(3):833-42.
3. Regensteiner JG, Hiatt WR, Coll JR, Criqui MH, Treat-Jacobson D, McDermott MM, et al. The impact of peripheral arterial disease on health-related quality of life in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) Program. *Vasc Med.* 2008 Feb;13(1):15-24.
4. Muluk SC, Muluk VS, Kelley ME, Whittle JC, Tierney JA, Webster MW, et al. Outcome events in patients with claudication: a 15-year study in 2777 patients. *J Vasc Surg.* 2001 Feb;33(2):251-7; discussion 7-8.
5. Diehm C, Allenberg JR, Pittrow D, Mahn M, Tepohl G, Haberl RL, et al. Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. *Circulation.* 2009 Nov 24;120(21):2053-61.
6. Rehring TF, Sandhoff BG, Stolcpart RS, Merenich JA, Hollis HW, Jr. Atherosclerotic risk factor control in patients with peripheral arterial disease. *J Vasc Surg.* 2005 May;41(5):816-22.
7. Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *J Am Coll Cardiol.* 2006 Mar 21;47(6):1239-312.

8. Tilloy E, Montaye M, Kee F, Bingham A, Arveiler D, Ruidavets JB, et al. Contribution of cardiovascular risk factors to coronary risk in patients with intermittent claudication in the PRIME Cohort Study of European men. *Atherosclerosis*. 2009 Oct;206(2):563-8.
9. Duran NE, Duran I, Gurel E, Gunduz S, Gol G, Biteker M, et al. Coronary artery disease in patients with peripheral artery disease. *Heart Lung*. 2010 Mar-Apr;39(2):116-20.
10. Sukhija R, Yalamanchili K, Aronow WS. Prevalence of left main coronary artery disease, of three- or four-vessel coronary artery disease, and of obstructive coronary artery disease in patients with and without peripheral arterial disease undergoing coronary angiography for suspected coronary artery disease. *Am J Cardiol*. 2003 Aug 1;92(3):304-5.
11. St-Pierre AC, Cantin B, Lamarche B, Auger D, Despres JP, Dagenais GR. Intermittent claudication: From its risk factors to its long-term prognosis in men. The Quebec Cardiovascular Study. *Can J Cardiol*. 2010 Jan;26(1):17-21.
12. Watson L, Ellis B, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2008(4):CD000990.
13. Leng GC, Fowler B, Ernst E. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2000(2):CD000990.
14. Wind J, Koelemay MJ. Exercise therapy and the additional effect of supervision on exercise therapy in patients with intermittent claudication. Systematic review of randomised controlled trials. *Eur J Vasc Endovasc Surg*. 2007 Jul;34(1):1-9.
15. Bendermacher BL, Willigendael EM, Teijink JA, Prins MH. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev*. 2006(2):CD005263.
16. Gardner AW, Parker DE, Montgomery PS, Scott KJ, Blevins SM. Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication: a randomized controlled trial. *Circulation*. 2011 Feb 8;123(5):491-8.
17. Fokkenrood HJ, Bendermacher BL, Lauret GJ, Willigendael EM, Prins MH, Teijink JA. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev*. 2013 Aug 23;8:CD005263.
18. Sakamoto S, Yokoyama N, Tamori Y, Akutsu K, Hashimoto H, Takeshita S. Patients with peripheral artery disease who complete 12-week supervised exercise training program show reduced cardiovascular mortality and morbidity. *Circ J*. 2009 Jan;73(1):167-73.

19. Makris GC, Lattimer CR, Lavidia A, Geroulakos G. Availability of supervised exercise programs and the role of structured home-based exercise in peripheral arterial disease. *Eur J Vasc Endovasc Surg.* 2012 Dec;44(6):569-75; discussion 76.
20. Lauret GJ, van Dalen HC, Hendriks HJ, van Sterkenburg SM, Koelemay MJ, Zeebregts CJ, et al. When is supervised exercise therapy considered useful in peripheral arterial occlusive disease? A nationwide survey among vascular surgeons. *Eur J Vasc Endovasc Surg.* 2012 Mar;43(3):308-12.
21. Shalhoub J, Hamish M, Davies AH. Supervised exercise for intermittent claudication - an under-utilised tool. *Ann R Coll Surg Engl.* 2009 Sep;91(6):473-6.
22. Jongert MWA, Hendriks HJM, van Hoek J, Klaasboer-Kogelman K, Robeer GG, Simens B, et al. [KNGF-Guideline Intermittent Claudication (author's transl)]. *Ned Tijdschr Fysiother.* 2003;113(6).
23. Frans FA, Bipat S, Reekers JA, Legemate DA, Koelemay MJ. Systematic review of exercise training or percutaneous transluminal angioplasty for intermittent claudication. *Br J Surg.* 2012 Jan;99(1):16-28.
24. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. *N Engl J Med.* 2002 Dec 12;347(24):1941-51.
25. Fakhry F, van de Luijngaarden KM, Bax L, den Hoed PT, Hunink MG, Rouwet EV, et al. Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg.* 2012 Oct;56(4):1132-42.
26. Pavy B, Iliou MC, Meurin P, Tabet JY, Corone S. Safety of exercise training for cardiac patients: results of the French registry of complications during cardiac rehabilitation. *Arch Intern Med.* 2006 Nov 27;166(21):2329-34.
27. Myers J, Arena R, Franklin B, Pina I, Kraus WE, McInnis K, et al. Recommendations for clinical exercise laboratories: a scientific statement from the american heart association. *Circulation.* 2009 Jun 23;119(24):3144-61.
28. Skinner JS, Smeeth L, Kendall JM, Adams PC, Timmis A. NICE guidance. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. *Heart.* 2010 Jun;96(12):974-8.
29. Faisal AW, Abid AR, Azhar M. Exercise Tolerance Test: a comparison between true positive and false positive test results. *J Ayub Med Coll Abbottabad.* 2007 Oct-Dec;19(4):71-4.

30. Megnien JL, Simon A. Exercise tolerance test for predicting coronary heart disease in asymptomatic individuals: A review. *Atherosclerosis*. 2009 Aug;205(2):579-83.
31. McDermott MM, Ades P, Guralnik JM, Dyer A, Ferrucci L, Liu K, et al. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial. *JAMA*. 2009 Jan 14;301(2):165-74.
32. Gibbons LW, Mitchell TL, Gonzalez V. The safety of exercise testing. *Prim Care*. 1994 Sep;21(3):611-29.
33. Ahmed AH, Shankar K, Eftekhari H, Munir M, Robertson J, Brewer A, et al. Silent myocardial ischemia: Current perspectives and future directions. *Exp Clin Cardiol*. 2007 Winter;12(4):189-96.
34. Zellweger MJ. Prognostic significance of silent coronary artery disease in type 2 diabetes. *Herz*. 2006 May;31(3):240-5.
35. Ditchburn CJ, Hall JA, de Belder M, Davies A, Kelly W, Bilous R. Silent myocardial ischaemia in patients with proved coronary artery disease: a comparison of diabetic and non-diabetic patients. *Postgrad Med J*. 2001 Jun;77(908):395-8.
36. Moskowitz RM, Chatterjee K, Parmley WW. Silent myocardial ischemia: an update. *Med Clin North Am*. 1988 Sep;72(5):1033-54.
37. Sayer JW, Timmis AD. Investigation of coronary artery disease in diabetes: is screening of asymptomatic patients necessary? *Heart*. 1997 Dec;78(6):525-6.
38. Messerli FH, Bangalore S, Yao SS, Steinberg JS. Cardioprotection with beta-blockers: myths, facts and Pascal's wager. *J Intern Med*. 2009 Sep;266(3):232-41.
39. Schweizer J, Kaulen R, Altmann E, Nierade A, Nanning T. [Are beta-blockers generally contraindicated in patients with peripheral arterial occlusive disease?]. *Z Kardiol*. 1996 Mar;85(3):193-7.
40. Paravastu SC, Mendonca DA, da Silva A. Beta blockers for peripheral arterial disease. *Eur J Vasc Endovasc Surg*. 2009 Jul;38(1):66-70.
41. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009 Apr 8;301(14):1439-50.
42. Hambrecht R, Walther C, Mobius-Winkler S, Gielen S, Linke A, Conradi K, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. *Circulation*. 2004 Mar 23;109(11):1371-8.

APPENDIX I Studies included in the review

- Andreozzi GM, Leone A, Martini R, Laudani R, Salimistraro G, Deinite G. Effectiveness and costs of a short-course supervised training program in claudicants: proposal for a shared protocol with aerobic working load. *Int Angiol.* 2008 Oct;27(5):401-7.
- Andreozzi GM, Leone A, Laudani R, Deinite G, Martini R. Acute impairment of the endothelial function by maximal treadmill exercise in patients with intermittent claudication, and its improvement after supervised physical training. *Int Angiol.* 2007 Mar;26(1):12-7.
- Arosio E, Minuz P, Prior M, Zuliani V, Gaino S, De Marchi S, et al. Vascular adhesion molecule-1 and markers of platelet function before and after a treatment with iloprost or a supervised physical exercise program in patients with peripheral arterial disease. *Life Sci.* 2001 Jun 15;69(4):421-33.
- Badger SA, Soong CV, O'Donnell ME, Boreham CA, McGuigan KE. Benefits of a supervised exercise program after lower limb bypass surgery. *Vasc Endovascular Surg.* 2007 Feb-Mar;41(1):27-32.
- Beckitt TA, Day J, Morgan M, Lamont PM. Skeletal muscle adaptation in response to supervised exercise training for intermittent claudication. *Eur J Vasc Endovasc Surg.* 2012 Sep;44(3):313-7.
- Beckitt TA, Day J, Morgan M, Lamont PM. Calf muscle oxygen saturation and the effects of supervised exercise training for intermittent claudication. *J Vasc Surg.* 2012 Aug;56(2):470-5.
- Bendermacher BL, Willigendael EM, Nicolai SP, Kruidenier LM, Welten RJ, Hendriks E, et al. Supervised exercise therapy for intermittent claudication in a community-based setting is as effective as clinic-based. *J Vasc Surg.* 2007 Jun;45(6):1192-6.
- Cachovan M, Scheffler P, Gruss J, Diehm C, Rogatti W. Efficacy of a standardized physical training programme in intermittent claudication [author's translation]. *Wien Klin Wochenschr.* 1994;106(16):3.
- Carlon R, Olivieri A, Benacchio L, Zanchetta M. [Short and medium term functional capacity after single cycle of controlled physical training in subjects with claudication]. *Monaldi Arch Chest Dis.* 2008 Jun;70(2):76-83.
- Cheetham DR, Burgess L, Ellis M, Williams A, Greenhalgh RM, Davies AH. Does supervised exercise offer adjuvant benefit over exercise advice alone for the treatment of intermittent claudication? A randomised trial. *Eur J Vasc Endovasc Surg.* 2004 Jan;27(1):17-23.

- Ciuffetti G, Paltriccia R, Lombardi R, Lupattelli G, Pasqualini L, Mannarino E. Treating peripheral arterial occlusive disease: pentoxifylline vs exercise. *Int Angiol.* 1994;13(1):6.
- Collins EG, Langbein WE, Orebaugh C, Bammert C, Hanson K, Reda D, et al. Cardiovascular training effect associated with polestriding exercise in patients with peripheral arterial disease. *J Cardiovasc Nurs.* 2005 May-Jun;20(3):177-85.
- Collins EG, O'Connell S, McBurney C, Jelinek C, Butler J, Reda D, et al. Comparison of walking with poles and traditional walking for peripheral arterial disease rehabilitation. *J Cardiopulm Rehabil Prev.* 2012 Jul-Aug;32(4):210-8.
- Collins TC, Lunos S, Carlson T, Henderson K, Lightbourne M, Nelson B, et al. Effects of a home-based walking intervention on mobility and quality of life in people with diabetes and peripheral arterial disease: a randomized controlled trial. *Diabetes Care.* 2011 Oct;34(10):2174-9.
- Cousin A, Popielarz S, Wieczorek V, Tiffreau V, Mounier-Vehier C, Thevenon A. Impact of a rehabilitation program on muscular strength and endurance in peripheral arterial occlusive disease patients. *Ann Phys Rehabil Med.* 2011 Oct;54(7):429-42.
- Crowther RG, Spinks WL, Leicht AS, Sangla K, Quigley F, Golledge J. Effects of a long-term exercise program on lower limb mobility, physiological responses, walking performance, and physical activity levels in patients with peripheral arterial disease. *J Vasc Surg.* 2008 Feb;47(2):303-9.
- Degischer S, Labs KH, Aschwanden M, Tschoepf M, Jaeger KA. Reproducibility of constant-load treadmill testing with various treadmill protocols and predictability of treadmill test results in patients with intermittent claudication. *J Vasc Surg.* 2002 Jul;36(1):83-8.
- Franz RW, Garwick T, Haldeman K. Initial results of a 12-week, institution-based, supervised exercise rehabilitation program for the management of peripheral arterial disease. *Vascular.* 2010 Nov-Dec;18(6):325-35.
- Gardner AW, Montgomery PS, Flinn WR, Katzel LI. The effect of exercise intensity on the response to exercise rehabilitation in patients with intermittent claudication. *J Vasc Surg.* 2005 Oct;42(4):702-9.
- Gardner AW, Parker DE, Montgomery PS, Scott KJ, Blevins SM. Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication: a randomized controlled trial. *Circulation.* 2011 Feb 8;123(5):491-8.

- Gardner AW, Katzel LI, Sorkin JD, Goldberg AP. Effects of long-term exercise rehabilitation on claudication distances in patients with peripheral arterial disease: a randomized controlled trial. *J Cardiopulm Rehabil.* 2002 May-Jun;22(3):192-8.
- Gardner AW, Montgomery PS, Parker DE. Optimal exercise program length for patients with claudication. *J Vasc Surg.* 2012 May;55(5):1346-54.
- Gibellini R, Fanello M, Bardile AF, Salerno M, Aloï T. Exercise training in intermittent claudication. *Int Angiol.* 2000 Mar;19(1):8-13.
- Greenhalgh RM, Belch JJ, Brown LC, Gaines PA, Gao L, Reise JA, et al. The adjuvant benefit of angioplasty in patients with mild to moderate intermittent claudication (MIMIC) managed by supervised exercise, smoking cessation advice and best medical therapy: results from two randomised trials for stenotic femoropopliteal and aortoiliac arterial disease. *Eur J Vasc Endovasc Surg.* 2008 Dec;36(6):680-8.
- Grizzo Cucato G, de Moraes Forjaz CL, Kanegusuku H, da Rocha Chehuen M, Riani Costa LA, Wolosker N, et al. Effects of walking and strength training on resting and exercise cardiovascular responses in patients with intermittent claudication. *Vasa.* 2011 Sep;40(5):390-7.
- Hiatt WR, Regensteiner JG, Wolfel EE, Carry MR, Brass EP. Effect of exercise training on skeletal muscle histology and metabolism in peripheral arterial disease. *J Appl Physiol.* 1996 Aug;81(2):780-8.
- Hiatt WR, Regensteiner JG, Hargarten ME, Wolfel EE, Brass EP. Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation.* 1990 Feb;81(2):602-9.
- Hiatt WR, Creager MA, Amato A, Brass EP. Effect of propionyl-L-carnitine on a background of monitored exercise in patients with claudication secondary to peripheral artery disease. *J Cardiopulm Rehabil Prev.* 2011 Mar-Apr;31(2):125-32.
- Hobbs SD, Marshall T, Fegan C, Adam DJ, Bradbury AW. The effect of supervised exercise and cilostazol on coagulation and fibrinolysis in intermittent claudication: a randomized controlled trial. *J Vasc Surg.* 2007 Jan;45(1):65-70; discussion.
- Hodges LD, Sandercock GR, Das SK, Brodie DA. Randomized controlled trial of supervised exercise to evaluate changes in cardiac function in patients with peripheral atherosclerotic disease. *Clin Physiol Funct Imaging.* 2008 Jan;28(1):32-7.

- Jones WS, Duscha BD, Robbins JL, Duggan NN, Regensteiner JG, Kraus WE, et al. Alteration in angiogenic and anti-angiogenic forms of vascular endothelial growth factor-A in skeletal muscle of patients with intermittent claudication following exercise training. *Vasc Med*. 2012 Apr;17(2):94-100.
- Kakkos SK, Geroulakos G, Nicolaides AN. Improvement of the walking ability in intermittent claudication due to superficial femoral artery occlusion with supervised exercise and pneumatic foot and calf compression: a randomised controlled trial. *Eur J Vasc Endovasc Surg*. 2005 Aug;30(2):164-75.
- Kiesewetter H, Blume J, Jung F, Gerhards M, Leipnitz G. [Walk training and drug therapy in peripheral arterial occlusive disease. A randomized, prospective, placebo-controlled double-blind study]. *Dtsch Med Wochenschr*. 1987 May 29;112(22):873-8.
- Krause D, Dittmar K. [Active therapeutic exercises in combination with vasoactive drug in intermittent claudication (author's transl)]. *MMW Munch Med Wochenschr*. 1978 Jan 20;120(2-3):69-72.
- Krause D, Dittmar K. [Combination of physiotherapeutic exercise therapy with bencyclane in intermittent claudication (author's transl)]. *MMW Munch Med Wochenschr*. 1976 Oct 1;118(40):1281-4.
- Kruidenier LM, Nicolai SP, Rouwet EV, Peters RJ, Prins MH, Teijink JA. Additional supervised exercise therapy after a percutaneous vascular intervention for peripheral arterial disease: a randomized clinical trial. *J Vasc Interv Radiol*. 2011 Jul;22(7):961-8.
- Lee HL, Mehta T, Ray B, Heng MS, McCollum PT, Chetter IC. A non-randomised controlled trial of the clinical and cost effectiveness of a Supervised Exercise Programme for claudication. *Eur J Vasc Endovasc Surg*. 2007 Feb;33(2):202-7.
- Leicht AS, Crowther RG, Golledge J. Influence of peripheral arterial disease and supervised walking on heart rate variability. *J Vasc Surg*. 2011 Nov;54(5):1352-9.
- Lundgren F, Dahllof AG, Lundholm K, Schersten T, Volkmann R. Intermittent claudication-surgical reconstruction or physical training? A prospective randomized trial of treatment efficiency. *Ann Surg*. 1989 Mar;209(3):346-55.
- Mannarino E, Pasqualini L, Innocente S, Scricciolo V, Rignanese A, Ciuffetti G. Physical training and antiplatelet treatment in stage II peripheral arterial occlusive disease: alone or combined? *Angiology*. 1991 Jul;42(7):513-21.

- Mannarino E, Pasqualini L, Menna M, Maragoni G, Orlandi U. Effects of physical training on peripheral vascular disease: a controlled study. *Angiology*. 1989 Jan;40(1):5-10.
- Martinez CA, Carmeli E, Barak S, Stopka CB. Changes in pain-free walking based on time in accommodating pain-free exercise therapy for peripheral arterial disease. *J Vasc Nurs*. 2009 Mar;27(1):2-7.
- Mazari FA, Khan JA, Carradice D, Samuel N, Abdul Rahman MN, Gulati S, et al. Randomized clinical trial of percutaneous transluminal angioplasty, supervised exercise and combined treatment for intermittent claudication due to femoropopliteal arterial disease. *Br J Surg*. 2012 Jan;99(1):39-48.
- McDermott MM, Ades P, Guralnik JM, Dyer A, Ferrucci L, Liu K, et al. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial. *JAMA*. 2009 Jan 14;301(2):165-74.
- McDermott MM, Tiukinhoy S, Greenland P, Liu K, Pearce WH, Guralnik JM, et al. A pilot exercise intervention to improve lower extremity functioning in peripheral arterial disease unaccompanied by intermittent claudication. *J Cardiopulm Rehabil*. 2004 May-Jun;24(3):187-96.
- McGuigan MR, Bronks R, Newton RU, Sharman MJ, Graham JC, Cody DV, et al. Resistance training in patients with peripheral arterial disease: effects on myosin isoforms, fiber type distribution, and capillary supply to skeletal muscle. *J Gerontol A Biol Sci Med Sci*. 2001 Jul;56(7):B302-10.
- Mika P, Wilk B, Mika A, Marchewka A, Nizankowski R. The effect of pain-free treadmill training on fibrinogen, haematocrit, and lipid profile in patients with claudication. *Eur J Cardiovasc Prev Rehabil*. 2011 Oct;18(5):754-60.
- Mika P, Spodaryk K, Cencora A, Unnithan VB, Mika A. Experimental model of pain-free treadmill training in patients with claudication. *Am J Phys Med Rehabil*. 2005 Oct;84(10):756-62.
- Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) study. *Circulation*. 2012 Jan 3;125(1):130-9.

- Nawaz S, Walker RD, Wilkinson CH, Saxton JM, Pockley AG, Wood RF. The inflammatory response to upper and lower limb exercise and the effects of exercise training in patients with claudication. *J Vasc Surg.* 2001 Feb;33(2):392-9.
- Ng PW, Hollingsworth SJ, Luery H, Kumana TJ, Chaloner EJ. Intermittent claudication: exercise-increased walking distance is not related to improved cardiopulmonary fitness. *Eur J Vasc Endovasc Surg.* 2005 Oct;30(4):391-4.
- Nicolai SP, Hendriks EJ, Prins MH, Teijink JA. Optimizing supervised exercise therapy for patients with intermittent claudication. *J Vasc Surg.* 2010 Nov;52(5):1226-33.
- Parr BM, Noakes TD, Derman EW. Peripheral arterial disease and intermittent claudication: efficacy of short-term upper body strength training, dynamic exercise training, and advice to exercise at home. *S Afr Med J.* 2009 Nov;99(11):800-4.
- Patterson RB, Pinto B, Marcus B, Colucci A, Braun T, Roberts M. Value of a supervised exercise program for the therapy of arterial claudication. *J Vasc Surg.* 1997 Feb;25(2):312-8; discussion 8-9.
- Perkins JM, Collin J, Creasy TS, Fletcher EW, Morris PJ. Exercise training versus angioplasty for stable claudication. Long and medium term results of a prospective, randomised trial. *Eur J Vasc Endovasc Surg.* 1996 May;11(4):409-13.
- Regensteiner JG, Meyer TJ, Krupski WC, Cranford LS, Hiatt WR. Hospital vs home-based exercise rehabilitation for patients with peripheral arterial occlusive disease. *Angiology.* 1997 Apr;48(4):291-300.
- Ritti-Dias RM, Wolosker N, de Moraes Forjaz CL, Carvalho CR, Cucato GG, Leao PP, et al. Strength training increases walking tolerance in intermittent claudication patients: randomized trial. *J Vasc Surg.* 2010 Jan;51(1):89-95.
- Sanderson B, Askew C, Stewart I, Walker P, Gibbs H, Green S. Short-term effects of cycle and treadmill training on exercise tolerance in peripheral arterial disease. *J Vasc Surg.* 2006 Jul;44(1):119-27.
- Savage P, Ricci MA, Lynn M, Gardner A, Knight S, Brochu M, et al. Effects of home versus supervised exercise for patients with intermittent claudication. *J Cardiopulm Rehabil.* 2001 May-Jun;21(3):152-7.
- Saxton JM, Zwierska I, Blagojevic M, Choksy SA, Nawaz S, Pockley AG. Upper- versus lower-limb aerobic exercise training on health-related quality of life in patients with symptomatic peripheral arterial disease. *J Vasc Surg.* 2011 May;53(5):1265-73.

- Scheffler P, de la Hamette D, Gross J, Mueller H, Schieffer H. Intensive vascular training in stage IIb of peripheral arterial occlusive disease. The additive effects of intravenous prostaglandin E1 or intravenous pentoxifylline during training. *Circulation*. 1994 Aug;90(2):818-22.
- Schlager O, Giurgea A, Schuhfried O, Seidinger D, Hammer A, Groger M, et al. Exercise training increases endothelial progenitor cells and decreases asymmetric dimethylarginine in peripheral arterial disease: a randomized controlled trial. *Atherosclerosis*. 2011 Jul;217(1):240-8.
- Slordahl SA, Wang E, Hoff J, Kemi OJ, Amundsen BH, Helgerud J. Effective training for patients with intermittent claudication. *Scand Cardiovasc J*. 2005 Sep;39(4):244-9.
- Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Intermittent claudication: clinical effectiveness of endovascular revascularization versus supervised hospital-based exercise training--randomized controlled trial. *Radiology*. 2009 Feb;250(2):586-95.
- Stewart AH, Smith FC, Baird RN, Lamont PM. Local versus systemic mechanisms underlying supervised exercise training for intermittent claudication. *Vasc Endovascular Surg*. 2008 Aug-Sep;42(4):314-20.
- Streminski JA, de la Haye R, Rettig K, Kuntz G. [Comparison of the effectiveness of physical training with parenteral drug therapy in Fontaine stage IIb peripheral arterial occlusive disease]. *Vasa*. 1992;21(4):392-402.
- Tew G, Nawaz S, Zwierska I, Saxton JM. Limb-specific and cross-transfer effects of arm-crank exercise training in patients with symptomatic peripheral arterial disease. *Clin Sci (Lond)*. 2009 Dec;117(12):405-13.
- Tisi PV, Hulse M, Chulakadabba A, Gosling P, Shearman CP. Exercise training for intermittent claudication: does it adversely affect biochemical markers of the exercise-induced inflammatory response? *Eur J Vasc Endovasc Surg*. 1997 Nov;14(5):344-50.
- Treat-Jacobson D, Bronas UG, Leon AS. Efficacy of arm-ergometry versus treadmill exercise training to improve walking distance in patients with claudication. *Vasc Med*. 2009 Aug;14(3):203-13.
- Tsai JC, Chan P, Wang CH, Jeng C, Hsieh MH, Kao PF, et al. The effects of exercise training on walking function and perception of health status in elderly patients with peripheral arterial occlusive disease. *J Intern Med*. 2002 Nov;252(5):448-55.

- Villemur B, Marquer A, Gailledrat E, Benetreau C, Bucci B, Evra V, et al. New rehabilitation program for intermittent claudication: Interval training with active recovery: pilot study. *Ann Phys Rehabil Med*. 2011 Jul;54(5):275-81.
- Wang J, Zhou S, Bronks R, Graham J, Myers S. Supervised exercise training combined with ginkgo biloba treatment for patients with peripheral arterial disease. *Clin Rehabil*. 2007 Jul;21(7):579-86.
- Winterfeld HJ, Siewert H, Strangfeld D, Schmidt HH. [Experiences with the application of physiotherapy in peripheral arterial circulatory disorders of the lower extremities (stage I and IIa) under ambulatory conditions]. *Z Gesamte Inn Med*. 1983 Apr 1;38(7):221-5.
- Wood RE, Sanderson BE, Askew CD, Walker PJ, Green S, Stewart IB. Effect of training on the response of plasma vascular endothelial growth factor to exercise in patients with peripheral arterial disease. *Clin Sci (Lond)*. 2006 Dec;111(6):401-9.

CHAPTER 4

Gender differences following supervised exercise therapy in patients with intermittent claudication

L.N.M. Gommans
M.R.M. Scheltinga
M.R.H.M. van Sambeek
A.H.E.M. Maas
B.L.W. Bendermacher
J.A.W. Teijink

ABSTRACT

Background: Prevalence of peripheral arterial disease is equal in men and women. However, women seem to suffer more from the burden of disease. Current studies on gender-related outcomes following supervised exercise therapy (SET) for intermittent claudication (IC) yield conflicting results.

Methods: A follow-up analysis on data from the 2010 Exercise Therapy in Peripheral Arterial Disease (EXITPAD) study: a multicentre randomized controlled trial including IC patients following SET, was performed. The SET program was supervised by physiotherapists and included interval-based treadmill walking approximating maximal pain, combined with activities such as cycling and rowing. Patients usually started with three 30 minutes sessions a week. Training frequency was adapted during the following year on the basis of individual needs. Primary outcome was gender differences regarding the change in absolute claudication distance (ACD) following SET. ACD was defined as the number of meters that a patient had covered just before he/she was forced to stop walking because of intolerable pain. Secondary outcomes were gender differences in change of functional walking distance (FWD), quality of life and walking (dis)ability following SET. Walking distances were obtained by standardized treadmill testing according the Gardner-Skinner protocol. Quality of life was measured by the Short Form (36) Health Survey and walking (dis)ability was determined by the Walking Impairment Questionnaire (WIQ). Measurements were performed at baseline and after 3, 6, 9 and 12 months. Only patients who met the 12 months follow-up measure were included in the analysis.

Results: A total of 113 men and 56 women were available for analysis. At baseline, groups were similar in terms of clinical characteristics and ACD walking distances (men: 250 meters vs. women: 270 meters; $P=.45$). ACD improved for both sexes. However, ACD increase was significantly lower for women than for men, during the first 3 months of SET (men: Δ 280 meters vs. women: Δ 220 meters, $P=.04$). Moreover, absolute walking distance was significantly shorter for women compared to men after 1 year (565 meters vs. 660 meters, $P=.032$). Women also reported less on several WIQ subdomains, although total WIQ score was similar (men: 0.69 vs. women: 0.61; $P=.592$). No differences in quality of life after SET were observed.

Conclusion: Women with IC benefit less during the first 3 months of SET and have lower absolute walking distances after twelve months of follow-up compared to men. More research is needed to determine whether gender-based IC treatment strategies are required.

INTRODUCTION

Peripheral arterial disease (PAD) affects more than 12% of the aging population¹, and was initially thought to be more prevalent in men than in women.² However, recent population-based studies demonstrated an almost equal sex distribution (men: 13.4% vs. women: 15.6%).³ Interestingly, women may suffer more from the consequences of PAD. For instance, they were found to perceive a lower physical function, experience greater impact on hampered daily activities and mood state, and report greater bodily pain compared to men with PAD.⁴ Moreover, a faster functional decline with greater mobility loss⁵, poorer outcomes after lower extremity revascularisation procedures⁶ and a twofold higher mortality rate with symptomatic disease were found in PAD females compared to their male counterparts.⁷ Conversely, no gender-related differences were observed regarding self-reported community-based walking ability.⁴

Intermittent claudication (IC) is the most common manifestation of PAD. A growing number of reports consistently demonstrates beneficial effects of supervised exercise therapy (SET) on overall walking ability in patients with IC.^{8, 9} Most studies compared the efficacy of (various types of) SET to controls receiving pharmacological therapy or a revascularization procedure.^{8, 10-13} However, gender-specific outcomes following SET for patients with IC are seldom reported and results are conflicting.¹⁴⁻¹⁶ Two studies suggested that gender did not influence walking performance¹⁴ and that both sexes equally benefitted from SET.¹⁵ In contrast, a third study found that women responded less favourably to a program of exercise rehabilitation compared to men.¹⁶ No study addressed a possible gender-specific response to SET in terms of absolute walking distances or perceived walking (dis)ability. The paucity of data so far is likely due to a consistent female underrepresentation in randomized controlled trials. In a recent scientific statement, the American Heart Association released a 'call to action' for more research into gender-based differences of patients with PAD.¹⁷

The present study evaluated whether men and women with IC responded differently to SET with respect to walking distance, walking (dis)ability and quality of life. It was hypothesized that women have inferior outcomes after SET associated with an accelerated functional decline.⁵

METHODS

This study consists of a follow-up analysis of data that were generated by the 2010 Exercise Therapy in Peripheral Arterial Disease (EXITPAD) study. This multicentre randomized clinical trial, approved by the institutional review board of the Atrium medical center and at each of the participating sites, was undertaken to study the effect of either SET or a walking advice in IC patients. Methods and results in terms of walking distance and quality of life were previously published.¹⁸ The EXITPAD study included patients with Fontaine stage II PAD (e.g. IC), defined as having an ankle-brachial index (ABI) <0.9 who were considered for conservative therapy. Exclusion criteria were an absolute CI distance (ACD) >500 meters, prior exercise therapy or vascular interventions, insufficient command of the Dutch language, serious cardiopulmonary limitations (NYHA 3-4), leg amputation, psychiatric instability, and other serious comorbidities prohibiting physical exercise therapy.

In the EXITPAD study, all eligible patients standardly received cardiovascular risk management including cholesterol lowering medication and antiplatelet therapy. They were also counselled regarding management of additional atherosclerotic risk factors (e.g. smoking, body weight). Patients were randomized into three groups after written informed consent was obtained. A first group receiving a walking advice (WA, 'go home and walk'), a second group underwent SET 'with feedback' whereas the third group received SET 'without feedback'. Patients of the WA group were advised by a vascular surgeon to walk as often as possible. Patients of the two SET study groups were referred to regional physiotherapists (PT) who were previously selected and had undergone training to participate in the EXITPAD study. These PT's were educated according to the guideline on 'Intermittent Claudication' of the Royal Dutch Society for Physical Therapy and were asked to administer SET according to this guideline.¹⁹ Main goal of SET was to increase maximum walking distance. Additional goals were improvement of aerobic endurance, pain tolerance, gait pattern and specific activities (e.g. stair climbing). Lastly, information on lifestyle changes was provided by these PT's in order to stimulate healthy behaviour.²⁰ The training program predominately consisted of interval-based treadmill walking approximating (sub)maximal pain. An example of the training protocol is provided in table 1. Patients assigned to the SET 'with feedback' group received similar SET program

and also carried a Personal Activity Monitor (PAM) accelerometer (PAM B.V. Doorwerth, The Netherlands) to monitor physical activity during daily life.

Detailed therapy evaluation and documentation sheets determining frequency, duration, and content of the therapy were completed by the physiotherapists after 6, 12, 26 and 52 weeks of SET.

Table 1. Example of the SET trainings protocol for intermittent claudication

Frequency	Started at 3 times a week. Frequency is then adapted to the individual need, meaning that patients who perform well and comply with the exercise recommendations can phase down the therapy frequency sooner than other patients
Duration	20-40 minutes per training session
Intensity	40-70% of VO_2max or Borg RPE score 11-15
Content	Interval training: regimen included 2-5 minutes of walking (near to ACSM Claudication Pain Rating Scale score 2-3) and a subsequent 2-5 minutes of passive rest. Three to five cycles per training session. Aerobic endurance training
Activities	Primarily walking (on a treadmill, with slope of 2-8°) Combined with cycling, rowing, stepping and sports activities in general
Progression	Duration (i.e. amount of interval cycles) and intensity (i.e. duration of interval cycles) of training is increased as based on individual progression. In general, first intensification takes place when a patient is able to exercise for 20 minutes (e.g. 5 cycles of 4 minutes)
Home work	Moderate exercising for 30 minutes (in bouts of at least 10 minutes): 5 days per week
Evaluation	Continuous evaluation. Treadmill testing at least after 6 and 12 weeks
Termination	Program ends when patient is satisfied and the physiotherapist expects no further progression

VO_2max = maximal oxygen consumption. Reflects the aerobic physical fitness; Borg RPE = Borg Ratings of Perceived Exertions. Score ranges from 6 to 20 (respectively: no exertion at all to maximal exertion); ACSM = American College of Sport Medicine. Claudication Pain scores range from 1 to 4 (respectively: minimal discomfort to unbearable pain).

Outcome measurements of present study

Since the EXITPAD trial found no additional improvement in patients receiving extra feedback¹⁸, it was allowed to combine data of both SET groups for the purpose of the present study. Data of patients receiving a WA were not used. Evaluation of data generated at baseline and after 3, 6, 9 and 12 months of SET was performed by a blinded observer (LG). Primary outcome was a gender difference in absolute claudication distance (ACD). Secondary outcomes were gender-differences regarding functional claudication distance (FCD) and scores obtained by the Walking Impairment Questionnaire (WIQ) and the Short Form (36) Health Survey (SF-36).

The ACD was defined as the number of meters that a patient had covered just before he/she was forced to stop walking because of intolerable pain. A FCD was defined as the number of meters that a patient had walked until it was subjectively decided to stop due to a certain level of pain.²¹ Both parameters are reliable tools to quantify walking distance in patients with IC.²¹ These distances were determined by a standardized graded treadmill test according to the Gardner-Skinner protocol, most reliable measure for walking ability.²²

The WIQ is a questionnaire that is validated for the Dutch language in patients with PAD.²³ The self-administered revised Dutch version was used in the present study.²³ A WIQ assesses impairment regarding three domains: walking distance, walking speed and stair climbing.²⁴ WIQ scores range from 0 to 1 and lower scores correspond with more severe walking disability. The total WIQ score is the mean of scores of these domains.

The SF-36 is a general, often used, questionnaire determining quality-of-life (QOL).²⁵ It contains eight subscales evaluating physical function and role, general health, social function, emotional role, mental health, vitality and pain. Scores were calculated using a common scoring algorithm.²⁶

Statistical analysis

Analysis was conducted according to the intention-to-treat principle and included data from patients who were randomized (for SET) and who completed the treadmill assessment for quantifying walking distance after 12 months of follow-up. Therefore, patients who terminated the SET program but who performed the treadmill assessment were also incorporated in the analysis. Categorical variables were presented as percentages, and continuous variables as means $\pm$ standard deviations if normally distributed, or as medians with interquartile ranges (IQR) in case of a skewed distribution. Missing values of walking distances at 3, 6 and 9 months were imputed based on a multivariate linear regression analysis. Depending on the data's measuring level and distribution, Pearson's Chi-square, one-way analysis of variance (ANOVA), Kruskal-Wallis or Wilcoxon-Signed Rank Test were used to determine gender differences in baseline characteristics and both primary and secondary outcomes. Multivariate analysis were conducted to determine influence of potential confounders. A significance level of $P < .05$ was applied. Analyses were performed using SPSS 20.0 (SPSS Inc, Chicago, 11).

RESULTS

Study population

Between December 2005 and May 2008, the EXITPAD study enrolled 304 patients (WA group, n=102 patients; SET group, n=202). Follow-up ended in May 2009. Three patients eventually did not participate in the SET program leading to a total number of 199 patients receiving SET. As 26 were lost to follow up whereas four had died, 169 patients (men n=113, women n=56) were analysed in the present study (*figure 1*).

Males were not different compared to females in terms of age, BMI, ABI and comorbidities (*table 2*). A total of 30 men (26.5%) and 17 women (30.4%) discontinued the SET program at various time points during the 12 months follow-up period ($P=.692$). Insufficient motivation was a commonly reported reason (men: n=7, 23.2%; women: n=4, 23.5%. $P=.525$).

Figure 1. Flow chart of study population

Content of the SET program

Mean number of sessions per week (men: 1.8 to 0.8 vs. women: 1.7 to 0.7, $P=.61$) and total number did not differ between men and women (*table 3*). However, session duration during the first 12 weeks was significantly longer for men (men: 43 minutes vs. women: 37 minutes, Δ 6 minutes, $P=.03$). The amount of training on the treadmill training and program compliance ($>70\%$ compliance: men: 71% vs. women: 58%, $P=.17$) were similar for both groups.

Table 2. Baseline characteristics of study population (n=169)

Variables	Men (n=113)	Women (n=56)	P-values
Age (years) - mean (SD)	65 (9.2)	67 (9.7)	0.21
BMI (kg/m ²) - mean (SD)	28 (4.1)	27 (4.8)	0.59
ABI - mean (SD)	0.66 (0.19)	0.70 (0.14)	0.21
ACD - median (IQR)	250 (170-395)	270 (153-340)	0.45
Current smokers - %	53	60	0.35
Diabetes mellitus - %	21	23	0.79
Cardiac disease - %	27	14	0.07
CVA or TIA - %	15	14	0.88
COPD - %	20	18	0.78
LE orthopaedic disease - %	13	18	0.42

BMI = body mass index, CVA = cerebrovascular accident, TIA = transient ischemic attack, COPD = chronic obstructive pulmonary disease, LE = lower extremities. LE orthopaedic diseases included: osteoarthritis, rheumatoid arthritis, a total knee or hip prosthesis and other problems related to the bone or muscular tissue.

Walking distance before and after one year of SET

Prior to SET initiation, ACD and FCD were not different in men compared to women (ACD: men 250 meters vs. women 270 meters, $P=.451$; FCD: men 150 vs. women 140, $P=.332$). Following one year of SET, both groups demonstrated increased ACDs as well as FCDs (both $P<.05$). The largest increase in both ACD and FCD was observed during the first 3 months of SET (*table 4*). The improvement of ACD of this first interval was significantly greater for men (men: Δ 280 meters vs. women: Δ 220 meters; $P=.04$) (*figure 2A*). Furthermore, improved walking distances maximized at 9 months of follow-up and no further improvement was found later on, neither for men nor for women (*table 4*). Towards the end of a year of SET, FCD in women already started to decrease (*figure 2B*).

Furthermore, men revealed larger ACD and FCD at each of the 3-month intervals compared to women (*figure 2*). However, gender differences were only significant regarding absolute ACD at the 12 months follow-up point (men: ACD 660 meters vs. women: ACD 565 meters, $P=.032$) (*table 4, figure 2A*). Compared to ACD baseline values, men had increased by +264%, while for women a +209% increase was found at the 12 months follow-up point ($P=.042$).

Table 3. Content of and adherence to the supervised exercise program

	Men (n=113)				Women (n=56)			
	week 1-6 (n=97)	week 7-12 (n=88)	week 13-26 (n=88)	week 27-52 (n=82)	week 1-6 (n=52)	week 7-12 (n=49)	week 13-26 (n=46)	week 27-52 (n=39)
Participants ^a – %	86	78	78	73	93	88	82	70
Sessions per week – mean (sd)	1.8 (0.6)	1.6 (0.7)	1.1 (0.7)	0.8 (0.7)	1.7 (0.6)	1.4 (0.6)	0.9 (0.7)	0.7 (0.7)
P-value ^b	0.42	0.39	0.31	0.61				
Duration per session ^c – mean (sd)	41 (15)	43 (15)	40 (19)	37 (21)	35 (14)	37 (16)	37 (18)	35 (19)
P-value ^d	0.02	0.03	0.41	0.53				
Cumulative sessions ^e – mean (sd)	10.6 (3.7)	9.4 (4.5)	15.8 (10.4)	21.1 (18.6)	10.1 (3.4)	8.7 (3.9)	13.9 (9.7)	19.2 (17.5)
P-value ^f	0.43	0.39	0.31	0.61				
Training on treadmill ^g – mean (sd)	24 (11.5)	25 (11.4)	24 (13.5)	23 (14.6)	22 (11.4)	23 (12.5)	24 (10.9)	22 (13.4)
P-value ^h	0.49	0.62	0.85	0.49				
Individual training – %	79	75	79	82	85	80	83	77
P-value ⁱ	0.40	0.31	0.32	0.64				
Adequate compliance ^j – %	74	73	72	71	72	73	64	58
P-value ^k	0.48	0.96	0.40	0.17				

a = number of patients who completed SET program for given duration. SET program ended on initiative of the patient: when satisfied with the result or on initiative of the physiotherapist: when no further progression was expected. b,d,f,h = independent-samples T-test; c,g = duration in minutes; e = cumulative number of training session for given duration. i,k = Pearson Chi-square test; j = adequate compliance was defined as >70 % adherence to the training program.

At baseline and follow-up measures for men (n=113; dashed line) and women (n=56; solid line) separately. Error bars (grey for men; black for women) represent interquartile ranges. x = significant difference in change of walking distance from baseline to 3 months of follow-up; * = significant difference in absolute walking distance at 12 months of follow-up.

Figure 2. Median walking distances. A: Absolute claudication distance (ACD); B: Functional claudication distance (FCD).

Table 4. Walking distance and change in walking distance at baseline and during follow-up measures (meters; median and IQR)

	Men (n=113)	Women (n=56)	P-value
Baseline			
FCD	150 (100-250)	140 (83-225)	0.33
ACD	250 (170-395)	270 (153-340)	0.45
3 m follow-up			
FCD	390 (267-565)	365 (203-495)	0.13
Δ FCD ^a	220	130	0.07
ACD	535 (395-880)	460 (333-620)	0.06
Δ ACD ^a	280	220	0.04
6 m follow-up			
FCD	480 (283-670)	453 (253-658)	0.55
Δ FCD ^b	50	60	0.38
ACD	630 (398-1045)	560 (365-815)	0.32
Δ ACD ^b	60	70	0.76
9 m follow-up			
FCD	505 (350-807)	475 (290-625)	0.13
Δ FCD ^c	30	0	0.17
ACD	660 (490-1320)	575 (405-818)	0.05
Δ ACD ^c	50	14	0.12
12 m follow-up			
FCD	490 (315-770)	425 (255-638)	0.06
Δ FCD ^d	0	0	0.55
ACD	660 (450-1600)	565 (388-768)	0.03
Δ ACD ^d	0	0	0.51

m = months. a: change from baseline; b = change from 3 to 6 months; c = change from 6 to 9 months; d = change from 9 to 12 months. Significant differences are depicted in bold ($P < .05$).

Walking Impairment Questionnaire

At baseline, group scores were not different (*table 5*). After 12 months of SET, men and women demonstrated similar increased scores (men: $+0.19 \pm 0.22$ vs. women: $+0.21 \pm 0.2$, $P = .592$). However, 3, 6 and 12 months scores for walking speed, 3 months scores for stair climbing and 3 and 6 months total WIQ scores were significant lower in women (*table 5*).

Quality of life

Prior to SET, mental health as scored by the SF-36 was significantly lower in women compared to men (men: 78.3 vs. women: 71.9, $P=.031$). In contrast, all seven other domains were similar for both sexes prior to the therapy. Gender-related differences in change of QOL after 12 months of SET were not observed (*table 5*). Mental health at baseline did not contribute to the gender differences in ACD (multivariate analysis, $P=.795$).

Table 5. Walking Impairment Questionnaire (WIQ) in men and women (mean and (standard deviation))

	Men ^a					Women ^a				
	Baseline	3 m	6 m	9 m	12 m	Baseline	3 m	6 m	9 m	12 m
Distance	0.36 (0.29)	0.58 (0.29)	0.67 (0.29)	0.67 (0.30)	0.69 (0.29)	0.33 (0.24)	0.53 (0.34)	0.62 (0.35)	0.69 (0.33)	0.68 (0.30)
Speed	0.46 (0.24)	0.59 (0.24)	0.61 (0.23)	0.60 (0.25)	0.62 (0.25)	0.42 (0.21)	0.44 (0.23)	0.50 (0.26)	0.54 (0.23)	0.52 (0.24)
Stairs	0.63 (0.28)	0.76 (0.26)	0.80 (0.24)	0.76 (0.25)	0.78 (0.24)	0.57 (0.30)	0.64 (0.31)	0.71 (0.27)	0.74 (0.29)	0.72 (0.30)
Total score	0.48 (0.22)	0.63 (0.22)	0.69 (0.21)	0.66 (0.22)	0.69 (0.21)	0.44 (0.20)	0.52 (0.25)	0.60 (0.24)	0.66 (0.24)	0.61 (0.25)
Change in total score from baseline after FU					Change in total score from baseline after FU					
		0.14 (0.16)	0.17 (0.23)	0.16 (0.21)	0.19 (0.22)		0.12 (0.25)	0.17 (0.23)	0.21 (0.27)	0.21 (0.24)

M = months, FU= follow-up. a= significant differences ($P<.05$), depicted in bold. The WIQ scores range from 0 to 1. Lower scores correspond with more severe walking disability.

Table 6. Short Form 36 (SF-36) Health Survey in men and women (means and (standard deviation))

	Men ^a			Women ^a		
	Baseline	12 m FU	Change	Baseline	12 m FU	Change
Physical function	53.0 (15.9)	68.4 (18.7)	13.8 (21.7)	48.8 (15.7)	63.6 (19.5)	13.8 (19.7)
Physical role	48.4 (40.4)	64.8 (38.9)	15.0 (46.9)	41.0 (38.6)	58.7 (39.9)	18.9 (44.1)
General health	51.6 (12.0)	53.4 (12.3)	1.2 (12.8)	54.4 (12.7)	52.3 (11.9)	-2.0 (13.4)
Social function	78.3 (23.2)	82.5 (21.5)	4.3 (27.6)	76.1 (21.8)	83.4 (19.3)	8.3 (22.1)
Emotional role	88.4 (30.1)	87.1 (30.7)	-0.9 (40.6)	78.4 (37.8)	83.6 (34.3)	3.8 (15.8)
Mental health	78.3 (18.3)	77.1 (18.4)	-0.4 (17.5)	71.9 (16.5)	74.7 (19.7)	3.7 (15.8)
Vitality	63.3 (19.7)	63.0 (18.5)	0.40 (17.6)	58.8 (17.5)	59.7 (18.6)	1.7 (16.3)
Pain	53.8 (20.9)	71.6 (22.3)	17.8 (28.5)	56.4 (15.8)	67.0 (21.9)	11.0 (21.5)

a = significant differences ($P < .05$), depicted in bold. M = months. FU = follow-up. Follow-up at 3, 6 and 9 months not shown.

DISCUSSION

The aim of this study was to investigate whether outcomes of SET in patients with IC were gender-related. The scarce literature reports conflicting results. The present study is the first to address gender-based outcomes of SET in terms of subjective walking (dis)ability, quality of life and absolute walking distances. Our study showed that women benefit less from SET during the first 3 months of SET, in terms of change in absolute walking distance. Moreover, women's ACD was almost 15% less after one year compared to men's ACD (660 vs. 565 meters). Our findings support the results of recent studies reporting a less favourable response following SET in women, although both their follow-up included only three months.^{4, 16}

In general, SET is known to improve walking disability.¹⁸ Interestingly, previous research suggested lower baseline WIQ scores in women.²⁷ These baseline gender differences were not observed in the present study. Moreover, the magnitude of change in woman's total WIQ score after 12 months of SET also did not differ from men. A higher prevalence of comorbidities and advanced female age in previous research could explain

these opposing results, as these factors have influence on WIQ scores.²⁷ Furthermore, women had lower walking ability scores in various subdomains, most strikingly with regard to walking speed. Previous studies also reported that women with IC ambulate slower in a community setting.²⁸ Therefore, women should possibly be encouraged to train at a faster pace than preferred as also suggested in one other study.²⁸

Reduced quality of life (QOL) in an IC patient is a conflicting issue. Similar to our findings, Serracino-Inglot et al. also found no gender differences in QOL after SET.¹⁵ A significantly lower mental health in women at baseline was identified in our study, although these differences disappeared at later time points, possibly due to small sample sizes. This novel finding of poorer mental health in women with IC at baseline parallels with recent data suggesting depression as one of the strongest risk factors for PAD in women.²⁹ Poorer mental health parameters contribute to greater physical inactivity, which in turn induces insulin resistance and microvascular dysfunction³⁰ rendering women more susceptible to develop PAD.

There is evidence regarding microvascular gender differences in IC patients. Women have greater muscular ischemia during exercise than men. Due to lower hemoglobin oxygen saturation of the calf musculature³¹ and a more impaired microvascular function.³² These phenomena might explain a differential improvement of walking distance after SET between men and women as found in this study. This may also explain why only ACD and not FCD was significantly lower in our study as FCD is more closely reflecting the actual functional impairment²¹ rather than the patients' absolute capacity. However, differences between men and women regarding motivation, willingness to push through discomfort and pain tolerance, might play a role. In addition, lowered hemoglobin oxygen saturation during ambulation, next to poorer leg strength³³ in women possibly contribute to a restricted walking pace, and may explain differences in WIQ scores regarding the walking speed subdomain.

Other biochemical mechanisms might be involved in the gender issue too. Higher levels of oxidative stress, insulin resistance and inflammation are present in postmenopausal women compared to similar aged men and may contribute to lower claudication threshold levels.³¹ These findings are in line with gender-based functional differences in coronary artery disease.³⁴ Oxidative stress and inflammation affect women with diabetes mellitus (DM) more compared to men and result in a relatively greater impairment of the

peripheral microcirculation. As a consequence, women with IC and DM respond worse to SET compared to IC women without DM.¹⁶ Unfortunately, current diagnostic ABIs are not suitable to determine the degree of peripheral microvascular dysfunction³², and alternatives are not available yet. Our post-hoc analysis in this relatively small sample size (n=56) also found a similar association with DM in women but not in men (women; $P=.058$ vs. men; $P=.554$).

The knowledge gap and lack of research in gender-based differences in patients with PAD were recently highlighted by the American Heart Association.¹⁷ Women are under-represented in cardiac rehabilitation (CR) programs whereas success rates in terms of mortality reduction are higher than in men.³⁵ Reasons for diminished female participation in CR programs may also apply to PAD rehabilitation programs and may be related to women's older age, lower socio-economic status and restricted psychosocial wellbeing.³⁶ Interestingly, group-based intervention programs may be more effective in women as sharing of emotions and experiences tends to increase intrinsic motivation for exercise.³⁷

There is uncertainty on the optimal duration of SET resulting in maximally improved walking distances.³⁸ Previous research on optimal length of SET programs has found the greatest improvement in walking distance during the first two months of therapy³⁹, which is in accordance with our findings. Both groups of the present study received similar number of training sessions and were engaged in a similar amount of treadmill walking. However, duration in terms of minutes per sessions during the first 12 weeks was on average 6 minutes longer for men compared to women. The effect of duration per single session in couple of minutes has not been explored yet. However, it is quite unlikely that this small difference, though statistical significant, is the single factor explaining the difference in ACD after 3 or 12 months.

Smoking behaviour, BMI, comorbidities and baseline walking distances are potential confounders in the relationship between gender and walking distance. However, these factors were the same or equally distributed among both groups, allowing for a valid comparison. However, the present study may suffer from shortcomings. Gender-based analyses were not considered at the time of data collection, observer bias is therefore unlikely. Selection bias was absent as only patients participating in SET programs were analysed. The present study was a follow-up analysis of previously accumulated clinical trial data precluding a power calculation based on our main outcome. However, previous

power calculations for the EXITPAD trial revealed a sample size of 81 patients per group to demonstrate a difference of 150 meters.¹⁸ By combining both groups of SET (e.g. with and without feedback), we were able to meet this minimal number of patients for the male group (n=113) but not for females (n=56). Limited numbers of women may possibly explain the lack of significant differences regarding short term follow-up data. Restricted numbers of women in our study reflect current misperception on gender differences in PAD prevalence. Besides, it accents the general problem of under-representation of women in clinical trials,¹⁷ which is mainly due to current underdiagnoses of PAD in women caused by misleading clinical presentation and the contribution of alternative risk factors to cardiovascular diseases.⁴⁰ Last, we proposed several reasons to explain our results. However, motivation, pain tolerance and differential use of medications (i.e. statins or beta-blockers) were not assessed in this study and require further investigation.

CONCLUSION

Women with IC benefit less from SET during the first 3 months and have significant lower absolute walking distances after twelve months of follow-up. More research is needed to expand our understanding on gender-based differences in IC. This knowledge may be used to determine the necessity and/or requirement of gender-based exercise programs for patients with IC.

REFERENCES

1. Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *J Am Coll Cardiol* 2006;47:1239-312.
2. Higgins JP, Higgins JA. Epidemiology of peripheral arterial disease in women. *J Epidemiol* 2003;13:1-14.
3. Vavra AK, Kibbe MR. Women and peripheral arterial disease. *Womens Health (Lond Engl)* 2009;5:669-83.
4. Oka RK, Szuba A, Giacomini JC, Cooke JP. Gender differences in perception of PAD: a pilot study. *Vasc Med* 2003;8:89-94.
5. McDermott MM, Ferrucci L, Liu K, Guralnik JM, Tian L, Kibbe M, et al. Women with peripheral arterial disease experience faster functional decline than men with peripheral arterial disease. *J Am Coll Cardiol* 2011;57:707-14.
6. Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication: the Framingham Study. *J Am Geriatr Soc* 1985;33:13-8.
7. Nguyen LL, Hevelone N, Rogers SO, Bandyk DE, Clowes AW, Moneta GL, et al. Disparity in outcomes of surgical revascularization for limb salvage: race and gender are synergistic determinants of vein graft failure and limb loss. *Circulation* 2009;119:123-30.
8. Fokkenrood HJ, Bendermacher BL, Lauret GJ, Willigendael EM, Prins MH, Teijink JA. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev* 2013;8:CD005263.
9. Gommans LN, Saarloos R, Scheltinga MR, Houterman S, de Bie RA, Fokkenrood HJ, et al. Editor's choice--The effect of supervision on walking distance in patients with intermittent claudication: a meta-analysis. *Eur J Vasc Endovasc Surg* 2014;48:169-84.

10. Ahimastos AA, Pappas EP, Buttner PG, Walker PJ, Kingwell BA, Golledge J. A meta-analysis of the outcome of endovascular and noninvasive therapies in the treatment of intermittent claudication. *J Vasc Surg* 2011;54:1511-21.
11. Al-Jundi W, Madbak K, Beard JD, Nawaz S, Tew GA. Systematic Review of Home-based Exercise Programmes for Individuals with Intermittent Claudication. *Eur J Vasc Endovasc Surg* 2013.
12. Bendermacher BL, Willigendael EM, Nicolai SP, Kruidenier LM, Welten RJ, Hendriks E, et al. Supervised exercise therapy for intermittent claudication in a community-based setting is as effective as clinic-based. *J Vasc Surg* 2007;45:1192-6.
13. Beebe HG, Dawson DL, Cutler BS, Herd JA, Strandness DE, Jr., Bortey EB, et al. A new pharmacological treatment for intermittent claudication: results of a randomized, multicenter trial. *Arch Intern Med* 1999;159:2041-50.
14. Lundgren F, Dahllöf AG, Lundholm K, Schersten T, Volkmann R. Intermittent claudication-surgical reconstruction or physical training? A prospective randomized trial of treatment efficiency. *Ann Surg* 1989;209:346-55.
15. Serracino-Inglott F, Owen G, Carter A, Dix F, Smyth JV, Mohan IV. All patients benefit equally from a supervised exercise program for claudication. *Vasc Endovascular Surg* 2007;41:212-6.
16. Gardner AW, Parker DE, Montgomery PS, Blevins SM. Diabetic women are poor responders to exercise rehabilitation in the treatment of claudication. *J Vasc Surg* 2014;59:1036-43.
17. Hirsch AT, Allison MA, Gomes AS, Corriere MA, Duval S, Ershow AG, et al. A call to action: women and peripheral artery disease: a scientific statement from the American Heart Association. *Circulation* 2012;125:1449-72.
18. Nicolai SP, Teijink JA, Prins MH, Exercise Therapy in Peripheral Arterial Disease Study G. Multicenter randomized clinical trial of supervised exercise therapy with or without feedback versus walking advice for intermittent claudication. *J Vasc Surg* 2010;52:348-55.
19. Merry AH, Teijink JA, Jongert MW, Poelgeest A, van der Voort SS, Bartelink ME, et al. [KNGF-guideline Symptomatic peripheral arterial disease (author's translation)]. 2014.
20. Jongert MW, Hendriks HJ, van Hoek J, Klaasboer-Kogelman K, Robeer GG, Simens B. [KNGF-Guideline Intermittent Claudication (author's translation)]. *Ned Tijd Fysiother* 2003;113:3-50.
21. Kruidenier LM, Nicolai SP, Willigendael EM, de Bie RA, Prins MH, Teijink JA. Functional claudication distance: a reliable and valid measurement to assess functional limitation in patients with intermittent claudication. *BMC Cardiovasc Disord* 2009;9:9.

22. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007;45 Suppl S:S5-67.
23. Verspaget M, Nicolai SP, Kruidenier LM, Welten RJ, Prins MH, Teijink JA. Validation of the Dutch version of the Walking Impairment Questionnaire. *Eur J Vasc Endovasc Surg* 2009;37:56-61.
24. Nicolai SP, Kruidenier LM, Rouwet EV, Graffius K, Prins MH, Teijink JA. The walking impairment questionnaire: an effective tool to assess the effect of treatment in patients with intermittent claudication. *J Vasc Surg* 2009;50:89-94.
25. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055-68.
26. Ware JE, Jr., Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. *Med Care* 1995;33:AS264-79.
27. Lozano FS, Gonzalez-Porras JR, March JR, Carrasco E, Lobos JM. Differences between women and men with intermittent claudication: a cross-sectional study. *J Womens Health (Larchmt)* 2014;23:834-41.
28. Gardner AW, Parker DE, Montgomery PS, Khurana A, Ritti-Dias RM, Blevins SM. Gender differences in daily ambulatory activity patterns in patients with intermittent claudication. *J Vasc Surg* 2010;52:1204-10.
29. Grenon SM, Cohen BE, Smolderen K, Vittinghoff E, Whooley MA, Hiramoto J. Peripheral arterial disease, gender, and depression in the Heart and Soul Study. *J Vasc Surg* 2014;60:396-403.
30. Hamburg NM, McMackin CJ, Huang AL, Shenouda SM, Widlansky ME, Schulz E, et al. Physical inactivity rapidly induces insulin resistance and microvascular dysfunction in healthy volunteers. *Arterioscler Thromb Vasc Biol* 2007;27:2650-6.
31. Gardner AW, Parker DE, Montgomery PS, Blevins SM, Nael R, Afaq A. Sex differences in calf muscle hemoglobin oxygen saturation in patients with intermittent claudication. *J Vasc Surg* 2009;50:77-82.

32. Gardner AW, Montgomery PS, Blevins SM, Parker DE. Gender and ethnic differences in arterial compliance in patients with intermittent claudication. *J Vasc Surg* 2010;51:610-5.
33. McDermott MM, Greenland P, Liu K, Criqui MH, Guralnik JM, Celic L, et al. Sex differences in peripheral arterial disease: leg symptoms and physical functioning. *J Am Geriatr Soc* 2003;51:222-8.
34. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. *Eur Heart J* 2014;35:1101-11.
35. Colbert JD, Martin BJ, Haykowsky MJ, Hauer TL, Austford LD, Arena RA, et al. Cardiac rehabilitation referral, attendance and mortality in women. *Eur J Prev Cardiol* 2014.
36. Leifheit-Limson EC, Reid KJ, Kasl SV, Lin H, Jones PG, Buchanan DM, et al. The role of social support in health status and depressive symptoms after acute myocardial infarction: evidence for a stronger relationship among women. *Circ Cardiovasc Qual Outcomes* 2010;3:143-50.
37. Orth-Gomer K, Schneiderman N, Wang HX, Walldin C, Blom M, Jernberg T. Stress reduction prolongs life in women with coronary disease: the Stockholm Women's Intervention Trial for Coronary Heart Disease (SWITCHD). *Circ Cardiovasc Qual Outcomes* 2009;2:25-32.
38. Gardner AW, Montgomery PS, Parker DE. Optimal exercise program length for patients with claudication. *J Vasc Surg* 2012;55:1346-54.
39. Fakhry F, van de Luijngaarden KM, Bax L, den Hoed PT, Hunink MG, Rouwet EV, et al. Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg* 2012;56:1132-42.
40. Hiramoto JS, Katz R, Weisman S, Conte M. Gender-specific risk factors for peripheral artery disease in a voluntary screening population. *J Am Heart Assoc* 2014;3:e000651.

CHAPTER 5

Effect of diabetes on outcomes of supervised exercise therapy for intermittent claudication

D. Hageman
L.N.M. Gommans
J.A.W. Teijink

Submitted to J Vasc Surg.

ABSTRACT

Background: To summarize literature and to address the lack of evidence on the potential influence of diabetes mellitus (DM) on the response to supervised exercise therapy (SET) in patients with intermittent claudication (IC).

Methods: Studies were obtained from MEDLINE, EMBASE, and CENTRAL. Two authors independently assessed randomized and nonrandomized studies investigating the effect of DM on walking distance outcomes after SET in patients with IC. Eligible studies examined SET in diabetic and nondiabetic patients with IC. Studies were evaluated for methodological quality using the Cochrane Collaboration's tool for assessing risk of bias. Outcome measures were expressed in walking distance (meters), absolute increase (meters) and relative increase (percentage).

Results: The literature search identified 903 potentially relevant and unique articles. After screening of the titles and abstracts, and full-text evaluation, 3 articles were included. Methodological quality assessment revealed that all studies were having a low risk of bias. Of these three studies, all reported on maximal walking distance (MWD, n=845), two reported on pain-free walking distance (PFWD, n=87), and one reported on functional walking distance (FWD, n=758). Studies reported improvement in MWD, PFWD and FWD for both the diabetic and the nondiabetic group. One study reported a nearly significant effect of DM on MWD ($P=.056$). Another study demonstrated a difference in PFWD between diabetic and nondiabetic IC patients. On the contrary, the largest study of this review did not find any effect of DM on MWD and FWD after SET.

Conclusion: IC patients with DM demonstrate improvement on walking distance outcomes after SET. Conflicting results were reported when comparing diabetic and nondiabetic IC patients.

INTRODUCTION

Peripheral arterial disease (PAD) is a major manifestation of systemic atherosclerosis, characterized by obstruction or occlusion of the lower extremity arteries. PAD affects approximately 202 million individuals worldwide.¹ As the population ages, the prevalence of PAD is expected to increase.^{2, 3} Well-known risk factors for PAD include cigarette smoking, diabetes mellitus (DM), advanced age (≥ 40), hypertension, hyperlipidemia, and hyperhomocystenemia.^{4, 5} Cigarette smoking and DM in particular have a strong association with the development of PAD.⁶

The most common symptom of PAD is intermittent claudication (IC), which results from poor oxygenation of the muscles of the lower extremities and is typically experienced as pain, cramping or aching in the calves, thighs, or buttocks. Symptoms are induced by exercise (i.e. walking) and are relieved by rest.⁷ More extreme presentations of PAD include rest pain, tissue loss, or gangrene. These limb-threatening manifestations of PAD are collectively termed critical limb ischemia (CLI). It has been reported that of those with PAD, over one-half are asymptomatic or have atypical symptoms, about one-third have IC, and the remainder present with more severe symptoms.⁸

PAD comes with increased cardiovascular mortality rates due to the concomitant presence of coronary artery disease and/or cerebrovascular disease. Patients with PAD have a significantly higher risk of cardiovascular events (myocardial infarction, stroke).⁹ The precise prevalence of DM in patients with PAD is unclear. Data from the Framingham Heart Study revealed that 20% of symptomatic PAD patients had DM.¹⁰ In addition, it has been estimated that PAD is 2 to 4 times more prevalent in individuals with DM.^{11, 12} A study aimed to assess the risk of mortality for individuals with both DM and PAD compared to individuals with either conditions alone, showed that the adjusted risk of death when having both conditions was 2.2 times higher than when having only PAD, further indicating that DM is a strong risk factor for PAD-associated mortality.¹³

DM is known to affect nearly every vascular bed. The associated proatherogenic changes include increased vascular inflammation, derangements of cellular components of the vasculature, generalized endothelial cell dysfunction, as well as alterations in blood cells and hemostatic factors.¹⁴ Moreover, in diabetic patients atherosclerotic lesions are more likely to be diffuse and more distal, accounting for an atypical IC presentation.¹⁵

Patients with PAD and DM also experience worse lower-extremity function than those with PAD alone.¹⁶ Other studies have shown faster disease progression, high rates of foot ulcers, and more lower-limb amputations in patients with PAD and DM.^{17, 18}

Treatment of IC, irrespective of the presence of DM, should consist of two components. First, cardiovascular risk management (smoking cessation, antiplatelet therapy, statin therapy, glycemic control, hypertension and treatment of hyperlipidemia) to minimize the risk of future cardiovascular and cerebrovascular ischemic events, and second, symptomatic treatment of IC complaints. Recent international guidelines on the management of IC recommend supervised exercise therapy (SET) as the cornerstone therapy.¹⁹⁻²¹ It is known for more than a decade that the best results with exercise therapy are achieved under supervision.^{22, 23} In nearly all studies, unsupervised exercise regimens have shown lack of efficacy in improving functional capacity. Invasive revascularization procedures should be considered only when SET fails to achieve sufficient results.

Although the benefits of SET for IC have been documented, these findings have limited generalizability for patients with IC and DM. Characteristics specific to DM may influence the results of SET. However, in contemporary literature, information regarding the influence of DM on SET is limited. We conducted a review to summarize literature and to address the lack of evidence on the potential influence of DM on the response to SET in patients with IC. We hypothesized that SET may be less effective in IC patients with DM compared to those without DM.

METHODS

Participants

We included studies that investigated the effect of DM on walking distance outcomes after SET in patients with IC (Fontaine II/Rutherford 1-3).

Types of studies

Eligible studies examined SET in diabetic and nondiabetic patients with IC. Randomized and nonrandomized studies were included. Although treadmill walking is considered an important component of a SET program, uncertainty remains regarding the most

effective content of such a program.²⁴ Therefore, all types of SET programs were included. The search was limited to studies in humans and articles written in English or Dutch. No limitation to the date of publication was considered.

Search strategy

We performed a search in MEDLINE, EMBASE, and CENTRAL in July 2015, using the following Medical Subject Headings (MeSH), Emtree terms, and free terms: “peripheral arterial disease”, “peripheral occlusive artery disease”, “intermittent claudication”, “diabetes mellitus”, “diabetes mellitus, type 1”, “diabetes mellitus, type 2”, “diabetes”, “exercise”, “exercise therapy”, “walking”, “exercise movement techniques”, “physical therapy modalities”, “treadmill”, “treadmill exercise”, “kinesiotherapy”, “physiotherapy”, “supervised exercise therapy”, “home-based exercise therapy”, “walking advice”, and “exercise training”. We also hand-searched bibliographies of included articles. Two authors (D.H. and L.G.) independently screened titles and abstracts, and selected articles, based on full-text evaluation. Disagreement between reviewers was discussed and resolved by consensus. Studies were evaluated for methodological quality using the Cochrane Collaboration’s tool for assessing risk of bias.

Data extraction and management

Same authors used a standardized data extraction form to extract the following data: details of the study population: country, study design, number of participants, gender, age, diabetic status, and inclusion and exclusion criteria; description of the SET protocol: content, frequency, duration, intensity, and amount of supervision; and outcome measures: walking distance, walking time, walking speed and quality of life.

Data analysis

Data were analyzed using SPSS 19 software (IBM Corporation, Armonk, New York). Outcome measures were expressed in walking distance (meters), absolute increase (meters) and relative increase (percentage) for the different follow-up moments. If studies reported walking capacity in walking time (seconds), we converted the outcome to walking distance in meters using the information on the treadmill protocol. Also, if improvements in walking capacity were reported in increase in walking time (seconds), outcomes were converted to absolute increase in meters and relative increase in percentage.

RESULTS

Study selection

The literature search identified 903 potentially relevant and unique articles (*figure 1*). After screening of the titles, 841 articles were excluded. The abstracts of the remaining 62 articles were screened, resulting in the exclusion of another 58 articles. Full-text evaluation of the remaining 4 articles followed, which resulted in the exclusion of 1 article. Finally, 3 studies with a total of 845 patients with IC were included. Among them, 268 patients were diabetic and 577 patients were nondiabetic. Methodological quality assessment revealed that all studies were having a low risk of bias.

Figure 1. Flow diagram of study inclusion

Study characteristics

Of the included studies, two were performed in the USA and one was performed in the Netherlands (*table 1*). Among diabetic patients, the mean age ranged from 61 to 68 years, whereas for nondiabetic patients, the mean age ranged from 67 to 69 years. Overall, more men than women participated.

Interventions

All studies included a SET program, predominantly treadmill walking under supervision (*table 1*). The SET programs were designed to increase the patient's walking distance. This was mainly achieved by walking in intervals up to submaximal pain, followed by a short resting period. In one study, patients were randomized to either a home-based exercise therapy (HBET) program or a SET program.²⁵ The HBET program was designed to be as similar to the SET program as possible. In all studies, SET was performed at least three times per week for at least three months.

Outcome measures

To evaluate therapy progress, the maximum walking distance (MWD), pain-free walking distance (PFWD) and/or functional walking distance (FWD) were assessed at baseline and at least after three months of follow-up. The MWD was defined as the distance that a patient had covered before he/she was forced to stop walking because of intolerable claudication pain. The PFWD was defined as the distance that a patient had covered when he/she first experienced claudication pain. The FWD was defined as the distance that the patient had covered until he/she preferred to stop walking because of a certain level of claudication pain. To assess walking distances, all studies used the standardized Gardner maximal treadmill test protocol with a constant speed of 3.2 km/h (or 2 m/h) and an increasing slope of 2% every 2 minutes to a maximum slope of 10%.^{26, 27} The maximum test duration was 30 minutes.

Effect of DM on maximum walking distance (MWD)

All three studies included outcomes on MWD after SET, and all studies reported improvement in MWD for both the nondiabetic and the diabetic group (n=845).^{25, 28, 29} One study reported a tendency for greater improvement in the nondiabetic group

compared to the diabetic group.²⁵ In the study by Allen et al., following the completion of three months of SET, the non-DM group showed a mean increase in MWD of 52% (233 meter, $P < .01$), while the DM group increased by 29% (152 meter, $P < .01$).²⁸ No comparison between groups was provided. In the study by Gardner et al. patients were classified according to their diabetic status and then further separated by gender, leading to the formation of four study groups.²⁵ All groups demonstrated a significant improvement ($P < .05$) in MWD after three months of exercise therapy, except for diabetic women ($P > .05$). The mean MWD of the overall non-DM group increased with 57% (198 meter), compared to a 30% (87 meter) increase for the overall DM group. There was a trend for less improvement in diabetic IC patients ($P = .056$), as nondiabetic men and women had larger increases than their diabetic counterparts. Furthermore, in the study by Gardner et al. only 56% of diabetic women had an increase in MWD versus 78% of diabetic men. At baseline and at one, three and six months follow-up, Van Pul et al. found that the median MWD in patients with DM was significantly lower ($P < .001$) compared to patients without DM.²⁹ However, relative and absolute increase in median MWD were not significantly different between both groups. After three months, median MWD increased by 73% in the non-DM group (median increase of 300 meter), compared to 67% in the DM group (median increase of 200 meter, $P = .48$). At six months follow-up, median MWD increased with 100% in the non-DM group (median increase of 400 meter) compared to 91% in the DM group (median increase of 270 meter, $P = .48$).

Effect of DM on pain-free walking distance (PFWD)

Of the three included studies, two studies reported on PFWD outcomes ($n = 87$).^{25, 28} In the study by Allen et al. the non-DM group demonstrated a mean increase in PFWD of 59% (114 meter, $P < .05$), whereas there was no statistically significant increase in PFWD for the DM group (19%, 54 meter).²⁸ Again, no comparison between groups was provided. In the study by Gardner et al. all groups had significant improvement ($P < .05$) in mean and median PFWD after three months of exercise therapy, except for diabetic women ($P > .05$).²⁵ The mean PFWD of the overall non-DM group increased with 84% (148 meter) compared to 67% (117 meter) for the overall DM group ($P = .982$). In patients with DM, the increase in mean PFWD was 425% (196 meter) greater in men than in women ($P < .05$), whereas in those without DM, the increase in mean PFWD was only 35% (44

meter) greater in men ($P>.05$). Similar to the MWD results, the diabetic women had the lowest percentage of responders to exercise therapy. Only 37% of women with DM had an increase in PFWD versus 100% of men with DM ($P<.01$).

Effect of DM on functional walking distance (FWD)

Of the three included studies, one study reported on FWD outcomes ($n=758$).²⁹ Improvement in FWD after SET was found in both the nondiabetic group and the diabetic group. At baseline and at one, three and six months follow-up, Van Pul et al. found that the median FWD in patients with DM was significantly lower ($P<.001$) compared to patients without DM.²⁹ However, relative and absolute increase in median MWD were not significantly different between both groups. After three months of SET, median FWD increased by 100% in both groups, corresponding to a median increase of 200 meter in the non-DM group and a median increase of 180 meter in the DM group ($P=.72$). At six months follow-up, median FWD increased with 148% in the non-DM group (median increase of 332 meter), compared to 140% in the DM group (median increase of 280 meter, $P=.72$).

Table 1. Characteristics of included studies

Author	Year	Country	Design	N	Diabetic group			Nondiabetic group			Intervention	Outcomes
					N	Male (%)	Age (years)	N	Male (%)	Age (years)		
Allen ²⁸	2014	USA	CCS	27	13	46	66	14	71	69	Supervised intermittent treadmill walking, 30 to 40 min, 3 times per week, for 3 months	COT, PWT: 3 months follow-up
Gardner ²⁵	2014	USA	RCT/CCS ^a	60	25	36	61	35	54	69	HBET: intermittent walking, 20 to 45 min, 3 times per week, for 3 months SET: supervised intermittent treadmill walking, 15-40 min, 3 times per week, for 3 months	COT, PWT: 3 months follow-up
Van Pul ²⁹	2012	NL	CCS	758	230	67	68	528	61	67	Supervised intermittent treadmill walking, for 6 months: months 1-3, 2 to 3 times per week, 30 min; months 4-6, 0-2 times per week, 30 min; encouragement to walk on daily basis to submaximal pain	FCD, ACD: 1, 3, and 6 months follow-up

a = case control analysis of prospectively collected RCT data. CCS = case control study; RCT = randomized controlled trial; NL = the Netherlands; HBET = home-based exercise therapy; SET = supervised exercise therapy; COT = claudication onset time; PWT = peak walking time; FCD = functional claudication distance; ACD = absolute claudication distance.

DISCUSSION

The results of this review showed that IC patients with DM improve in maximal walking distance (MWD), pain-free walking distance (PFWD), and functional walking distance (FWD) after SET. However, conflicting results were found when comparing the effect of SET on walking distances between diabetic and nondiabetic IC patients. One study reported a nearly significant effect of DM on MWD.²⁵ Another study demonstrated a difference in PFWD between diabetic and nondiabetic IC patients.²⁸ On the contrary, the largest study of this review did not find any effect of DM on improvement in FWD and MWD after SET.²⁹ Consequently, still some controversy exists regarding the effect of DM on walking distance outcomes in patients with IC.

The results of this review are in contrast to the results of Ubels et al., who reported that IC patients with DM gained even more from exercise therapy than their counterparts without DM.³⁰ This study was intentionally excluded from the current review since patients did not receive a true SET program, but just a training schedule which was adapted every two months. Besides, Ubels et al. used a corridor-based test to assess walking distance, hardly comparable to the results obtained with a treadmill test.³¹ In a study by Collins et al., who included only diabetic IC patients, no improvement in MWD and PFWD after a six months HBET program was found.³² These findings add to current evidence that HBET programs may not be as efficacious as SET programs.³³

DM is associated with an impaired microvascular function in patients with IC. As a consequence, reduced capillary volume expansion of the calf musculature and a transient imbalance of muscle oxygen delivery relative to oxygen uptake during exercise have been found.^{34, 35} This suboptimal metabolic environment might contribute to a lower baseline walking capacity in diabetic IC patients and less improvement after SET, as found by some authors.^{28, 29}

In the study by Gardner et al., patients were classified according to their diabetic status and then further separated by gender, leading to the formation of four study groups.²⁵ Of these two factors, gender turned out to be more closely related to the exercise response than DM, as demonstrated by the significant gender effect for mean MWD and mean PFWD. However, a trend for a DM effect on the mean MWD was found. Of the four subgroups, only diabetic women did not significantly improve their MWD and PFWD after three months of exercise therapy. It has been increasingly recognized that female IC patients have greater baseline limitations of IC, less calf muscle hemoglobin oxygen saturation, and lower daily ambulatory activity.³⁶⁻³⁸ These mechanisms probably contribute to the less favorable response in women. However, the worse response to exercise therapy in women was only found in those with DM.²⁵ Thus, an effect of DM itself cannot be excluded yet.

SET in people with IC has been shown to be highly beneficial in terms of increasing walking distance and improving quality of life.^{23, 39} According to current international guidelines SET is considered to be the first choice therapy for all patients with IC.¹⁹⁻²¹ This is in contrast with a recent editorial that claimed that many IC patients may be unsuitable for SET, based on the presence of comorbidities and the possibly increased risks.⁴⁰ However, based on the results of this review, no arguments can be found to retain diabetic IC patients from SET.

Besides improvement on walking distance, exercise therapy may have some other benefits for IC patients with DM. Exercise has been found to reduce hyperglycemia, insulin resistance, dyslipidemia, and hypertension.⁴¹⁻⁴³ These benefits may lead to an improved vascular disease risk profile in these patients. Exercise may also aid in weight loss and may improve glycemic and lipemic control in people with DM.⁴⁴ Additionally, exercise improves physical function and quality of life in people with DM.^{45, 46}

This review has some limitations. First, just few studies examined the effect of DM on walking distance outcomes after SET in IC patients so far. Second, the studies of Allen et al. and Gardner et al. included just small sample sizes (n=27 and n=60, respectively) and may therefore be underpowered to demonstrate true differences in walking distance outcomes after SET between IC patients with and without DM.^{25, 28} Third, the patients of included studies were not evenly matched for gender. Since evidence exists that women with IC, particularly those with DM, represent a vulnerable subgroup of IC patients who respond poorly to an exercise program, bias might have been introduced.²⁵ Fourth, the study by Gardner et al. used two different exercise interventions.²⁵ Patients were randomized to either a HBET program or a SET program. Although the HBET program was designed to be as similar to the SET program as possible, patients did not receive supervision during exercise. Unfortunately, authors did not report which patients participated in what program, and results did not include subgroup analyses. The lack of supervision in the HBET group might have influenced the overall outcomes. Besides these limitations, studies examining the effect of DM on quality of life after SET, as well as reports on long term results (>6 months) of SET in diabetic patients are currently lacking.

In conclusion, IC patients with DM demonstrate improvement on walking distance outcomes after SET. Although conflicting results were reported when comparing diabetic and nondiabetic IC patients, no arguments can be found to retain diabetic IC patients from SET. Future studies are warranted to investigate the influence of DM on SET outcomes.

REFERENCES

1. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382(9901):1329-40.
2. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 2001;286(11):1317-24.
3. Levy PJ. Epidemiology and pathophysiology of peripheral arterial disease. *Clin Cornerstone*. 2002;4(5):1-15.
4. Criqui MH. Peripheral arterial disease--epidemiological aspects. *Vascular medicine (London, England)*. 2001;6(3 Suppl):3-7.
5. Gey DC, Lesho EP, Manngold J. Management of peripheral arterial disease. *Am Fam Physician*. 2004;69(3):525-32.
6. Cimminiello C. PAD. Epidemiology and pathophysiology. *Thromb Res*. 2002;106(6):V295-301.
7. Schainfeld RM. Management of peripheral arterial disease and intermittent claudication. *J Am Board Fam Pract*. 2001;14(6):443-50.
8. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med*. 2001;344(21):1608-21.
9. Kim CK, Schmalfuss CM, Schofield RS, Sheps DS. Pharmacological treatment of patients with peripheral arterial disease. *Drugs*. 2003;63(7):637-47.
10. Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from The Framingham Heart Study. *Circulation*. 1997;96(1):44-9.
11. Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication: the Framingham Study. *Journal of the American Geriatrics Society*. 1985;33(1):13-8.
12. Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Health Study (CHS) Collaborative Research Group. *Circulation*. 1993;88(3):837-45.
13. Leibson CL, Ransom JE, Olson W, Zimmerman BR, O'Fallon W M, Palumbo PJ. Peripheral arterial disease, diabetes, and mortality. *Diabetes Care*. 2004;27(12):2843-9.

14. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA*. 2002;287(19):2570-81.
15. Peripheral arterial disease in people with diabetes. *Diabetes Care*. 2003;26(12):3333-41.
16. Dolan NC, Liu K, Criqui MH, Greenland P, Guralnik JM, Chan C, et al. Peripheral artery disease, diabetes, and reduced lower extremity functioning. *Diabetes Care*. 2002;25(1):113-20.
17. Bird CE, Criqui MH, Fronck A, Denenberg JO, Klauber MR, Langer RD. Quantitative and qualitative progression of peripheral arterial disease by non-invasive testing. *Vascular medicine (London, England)*. 1999;4(1):15-21.
18. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. *Diabetes Care*. 2001;24(8):1433-7.
19. Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease (lower extremity, renal, mesenteric, and abdominal aortic): A collaborative report from the American Associations for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology. *Journal of Vascular and Interventional Radiology*. 2006;17(9):1383-98.
20. Layden J, Michaels J, Bermingham S, Higgins B. Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance. *BMJ (Clinical research ed)*. 2012;345:e4947.
21. Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JE, Mills JL, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *Journal of vascular surgery*. 2015;61(3 Suppl):2S-41S.
22. Bendermacher BL, Willigendael EM, Teijink JA, Prins MH. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *The Cochrane database of systematic reviews*. 2006(2):CD005263.
23. Fokkenrood HJ, Bendermacher BL, Lauret GJ, Willigendael EM, Prins MH, Teijink JA. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *The Cochrane database of systematic reviews*. 2013;8:CD005263.

24. Fakhry F, van de Luijngaarden KM, Bax L, den Hoed PT, Hunink MG, Rouwet EV, et al. Supervised walking therapy in patients with intermittent claudication. *Journal of vascular surgery*. 2012;56(4):1132-42.
25. Gardner AW, Parker DE, Montgomery PS, Blevins SM. Diabetic women are poor responders to exercise rehabilitation in the treatment of claudication. *Journal of vascular surgery*. 2014;59(4):1036-43.
26. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc*. 1991;23(4):402-8.
27. Nicolai SP, Viechtbauer W, Kruidenier LM, Candel MJ, Prins MH, Teijink JA. Reliability of treadmill testing in peripheral arterial disease: a meta-regression analysis. *Journal of vascular surgery*. 2009;50(2):322-9.
28. Allen JD, Stabler T, Kenjale AA, Ham KL, Robbins JL, Duscha BD, et al. Diabetes status differentiates endothelial function and plasma nitrite response to exercise stress in peripheral arterial disease following supervised training. *J Diabetes Complications*. 2014;28(2):219-25.
29. van Pul KM, Kruidenier LM, Nicolai SP, de Bie RA, Nieman FH, Prins MH, et al. Effect of supervised exercise therapy for intermittent claudication in patients with diabetes mellitus. *Ann Vasc Surg*. 2012;26(7):957-63.
30. Ubels FL, Links TP, Slutter WJ, Reitsma WD, Smit AJ. Walking training for intermittent claudication in diabetes. *Diabetes Care*. 1999;22(2):198-201.
31. Gardner AW, Katzel LI, Sorkin JD, Bradham DD, Hochberg MC, Flinn WR, et al. Exercise rehabilitation improves functional outcomes and peripheral circulation in patients with intermittent claudication: a randomized controlled trial. *Journal of the American Geriatrics Society*. 2001;49(6):755-62.
32. Collins TC, Lunos S, Carlson T, Henderson K, Lightbourne M, Nelson B, et al. Effects of a Home-Based Walking Intervention on Mobility and Quality of Life in People With Diabetes and Peripheral Arterial Disease: A randomized controlled trial. *Diabetes Care*. 2011;34(10):2174-9.
33. Savage P, Ricci MA, Lynn M, Gardner A, Knight S, Brochu M, et al. Effects of home versus supervised exercise for patients with intermittent claudication. *Journal of cardiopulmonary rehabilitation*. 2001;21(3):152-7.
34. Mohler ER, 3rd, Lech G, Supple GE, Wang H, Chance B. Impaired exercise-induced blood volume in type 2 diabetes with or without peripheral arterial disease measured by continuous-wave near-infrared spectroscopy. *Diabetes Care*. 2006;29(8):1856-9.

35. Bauer TA, Reusch JE, Levi M, Regensteiner JG. Skeletal muscle deoxygenation after the onset of moderate exercise suggests slowed microvascular blood flow kinetics in type 2 diabetes. *Diabetes Care*. 2007;30(11):2880-5.
36. Gardner AW. Sex differences in claudication pain in subjects with peripheral arterial disease. *Med Sci Sports Exerc*. 2002;34(11):1695-8.
37. Gardner AW, Parker DE, Montgomery PS, Blevins SM, Nael R, Afaq A. Sex differences in calf muscle hemoglobin oxygen saturation in patients with intermittent claudication. *Journal of vascular surgery*. 2009;50(1):77-82.
38. Gardner AW, Parker DE, Montgomery PS, Khurana A, Ritti-Dias RM, Blevins SM. Gender differences in daily ambulatory activity patterns in patients with intermittent claudication. *Journal of vascular surgery*. 2010;52(5):1204-10.
39. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, 3rd, Cohen DJ, Reynolds MR, et al. Supervised Exercise, Stent Revascularization, or Medical Therapy for Claudication Due to Aortoiliac Peripheral Artery Disease: The CLEVER Study. *Journal of the American College of Cardiology*. 2015;65(10):999-1009.
40. Popplewell MA, Bradbury AW. Why do health systems not fund supervised exercise programmes for intermittent claudication? *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery*. 2014;48(6):608-10.
41. Giannini C, de Giorgis T, Mohn A, Chiarelli F. Role of physical exercise in children and adolescents with diabetes mellitus. *J Pediatr Endocrinol Metab*. 2007;20(2):173-84.
42. O'Gorman DJ, Karlsson HK, McQuaid S, Yousif O, Rahman Y, Gasparro D, et al. Exercise training increases insulin-stimulated glucose disposal and GLUT4 (SLC2A4) protein content in patients with type 2 diabetes. *Diabetologia*. 2006;49(12):2983-92.
43. Sato Y, Nagasaki M, Kubota M, Uno T, Nakai N. Clinical aspects of physical exercise for diabetes/metabolic syndrome. *Diabetes Res Clin Pract*. 2007;77 Suppl 1:S87-91.
44. Ivy JL. Role of exercise training in the prevention and treatment of insulin resistance and non-insulin-dependent diabetes mellitus. *Sports Med*. 1997;24(5):321-36.
45. Bruce DG, Davis WA, Davis TM. Longitudinal predictors of reduced mobility and physical disability in patients with type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care*. 2005;28(10):2441-7.
46. Smith DW, McFall SL. The relationship of diet and exercise for weight control and the quality of life gap associated with diabetes. *J Psychosom Res*. 2005;59(6):385-92.

CHAPTER 6

The minimally important difference of absolute and functional claudication distance in patients with intermittent claudication

M.M.L. van den Houten

L.N.M. Gommans

P.J. van der Wees

J.A.W. Teijink

Accepted in Eur J Vasc Endovasc Surg.

ABSTRACT

Background: Disease severity and treatment outcomes in patients with intermittent claudication (IC) are commonly assessed using walking distance measured with a standardized treadmill test. It is unclear what improvement or deterioration in walking distance constitutes a meaningful, clinically relevant, change from the patients' perspective. The purpose of our study was to estimate the minimally important difference (MID) for the absolute claudication distance (ACD) and functional claudication distance (FCD) in patients with IC.

Methods: The MIDs were estimated using an anchor-based approach with a previously defined clinical anchor derived from scores of the walking impairment questionnaire (WIQ) in a similar IC population. We used baseline and three-month follow-up data on WIQ scores and walking distances (ACD and FCD) from 202 patients receiving supervised exercise therapy from the 2010 EXITPAD randomized controlled trial. The external WIQ anchor was used to form three distinct categories: patients with 'clinically relevant improvement', 'clinically relevant deterioration' and 'no clinically relevant change'. The MIDs for improvement and deterioration were defined by the upper and lower limits of the 95% confidence interval of the mean change in ACD and FCD, for the group of IC patients that remained unchanged according to the WIQ anchor.

Results: For the estimation of the MID of the ACD and FCD 102 and 101 patients were included, respectively. The MID for the ACD was 305m for improvement, and 147m for deterioration. The MID for the FCD was 250m for improvement, and 120m for deterioration.

Conclusion: The MIDs for the treadmill-measured ACD and FCD can be used to interpret the clinical relevance of changes in walking distances after supervised exercise therapy and may be used in both research and individual care.

INTRODUCTION

Intermittent claudication (IC) is the most common symptom of peripheral arterial disease (PAD). Atherosclerosis in the major vessels supplying the lower extremities causes muscle discomfort provoked by exercise in IC patients. Exertional limitations of walking ability lead to functional disability in daily life.¹ Treatment of IC aims at reducing symptoms and thereby improving walking capacity and health related quality of life (HRQoL).^{1,2} Disease severity and treatment outcomes are commonly assessed by walking distance with standardized treadmill tests, and patient-reported outcome measures reflecting HRQoL.^{1,3}

However, the clinical value of different outcome parameters in IC is currently under debate. Treadmill-measured walking distances have been disputed for being an inadequate reflection of walking capacity in daily life^{4,5}, and for failing to address actual physical activity limitations.⁶ Additionally, walking distances correlate moderately with HRQoL measures.⁵ Notwithstanding these concerns, changes in walking distance remain an important indicator of treatment effect in clinical decision-making.^{1,2} Moreover, it functions as primary end point in most trials assessing IC.^{1,3} Despite this important role, it is unclear what improvement or deterioration in walking performance constitutes a meaningful, clinically relevant, change from a patient's perspective.

The concept of the minimally important difference (MID) represents the smallest change on an outcome measure which patients value as important.⁷ It was first described by Jaeschke et al.⁸ in an attempt to elucidate what change in an asthma QoL questionnaire score would be meaningful. Recently, Conijn et al.⁹ introduced the MID for an IC population. In their study, the MID was calculated for the Walking Impairment Questionnaire (WIQ); a patient reported assessment of walking impairment. The MID can be used to estimate clinically relevant improvement and deterioration, thus giving meaning to outcome measures such as walking distance. Hiatt et al.¹⁰ postulated an established MID as a requirement for an optimal functional test in PAD. Determination of the MID of walking distance could facilitate clinicians and researchers in their interpretation of this widely used outcome measure.

The purpose of the present study was to estimate the MID for the absolute claudication distance (ACD) and functional claudication distance (FCD) in patients with IC.

METHODS

Study population

We used data from the 2010 'Exercise Therapy in Peripheral Arterial Disease' (EXITPAD) trial. The EXITPAD study was a multicenter, randomized controlled trial of supervised exercise therapy (SET) versus a verbal walking advice. Patients with Fontaine stage II peripheral arterial disease (PAD), an ankle brachial index (ABI) <0.9 and an ACD of <500 meters were included from eleven outpatient vascular surgery clinics in the Netherlands. Their respective institutional review boards approved the trial and all patients gave written informed consent. Details on methodology were previously published¹¹; below we will briefly describe aspects relevant to the current study.

In the present study, we used the baseline and three-month follow-up data on WIQ scores and walking distances from the 202 patients receiving SET in the former EXITPAD study. Patients were referred to a local physical therapist and received a SET programme according to recommendations in the guidelines of the Royal Dutch Society for Physical Therapy.¹² Prior to SET, all patients received cardiovascular risk management including cholesterol lowering medication, antiplatelet therapy, a 'stop smoking' advice and modification of other atherosclerotic present risk factors.

Walking distances

The ACD is defined as the walking distance where intolerable claudication pain forces a patient to stop. An alternative term for ACD is maximal walking distance. The FCD is defined as the distance at which the patient preferred to stop walking due to pain.¹³ Walking distances were determined by a standardized progressive treadmill test (i.e. Gardner-Skinner protocol) with a constant speed of 3.2 km/h starting with 0% inclination, increasing every 2 minutes by 2%.¹⁴ The maximum inclination was 10%, maximum duration of the test 30 minutes (1600 meters).¹¹

The walking impairment questionnaire

The WIQ is a patient-reported outcome measure designed to assess the functional capacity of IC patients. It asks patients to rate their perceived difficulty regarding walking speed, distance and stair climbing. The total WIQ score constitutes a value ranging from

0 to 1. Lower scores represent more impairment. The validated Dutch version of the WIQ was used.^{15, 16}

Determination of the MID

As per current recommendations we used an anchor-based approach, as opposed to a distribution-based approach, in estimating the MID, using longitudinal prospective data.¹⁷ An anchor is an external criterion for a meaningful change, and can be based on patient reported outcome measures that have demonstrated MID in the target population.¹⁸ We used a previously defined MID for the WIQ as an anchor. A study by Conijn et al.⁹ reported a MID of -0.03 for deterioration and 0.11 for improvement. Meaning a decrease in WIQ score of ≥ 0.03 is clinically relevant, as is an improvement of ≥ 0.11 . Based on this anchor the current study population was divided into three categories: patients with 'clinically relevant improvement', 'clinically relevant deterioration' and 'no clinically relevant change'. Analogous to Conijn et al.⁹ the MID for improvement was determined using the upper limit of the 95% confidence interval (CI) of the mean change in walking distance of patients who experienced 'no clinically relevant change' according to the WIQ-anchor. The MID for deterioration was defined by the lower limit of the 95% CI in this 'unchanged' category.

Statistical analysis

It is advised that the anchor (WIQ data) and the outcome measure (treadmill-based walking distances) are correlated at ≥ 0.3 to ensure that an appropriate association between the two variables exists.¹⁸ So, the Pearson correlation coefficient was calculated between the change in walking distance (between baseline and after 3 months of SET) and the anchor. Categorical variables were presented as numbers with percentages. Continuous variables were reported as means $\pm$ standard deviations if normally distributed, or as medians with interquartile ranges (IQR) in case of a skewed distribution. Our methodology required the calculation of 95% CIs in the 'no clinically relevant change' category. Thus, when changes in ACD or FCD for the 'unchanged' patients demonstrated a distribution that was not normal, these variables were assessed for outliers. One patient, who deviated approximately 4 standard deviations from the mean change in ACD, was excluded for this reason. Baseline characteristics were compared using a Pearson's Chi-

square test for categorical variables and a student's *t*-test for continuous variables. A statistical significance level of $P < .05$ was applied. All analyses were performed with SPSS version 22.0 (SPSS Inc, Chicago, Ill).

RESULTS

Out of a total of 202 patients, data on WIQ scores as well as ACD and FCD were available for 103 and 102 patients, respectively. After removal of the one outlier, estimation of the MID for the ACD was based on 102 patients, and for the FCD on 101 patients. Baseline characteristics of in- and excluded patients are reported in table 1. There were no statistically significant differences between baseline characteristics of patients included and excluded from analysis, except for chronic obstructive pulmonary disease (COPD) prevalence, baseline FCD values and follow-up WIQ scores. Based on the WIQ-anchor, 56.9% of the included patients had a clinically relevant improvement after 3 months of SET, 23.5% remained unchanged, and 19.6% of the patients deteriorated.

MID of the ACD

Three-month change in ACD was significantly correlated to the anchor (Pearson $r = 0.31$, $P = .001$), thus complying with the criterion of Revicki.¹⁸ Table 2 presents the distribution of the ACD over the three categories (i.e. improved, unchanged, deteriorated) defined by the WIQ-anchor. The MID for the ACD was 305m for improvement, and 147m for deterioration. The MID for deterioration is a positive value and implicates that a small numerical improvement in ACD (< 147 m) is still perceived as clinical deterioration by the patient.

MID of the FCD

Three-month change in FCD was significantly correlated to the anchor as well (Pearson $r = 0.30$, $P = .001$). Table 3 presents the distribution of the FCD over the three categories defined by the WIQ-anchor. The MID for the FCD was 250m for improvement, and 120m for deterioration. Thus, a numerical improvement in FCD of < 120 m is considered as a clinical deterioration by the patient. Figure 1 shows a visual representation of the MIDs for both the ACD and FCD.

Table 1. Baseline characteristics

Variable ^a	Included patients (n=102)	Excluded patients (n=99)	P-value ^b
Age, y	66.3 ±10	65.3 ±9.3 (n=98)	.471
Body mass index, kg/m ²	28.0 (5.3) (n=99)	27.0 (5.7) (n=93)	.374
Ankle brachial index	0.70 (0.23) (n=100)	0.66 (0.22) (n=95)	.229
Baseline WIQ score	0.46 ±0.21	0.44 ±0.22 (n=51)	.427
Follow-up WIQ score ^c	0.61 ±0.22	0.49 ±0.26 (n=27)	.016
Baseline ACD, m	280 (210)	249 (190) (n=97)	.176
Baseline FCD, m	164 (150)	130 (110) (n=97)	.006
Male sex	73 (71.6)	62 (62.2)	.177
Arterial hypertension	63 (61.8)	57 (57.6) (n=96)	.731
Diabetes mellitus	25 (24.5)	19 (19.2)	.362
Hyperlipidemia	69 (67.6) (n=101)	64 (64.6) (n=94)	.972
Orthopedic disease	15 (14.7)	17 (17.2) (n=95)	.544
Cerebrovascular disease	13 (12.7)	12 (12.1) (n=96)	.959
Cardiac disease	26 (25.5) (n=99)	22 (22.2) (n=95)	.616
COPD	27 (26.5)	9 (9.1) (n=96)	.002
Smoking			
Current	41 (40.2) (n=101)	40 (40.4) (n=94)	.781
Former	54 (52.9) (n=101)	43 (43.3) (n=94)	.501
Never	6 (5.9) (n=101)	11 (11.1) (n=94)	.154

Inclusion of patients was based on presence of both WIQ data (baseline and 3 months follow-up) and walking distance measures. ACD, absolute claudication distance; COPD, chronic obstructive pulmonary disease; FCD, functional claudication distance; IQR, interquartile range; SD, standard deviation; WIQ, walking impairment questionnaire; a = Normally distributed continuous values are presented as mean ±SD, and as median (IQR) in case of a skewed distribution. Categorical values are presented as number (percentages). b = By student's t-test for parametric continuous variables, by Mann-Whitney U test for non-parametric continuous variables, and by Pearson's Chi-square test for categorical variables. c = WIQ data after 3 months of SET.

Table 2. Distribution and MID of the ACD (meters) after 3 months of SET

ACD baseline (IQR)	Follow up	Median change	Correlation with anchor
280 (210)	507 (340)	210 (253)	0.31 ^a

Compared with anchor	Patients, n	Mean change ACD	
Improved	58	245 ^b	IQR: 456
Unchanged	24	226	95% CI: 147 to 305
Deteriorated	20	125	95% CI: 39 to 212

MID of the ACD	
Improvement	305
Deterioration	147

ACD = absolute claudication distance; CI = confidence interval; IQR = interquartile range; MID = minimally important difference; SET = supervised exercise therapy; a = Pearson correlation coefficient; b = value represents a median.

Table 3. Distribution and MID of the FCD (meters) after 3 months of SET

ACD baseline (IQR)	Follow up	Median change	Correlation with anchor
167 (145)	370 (315)	200 (240)	0.30 ^a

Compared with anchor	Patients, n	Mean change ACD	
Improved	58	200 ^b	IQR: 238
Unchanged	24	185	95% CI: 120 to 250
Deteriorated	19	107	95% CI: 37 to 178

MID of the ACD	
Improvement	250
Deterioration	120

FCD = functional claudication distance; CI = confidence interval; IQR = interquartile range; MID = minimally important difference; SET = supervised exercise therapy; a = Pearson correlation coefficient; b = value represents a median.

Threshold values at which the change in absolute claudication distance (ACD) and functional claudication distance (FCD) after three months of supervised exercise therapy (SET) is perceived as a clinically relevant improvement or deterioration by the patient.

Figure 1. The MID of walking distance

DISCUSSION

This study was the first to estimate MID for the ACD and FCD in patients with IC. Our results can facilitate clinicians and researchers in appointing what numerical changes in walking distance indicate a clinically meaningful change. Recently, Hiatt et al. underlined the importance of estimating MID for treadmill walking performance in the PAD population, as a change in performance on a test should be related to a patient's perception of his or her limitations.¹⁰ Currently, these MID are unknown for the IC population. Based on our estimations a change in ACD of more than 305m, and FCD of more than 250m, is viewed as meaningful by the patient. Interestingly, the MID for deterioration were positive values (ACD: 147m; FCD: 120m) as well. This indicates that small improvements in walking distance are apparently not satisfactory in the patients' eyes. This may not be surprising as SET demands a considerable investment of time and effort, therefore patients' expectations of treatment effect are not readily met. On the other hand, patients might also have unrealistic expectations, in general a 50% to 200%

improvement of ACD has been reported.¹⁹ Besides, as overground walking requires higher ground reaction forces and movement power as compared to treadmill walking²⁰, it may also be possible that an increase in treadmill-based walking distance of approximately 100 meters is insufficient to reveal any effect on walking distance in daily life. These findings might suggest that SET should not only be focused on treadmill walking, but should additionally include for instance outdoor walking and strength training.

MIDs are population specific¹⁸, and users should consider several factors before applying our MID values to their own patient population. There is a plethora of ways of measuring walking distance in IC. Notably, walking capacity can be determined using a treadmill test¹⁰, a corridor-based 6-minute walking test³, or by tracking outside walking via global positioning system (GPS) devices.^{21, 22} Walking distance values measured for the same patient with different tests generally do not correspond well.^{4,23} Likely, the MID values found in this study are only transferable to walking distances measured using a graded treadmill protocol.

Treadmill training has been criticized for being an artificial form of walking that does not necessarily translate to improved ambulatory function in daily life.²⁴ However, others found excellent agreement with values measured during outside walking, implying agreement with daily life impairment.²³ SET treatment largely takes place on a treadmill, thus another argument opposing treadmill tests is that a learning effect for treadmill walking cannot be ruled out. This may have influenced the reported MID values. Yet it does not hamper their use, as such learning effect would also exist in daily practice. The use of a standardized treadmill protocol with a graded inclination, such as the one used in the present study¹⁴, is well established¹⁰ and advised in current guidelines.¹ It is the most reliable treadmill test²⁵ and demonstrates the best agreement to outside walking when compared with a non-graded treadmill protocol.²⁶ Accordingly, it is widely used to assess the effect of SET.¹² Thus, the MIDs found in this study are likely applicable to the majority of the IC patients, in both research and daily clinical practice, after three months of SET. Limitations in walking distance are, irrespective of measuring method, not necessarily a true reflection of disease severity in patients with IC. Other authors reported important discrepancies between treadmill measurements and walking impairment as perceived by the patient.^{4, 24} Moreover, an improvement of walking distance does not necessarily equal increased physical activity levels in patients with IC⁶, and it lacks correlation with

IC-specific HRQoL.⁵ Evidently, walking distance is an imperfect outcome parameter. Nonetheless, it is widely used in clinical trials, as its value in assessing treatment effect has been well established.^{13,25} Indeed, assessment of walking distance provides the means to directly measure the primary treatment goal in IC: improvement of ambulatory (dis) function. The MIDs found in the current study strengthen the connection between this widely used outcome measure and patients' perception of treatment effect.

Our study had some important limitations. First, a single MID may be insufficient for all study applications as multiple approaches to estimating the MID will produce a range of different values. Besides, MIDs may vary by context and MID values will therefore differ for various treatment strategies (i.e. endovascular intervention).¹⁸ So, final selection of MID values for a specific outcome measure should be based on several methods. Second, the MID is preferably determined using an anchor that has been established in the target population. Preferably, the anchor provides a direct measurement of the patient's perspective on the results of treatment. A 'global rating of change'-question seems best-suited for this purpose in IC. Unfortunately, our data did not include such a question, thus we used an external anchor established in a separate study.⁹ Patient populations were similar, thereby approving the current external anchor strategy. Third, to ensure the greatest agreement between the external anchor's population and our study subjects we used outcome data after three months of SET. Yet, most IC patients are treated over prolonged periods in clinical practice. Preferably, future studies should incorporate a longer follow-up duration to ensure optimal translation to the real world population. Fourth, almost half of the study population had to be excluded for failing to complete the WIQ at both baseline and after three months of SET. Although few differences in baseline characteristics between the in- and excluded population were found, MID values may have been influenced by unknown confounders. Notably, a similar amount of exclusions were found in the study by Conijn et al.⁹, highlighting the problem of early drop-out in this specific population. Finally, the correlation between the WIQ-anchor and ACD or FCD just barely fulfilled Revicki's criterium (a correlation of ≥ 0.3).¹⁸

Future research is needed to validate our findings by directly relating data on ACD and FCD to an anchor in the same population. Ideally, this anchor should incorporate aspects beyond walking capacity, like disease-specific quality of life (i.e. VasculQoL-6 or -25), to include a broader perceived health status. As various methods for estimating

MIDs often converge, repetition is supported for the generalizability of MID estimates in similar applications.

In conclusion, the MID of treadmill-measured ACD in patients with IC was 305m for improvement and 147m for deterioration. The MID for FCD was 250m for improvement and 120m for deterioration. The MIDs as found may be helpful to interpret the clinical relevance of changes in walking distances, which may be used in both research and the individual care setting.

REFERENCES

1. Society for Vascular Surgery Lower Extremity Guidelines Writing G, Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JF, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg* 2015;61:2S-41S.
2. Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;127:1425-43.
3. Kinlay S. Outcomes for clinical studies assessing drug and revascularization therapies for claudication and critical limb ischemia in peripheral artery disease. *Circulation* 2013;127:1241-50.
4. Frans FA, Zagers MB, Jens S, Bipat S, Reekers JA, Koelemay MJ. The relationship of walking distances estimated by the patient, on the corridor and on a treadmill, and the Walking Impairment Questionnaire in intermittent claudication. *J Vasc Surg* 2013;57:720-7 e1.
5. Nordanstig J, Broeren M, Hensater M, Perlander A, Osterberg K, Jivegard L. Six-minute walk test closely correlates to "real-life" outdoor walking capacity and quality of life in patients with intermittent claudication. *J Vasc Surg* 2014;60:404-9.
6. Fokkenrood HJ, Lauret GJ, Verhofstad N, Bendermacher BL, Scheltinga MR, Teijink JA. The effect of supervised exercise therapy on physical activity and ambulatory activities in patients with intermittent claudication. *Eur J Vasc Endovasc Surg* 2015;49:184-91.
7. Frans FA, Nieuwkerk PT, Met R, Bipat S, Legemate DA, Reekers JA, et al. Statistical or clinical improvement? Determining the minimally important difference for the vascular quality of life questionnaire in patients with critical limb ischemia. *Eur J Vasc Endovasc Surg* 2014;47:180-6.
8. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989;10:407-15.
9. Conijn AP, Jonkers W, Rouwet EV, Vahl AC, Reekers JA, Koelemay MJ. Introducing the Concept of the Minimally Important Difference to Determine a Clinically Relevant Change on Patient-Reported Outcome Measures in Patients with Intermittent Claudication. *Cardiovasc Intervent Radiol* 2015.

10. 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.
11. Nicolai SP, Teijink JA, Prins MH, Exercise Therapy in Peripheral Arterial Disease Study G. Multicenter randomized clinical trial of supervised exercise therapy with or without feedback versus walking advice for intermittent claudication. *J Vasc Surg* 2010;52:348-55.
12. Merry AH, Teijink JA, Jongert MW, Poelgeest A, van der Voort SS, Bartelink ME, et al. [KNGF-guideline Symptomatic peripheral arterial disease (author's translation)]. 2014.
13. Kruidenier LM, Nicolai SP, Willigendael EM, de Bie RA, Prins MH, Teijink JA. Functional claudication distance: a reliable and valid measurement to assess functional limitation in patients with intermittent claudication. *BMC Cardiovasc Disord* 2009;9:9.
14. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc* 1991;23:402-8.
15. Nicolai SP, Kruidenier LM, Rouwet EV, Graffius K, Prins MH, Teijink JA. The walking impairment questionnaire: an effective tool to assess the effect of treatment in patients with intermittent claudication. *J Vasc Surg* 2009;50:89-94.
16. Verspaget M, Nicolai SP, Kruidenier LM, Welten RJ, Prins MH, Teijink JA. Validation of the Dutch version of the Walking Impairment Questionnaire. *Eur J Vasc Endovasc Surg* 2009;37:56-61.
17. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol* 2003;56:395-407.
18. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J Clin Epidemiol* 2008;61:102-9.
19. Fakhry F, van de Luijngaarden KM, Bax L, den Hoed PT, Hunink MG, Rouwet EV, et al. Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg* 2012;56:1132-42.
20. Riley PO, Paolini G, Della Croce U, Paylo KW, Kerrigan DC. A kinematic and kinetic comparison of overground and treadmill walking in healthy subjects. *Gait Posture* 2007;26:17-24.
21. Gernigon M, Le Faucheur A, Noury-Desvaux B, Mahe G, Abraham P, Post GPSSCG. Applicability of global positioning system for the assessment of walking ability in patients with arterial claudication. *J Vasc Surg* 2014;60:973-81 e1.

22. Le Faucheur A, Abraham P, Jaquinandi V, Bouye P, Saumet JL, Noury-Desvaux B. Measurement of walking distance and speed in patients with peripheral arterial disease: a novel method using a global positioning system. *Circulation* 2008;117:897-904.
23. Montgomery PS, Gardner AW. The clinical utility of a six-minute walk test in peripheral arterial occlusive disease patients. *J Am Geriatr Soc* 1998;46:706-11.
24. McDermott MM, Guralnik JM, Criqui MH, Liu K, Kibbe MR, Ferrucci L. Six-minute walk is a better outcome measure than treadmill walking tests in therapeutic trials of patients with peripheral artery disease. *Circulation* 2014;130:61-8.
25. Nicolai SP, Viechtbauer W, Kruidenier LM, Candel MJ, Prins MH, Teijink JA. Reliability of treadmill testing in peripheral arterial disease: a meta-regression analysis. *J Vasc Surg* 2009;50:322-9.
26. Fokkenrood HJ, van den Houten MM, Houterman S, Breek JC, Scheltinga MR, Teijink JA. Agreements and Discrepancies between the Estimated Walking Distance, Nongraded and Graded Treadmill Testing, and Outside Walking in Patients with Intermittent Claudication. *Ann Vasc Surg* 2015;29:1218-24.

CHAPTER 7

Minimal correlation between physical exercise capacity and daily activity in patients with intermittent claudication

L.N.M. Gommans
D. Hageman
I. Jansen
R. de Gee
R.C. van Lummel
N. Verhofstad
M.R.M. Scheltinga
J.A.W. Teijink

ABSTRACT

Introduction: Walking capacity measured by a treadmill test (TT) reflects the patient's maximal capacity in a controlled setting and is part of the physical exercise capacity (PEC). On the other hand, daily physical activity (PA) is defined as the total of actively produced freely movements per day. A lower PA level has been increasingly recognized as a strong predictor of increased morbidity and mortality in patients with IC. Recent insights suggested that an increased PEC does not automatically leads to an increase in daily PA. However, the precise relation between PEC and PA in patients with IC is still unclear.

Methods: A cross-sectional study was conducted to assess the association between several PEC outcomes and PA in a general IC population. PEC was determined by well-established tests (Gardner-Skinner treadmill test (TT), a physical performance battery, a timed up and go test, and a six-minute walk test (6-MWT)). PA was obtained during seven consecutive days using a tri-axial accelerometer (Dynaport MoveMonitor). Five PA components (lying, sitting, standing, shuffling and locomotion) and four parameters (total duration, number of periods, mean duration per period and mean movement intensity per period) were analysed. Correlation coefficients between PEC and PA components were calculated.

Results: Data of 46 patients were available for analysis. Patients were sedentary (sitting and lying) during 81% of the day, and physically active (standing, shuffling and locomotion) for the remaining 19% of the time. Overall, correlations between PEC outcomes and PA ranged from very weak (.025) to moderate (.663). Moderate correlations (as therefore assumed to be relevant) were only found for both TT and 6-MWT outcomes and locomotion components of PA. For instance, functional walking distance (measured by TT) and number of steps per day correlated reasonably well (Spearman correlation $\rho=.663$, $P<.01$).

Conclusion: Exercise capacity and physical activity correlate minimally in patients with intermittent claudication. Physical activity may be preferred as a novel outcome measure and future treatment target in patients with IC.

INTRODUCTION

Intermittent claudication (IC) is the most common symptom of peripheral artery disease (PAD) and results from atherosclerosis in large peripheral arteries.¹ Among conservative therapies, supervised exercise therapy (SET) was found the most effective tool in decreasing IC symptoms and increasing physical exercise capacity (PEC).² The term PEC actually reflects what a person is maximally capable of in a controlled laboratory setting.³ In patients with IC, PEC is usually determined by a standardized treadmill test (TT).⁴ With this test, a physician is able to evaluate a patient's individual walking capacity (i.e. maximum walking distance), which is especially useful to determine the effect of SET.⁴ Moreover, TT-based walking capacity is frequently used to assess the effect of novel treatment strategies in clinical trials.

A recent study demonstrated that an improvement in PEC does not automatically lead to an increase in daily physical activity (PA).⁵ These insights are in line with a recent study that also found no increase in daily PA levels after SET in patients with IC.⁶ These results may have important implications as daily PA level is a strong predictor of morbidity and mortality, in patients with IC.⁷ Several studies have now demonstrated that patients with IC exhibit lower daily PA levels than healthy controls,^{8,9} and the majority does not meet the internationally recommended standard for PA.⁸ The World Health Organisation defines PA as 'any bodily movement produced by skeletal muscles that requires energy expenditure'.¹⁰ The different aspects of PA include mode, frequency, duration, intensity and context in which the activities occur. Hence, daily PA reflects the total of actively produced movements a person actually performs on a daily basis.

In current practice, PA levels are most commonly determined by interviews or questionnaires. These self-report tools proved to be poorly reproducible¹¹ and seem insensitive for assessing IC symptoms.¹² Despite the current possibility to objectively measure PA with the use of activity monitors (i.e. pedometers and accelerometers), this approach is rarely applied in daily clinical practice. Although, such devices are small, easily wearable, and found to provide reliable information on PA.¹³ Patients only need to wear the device for multiple days in order to obtain an accurate measure of daily PA levels, since PA can fluctuate over days.¹⁴

For both research and clinical purposes, it might be important to focus more on daily PA as an outcome parameter.^{7, 15} Whether PEC outcomes however could serve as a surrogate marker for PA is currently unknown in patients with IC, as the relation between PEC and daily PA is still unclear. For chronic obstructive pulmonary disease (COPD), research already showed that PEC and daily PA are two completely different entities.¹⁶ These results underscored the importance of measuring daily PA in order to optimize treatment for COPD, which might be the same for IC patients. The current study therefore aims to evaluate how different PEC measures relate to daily PA in a general IC population. In line with previously results obtained from a COPD population, we hypothesized that PEC outcomes are poorly associated with daily PA behaviour.

METHODS

Participants

Between February and May 2015, patients with symptoms of IC were recruited at the vascular surgery outpatient clinic of the Catharina Hospital, Eindhoven, the Netherlands, and from two physical therapy centres in respectively Eindhoven and Veenendaal (the Netherlands). Inclusion criteria were PAD Rutherford stage 1-3 and an ankle-brachial index (ABI) <0.90 at rest and/or a drop of >0.15 after a graded TT, or a duplex or magnetic resonance angiography (MRA) demonstrating a significant arterial stenosis ($>50\%$). Exclusion criteria were serious cardiopulmonary comorbidities (NYHA 3-4), PAD Rutherford stage 4-6, previous lower-limb amputation, use of walking aids, high probability of non-adherence to protocol (e.g. for instance due to dementia), other comorbidities that might limit the patient's walking ability (e.g. severe arthritis, Parkinson's disease, recent trauma to the lower extremities), and wearing the PA device for less than five days, as that is the minimum number of days for obtaining accurate data on locomotion bouts.¹⁷

Patients who were willing to participate were counselled regarding the study protocol prior to providing written informed consent. All procedures were approved by the Medical Ethical Committee of the Catharina Hospital, Eindhoven, the Netherlands.

Study protocol

A cross-sectional design was used to investigate the relation between PEC outcomes and components of daily PA. All participants were extensively instructed how to wear the PA device properly. Patients returned to our hospital once for the PEC measurements. Assessment of PEC and PA was scheduled in random order. Three researchers (LG, IJ, RG) were responsible for the data collection.

Measurements

Ankle-brachial index

According to standardized institutional protocols, ABIs were measured by experienced nurses at the vascular laboratory of the Catharina Hospital. Using a hand-held 8 MHz Doppler probe, systolic pressures were measured at the brachial artery of both arms, followed by the posterior tibial artery and dorsal pedal artery at the level of both ankles. A baseline measurement was performed at rest. Subsequently, a post-exercise ABI was obtained (i.e. treadmill test at 3.2 km/h, and a 6-degree slope for a maximum of six minutes). The ABI was calculated by dividing the highest obtained ankle pressure by the highest obtained arm pressure.

Physical exercise capacity

PEC was determined through a sequence of tests. Patients performed a TT, a short physical performance battery (SPPB), a timed up and go (TUG) test and a six-minute walk test (6-MWT).

- A standard TT was based on the graded Gardner-Skinner protocol.¹⁸ Patients started walking on a flat treadmill with a constant speed of 3.2 km/h. The incline was increased by 2% every two minutes until a maximum of 10% was reached. The test ends at a maximum of thirty minutes (1600 meters). The functional claudication distance (FCD) and absolute claudication distance (ACD) were recorded. FCD was defined as the distance at which a patient prefers to stop because of claudication symptoms.¹⁹ ACD was defined as the maximal walking distance limited by intolerable pain.

- The SPPB, developed by Guralnik et al.²⁰, is a battery that consists of three tests and aims to assess general lower extremity function. In a 3-meter walking velocity test, patients were asked to walk three meters at their usual speed. Participants performed the test twice, whereupon the fastest result was selected. In a repeated chair rise test, patients were instructed to stand up and sit down five times as fast as possible, with arms folded across the chest. The time for completing was recorded and results generally reflect leg strength and balance.²⁰ In the standing balance test, patients were asked to maintain balance for ten seconds in the following three positions; feet together (side-by-side position), heel of one foot next to the big toe of the other foot (semi-tandem position) and the heel of one foot in front of the toe of the other foot (tandem position). A maximum of 4 points can be scored in each of these three tests, leading to a 12 points maximum score.
- During a TUG test, patients were instructed to rise from a chair, walk three meters, turn around, walk back to sit again, all at their fastest pace. The total time was recorded as a result.
- A 6-MWT was based on the standardized Montgomery and Gardner protocol.²¹ Patients were asked to walk up and down a twenty meter distance for six minutes, covering as much distance as possible. Total walking distance was registered as well as the number of stops due to IC symptoms.

Daily physical activity

PA was measured using the Dynaport MoveMonitor®, a tri-axial seismic accelerometer (McRoberts BV, The Hague, the Netherlands). This device has been validated to objectively measure physical activity in patients with IC.¹³ It consists of a rechargeable battery, USB connection and raw data storage capability on a micro secure digital card. Participants wore the device with a belt around the waist for seven consecutive days, except when showering or bathing. The MoveMonitor (MM) includes three orthogonal accelerometers that measure acceleration in three axes: x (longitudinal), y (mediolateral) and z (anterior-posterior), at a sample rate of 100 samples per second. Raw data were processed using pattern recognition algorithms (Movemonitor analysis software, version 1.0.7.21), and expressed in terms of body posture (i.e. lying and sitting), locomotion, and movement parameters (i.e. movement duration, intensity and frequency). Following PA categories

were retrieved: lying, sitting, standing, shuffling and locomotion. Shuffling separation divides the active (not walking) parts into two categories: shuffling and transitions. So shuffling is defined as all movement from A to B that is not walking. Thus, if the number of steps is fewer than three, or the intensity and direction of the motion do not comply with the characteristics of walking, the movements are classified as shuffling.¹³ Four subsequent parameters were reported for each activity category: total duration, number of periods, mean duration per period and the weighted mean movement intensity (MI) per period.

Data analysis

Continuous variables were expressed as means ($\pm$ standard deviation) when normally distributed, and as medians with interquartile ranges (IQR) in the case of a skewed distribution. For categorical variables, percentages were presented. Normality checks were performed visually using histograms and with a Kolmogorov-Smirnov test. The relation between daily PA (variables being lying, sitting, standing, shuffling and locomotion) and PEC (variables being the outcomes measures of a TTT, SPPB, TUG and 6-MWT) was determined by calculating Spearman correlation coefficients (ρ) as PEC data revealed a skewed distribution. According to Zou et al. correlations of ≥ 0.50 and ≥ 0.80 were considered as respectively, moderate and strong associations.²² Multivariate regression analysis was conducted to study the potential influence of gender and age on the relation between PEC and PA. All data was analysed using SPSS Statistics for Windows, version 21.0 (IBM, Armonk, NY, USA). A P-value < 0.05 was regarded as being statistically significant. Sample size calculation (with $\alpha = 0.05$ and $\beta = 0.80$) revealed a sample size of 46 subjects to realize statistical significant correlations of ≥ 0.4 between PEC and PA.

RESULTS

Recruitment and response

A total of 55 patients met eligibility criteria and were willing to participate. Inclusion of nine patients was based on duplex or MRA images. A total of nine patients (~17%) were excluded (MM worn < 5 days ($n=2$), technical failure ($n=1$), withdrawal due to personal

reasons (n=4), and unanticipated operative interventions during the MM measurement period (n=2)). Therefore, complete data sets of 46 patients were available for analysis.

Sample characteristics

Baseline characteristics are depicted in table 1. Mean age was 66 years (± 9 years), and the majority were men (n=35, 76%). About half demonstrated bilateral complaints (n=21, 46%). The lowest mean ABI in rest was 0.63 (± 0.17), dropping to 0.38 (± 0.19) after exercising. Cardiovascular risk factors (smoking, diabetes mellitus) were commonly observed (*table 1*).

Table 1. Baseline characteristics of the study population (n=46)

Gender, male (n, %)	35 (76)
Age, years (mean $\pm$ SD)	66 $\pm$ 9
BMI, kg/m ² (mean $\pm$ SD)	25.1 $\pm$ 4.9
Affected side (n, %)	
Left	16 (35)
Right	9 (20)
Both	21 (45)
Lowest ABI (mean $\pm$ SD) ^a	
Rest	0.63 $\pm$ 0.17
Post-exercising	0.38 $\pm$ 0.19
Comorbidity (n, %)	
Pulmonary	7 (15)
Cardiac	10 (22)
TIA/stroke	5 (11)
Diabetes mellitus	10 (22)
Hypertension (n, %)	32 (70)
Current smokers (n,%)	14 (30)

a=based on ABI values of 37 IC patients, ABI=ankle-brachial index, TIA=transient ischemic accident

Physical exercise capacity

The median functional and absolute claudication distances on the TT were 360 meters (IQR: 160.00-536.50) and 438 meters (IQR: 298.25-714.50), respectively. Six patients (13%) achieved the maximum walking distance of 1600 meters. The median walking distance assessed by a 6-MWT was 400 meters (IQR: 320.50-468.50). For the TUG test a median of 7.58 seconds for completion was found. A total of 87% patients attained a SPPB total score of 10 (out of 12, range 8-12). The SPPB subtests revealed that 76% had a maximum score for balance, 98% had a maximum score for walking speed, but just 18% scored maximal points on the repeated chair rise test (*table 2*).

Physical activity in IC patients

Patients were physically active for 4.46 hours per day (standing, shuffling, locomotion), equivalent to 19% of a 24-hour day. On the other hand, mean number of hours that patients spent in a sedentary mode (lying or sitting) was 18.98, corresponding with the remaining 81% of a day. Note that this also includes sleeping overnight. Patients initiated a median number of 408 (IQR: 264-611) locomotion periods per day, with a mean movement intensity of 0.187 m/s² (SD: $\pm$.022) and a median time of 9.88 seconds (IQR: 8.81-12.02) per period. The median number of transitions from sitting to standing was 52 (IQR: 40-69). A detailed overview of the median daily PA levels is shown in table 3.

Table 2. Physical exercise capacity of the study population

	median (IQR)
Treadmill test	
FCD (m)	360 (160-537)
ACD (m)	438 (298-715)
6-MWT walking distance (m)	400 (321-469)
TUG (s)	7.58 (6.66-9.86)
SPPB	
Balance (1-4)	4 (3-4)
Velocity (1-4)	4 (4-4)
Chair rise test (1-4)	3 (2-3)
Total score (1-12)	11 (10-12)

IQR=interquartile range; m=meters; s=seconds, FCD=functional claudication distance, ACD=absolute claudication distance, TUG=timed up and go test, SPPB=short physical performance battery

Table 3. Physical activity outcomes of the study population

	Mean duration per day (h) ± SD	Median number of periods per day + IQR	Median time per period (s or m) + IQR	Mean movement intensity (m/s ²) ± SD
Lying	10.1 (+/- 1.92)	9 (6-15)	60.8 (41.6-91.6) ^a	0.005 (+/- 0.002)
Sitting	8.52 (+/- 1.87)	109 (90-141)	4.38 (3.0-6.1) ^a	0.023 (+/- 0.013)
Standing	2.67 (+/- 1.19)	756 (528-1202)	11.02 (9.4-15.9) ^b	0.052 (+/- 0.012)
Shuffling	0.40 (+/- 0.26)	409 (277-686)	2.77 (2.6-3.0) ^b	0.139 (+/- 0.028)
Locomotion	1.30 (+/- 0.72)	408 (264-611)	9.88 (8.8-12.0) ^b	0.187 (+/- 0.022)
Mean activity time per day (h) ^c		4.46 (+/- 2.0)		
Mean sedentary time per day (h) ^{c,d}		18.98 (+/- 1.9)		
Median number of sit-to-stand		52 (40-69)		
Median number of steps per day		6,315 (3,364-9,207)		
Mean MM not worn per day (m) ^c		36,9 (+/- 62,1)		

h=hours; m=minutes; s=seconds; IQR=interquartile range; SD=standard deviation; a=minutes; b=seconds; c=add up to 100%; d=note that the sedentary time also includes sleeping overnight.

Correlation between PEC and daily PA

No significant or relevant correlations ($\rho \geq .4$) were present between SPPB/TUG test outcomes and any of the PA components (data not shown), except for a weak inverse correlation ($\rho = -.492$, $P < .01$) between locomotion movement intensity and the results of the TUG test.

ACD (using a TT) and duration of locomotion per day were moderately correlated ($\rho = .561$, $P < .01$). In contrast, corridor-based walking distance (using a 6-MWT) and duration of locomotion per day showed just a weak correlation ($\rho = .375$, $P < .01$). Stronger correlations were present between total number of steps per day and TT outcomes (FCD: $\rho = .663$; ACD: $\rho = .621$, both $P < .01$). In addition, outcome of 6-MWT was moderately associated with locomotion movement intensity ($\rho = .599$, $P < .01$). The sedentary activity modes did not show any relevant correlations with either TT or 6-MWT outcomes (table 4).

Multivariate regression analysis did not reveal any significant contribution of gender or age to the PEC and PA correlations.

Table 4. Spearman correlation coefficients between PEC and PA

		Treadmill test		6-MWT
		FCD	ACD	
Lying	Duration	-.173	-.138	-.234
	No of periods	-.297*	-.245	-.137
	Time/period	.306*	.257	.114
	Intensity	-.230	-.190	.029
Sitting	Duration	-.163	-.196	-.060
	No of periods	.305	.153	.303*
	Time/period	-.116	-.183	-.204
	Intensity	-.103	.025	.157
Standing	Duration	.253	.281	.228
	No of periods	.439**	.422**	.343*
	Time/period	-.459**	-.387**	-.245
	Intensity	.251	.286	.359*
Shuffling	Duration	.449**	.438**	.406**
	No of periods	.431**	.417**	.356*
	Time/period	.088	.093	.256
	Intensity	.094	.168	.237
Locomotion	Duration	.617**	.561**	.375*
	No of periods	.463**	.422**	.245
	Time/period	.596**	.549*	.499*
	Intensity	.277	.323*	.599**
Steps per day	Total number	.663**	.621**	.425**

No=number; * indicates a significance $P<.05$; ** indicates a significance of $P<.01$, FCD=functional claudication distance, ACD=absolute claudication distance.

DISCUSSION

In this study we investigated the relation between PEC outcomes and daily PA in patients with IC. Overall, only weak to moderate correlations between these parameters were found. A substantial portion of the correlations was therefore considered of minor relevance ($\rho \leq 0.5$), despite their statistical significance.²² Among relevant correlations, results of a treadmill test (TT, i.e. FCD and ACD) showed strongest association with locomotion (i.e. total amount of locomotion and duration of locomotion per period).

These findings possibly imply that ‘the better a TT performance, the more a patient walks in daily life’. Similar conclusions may be drawn from the correlations between TT-based FCD and ACD and number of steps per day. A moderate correlation was also found between a 6-MWT walking distance and locomotion movement intensity (MI). MI as determined by the acceleration and deceleration signals indicates movement power. A comparison between corridor-based walking and treadmill walking demonstrated reduced anterior-posterior ground reaction forces during the latter protocol.²³ Therefore, it may be expected that results of MI and 6-MWT demonstrate stronger correlations when compared to MI and TT outcomes. Besides, other authors also reported that 6-MWT results correlated well with PA levels as expressed in general ‘activity units’.²⁴ In general, correlations of FCD and PA were stronger than the correlations between ACD and PA. It may therefore be proposed that a measurement of FCD is currently the most optimal predictor of daily walking activity.

Understanding of the underlying motives of physical activity behaviour is an aid for optimizing intervention strategies.²⁵ This assumption may particularly be true in sedentary populations including IC patients⁸, as health benefits of increased PA are likely substantial. However, PA is a complex endpoint that is influenced by a range of factors (e.g. personal, exercise-related, environment and policy).²⁵ Moreover, there is still uncertainty about the exact factors defining someone’s behaviour to be physically active. A poor relation between PEC and PA as shown in this study may be not surprising, as it was also demonstrated in other populations including healthy elderly¹⁴ and COPD.¹⁶ The concepts of PEC and PA may therefore be different.^{26, 27} Our results indicate that the parameter PEC is able to predict 44% of the variance in PA (FCD versus numbers of steps per day) at best. Leaving more than half for others factors to explain PA behaviour. Considering these results and knowing that a low PA level is a strong risk factor for developing comorbidities⁷, assessment of PA as an additional outcome measure may have important implications for IC care.

Correct assessment of PA in patients with IC seems to be a challenge. Questionnaires may help to identify a severely inactive patient, but these tools largely fail to provide a correct reflection of an entire patient population. Moreover, self-reported responses on daily PA are subject to social desirability bias.²⁸ In contrast, activity monitors were found to be reliable tools for PA assessment and are currently widely available.¹³ These

devices are easy to wear, whereas the number of problems that were encountered in the present study was minimal. A unique aspect of our methodology was the quantification of a range of different activity components (e.g. sitting and standing) rather than more general measures of PA (e.g. activity units or metabolic equivalents of a task; MET).^{24, 29} A precise measurement of PA is important as recent insights revealed that prolonged sitting (i.e. sedentary behaviour) predicts all-cause mortality, independent of these overall physical activity levels in METs.³⁰ Prolonged sitting is found to disrupt metabolic functions, resulting in increased plasma triglyceride levels, decreased levels of high-density lipoprotein cholesterol, and decreased insulin sensitivity.³⁰ Based on the results from molecular biology and medical chemistry studies, physical activity and sedentary behavior are thought to have different influences on the body, supporting their independent effects on health.³¹ Consequently, the positive effect of (vigorous) physical activity for a couple of times per week (for instance during SET) does not seem to compensate for the independent negative effect when one is predominantly sedentary for the remaining time. Thus, incorporating different activity components of PA in patients with IC, in particular time spent in sedentary modes, may be more predictive compared to measurements of just energy consumption.

Previous studies failed to demonstrate beneficial effects of SET on daily PA in patients with IC. Both Fokkenrood et al. and Crowther et al. concluded that PA levels did not increase following three and twelve months of SET, respectively.^{6, 32} The finding that an exercise program primarily focussing on stimulating physical capacity does not improve daily PA is explainable. When PAD gradually progresses over the years, the patient likely develops a sedentary lifestyle requiring more than just an increase in exercise capacity to change. This explanation is in line with a previous conclusion from a COPD study.⁵ Exercise interventions require targeting to exercise capacity as well as to behavior change with regard to daily physical activity, in order to achieve improvement in PA.⁵ Behavioural changing techniques such as motivational interviewing might be helpful in achieving and maintaining improved PA levels. A brief psychological intervention of just two 1-hour sessions significantly increased daily walking in patients with IC³³, an effect that was sustained for over two years.³⁴ SET provides an ideal opportunity for incorporation of such psychological interventions (i.e. health behaviour changing techniques), thereby probably optimizing SET programs and improving patient outcome. However, high-

quality trials examining the effectiveness of these health behaviour changing techniques in patients with IC are urgently needed.³⁵ The additional value of health technology applications (e.g. incorporated in smart phones) for enhancing PA also require detailed studies.

Based on present results one may argue that measurement of PEC does not have an additional role in an improved understanding of daily PA in patients with IC. However, such a functional assessment was found to reflect the IC patients' abilities and limitations³⁶, and may therefore provide valuable information. Evidently, walking distance as measured using a TT has limitations, as discrepancies between treadmill measures and perceived walking impairment are reported.³⁷ It must also be appreciated that treadmill based walking distance is the most widely used outcome parameter to evaluate treatment effects of SET in both clinical trials and daily practice.³⁶ Both the TUG and SPPB measures may be of less relevance and/or suitable for this patient population. The high number of maximum scores ('ceiling effect') imply that patients were not really challenged during these tests, both protocols require just a very short period of activity (usually <15 seconds), whereas most IC patients experience pain at a later time point. PEC is considered to determine someone's maximal capacity and may therefore be inadequately estimated by these tests. As also indicated by the lack of correlations with PA. Consequently, we propose to incorporate PA as a novel outcome measure and treatment goal for IC alongside current walking (TT or 6-MWT) PEC measurements.

The present study must be interpreted in view of the fact that PEC results may be overestimated as persons are generally thought to push to their limits when challenged during a test setting, as compared to a normal day-to-day situation. It may therefore be possible that this has influenced correlation strength. Moreover, several factors apart from age and gender might influence potential correlations between PEC and PA. Variance in the use of sort and type of medication, presence of comorbidities and BMI for instance have a possible effect on PA and correlations with PEC might be different for certain subgroups of patients with IC. Unfortunately, the study's cross-sectional design does not allow for studying causality. Future research should preferably explore determinants which possibly contribute to PA. Such an analysis may allow for a more selective use of monitoring equipment.

In conclusion, walking distance as determined with a 6-MWT or graded TT protocol revealed weak to moderate correlations with locomotion components of PA. Whereas, no to weak correlations were found with sedentary PA components. On the basis of the present study results, the sedentary nature of IC patients, and the increased mortality risks accompanied with these low PA levels, we suggest including of objectively measured PA as an additional outcome measure and treatment target in patients with IC.

CONFLICT OF INTEREST

R.C. van Lummel is owner of McRoberts BV, The Hague, the Netherlands; distributor of the DynaPort® MoveMonitor.

ACKNOWLEDGEMENTS

Authors would like to thank Dirk van Dooren for his support in the data analysis. We also greatly appreciated the help of Natasja Huls (physical therapist at Fysiotherapie De Jong, Eindhoven, the Netherlands) and Sander van de Hoef (Paramedisch Instituut Rembrandt, Veenendaal, the Netherlands) for the recruitment of study participants.

REFERENCES

1. Cooke JP, Chen Z. A compendium on peripheral arterial disease. *Circ Res* 2015;116:1505-8.
2. Society for Vascular Surgery Lower Extremity Guidelines Writing G, Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JE, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg*. 2015;61(3 Suppl):2S-41S.
3. Goldstein RE. Exercise capacity. In: Walker HK, Hall WD, Hurst JW, editors. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3 ed. Boston: Butterworths; 1990.
4. Hiatt WR, Rogers K, Brass EP. Response to McDermott. *Circulation*. 2014;130(1):68.
5. Zwerink M, van der Palen J, van der Valk P, Brusse-Keizer M, Effing T. Relationship between daily physical activity and exercise capacity in patients with COPD. *Respir Med* 2013;107:242-8.
6. Fokkenrood HJ, Lauret GJ, Verhofstad N, Bendermacher BL, Scheltinga MR, Teijink JA. The effect of supervised exercise therapy on physical activity and ambulatory activities in patients with intermittent claudication. *Eur J Vasc Endovasc Surg*. 2015;49(2):184-91.
7. Garg PK, Tian L, Criqui MH, Liu K, Ferrucci L, Guralnik JM, et al. Physical activity during daily life and mortality in patients with peripheral arterial disease. *Circulation*. 2006;114(3):242-8.
8. Lauret GJ, Fokkenrood HJ, Bendermacher BL, Scheltinga MR, Teijink JA. Physical activity monitoring in patients with intermittent claudication. *Eur J Vasc Endovasc Surg*. 2014;47(6):656-63.
9. Gardner AW, Montgomery PS, Scott KJ, Afaq A, Blevins SM. Patterns of ambulatory activity in subjects with and without intermittent claudication. *J Vasc Surg*. 2007;46(6):1208-14.
10. Organisation WH. Physical activity. 2015; Available from: <http://www.who.int/mediacentre/factsheets/fs385/en/>.
11. Shephard RJ. Limits to the measurement of habitual physical activity by questionnaires. *Br J Sports Med*. 2003;37(3):197-206; discussion.
12. Gardner AW, Katzel LI, Sorkin JD, Bradham DD, Hochberg MC, Flinn WR, et al. Exercise rehabilitation improves functional outcomes and peripheral circulation in patients with intermittent claudication: a randomized controlled trial. *J Am Geriatr Soc*. 2001;49(6):755-62.

13. Fokkenrood HJ, Verhofstad N, van den Houten MM, Lauret GJ, Wittens C, Scheltinga MR, et al. Physical activity monitoring in patients with peripheral arterial disease: validation of an activity monitor. *Eur J Vasc Endovasc Surg.* 2014;48(2):194-200.
14. Nicolai S, Benzinger P, Skelton DA, Aminian K, Becker C, Lindemann U. Day-to-day variability of physical activity of older adults living in the community. *J Aging Phys Act.* 2010;18(1):75-86.
15. Gardner AW, Montgomery PS, Parker DE. Physical activity is a predictor of all-cause mortality in patients with intermittent claudication. *J Vasc Surg.* 2008;47(1):117-22.
16. Fastenau A, van Schayck OC, Gosselink R, Aretz KC, Muris JW. Discrepancy between functional exercise capacity and daily physical activity: a cross-sectional study in patients with mild to moderate COPD. *Prim Care Respir J.* 2013;22(4):425-30.
17. van Schooten KS, Rispens SM, Elders PJ, Lips P, van Dieen JH, Pijnappels M. Assessing physical activity in older adults: required days of trunk accelerometer measurements for reliable estimation. *J Aging Phys Act.* 2015;23(1):9-17.
18. Hiatt WR, Hirsch AT, Regensteiner JG, Brass EP. Clinical trials for claudication. Assessment of exercise performance, functional status, and clinical end points. *Vascular Clinical Trialists. Circulation.* 1995;92(3):614-21.
19. Kruidenier LM, Nicolai SP, Willigendael EM, de Bie RA, Prins MH, Teijink JA. Functional claudication distance: a reliable and valid measurement to assess functional limitation in patients with intermittent claudication. *BMC Cardiovasc Disord* 2009;9:9.
20. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol.* 1994;49(2):M85-94.
21. Montgomery PS, Gardner AW. The clinical utility of a six-minute walk test in peripheral arterial occlusive disease patients. *J Am Geriatr Soc.* 1998;46(6):706-11.
22. Zou KH, Tuncali K, Silverman SG. Correlation and simple linear regression. *Radiology.* 2003;227(3):617-22.
23. Riley PO, Paolini G, Della Croce U, Paylo KW, Kerrigan DC. A kinematic and kinetic comparison of overground and treadmill walking in healthy subjects. *Gait Posture.* 2007;26(1):17-24.

24. McDermott MM, Ades PA, Dyer A, Guralnik JM, Kibbe M, Criqui MH. Corridor-based functional performance measures correlate better with physical activity during daily life than treadmill measures in persons with peripheral arterial disease. *J Vasc Surg.* 2008;48(5):1231-7, 7 e1.
25. Bauman AE, Reis RS, Sallis JF, Wells JC, Loos RJ, Martin BW, et al. Correlates of physical activity: why are some people physically active and others not? *Lancet.* 2012;380(9838):258-71.
26. Leidy NK. Using functional status to assess treatment outcomes. *Chest.* 1994;106(6):1645-6.
27. Larson JL. Functional performance and physical activity in chronic obstructive pulmonary disease: theoretical perspectives. *COPD.* 2007;4(3):237-42.
28. Adams SA, Matthews CE, Ebbeling CB, Moore CG, Cunningham JE, Fulton J, et al. The effect of social desirability and social approval on self-reports of physical activity. *Am J Epidemiol.* 2005;161(4):389-98.
29. Clarke CL, Holdsworth RJ, Ryan CG, Granat MH. Free-living physical activity as a novel outcome measure in patients with intermittent claudication. *Eur J Vasc Endovasc Surg.* 2013;45(2):162-7.
30. van der Ploeg HP, Chey T, Korda RJ, Banks E, Bauman A. Sitting time and all-cause mortality risk in 222 497 Australian adults. *Arch Intern Med.* 2012;172(6):494-500.
31. Hamilton MT, Healy GN, Dunstan DW, Zderic TW, Owen N. Too little exercise and too much sitting: inactivity physiology and the need for new recommendations on sedentary behavior. *Curr Cardiovasc Risk Rep.* 2008;2(4):292-298.
32. Crowther RG, Spinks WL, Leicht AS, Sangla K, Quigley F, Golledge J. Effects of a long-term exercise program on lower limb mobility, physiological responses, walking performance, and physical activity levels in patients with peripheral arterial disease. *J Vasc Surg.* 2008;47(2):303-9.
33. Cunningham MA, Swanson V, O'Carroll RE, Holdsworth RJ. Randomized clinical trial of a brief psychological intervention to increase walking in patients with intermittent claudication. *Br J Surg.* 2012;99(1):49-56.
34. Cunningham MA, Swanson V, Holdsworth RJ, O'Carroll RE. Late effects of a brief psychological intervention in patients with intermittent claudication in a randomized clinical trial. *Br J Surg.* 2013;100(6):756-60.

35. Galea MN, Weinman JA, White C, Bearne LM. Do behaviour-change techniques contribute to the effectiveness of exercise therapy in patients with intermittent claudication? A systematic review. *Eur J Vasc Endovasc Surg.* 2013;46(1):132-41.
36. Nicolai SP, Viechtbauer W, Kruidenier LM, Candel MJ, Prins MH, Teijink JA. Reliability of treadmill testing in peripheral arterial disease: a meta-regression analysis. *J Vasc Surg.* 2009;50(2):322-9.
37. Frans FA, Zagers MB, Jens S, Bipat S, Reekers JA, Koelemay MJ. The relationship of walking distances estimated by the patient, on the corridor and on a treadmill, and the Walking Impairment Questionnaire in intermittent claudication. *J Vasc Surg.* 2013;57(3):720-7 e1.

CHAPTER 8

Intermittent claudication prolongs stance phase during walking

L.N.M. Gommans
A.T. Smid
M.R.M. Scheltinga
E. Cancrinus
F.A.M. Brooijmans
K. Meijer
J.A.W. Teijink

Submitted to Eur J Vasc Endovasc Surg.

ABSTRACT

Background: Patients with intermittent claudication (IC) tend to walk slower and consume about 40% more oxygen during walking compared to healthy individuals. An unfavourable locomotion pattern has been suggested to explain this metabolic inefficiency. However, knowledge on gait patterns in IC is limited.

Methods: In a cross-sectional study, the gait pattern of newly diagnosed IC patients was compared with similar healthy controls. Spatio-temporal gait parameters such as step length and duration of the stance phase were obtained by a photoelectric system (Optogait®). This system has shown a strong concurrent validity and test-re-test reliability in various study populations. Parameters were determined during pain-free and painful (in IC only) treadmill walking at comfortable self-determined walking pace. A total of 80 steps was selected for each participant to calculate averaged parameter values.

Results: A total of 28 patients and 28 controls were examined. IC patients walked 1.2 km/h (-27%) slower than controls ($P<.001$), coinciding with a significantly shorter step length (-20%) and lower cadence (-11%). IC patients demonstrated a longer stance and double support phase, even before the onset of ischemic pain. Differences were also observed in the segments of the stance phase, as a 14% shorter propulsion ($P<.001$) and 17% longer flat foot phase ($P<.001$) during painful walking was found. With respect to the absolute time however, differences were only present for the time for flat foot ($\Delta 0.10$ seconds, $P<.001$).

Conclusion: Patients with intermittent claudication demonstrate an altered gait pattern. Most striking differences include the prolonged relative and absolute duration of the flat foot position during the stance phase. This adaptation may be intuitive as arterial blood inflow to skeletal muscles takes place during the relaxation phase. Therefore, not only the lack of propulsion but also gain of relaxation may explain these gait disturbances to a certain part.

INTRODUCTION

The most common symptom of peripheral arterial disease (PAD) is intermittent claudication (IC), characterized by limb pain that is elicited by exercise and resolves after rest. Patients with IC demonstrate limited walking distance, lower physical activity levels,^{1, 2} less isokinetic distal muscles strength³ and reduced quality of life.⁴ Besides, patients with IC were found to consume more oxygen during walking compared to healthy controls.⁵⁻⁷ Researchers have suggested various mechanisms that may be responsible for this increased oxygen requirement. For instance, an unfavorable gait pattern and a reduced recovery of potential energy through the pendulum-like mechanism were implicated.⁸ Interestingly, a reduced metabolic efficiency was ruled out.⁵

Previous studies already found that IC patients walk slower, have lower cadence rates and smaller stride lengths, mainly caused by an increased double limb support and stride time.^{1, 9} However, only basic spatio-temporal parameters have been studied in IC so far. Distinct sub phases during the stance phase may also be interesting,¹⁰ particularly foot contact and toe off (propulsion).⁵ The calf muscles are known to contribute most to propulsion and constitute the main determinants of walking speed.¹¹ Precisely these muscles are considered the 'functional end organs' in the lower extremity ischemia of IC patients.¹² So, additional differences at this level may be plausible. Moreover, further insight in these sub phases might substitute to the development of rehabilitation strategies to restore the gait pattern and eventually walking distances, quality of life and possibly even survival. Since reduced exercise capacity is the most powerful harbinger of long-term mortality in PAD,¹³

One study on the potential effect of SET on altered gait pattern failed to demonstrate any improvement.¹⁴ However, consensus on which type of exercise is leading to optimally improved walking ability is lacking.¹⁵ Hence, current exercise protocols may be not tailored to elicit significant improvements in walking patterns, or gait pattern outcomes are not adequately specified. Moreover, previous research was mainly based on limited number of steps.^{1, 16} Fortunately, suitable gait analysis systems for continuous data capturing during treadmill walking have become available. These novel tools allow for optimizing accuracy and generalizability of collected data on the gait pattern.

The primary aim of this study was to explore spatio-temporal gait parameters in IC patients during continuous treadmill walking and compare these parameters with healthy controls. We hypothesized that patients with IC demonstrate changes of in particular the sub phases of the stance phase.

METHODS

Participants

Patients were recruited from a population presenting between October 2014 and March 2015 with new onset manifestations of IC at the Vascular Surgery outpatient departments of three regional Dutch hospitals (Catharina Hospital Eindhoven, Maxima Medical Center Veldhoven and St. Anna Hospital Geldrop). According to standardized institutional protocols, potential patients underwent an ankle-brachial index (ABI) measurement in rest and following exercise. Individuals demonstrating a resting ABI <0.90 or an ABI drop >0.15 after treadmill testing¹⁷ and typical symptoms of claudication in at least one leg, were eligible for study. Additional inclusion criteria were symptoms >4 weeks and the ability to walk on a treadmill for ≥ 1 minute. Patients were excluded if they suffered from a comorbid condition possibly influencing gait pattern such as lower extremity amputation, severe osteoarthritis (based on the American College of Rheumatology Osteoarthritis criteria),^{18, 19} previous knee or hip prosthesis, severe cardiopulmonary problems (i.e. chronic obstructive pulmonary disease $\geq$ Gold III and/or New York Heart Association $\geq$ III), neurological diseases including peripheral polyneuropathy (e.g. due to diabetes mellitus), Parkinson's disease, stroke, previous surgery of lower extremities, use of walking aids or orthopedic shoes or medication influencing walking pattern (e.g. psychotropic medication). Patients who experienced rest pain, suffered from chronic wounds or received more than five sessions of SET during the preceding three years were also excluded.

Control subjects of similar age, gender, height, and weight were recruited from family, friends and hospital personnel. They were exhibiting an ABI in rest >0.90 and did not experience pain or limitations during walking. Other exclusion criteria were similar as for the patients with IC. Participants that were willing to undergo the study protocol were

counseled prior to providing written informed consent. All procedures were approved by the Medical Ethical Committee of the Catharina Hospital, Eindhoven, the Netherlands.

Study protocol

Two researchers (LG and AS) were responsible for the data collection and performed all measurements. Height and weight allowed calculation of the Body Mass Index (BMI). Leg length was determined with a tape measure in standing position and defined as the distance from the trochanter major of the hip to the inferior aspect of the lateral malleolus.²⁰

After anthropometric measurements, participants walked for ten minutes (for IC patients, with intervals of rest, if necessary due to IC pain) on a treadmill to get accustomed to its specifics.²¹ The preferred walking pace was determined next, defined as ‘walk at a pace that is comfortable and comparable to your outside walking’.²¹ The treadmill was started at 2.4 km/h. Speed was increased in 0.1 km/h increments until self-selected comfortable walking speed was achieved. Speed was then further increased until fastest pace was attained, and again decreased until the comfortable speed was reached once more. Gait pattern measurements were obtained at this final, self-selected comfortable walking pace. After 20 minutes of rest, IC patients were specifically questioned whether IC pain was completely resolved, participants again started walking on the treadmill. During one minute of painless walking, gait parameters were obtained. Once IC patients experienced claudication pain as determined using a 4-point Claudication Pain Scale,²² gait parameters were again captured for one minute.

Control subjects underwent same measurements just once (i.e. pain-free trial). All participants walked bare feet on a flat treadmill to exclude differences based on variable footwear. Additionally, both patients and controls were interviewed regarding general health, cardiovascular risk factors (smoking) and comorbid conditions.

Gait pattern

Spatial and temporal gait parameters were collected using an OptoGait photoelectric cells system (Microgate S.r.l., Bolzano, Italy). The instrument consists of two bars of one meter each, a transmitting and receiving unit respectively. Both bars contain 96 LED diodes, one cm apart and 3 mm above floor level, and are positioned onto the side bars

of the treadmill (*figure 1*). Parameters are determined when LED diodes are interrupted by (one of) the feet during walking. Data were sampled at a frequency of 1000 Hz and saved on a laptop using OptoGait version 1.9.9.0 software (Mircogate S.r.l., Bolzano, Italy). The system is validated for spatio-temporal gait parameters on a treadmill and has shown strong concurrent validity and test-re-test reliability in various other populations including healthy adults, stroke patients and patients after knee arthroplasty.^{23, 24} Besides, reported minimum detectable changes are several times smaller than previously described differences in gait parameters of IC patients.

Following parameters were obtained: walking speed, cadence, gait cycle duration, step length, step time, duration of single and double limb support, swing and stance phase duration and contact, flat foot and propulsive phase (*figure 2*). Step length was defined as the distance from heel contact of the first foot to the heel contact of the subsequent contralateral foot.

Statistical analysis

Sample size calculation (with $\alpha=0.01$ and $\beta=0.80$) was based on both a spatial (stride length difference of 15 cm) and temporal (percentage stance phase difference of 2%) outcome variable⁹ and revealed a sample size of respectively 25 and 14 subjects per group, to realize a statistically significant difference between both groups.

Analyses and calculations of the data generated by the OptoGait software were performed in a customized program that was created in Matlab R2012a (Mathworks Inc, Natick, Massachusetts, USA). Eighty representative steps were obtained from each participant. Mean values and standard deviations were calculated for individual parameters per leg. In IC patients, the most symptomatic leg as based on the patients' history was considered the index leg. In healthy controls, the index leg was randomly selected. SPSS 20.0 (IBM, Armonk, NY, USA) was used for statistical analysis. Demographic characteristics were expressed as percentages or group means and standard deviations. Differences between patients and controls were studied. In addition, evaluation within the patient group was performed. The symptomatic (e.g. index leg) was compared to the asymptomatic leg (e.g. asymmetry), and the index leg was compared during the pain-free and painful one minute measuring period. Pearson's chi-square tests were used for analysis of categorical variables, whereas an independent-samples and paired t-tests

analyzed continuous variables. Variables that lacked normal distribution were expressed as median and corresponding interquartile ranges. Mann Whitney U-tests were used to compare these variables. Pearson correlation coefficients (Rho: ρ) were calculated to explore relations between spatio-temporal parameters and clinical determinants (walking speed, ABI values). Statistical significance was applied at $P < .01$ to control for multiple testing (type I error rate).

The transmitting (A) and receiving (B) bars are positioned on the side bars of the treadmill. Spatio-temporal parameters are obtained via interruptions in the LED signal between the bars, when a subject passes between the bars.

Figure 1. Study set-up including the OptoGait System

The gait cycle is divided in the stance phase and swing phase. The stance phase, which is defined as the heel to toe contact of the foot, accounts for around 60% of the gait cycle and the swing phase for the remaining 40%. The stance phase can be divided in heel strike: first contact of the heel with the floor; foot flat phase: period where the complete foot is in contact with the ground and the propulsion phase: termination of stance phase, starts when the heel leaves the ground and ends with complete set off of tip of the foot. (adapted from: R.C. Schafer, Clinical Biomechanics, 1987. Chap 4: Body alignment, Posture, and Gait – used with permission)

Figure 2. Phases of the normal gait cycle

RESULTS

Study population

The study population consisted of 28 IC patients and 28 controls of similar age (mean age: 68 years), gender distribution, height, weight and leg length (*table 1*). Hypertension rate however, was higher in the IC group. ABIs of patients during rest and after treadmill walking were 0.64 and 0.35, respectively. Almost half ($n=13$, 46%) of the IC patients had unilateral complaints.

IC patients versus control subjects

The IC patients walked at a 1.2 km/h slower pace (IC: 3.3 km/h vs. controls: 4.5 km/h, $P<.001$, *table 2*), coinciding with a significantly 24% shorter step length (IC: 49.2 cm vs. controls: 61.3 cm, $P<.001$), a 11% lower cadence (IC: 111 steps/min vs. controls: 122 steps/min, $P<.001$) and a 14% longer contact time (IC: 0.74 sec vs. controls: 0.65 sec, $P<.001$).

The relative duration of the single support phase was significantly shorter in IC patients compared to controls ($\Delta 2.3\%$ and $\Delta 3\%$ for respectively pain-free and painful ambulation), and the relative duration of the double support phase significantly longer ($\Delta 4.3\%$ and $\Delta 5\%$ for respectively pain-free and painful ambulation). Moreover, IC

patients had an evidently longer lasting foot flat phase (pain-free: $\Delta 4.9\%$; $P=.007$ and painful: $\Delta 7.4\%$; $P<.001$) and shorter propulsive phase than controls (pain-free: $\Delta 4.1\%$; $P=.016$ and painful: $\Delta 6.5\%$; $P<.001$). Reported differences between IC patients and controls increased during painful walking (*table 2*). Despite the difference in the relative duration of the propulsive phase, no difference was found in absolute propulsion time between IC patients and controls.

Table 1. Demographics of study groups undergoing gait analysis

Characteristics	IC patients (n=28)	Controls (n=28)	P-value
Gender (male) – n (%)	20 (71)	16 (57)	.27
Age (years) – mean (SD)	68 (6.8)	68 (6.7)	.75
Height (m) – mean (SD)	1.70 (0.08)	1.69 (0.08)	.64
Weight (kg) – mean (SD)	80 (13)	75 (11)	.10
Leg length (cm) – mean (SD)	80.6 (5.2)	80.5 (4.5)	.92
Index leg (left) – n (%) ^a	13 (46)	14 (50)	.79
ABI index leg – mean (SD)			
Rest	0.64 (0.19)	1.08 (0.16)	.00
After treadmill walking	0.35 (0.16)	-	
Duration of symptoms (months) – mean (SD)	17 (16)	-	
Uni- or bilateral complaints (unilateral) – n (%)	13 (46)	-	
BMI (kg/m ²) – mean (SD)	28.6 (4.9)	26.4 (4.7)	.10
Smoking			
Current smoker – n (%)	14 (50)	3 (11)	.02
Former smoker – n (%)	11 (39)	14 (50)	
Never smoker – n (%)	3 (11)	11 (39)	
Hypertension – n (%)	19 (68)	6 (21)	.00
Diabetes Mellitus – n (%)	7 (25)	1 (4)	.05
Cardiac disease – n (%) ^b	8 (29)	2 (7)	.08
Transient ischemic attack – n (%)	2 (7)	1 (4)	1.00
COPD – n (%)	4 (14)	3 (11)	1.00
Osteoarthritis – n (%)	4 (14)	1 (4)	.35

a: index leg = most symptomatic leg in IC patients and randomly selected for controls. b: cardiac. ABI = ankle-brachial index; BMI = body mass index; cardiac disease included coronary artery disease, arrhythmia, pacemaker; COPD = chronic obstructive pulmonary disease.

Pain-free versus painful walking in patients with IC

For the comparison between pain-free and painful walking in IC patients, differences were only found in the sub phases of the stance phase. The relative duration of flat foot increased significantly from 54.4% to 56.8% ($P=.002$), while the relative contribution of propulsion decreased from 34.0% to 31.6% ($P<.001$) when claudication pain presented. In addition, mean flat foot time increased by 0.02 seconds ($P<.001$) whereas mean propulsion time decreased by 0.02 seconds ($P<.001$) during painful walking.

No asymmetry in gait parameters was found when comparing the index leg (i.e. most symptomatic IC leg) and the contralateral leg, for both the pain-free and painful session (data not shown). A subanalysis of the unilateral IC patients ($n=13$) also revealed no significant differences between both legs of IC patients.

Table 2. Gait characteristics of IC patients compared to age-matched controls

Variables	IC patients (n=28)		P-value ¹	Controls (n=28)	P-value ²	P-value ³
	Pain-free	Painful				
Speed, km/h	3.3 (0.6)			4.5 (0.8)	<.001	
Step length, cm	49.2 (8.4)	50.0 (8.7)	.028	61.3 (9.8)	<.001	<.001
Stride length, cm	99.6 (3.0)	99.9 (3.0)	.615	123.6 (19.5)	<.001	<.001
Cadence, steps/min	111 (7.9)	110 (8.0)	.729	122 (9.6)	<.001	<.001
Contact time, sec	0.74 (0.06)	0.74 (0.07)	.748	0.65 (0.1)	<.001	<.001
Single support, %	32.4 (2.5)	31.7 (2.9)	.008	34.7 (2.2)	.001	<.001
Double support, %	35.3 (4.3)	36.0 (4.7)	.026	31.0 (4.4)	.001	<.001
Stance phase, %	67.7 (2.3)	67.6 (2.3)	.879	65.7 (2.5)	.003	.004
Swing phase, %	32.3 (2.3)	32.4 (2.3)	.966	34.3 (2.5)	.003	.003
Contact phase, %	11.6 (2.6)	11.6 (3.7)	.884	12.4 (2.5)	.217	.356
Contact phase, s	0.08 (0.02)	0.09 (0.03)	.777	0.08 (0.02)	.389	.422
Foot flat phase, %	54.4 (7.1)	56.8 (7.0)	.002	49.5 (6.1)	.007	<.001
Foot flat phase, s	0.40 (0.07)	0.42 (0.07)	.001	0.32 (0.06)	<.001	<.001
Propulsion, %	34.0 (6.5)	31.6 (5.9)	<.001	38.1 (5.9)	.016	<.001
Propulsion, %	0.25 (0.05)	0.23 (0.04)	.001	0.25 (0.04)	.810	.164

Step length = distance between heels of two subsequent feet. Contact time = time when the foot is in contact with the ground. Single support = time when only one foot touches the ground. Double support = sum of two partial double supports of one gait cycle. Stance phase = similar to the contact time but expressed as percentage of one gait cycle. Contact phase = moment between first contact of the heel (e.g. heel strike) to foot flat. Foot flat = moment that foot completely touches the ground. Propulsion = moment from lifting the heel to complete set off of the tip of the foot (figure 1). 1 = paired t-test: pain-free versus painful within IC patients group; 2 = independent-samples t-test: pain-free versus control; 3 = independent-samples t-test: painful versus control.

Correlations

No clinically relevant or significant correlations were found between ABI values and any gait parameters. In healthy controls walking speed was moderately correlated with relative duration of the propulsion phase ($\rho=.541$, $P=.005$). Whereas, no correlation was found for these variables in IC patients ($\rho=.187$, $P=.341$). Foot flat time on the other hand was significantly correlated to walking speed in both IC patients and controls (*figure 3*).

IC patients: $r = -.565$, $P = .002$; controls: $r = -.784$, $P < .001$.

Figure 3. Scatterplot of the time for flat foot and walking speed

DISCUSSION

The purpose of this study was to explore spatio-temporal gait parameters in patients with IC during continuous treadmill walking. This is the first study that also investigated individual phases of the stance phase in this patient population using this approach. Patients with IC walked 27% slower and spent a larger percentage in stance phase than

healthy controls. In addition, distinct differences were present for the separate segments of the stance phase. A 14% decrease in propulsion duration and a 17% increase in foot flat duration were observed in IC patients. Interestingly, these alterations were already present before claudication pain started.

Previous research reported contrasting findings regarding altered gait pattern in patients with IC. Most studies observed differences in percentage of stance phase and double support,⁹ walking speed and cadence^{25, 26} that are in line with our results. While some described no effect of claudication on several temporal and spatial gait measures.^{27, 28} However, the relatively small samples sizes²⁸ and the use of papered walkways with stopwatch recording²⁷ might explain the lack of differences in these latter studies, as study populations were comparable with our IC patients in terms of age and ABIs.

A unique aspect of the present study is the assessment of gait parameters during continuous treadmill walking. We based our results on 80 steps, while others obtained data from just a couple of steps during a short 4 to 7 meter walkway.^{1, 9} In the study of McCully et al., patients walked on a treadmill until a sufficient pain level was obtained followed by gait measurements during overground walking.²⁹ Our treadmill based methodology also allowed for data capturing immediately after the pain threshold was reached, thereby excluding confounding due to possible recovery processes. Based on this optimized and standardized methodology, we are confident that the results of the present study truly reflect the alterations in gait pattern that occur in patients with IC.

Differences in gait patterns between IC patients and controls are deemed important for several reasons. Walking is one of the most important activities of daily human life. From the very first step that is made, individual gait patterns are optimized as walking is the most economical means of locomotion. Gait speed is known to be an independent predictor of all-cause mortality³⁰ and gait speed differences between 0.36 km/h to 0.72 km/h are termed 'clinically relevant'.³¹ The difference as found in the present study was (at least) twice as large (1.2 km/h) and biomechanical gait alterations might contribute to the slower walking speed of IC. Insight and subsequent improvement of the gait pattern might therefore contribute to the prognosis of IC patients. The difference in propulsion (14%) between painful walking in IC and controls revealed a Cohen's d effect size of 0.48, which may be interpreted as a medium effect. So, even small differences may have a substantial impact.

The precise explanation for the gait changes in IC is still unknown. There may be a pathophysiological mechanism, related to the lower blood flow of IC patients,³² which partly explains the gait changes as observed in patients with IC. The present study showed that IC patients spend a significantly shorter percentage of the gait cycle in propulsion and a significantly longer percentage in flat foot position. Expressed in absolute time however, only a significantly longer flat foot position was found. Hence, the additional time per gait cycle as a consequence of the slower walking pace in IC, is completely used for the flat foot phase. This phenomenon may reflect an intuitive adaptation since skeletal muscles blood flow mainly occurs during the relaxation phase of dynamic exercising. The relaxation period in part determines the magnitude of arterial inflow.³³ It may therefore seem that, analogous to the definite walking stops when claudication pain maximizes, IC patients have already ‘discontinued’ walking for a longer period during every step, as a means to allow for sufficient blood inflow and supply of oxygen. This hypothesis may also explain why IC patients take fewer rather than shorter steps when claudication pain develops.²⁵

Calf muscle weakness has previously been described as a potential mechanism underlying IC gait adaptations.³⁴ The calf muscles are known to constitute most to the propulsion¹¹ and a recent study demonstrated a reduced dynamic capability of these muscles in IC.³⁵ These findings are in accordance with both the results of another study which reported a shorter time until maximum plantar flexion occurred³⁶ and our findings of reduced propulsion. Subsequently, propulsion is the main determinant of walking speed.¹¹ Reduced walking speed in IC might therefore be a consequence of decreased calf muscle strength and propulsion, as well as a compensatory strategy to allow for a longer relaxation phase.

Strategies to improve walking speed might be a valuable starting point for the clinical management of these patients. Walking at a higher speed during SET might increase training efficiency, as patients are thought to reach the claudication threshold earlier by superseding the compensatory mechanism. On the other hand, a higher walking speed might also be advantageous in terms of walking economy, since IC patients are known walking at a velocity below the optimal point of energy costs.³⁷ Future studies may focus on the value of treadmill training on a higher pace. Besides, effort to increase calf muscle strength could also be vital to improve propulsion and eventually the gait pattern of IC.

Last, the value of rollover footwear (i.e. MBT footwear) might be of particular interest for IC patients. Previous research described reduced peak internal plantarflexion ankle moments during propulsion, without change in metabolic costs or walking speed.³⁸

Some study limitations need to be addressed. First, we included only participants without additional comorbidities (e.g. osteoarthritis or previous lower limb surgery) potentially affecting the gait pattern. Therefore, the present findings were obtained in IC patients who were in a relatively good condition. As a consequence, the present results might be overestimated in favor of a relatively normal gait pattern. Besides, results may be not generalized to IC patients with numerous comorbid conditions. Second, we captured data during treadmill walking which is not necessarily similar to overground walking. However, Riley et al. reported identical kinematic and kinetic parameters during treadmill and overground gait.³⁹ It is thus felt that movement analysis during treadmill walking reveals valid results, all the more so when taking other advantages of treadmill-based protocols into account. One might question the influence of a treadmill protocol on the lack of asymmetry in spatio-temporal parameters, especially in unilateral IC patients, as found in this study. However, Gardner also found no asymmetry in IC patients during an overground walking protocol.⁹ Third, the present research included spatio-temporal analysis only. As data on kinematics, kinetics and surface electromyography were lacking, we were not able to provide additional views from alternative perspectives. However, our findings might serve as a starting point for further research to elucidate underlying mechanisms of impaired walking function in patients with IC. Future research should focus on muscle contraction patterns to address the exact relation between distal muscles relaxation during flat foot, and the subsequent contraction during propulsion.

In conclusion, patients with intermittent claudication demonstrate altered spatio-temporal gait parameters during treadmill walking that happen before the actual onset of claudication pain. The gait pattern is characterized by a slower walking pace and longer double support phase and stance phase. The prolonged flat foot phase might be a possibly compensatory mechanism contributing in a reduced walking speed. Future research should focus on strategies to improve walking speed.

ACKNOWLEDGEMENTS

We would like to thank Lode B.V. Groningen and Procure B.V. Groningen for providing a treadmill and Microgate Italy and Procure B.V. Groningen for the Optogait® system. We would like to thank Ingeborg Trul, human movement scientist at Procure B.V. for her technical support. Last, we greatly appreciated the help of Jos Swinkels, nurse practitioner at St. Anna Hospital Geldrop, for the recruitment of study participants.

REFERENCES

1. Crowther RG, Spinks WL, Leicht AS, Quigley F, Golledge J. Relationship between temporal-spatial gait parameters, gait kinematics, walking performance, exercise capacity, and physical activity level in peripheral arterial disease. *J Vasc Surg.* 2007;45(6):1172-8.
2. Lauret GJ, Fokkenrood HJ, Bendermacher BL, Scheltinga MR, Teijink JA. Physical activity monitoring in patients with intermittent claudication. *Eur J Vasc Endovasc Surg.* 2014;47(6):656-63.
3. Camara LC, Ritti-Dias RM, Meneses AL, D'Andrea Greve JM, Filho WJ, Santarem JM, et al. Isokinetic strength and endurance in proximal and distal muscles in patients with peripheral artery disease. *Ann Vasc Surg.* 2012;26(8):1114-9.
4. Mays RJ, Casserly IP, Kohrt WM, Ho PM, Hiatt WR, Nehler MR, et al. Assessment of functional status and quality of life in claudication. *J Vasc Surg.* 2011;53(5):1410-21.
5. Marconi C, Ferretti G, Anchisi S, Catalano M, Scandale G, Antico A, et al. Energetics of walking in patients with peripheral arterial disease: a proposed functional evaluation protocol. *Clin Sci (Lond).* 2003;105(1):105-11.
6. Gardner AW, Ritti-Dias RM, Stoner JA, Montgomery PS, Scott KJ, Blevins SM. Walking economy before and after the onset of claudication pain in patients with peripheral arterial disease. *J Vasc Surg.* 2010;51(3):628-33.
7. Womack CJ, Sieminski DJ, Katzel LI, Yataco A, Gardner AW. Improved walking economy in patients with peripheral arterial occlusive disease. *Med Sci Sports Exerc.* 1997;29(10):1286-90.
8. Cavagna GA, Thys H, Zamboni A. The sources of external work in level walking and running. *J Physiol.* 1976;262(3):639-57.
9. Gardner AW, Forrester L, Smith GV. Altered gait profile in subjects with peripheral arterial disease. *Vasc Med.* 2001;6(1):31-4.
10. Astephen JL, Deluzio KJ. Changes in frontal plane dynamics and the loading response phase of the gait cycle are characteristic of severe knee osteoarthritis application of a multidimensional analysis technique. *Clin Biomech (Bristol, Avon).* 2005;20(2):209-17.
11. Winter DA. Biomechanical motor patterns in normal walking. *J Mot Behav.* 1983;15(4):302-30.

12. Koutakis P, Johanning JM, Haynatzki GR, Myers SA, Stergiou N, Longo GM, et al. Abnormal joint powers before and after the onset of claudication symptoms. *J Vasc Surg.* 2010;52(2):340-7.
13. Leeper NJ, Myers J, Zhou M, Nead KT, Syed A, Kojima Y, et al. Exercise capacity is the strongest predictor of mortality in patients with peripheral arterial disease. *J Vasc Surg.* 2013;57(3):728-33.
14. King S, Vanicek N, Mockford KA, Coughlin PA. The effect of a 3-month supervised exercise programme on gait parameters of patients with peripheral arterial disease and intermittent claudication. *Clin Biomech (Bristol, Avon).* 2012;27(8):845-51.
15. Fakhry F, van de Luijngaarden KM, Bax L, den Hoed PT, Hunink MG, Rouwet EV, et al. Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg.* 2012;56(4):1132-42.
16. McCully K, Leiper C, Sanders T, Griffin E. The effects of peripheral vascular disease on gait. *J Gerontol A Biol Sci Med Sci.* 1999;54(7):B291-4.
17. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc.* 1991;23(4):402-8.
18. Centre JHA. ACR clinical classification criteria for OA of Hip. 2013; Available from: http://www.hopkinsarthritis.org/physician-corner/education/arthritis-education-diagnostic-guidelines/#class_hip.
19. Centre JHA. ACR clinical classification criteria for OA of Knee. 2013; Available from: http://www.hopkinsarthritis.org/physician-corner/education/arthritis-education-diagnostic-guidelines/#class_knee.
20. Vaughan CL, B.L.O.C. D. Dynamics of gait. 2 ed. Cape Town, South Africa: Kiboho publisher; 1999.
21. Van de Putte M, Hagemester N, St-Onge N, Parent G, de Guise JA. Habituation to treadmill walking. *Biomed Mater Eng.* 2006;16(1):43-52.
22. ACoS M. Guidelines for Exercise Testing and Prescription. Philadelphia: Wolters Kluwer/ Lippincott Williams & Wilkins; 2014.
23. Lienhard K, Schneider D, Maffiuletti NA. Validity of the Optogait photoelectric system for the assessment of spatiotemporal gait parameters. *Med Eng Phys.* 2013;35(4):500-4.

24. Lee MM, Song CH, Lee KJ, Jung SW, Shin DC, Shin SH. Concurrent Validity and Test-retest Reliability of the OPTOGait Photoelectric Cell System for the Assessment of Spatio-temporal Parameters of the Gait of Young Adults. *J Phys Ther Sci*. 2014;26(1):81-5.
25. Mockford KA, Vanicek N, Jordan A, Chetter IC, Coughlin PA. Kinematic adaptations to ischemic pain in claudicants during continuous walking. *Gait Posture*. 2010;32(3):395-9.
26. Scherer SA, Bainbridge JS, Hiatt WR, Regensteiner JG. Gait characteristics of patients with claudication. *Arch Phys Med Rehabil*. 1998;79(5):529-31.
27. Scherer SA, Hiatt WR, Regensteiner JG. Lack of relationship between gait parameters and physical function in peripheral arterial disease. *J Vasc Surg*. 2006;44(4):782-8.
28. Gardner AW, Montgomery PS, Ritti-Dias RM, Forrester L. The effect of claudication pain on temporal and spatial gait measures during self-paced ambulation. *Vasc Med*. 2010;15(1):21-6.
29. McCully KK, Landsberg L, Suarez M, Hofmann M, Posner JD. Identification of peripheral vascular disease in elderly subjects using optical spectroscopy. *J Gerontol A Biol Sci Med Sci*. 1997;52(3):B159-65.
30. Toots A, Rosendahl E, Lundin-Olsson L, Nordstrom P, Gustafson Y, Littbrand H. Usual gait speed independently predicts mortality in very old people: a population-based study. *J Am Med Dir Assoc*. 2013;14(7):529 e1-6.
31. Bohannon RW, Glenney SS. Minimal clinically important difference for change in comfortable gait speed of adults with pathology: a systematic review. *J Eval Clin Pract*. 2014;20(4):295-300.
32. Sorlie D, Myhre K. Lower leg blood flow in intermittent claudication. *Scand J Clin Lab Invest*. 1978;38(2):171-9.
33. Radegran G, Saltin B. Muscle blood flow at onset of dynamic exercise in humans. *Am J Physiol*. 1998;274(1 Pt 2):H314-22.
34. Chen SJ, Pipinos I, Johanning J, Radovic M, Huisinga JM, Myers SA, et al. Bilateral claudication results in alterations in the gait biomechanics at the hip and ankle joints. *J Biomech*. 2008;41(11):2506-14.
35. King S, Vanicek N, O'Brien TD. Dynamic muscle quality of the plantar flexors is impaired in claudicant patients with peripheral arterial disease and associated with poorer walking endurance. *J Vasc Surg*. 2015;62(3):689-97.

36. Celis R, Pipinos II, Scott-Pandorf MM, Myers SA, Stergiou N, Johanning JM. Peripheral arterial disease affects kinematics during walking. *J Vasc Surg.* 2009;49(1):127-32.
37. Womack CJ, Sieminski DJ, Katzel LI, Yataco A, Gardner AW. Oxygen uptake during constant-intensity exercise in patients with peripheral arterial occlusive disease. *Vasc Med.* 1997;2(3):174-8.
38. Forghany S, Nester CJ, Richards B, Hatton AL, Liu A. Rollover footwear affects lower limb biomechanics during walking. *Gait Posture.* 2014;39(1):205-12.
39. Riley PO, Paolini G, Della Croce U, Paylo KW, Kerrigan DC. A kinematic and kinetic comparison of overground and treadmill walking in healthy subjects. *Gait Posture.* 2007;26(1):17-24.

CHAPTER 9

Altered joint kinematics and increased electromyographic muscle activity during walking in patients with intermittent claudication

L.N.M. Gommans
A.T. Smid
M.R.M. Scheltinga
F.A.M. Brooijmans
E.M.J. van Disseldorp
F.Th.P.M. van der Linden
K. Meijer
J.A.W. Teijink

ABSTRACT

Background: Patients with intermittent claudication (IC) tend to walk at a slower pace, have less lower leg muscle strength and consume about 40% more oxygen during walking compared to healthy individuals. An unfavorable locomotion pattern has been suggested to explain this metabolic inefficiency. However, knowledge on gait patterns in IC is limited. Muscle activity patterns during walking as measured by surface electromyography (EMG) were never investigated in this patient population.

Methods: In this cross-sectional study, gait pattern of newly diagnosed IC patients and age-matched controls were evaluated using kinematic parameters and medial gastrocnemius (MG) and tibialis anterior (TA) muscles activity patterns. The protocol included pain-free and painful (only IC patients) treadmill walking sessions.

Results: A total of 22 IC patients and 22 healthy controls were included. Patients walked 1.4 km/h slower (3.2 km/h vs. 4.6 km/h, $P<.001$) than controls, coinciding with a 10% slower cadence (110 steps/min vs. 122 steps/min, $P<.001$). The kinematic analysis resulted in a patient's ankle plantar flexion reduction of 45% during the propulsion phase, and ankle dorsal flexion reduction of 41% at initial contact. No additional kinematic changes were observed once claudication pain presented. Interestingly, kinematic differences did not influence the muscle activity duration during walking, as equal duration of muscle activity was found in IC patients and healthy controls. However, amount of muscle activity in microvolts did significantly increase in IC patients when claudication pain presented (TA: $\Delta 23\%$, $P<.001$; MG: $\Delta 54\%$, $P=.007$).

Conclusion: Patients with IC demonstrate significant kinematic changes during walking. These alterations did not affect EMG activity duration of MG and TA muscles. However, EMG amplitude of both muscles did significantly increase during painful walking in IC patients.

INTRODUCTION

Peripheral arterial disease (PAD) is a chronic disease of the lower extremities caused by systemic atherosclerosis, affecting more than 12% of the population >65 years.¹ Intermittent claudication (IC) is the most common manifestation of PAD and is characterized by limb pain during exercise that resolves after a short period of rest. Patients with IC demonstrated reduced walking performance² and revealed higher prevalence of falls³ compared to non-IC patients. Studies have demonstrated several mechanisms for these impairments,^{4, 5} as patients were found to have less peak propulsion force, and a reduced ability to swing their legs forward.⁶

Other studies have suggested that the energy cost of locomotion is almost 40% greater in IC.⁷ Various mechanisms may be responsible for this higher cost of locomotion. For instance a maladapted and unfavorable gait pattern based on IC induced neuromuscular dysfunction. Patients with IC may use the same muscles, but with a different sequence of fibre recruitment⁷, as a result of chronic fibre changes following exercise induced ischemia.⁸ Previous studies already found that lower extremity ischemia has a direct, negative effect on calf muscle diameter, density and muscle fibre types.^{8, 9}

Surface electromyography (EMG) is a non-invasive technique that measures muscle action potentials that occur during muscle contraction while performing motor tasks, such as walking.¹⁰ The electrical activity is recorded by means of surface electrodes that are placed on the skin overlying a muscle or group of muscles.¹¹ It is a widely used method to determine activation patterns of different muscles (i.e. timing, 'on-off pattern') and it allows to study normal and pathological motor strategies.¹² Surface EMG has been demonstrated to be a feasible and valid method to record muscle activity.¹³ A recent study in patients after total hip arthroplasty also included EMG as an adjunctive tool that complements gait analysis.¹⁴ To our knowledge, surface EMG analyses during walking was not previously performed in patients with IC. This method may yield valuable information in IC patients as a means to investigate the previously suggested neuromuscular dysfunction. Chronic ischemia as present in IC, may lead to alterations in motor unit recruitment (EMG amplitudes) and/or muscle coordination patterns. EMG evaluation examined together with kinematics (joint angles) provides a thorough insight into muscle performance and their role in accomplishing motor tasks.¹⁰

The primary aim of the current study was to determine lower extremity joint angles and EMG patterns in patients with IC and in healthy controls during continuous treadmill walking. Besides, the effect of claudication pain on these gait parameters was studied. We hypothesized that patient with IC demonstrate less range of ankle and knee motion and generate a different pattern of muscle activity compared to healthy controls.

METHODS

Participants

Patients were recruited from a population presenting between October 2014 and March 2015 with new onset manifestations of IC at the Vascular Surgery outpatient departments of three regional Dutch hospitals (Catharina Hospital Eindhoven, Maxima Medical Center Veldhoven and St. Anna Hospital Geldrop). According to standardized institutional protocols, potential patients underwent an ankle-brachial index (ABI) measurement in rest and following exercise. Individuals demonstrating a resting ABI <0.90 and/or an ABI drop >0.15 after treadmill exercise¹⁵ and typical symptoms of claudication in at least one leg, were eligible for this study. Additional inclusion criteria were presence of symptoms >4 weeks and the ability to walk on a treadmill for ≥ 1 minute. Patients were excluded if they suffered from a comorbid condition possibly influencing the gait pattern, such as lower extremity amputation, severe osteoarthritis, knee or hip prosthesis, severe cardiopulmonary problems (i.e. chronic obstructive pulmonary disease $\geq$ Gold III and/or New York Heart Association $\geq$ III), neurological diseases such as peripheral polyneuropathy (based on history and eventual physical examination), Parkinson's disease, or stroke, previous lower extremities surgery (e.g. bypass, percutaneous vascular intervention), use of walking aids, orthopedic shoes or medication influencing walking pattern (e.g. psychotropic medication). Patients who experienced rest pain, suffered from chronic wounds or had received more than five sessions of supervised exercise therapy (SET) during the preceding three years were also excluded.

Age-matched control subjects were recruited from family, friends and hospital personnel. They were exhibiting an ABI in rest >0.90 and did not experience any pain or limitations during walking. Other exclusion criteria were similar as for the group of

patients. Participants that were willing to participate were counseled prior to providing written informed consent. All procedures were approved by the Medical Ethical Committee of the Catharina Hospital Eindhoven, the Netherlands.

Study protocol

Two researchers (LG and AS) were responsible for data collection. Height and weight measurements allowed calculation of the body mass index (BMI). Leg length was determined with a tape measure in standing position and defined as the distance from the major trochanter of the hip to the inferior aspect of the lateral malleolus.

After anthropometric measurements, participants walked for ten minutes (for IC patients, with intervals of rest if necessary) on a treadmill system to get familiarized with the system¹⁶ and to determine a 'preferred' walking pace, defined as 'walk at a pace that is comfortable and comparable to your outside walking'.¹⁶ The treadmill was started at 2.4 km/h and speed was increased in 0.1 km/h increments until this comfortable walking speed was achieved. Speed was then further increased until a rapid pace was attained, and decreased until the comfortable speed was reached once again. Gait measurements were obtained at this final, self-selected comfortable walking pace.

Following a short period of rest, participants received reflective markers that were placed at specific anatomical locations of each participants' lower limb (*figure 1*). The two-dimensional (2D) marker trajectories were captured with a high-speed real-time camera (Basler, 1394a/b, GigE) and its software system (Simi Aktysis version 1.4.1.2, Simi Reality Motion Systems GmbH, Unterschleissheim, Germany) sampling at 100 samples/seconds (hertz). Before placement of surface EMG probes, skin sites were cleaned with 70% isopropyl alcohol and hair was removed if necessary. The wireless EMG probes (BTS FreeEMG, BTS Bioengineering Corp., Brooklyn, USA) were attached to the skin via pre-gelled disposable Ag-electrodes (Kendall ECG electrodes H124SG) and positioned over the medial gastrocnemius (MG) muscle and tibialis anterior (TA) muscle following the SENIAM recommendations.¹¹ MG and TA were assessed as these muscles are considered main actuators of the ankle.¹⁷ Besides, the MG muscle is the most common site of ischemic pain that limits exercise tolerance in IC.¹⁸ Recording muscle electrical activity using surface EMG during gait has been found to demonstrate a sufficient repeatability, reliability and consistency.¹⁹ Data were captured at 1000 hertz and synchronized with the

kinematic data using a triggerbox. Data were real time stored and converted into digital signals by the EMG-Analyzer software program (BTS Bioengineering Corp., Brooklyn, USA).

After 20 minutes of rest following marker and electrode application, IC patients again started walking on the treadmill. During one minute of painless walking, gait parameters were obtained. Once IC patients experienced claudication pain as determined using a 4-point Claudication Pain Scale, gait parameters were again captured for one minute. Control subjects underwent similar measurements just once (i.e. pain-free trial). All participants walked bare feet on a flat treadmill.

Kinematic data analysis

The position of the reflective markers provided a proper 2D lower extremity segment orientation and knee and ankle joint angles during walking. The maximal forward trajectory of the lateral malleolus reflective marker in the sagittal plane was used as an indication of heel strike. All kinematic parameters were normalized to 100% of the gait cycle (e.g. 100 points representing heel strike to the following heel strike) using a cubic spline interpolation technique. Forty representative cycles were selected for each participant to determine following (averaged) parameters: range of motion (ROM), maximum and minimum joints' flexion and extension angles, and joints' angles at the moment of heel strike. All signal processing and calculations were performed using a customized program that was created in Matlab R2012a (Mathworks Inc, Natick, Massachusetts, USA).

EMG data analysis

After digitalization of the raw EMG signals, further processing and analysis were performed in a customized Matlab program. The EMG signal was high-pass filtered (cut-off frequency of 20 hertz) to suppress potential movement artifacts, full-wave rectified by subtracting the mean off-set value from the absolute signal values, and then low-passed filtered (cut-off frequency of 6 hertz) to create linear envelope EMG signals. A power spectrum analysis confirmed that chosen cut-off settings were appropriate. EMG data were normalized to a 100% gait cycle using the kinematic data of the lateral malleolus marker. Similarly, forty gait cycles were used to calculate the ensemble average percentage

of muscle activity and peak performance (in microvolts) for the MG and TA muscles per gait cycle. The threshold for muscle onset was based on a 25% of the mean peak value of the EMG signal during walking.²⁰

Left picture: LED lights are positioned on the bony landmarks of the lower limb, to determine the knee and ankle joint angles, respectively. A=knee joint angle; C=ankle joint angle. Current positions are set at zero degrees. B=EMG device on the tibialis anterior muscle. Middle picture: position of the EMG device on the tibialis anterior muscle, dashed circle indicated the muscle belly (D). Right picture: position of the EMG device on the medial gastrocnemius muscle, dashed circle indicated the muscle belly(E).

Figure 1. Measurement set up

Statistical analysis

Differences in kinematic and EMG parameters of the index leg in IC patients and controls were studied. In IC patients, the most symptomatic leg was considered the index leg. In controls, the index leg was randomly selected. Evaluation within the patient group was performed by comparing the values of the pain-free and painful trial, respectively. A Pearson's chi-square test was used for analysis of differences between categorical variables, whereas an independent samples t-test and paired t-test analyzed continuous

variables. Variables that lacked normal distribution were expressed as median and interquartile range. A Mann Whitney U-test and a Wilcoxon signed-rank test were used to study these variables. Pearson's correlation coefficients (Rho: ρ) were calculated to study associations between kinematic data and EMG data. Multivariate regression analyses were performed to study the effect of walking speed on kinematic and EMG outcomes. Statistical significance was applied at $P < .05$. SPSS software version 20.0 (IBM Corporation, Armonk, New York, USA) was used for the statistical analysis.

Sample size calculation was based on duration of muscle activity per gait cycle, which was considered the primary outcome. As data of IC patients are not available, data from patients after total hip arthroplasty instead were used.¹⁴ Calculation (using $\alpha = 0.05$ and $\beta = 0.80$) revealed that 16 subjects per group were required to attain a statistical significant difference of 5% gastrocnemius activity.

RESULTS

Study population

The study population consisted of 22 IC patients and 22 age-matched controls. Baseline characteristics were similar, except for current smoking and hypertension, which were more prevalent among IC patients (*table 1*). ABIs of patients during rest and after treadmill walking were 0.64 and 0.35, respectively (*table 1*). A total of 9 patients (41%) had unilateral IC complaints. IC patients walked at a 1.4 km/h slower pace and demonstrated a significantly lower cadence and shorter step length compared to the controls (*table 2*).

Kinematic parameters in IC

Except for a significant difference in total knee ROM ($\Delta 1.3^\circ$, $P < .019$), no differences were found when comparing pain-free and painful walking in patients with IC (*table 2*). However, evident differences were present between IC patients and controls. Patients with IC demonstrated approximately 7° less knee flexion after heel strike (IC: 10.9° vs. controls: 18.4° , $P < .001$, *figure 2*). There was also a significant difference in total ankle ROM ($\Delta 7^\circ$, IC: 18.3° vs. controls: 25.3° , $P < .001$), predominantly due to a decreased peak

plantar flexion ($\Delta 8.3^\circ$, IC: -10.2° vs. controls: -18.5° , $P < .001$, *figure 3*). Moreover, IC patients were found to exhibit less ankle ROM from initial heel contact to the flat foot position ($\Delta 2.3^\circ$, IC: 3.3° vs. controls: 5.6° , $P = .001$). No differences in variability of total ROM for respectively the knee and ankle joints between IC patients and controls were found (*table 2*).

In healthy controls, a significant correlation was found between walking speed and peak plantar flexion ($\rho = -.709$; $P < .001$). In contrast, this correlation was not found in IC patients ($\rho = -.388$, $P = .074$). Multivariate regression analyses revealed a significant contribution of walking speed to the difference in maximal ankle plantar flexion between IC and controls ($P < .001$), accounting for 64% of the explained variance.

Surface electromyography in IC

Analysis of the EMG signals included 19 controls (86%) and 18 IC patients (82%) as EMG data of 3 controls and 4 IC patients were corrupted and therefore not used. Figure 4 presents the EMG activity of the MG and TA muscles in a typical IC patient, as generated by the present study. In IC patients, no differences were found in MG muscle activity when comparing pain-free and painful walking. The TA muscle activity on the other hand, decreased significantly once claudication pain occurred (pain-free: 58% activity of the gait cycle, painful: 49% activity of the gait cycle; $P = .005$). In addition, a significant increase of peak muscle activity was found for both muscles during painful ambulation (MG: +54%, $P = .007$; TA: +23%, $P < .001$). For the comparison between patients and controls no differences were found for the MG muscle. Both groups used the MG muscle for approximately 43% of the gait cycle. Differences for the TA muscle tended to be more distinct, but were not significantly different (*table 3*).

For healthy controls, walking speed was significantly correlated to the position of peak MG muscle activity, as percentage of the gait cycle ($\rho = .543$, $P = .020$), whereas this correlation was not found in IC patients ($\rho = .068$, $P = .789$). In addition, no correlations were found between either EMG parameters and ABI indices or EMG parameters and kinematic outcomes.

Table 1. Demographics of study groups undergoing gait analysis

Characteristics	IC patients (n=22)	Controls (n=22)	P-value
Gender (male) – n (%)	17 (77)	16 (73)	.73
Age (years) – mean (SD)	69 (6.6)	69 (6.6)	.80
Height (m) – mean (SD)	1.70 (0.08)	1.70 (0.08)	.84
Weight (kg) – mean (SD)	80 (12)	76 (12)	.33
Leg length (cm) – mean (SD)	81 (4.3)	81 (5.8)	1.00
Index leg (left) – n (%) ^a	11 (50)	10 (46)	.76
ABI index leg – mean (SD)			
Rest	0.64 (0.2)	1.1 (0.2)	<.001
After treadmill walking	0.32 (0.13)	-	
Duration of symptoms (months) – mean (SD)	19 (17)	-	
Uni- or bilateral complaints (unilateral) – n (%)	9 (41)	-	
BMI (kg/m ²) – mean (SD)	27.3 (3.4)	26.3 (3.5)	.30
Smoking			
Current smoker – n (%)	12 (55)	2 (9)	.03 ^b
Former smoker – n (%)	8 (36)	11 (50)	
Never smoker – n (%)	2 (9)	9 (41)	
Hypertension – n (%)	15 (68)	6 (27)	.01
Diabetes Mellitus – n (%)	6 (27)	1 (5)	.10 ^c
Cardiac disease – n (%) ^d	6 (27)	2 (9)	.24 ^c
Transient ischemic attack – n (%)	2 (9)	1 (4.5)	1.00 ^c
COPD – n (%)	3 (14)	2 (9)	1.00 ^c
Osteoarthritis – n (%)	3 (14)	1 (5)	.61 ^c

ABI=ankle-brachial index; BMI=body mass index; COPD=chronic obstructive pulmonary disease; a=index leg, most symptomatic leg in IC patients, randomly selected for controls; b=Fisher's Exact test, calculation was based on never smoker and former smoker versus current smoker; c=Fisher's Exact test; d=cardiac diseases included coronary artery disease, arrhythmia, pacemaker.

Table 2. Gait parameters in IC patients (n=22) and healthy controls (n=22)

Variables Mean (±SD)	IC patients		P-value ^a	Controls	P-value ^b	P-value ^c
	Pain-free	Painful				
Walking speed, km/h	3.2 (0.6)			4.6 (0.8)		<.001
Cadance, steps/min	110 (7.1)			122 (9.2)		<.001
Step length, cm	48.2 (8.7)	48.8 (9.0)	.758	62.4 (10.6)		<.001
Knee heel strike ^d	12.0 (6.9)	11.2 (7.5)	.213	7.3 (5.2)	.014	.054
Knee heel strike to weight support ROM ^e	10.5 (5.7)	10.9 (6.0)	.238	18.4 (4.6)	<.001	<.001
Knee total ROM	56.2 (6.0)	57.5 (6.7)	.019	59.5 (5.2)	.056	.269
Knee sd total ROM	1.6 (0.2)	1.7 (0.3)	.138	1.6 (0.4)	.606	.231
Ankle plantar flexion	-10.6 (4.5)	-10.2 (3.8)	.372	-18.5 (6.5)	<.001	<.001
Ankle dorsiflexion	7.7 (4.2)	8.1 (3.9)	.156	6.7 (4.0)	.462	.265
Ankle heel strike ROM ^f	3.4 (2.0)	3.3 (2.2)	.643	5.6 (1.9)	.001	.001
Ankle total ROM	18.3 (3.5)	18.3 (3.6)	.961	25.3 (5.6)	<.001	<.001
Ankle sd ROM	1.2 (0.2)	1.2 (0.3)	.995	1.2 (0.3)	.446	.484

sd= standard deviation; a=paired t-test between pain-free and painful trial; b=independent samples t-test: pain-free versus control; c=independent samples t-test: painful versus control; d= knee angle during heel strike (initial contact); e=ROM between heel strike and complete weight support; f= ROM of the ankle between heel strike and flat foot position.

Table 3. Electromyographic analysis in IC patients (n=18) and healthy controls (n=19)

Variables Mean (±SD)	IC patients		P-value ^a	Controls	P-value ^b	P-value ^c
	Pain-free	Painful				
MG activity ^d , %	43.7 (7.0)	42.6 (9.6)	.497	43.1 (7.0)	.829	.773
TA activity ^d , %	58.0 (12.1)	49.0 (7.9)	.005	53.5 (11.6)	.268	.127
MG peak activity ^e , μV	67 (46-97)	103 (83-134)	.007 ^f	91 (57-156)	-	-
TA peak activity ^e , μV	105 (50-127)	129 (101-185)	<.001 ^f	135 (98-169)	-	-
MG peak position ^g , %	45.9 (11.4)	44.6 (14.1)	.604	45.3 (11.8)	.870	.866

IC=intermittent claudication; SD=standard deviation; a=paired t-test between pain-free and painful trial, except for f (see below); b=independent samples t-test: pain-free versus control; c=independent samples t-test: painful versus control; d= duration of muscle activation as percentage of the complete gait cycle, e=peak muscle activity in microvolts, represented in median and interquartile range, f=Wilcoxon signed-rank test, g=position of the peak muscular activity in percentage of the complete gait cycle.

Knee joint angles in the sagittal plane during the complete gait cycle (i.e. heel strike to heel strike) for IC patients during pain-free walking (x), painful walking (-), and healthy controls (*). Dashed vertical line separates the stance phase (~60%) and swing phase (~40%) of the gait cycle.

Figure 2. Knee joint angles in the sagittal plane during the complete gait cycle

Ankle joint angles in the sagittal plane during the complete gait cycle (i.e. heel strike to heel strike) for IC patients during pain-free walking (x), painful walking (-), and healthy controls (*). Dashed vertical line separates the stance phase (~60%) and swing phase (~40%) of the gait cycle. Plantar flexion angles were expressed as negative values, and dorsal flexion angles as positive values.

Figure 3. Ankle joint angles in the sagittal plane during the complete gait cycle

Graphs showing the level of muscle activity (microvolts) of a typical IC patient of the present study. Data of both the medial gastrocnemius (MG, black solid and dashed line) and tibialis anterior (TA, grey solid and dashed line) muscles, during the complete gait cycle for respectively pain-free and painful ambulation, is presented. The dashed vertical line separates the stance phase (~60%) and the swing phase (~40%) of the gait cycle.

Figure 4. Graphs showing the level of muscle activity (microvolts) of a typical IC patient

DISCUSSION

The purpose of this study was to evaluate kinematic gait parameters and muscle activity as assessed via EMG in patients with IC and age-matched controls. To our knowledge, this is the first study investigating both EMG and kinematic parameters using this type of methodology in this patient population. Patients with IC demonstrated a substantially reduced ankle joint displacement during initial contact (-41% dorsal flexion) and the propulsion phase (-45% plantar flexion), resulting in a significantly decreased total ankle ROM compared to healthy controls. Interestingly, no additional differences were found in the ankle joint angles once claudication pain presented itself. The surface EMG analysis revealed no significant differences between IC patients and controls regarding muscular activity duration of the MG and TA muscles. However, painful walking did result in an increased amount of muscle activity (i.e. EMG amplitude) within the group of IC patients. These findings suggest that IC pain due to ischemia coincides with an increased recruitment of motor units and muscle fatigue.

Limb movements are induced by muscles acting over a joint. The lesser ankle ROM as found in the present study might be considered as a compensatory mechanism to minimize the requested duration of muscle contraction (i.e. reduced work load). This

adaptation might be beneficial during painful walking in particular, as limited blood flow and oxygen (i.e. ischemia) are thought to hinder muscle contraction. Our data however indicated that IC patients use their lower limb muscles to a similar percentage of the gait cycle as controls do. Therefore, evidence for our assumption that such data are strongly coupled is not provided yet. These findings however support previous studies which also found no changes in calf muscle activity despite evident changes in ankle movements.²¹ A small number of studies analysing gait patterns in patients with IC reported conflicting results so far. For instance, one group described reduced plantar flexion and total ankle ROM, in line with our results.²² Whereas a second group found an increased ankle ROM²³, although they did not include peak plantar flexion during the start of the swing phase, a moment when the largest ankle plantar flexion is generally found (*figure 3*). It must be appreciated that the present study is unique in its assessment of gait parameters during continuous treadmill walking. Previous research groups based their conclusions on just a limited number of steps^{22,23} while larger number has been recommended.²⁴ Based on this optimized and standardized methodology, we are confident that the results of the present study reflect true alterations in the gait pattern of IC patients.

Walking in IC patients is known to occur at a much greater cost of transport (i.e. walking economy). As a consequence, IC patients consume more oxygen/energy per unit walking distance than matched controls.^{7,25} This phenomenon was judged by some as a consequence of an altered mechanical gait pattern.⁷ As slower walking speeds are known to decrease metabolic efficiency.²⁶ We observed evident kinematic differences in the ankle joint that can in part be explained by the difference in walking velocity between IC and controls. Causality cannot be tested by the cross-sectional nature of the present study, but results imply that both variables are related. Correction of the observed gait abnormalities may therefore contribute to an improved metabolic efficiency and will possibly allow IC patients to continue walking, whereas ischemic pain will likely be postponed. The present study found that gait abnormalities became evident before the onset of claudication pain. Therefore, mechanisms other than restricted blood flow and IC pain may be responsible for the observed ambulatory dysfunction. Reduced calf muscle strength for instance.²⁷ As oxidative damage due to exercise induced ischemia may contribute to metabolic myopathy in the lower extremity muscles.^{28,29} Alternatively, increased fatigability and predominance of type II muscle fibres (i.e. anaerobic and fatigue-prone) of the medial

gastrocnemius were also found in IC patients.³⁰ Muscle weakness and fatigue lead to an increased recruitment of motor units and a rise in EMG amplitude when similar work load (i.e. constant walking speed) is applied. These alterations may be reflected by significantly higher EMG amplitudes during painful ambulation, as found in this study. As fatigue is generally considered an important control parameter for muscular training, current results provide evidence for the beneficial effect of supervised exercise training (SET) recommended to performed at an intensity intensity near maximal pain level.³¹

The current research may fuel the search for novel training modalities of SET aimed to improve gait pattern. As plantar flexion is strongly associated with walking speed,³² one might first focus on improvement of plantar flexion during the pre-swing phase. It has been suggested that a reduced plantar flexion and subsequent inability to propel the body forward also contribute to the increased risk of falling in elderly.³³ Therefore, restoration of gait patterns may be beneficial from this perspective as well. Moreover, the effect of strength training on gait parameters in this patient population may be promising as well. A recent meta-analysis in IC already concluded that progressive resistance training with high intensities is a most effective exercise modality for improving gait speed.³⁴ Furthermore, lower limb strength training was shown to improve gait kinematics in elderly women.³⁵

Some limitations of the present study need to be addressed. First, only participants without additional comorbidities (e.g. osteoarthritis or previous lower limb surgery) were included thereby excluding factors potentially influencing the gait pattern. The present findings were obtained in patients who were in a relatively good condition, and results might be overestimated in favour of a relatively normal gait pattern. However, participants with diabetes mellitus (DM) were not excluded. One study reported lower ankle generative mechanical work in patients with DM, even in the absence of diabetic neuropathy.³⁶ As DM was more prevalent among IC, reduced joint ankle ROM is possibly overestimated in the IC group. Second, data as captured during treadmill walking may not necessarily be similar to data that is obtained during over ground walking. However, very equal characteristics of gait were reported³⁷, despite slight differences in stance duration and muscle activation.³⁸ It is thus reasoned that movement analysis during treadmill walking reveals outdoor day-to-day situations, all the more so when taking other advantages of treadmill-based protocols into account. However, caution should

be taken when comparing the present EMG data with results as acquired from over ground walking protocols. The same may be true regarding bare foot walking compared to walking using common footwear, as footwear is found to influence kinematic during walking. To exclude differences in gait pattern due to variable footwear, we decided to have all participants walk without shoes.³⁹ Third, we just studied two lower limb muscles. Although these muscles are considered main actuators of the ankle¹⁷ and being the 'functional end organs' in the lower extremity ischemia⁴⁰, it would be of interest to include additional muscles in future research. It must also be appreciated that surface EMG registration inherently has certain restrictions. EMG refers to the collective electric signal from muscles produced during contraction and the amplitude of an EMG signal is known to be dependent of several factors, such as the properties of the overlying tissue (e.g. thickness of overlying skin and adipose tissue). It is therefore not possible to compare raw EMG amplitudes across subjects. So, surface EMG should be used for studying muscle activation patterns and activity duration only. In contrast, muscle force is not reflected by this method. Last, we did not examine passive range of joint motion. Therefore, kinematic differences may possibly be attributed in part to a difference in passive range of motion. However, participants with a history of orthopaedic complaints, functional loss in range of motion, or observational abnormalities during walking were excluded.

CONCLUSION

Patients with IC demonstrate significant changes in kinematic parameters during walking, even before the onset of claudication pain. However, these changes did not influence EMG activity duration of the medial gastrocnemius and anterior tibialis muscles.

ACKNOWLEDGEMENTS

We would like to thank Roel ten Have for his technical assistance to synchronize measurement data. We also greatly appreciated the help of Jos Swinkels, nurse practitioner at St. Anna Hospital Geldrop, for the recruitment of study participants.

REFERENCES

1. Hirsch AT. Treatment of peripheral arterial disease--extending "intervention" to "therapeutic choice". *N Engl J Med*. 2006;354(18):1944-7.
2. Lauret GJ, Fokkenrood HJ, Bendermacher BL, Scheltinga MR, Teijink JA. Physical activity monitoring in patients with intermittent claudication. *Eur J Vasc Endovasc Surg*. 2014;47(6):656-63.
3. Gardner AW, Montgomery PS. Impaired balance and higher prevalence of falls in subjects with intermittent claudication. *J Gerontol A Biol Sci Med Sci*. 2001;56(7):M454-8.
4. Mockford KA, Vanicek N, Jordan A, Chetter IC, Coughlin PA. Kinematic adaptations to ischemic pain in claudicants during continuous walking. *Gait Posture*. 2010;32(3):395-9.
5. Gardner AW, Forrester L, Smith GV. Altered gait profile in subjects with peripheral arterial disease. *Vasc Med*. 2001;6(1):31-4.
6. Scott-Pandorf MM, Stergiou N, Johanning JM, Robinson L, Lynch TG, Pipinos II. Peripheral arterial disease affects ground reaction forces during walking. *J Vasc Surg*. 2007;46(3):491-9.
7. Marconi C, Ferretti G, Anchisi S, Catalano M, Scandale G, Antico A, et al. Energetics of walking in patients with peripheral arterial disease: a proposed functional evaluation protocol. *Clin Sci (Lond)*. 2003;105(1):105-11.
8. Koutakis P, Weiss DJ, Miserlis D, Shostrom VK, Papoutsis E, Ha DM, et al. Oxidative damage in the gastrocnemius of patients with peripheral artery disease is myofiber type selective. *Redox Biol*. 2014;2:921-8.
9. Regensteiner JG, Wolfel EE, Brass EP, Carry MR, Ringel SP, Hargarten ME, et al. Chronic changes in skeletal muscle histology and function in peripheral arterial disease. *Circulation*. 1993;87(2):413-21.
10. Benedetti MG, Agostini V, Knaflitz M, Bonato P. Muscle activation patterns during level walking and stair ambulation, applications for EMG in clinical and sports medicine Steele C, editor. Croatia: InTech; 2012.
11. Hermens HJ, Freriks B, Disselhorst-Klug C, Rau G. Development of recommendations for SEMG sensors and sensor placement procedures. *J Electromyogr Kinesiol*. 2000;10(5):361-74.
12. Spulak D, Cmejla R, Bacakova R, Kracmar B, Satrapova L, Novotny P. Muscle activity detection in electromyograms recorded during periodic movements. *Comput Biol Med*. 2014;47:93-103.

13. Chowdhury RH, Reaz MB, Ali MA, Bakar AA, Chellappan K, Chang TG. Surface electromyography signal processing and classification techniques. *Sensors (Basel)*. 2013;13(9):12431-66.
14. Agostini V, Ganio D, Facchin K, Cane L, Moreira Carneiro S, Knaflitz M. Gait parameters and muscle activation patterns at 3, 6 and 12 months after total hip arthroplasty. *J Arthroplasty*. 2014;29(6):1265-72.
15. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc*. 1991;23(4):402-8.
16. Van de Putte M, Hagemester N, St-Onge N, Parent G, de Guise JA. Habituation to treadmill walking. *Biomed Mater Eng*. 2006;16(1):43-52.
17. He H, Kiguchi K, Horikawa E. A Study on Lower-Limb Muscle Activities during Daily Lower-Limb Motions *Int J Bioelectromagn*. 2007;9(2):79-84.
18. Askew CD, Green S, Walker PJ, Kerr GK, Green AA, Williams AD, et al. Skeletal muscle phenotype is associated with exercise tolerance in patients with peripheral arterial disease. *J Vasc Surg*. 2005;41(5):802-7.
19. Bogey R, Cerny K, Mohammed O. Repeatability of wire and surface electrodes in gait. *Am J Phys Med Rehabil*. 2003;82(5):338-44.
20. Ozgunen KT, Celik U, Kurdak SS. Determination of an Optimal Threshold Value for Muscle Activity Detection in EMG Analysis. *J Sports Sci Med*. 2010;9(4):620-8.
21. Forghany S, Nester CJ, Richards B, Hatton AL, Liu A. Rollover footwear affects lower limb biomechanics during walking. *Gait Posture*. 2014;39(1):205-12.
22. Crowther RG, Spinks WL, Leicht AS, Quigley F, Golledge J. Relationship between temporal-spatial gait parameters, gait kinematics, walking performance, exercise capacity, and physical activity level in peripheral arterial disease. *J Vasc Surg*. 2007;45(6):1172-8.
23. Celis R, Pipinos II, Scott-Pandorf MM, Myers SA, Stergiou N, Johanning JM. Peripheral arterial disease affects kinematics during walking. *J Vasc Surg*. 2009;49(1):127-32.
24. Di Nardo F, Ghetti G, Fioretti S. Assessment of the activation modalities of gastrocnemius lateralis and tibialis anterior during gait: a statistical analysis. *J Electromyogr Kinesiol*. 2013;23(6):1428-33.
25. Gardner AW, Ritti-Dias RM, Stoner JA, Montgomery PS, Khurana A, Blevins SM. Oxygen uptake before and after the onset of claudication during a 6-minute walk test. *J Vasc Surg*. 2011;54(5):1366-73.

26. Malatesta D, Simar D, Dauvilliers Y, Candau R, Borrani F, Prefaut C, et al. Energy cost of walking and gait instability in healthy 65- and 80-yr-olds. *J Appl Physiol* (1985). 2003;95(6):2248-56.
27. Chen SJ, Pipinos I, Johanning J, Radovic M, Huisinga JM, Myers SA, et al. Bilateral claudication results in alterations in the gait biomechanics at the hip and ankle joints. *J Biomech*. 2008;41(11):2506-14.
28. Pipinos, II, Sharov VG, Shepard AD, Anagnostopoulos PV, Katsamouris A, Todor A, et al. Abnormal mitochondrial respiration in skeletal muscle in patients with peripheral arterial disease. *J Vasc Surg*. 2003;38(4):827-32.
29. Koutakis P, Myers SA, Cluff K, Ha DM, Haynatzki G, McComb RD, et al. Abnormal myofiber morphology and limb dysfunction in claudication. *J Surg Res*. 2015;196(1):172-9.
30. Gasparini M, Sabovic M, Gregoric ID, Simunic B, Pisot R. Increased fatigability of the gastrocnemius medialis muscle in individuals with intermittent claudication. *Eur J Vasc Endovasc Surg*. 2012;44(2):170-6.
31. Merry AH, Teijink JA, Jongert MW, Poelgeest A, van der Voort SS, Bartelink ME, et al. [KNGF-guideline Symptomatic peripheral arterial disease (author's translation)]. 2014.
32. Winter DA. Biomechanical motor patterns in normal walking. *J Mot Behav*. 1983;15(4):302-30.
33. McGibbon CA. Toward a better understanding of gait changes with age and disablement: neuromuscular adaptation. *Exerc Sport Sci Rev*. 2003;31(2):102-8.
34. Van Abbema R, De Greef M, Craje C, Krijnen W, Hobbelen H, Van Der Schans C. What type, or combination of exercise can improve preferred gait speed in older adults? A meta-analysis. *BMC Geriatr*. 2015;15(1):72.
35. Persch LN, Ugrinowitsch C, Pereira G, Rodacki AL. Strength training improves fall-related gait kinematics in the elderly: a randomized controlled trial. *Clin Biomech (Bristol, Avon)*. 2009;24(10):819-25.
36. Ko SU, Stenholm S, Chia CW, Simonsick EM, Ferrucci L. Gait pattern alterations in older adults associated with type 2 diabetes in the absence of peripheral neuropathy--results from the Baltimore Longitudinal Study of Aging. *Gait Posture*. 2011;34(4):548-52.
37. Riley PO, Paolini G, Della Croce U, Paylo KW, Kerrigan DC. A kinematic and kinetic comparison of overground and treadmill walking in healthy subjects. *Gait Posture*. 2007;26(1):17-24.

38. Lee SJ, Hidler J. Biomechanics of overground vs. treadmill walking in healthy individuals. *J Appl Physiol* (1985). 2008;104(3):747-55.
39. Franklin S, Grey MJ, Heneghan N, Bowen L, Li FX. Barefoot vs common footwear: A systematic review of the kinematic, kinetic and muscle activity differences during walking. *Gait Posture*. 2015.
40. Koutakis P, Pipinos, II, Myers SA, Stergiou N, Lynch TG, Johanning JM. Joint torques and powers are reduced during ambulation for both limbs in patients with unilateral claudication. *J Vasc Surg*. 2010;51(1):80-8.

CHAPTER 10

Summary & general discussion

SUMMARY & GENERAL DISCUSSION

Intermittent claudication

Intermittent claudication (IC) is the most common manifestation of peripheral arterial disease (PAD) and may be considered as a locoregional expression of systemic atherosclerosis. IC is defined as muscle discomfort in a lower limb that is predictably evoked by exercise and relieved after a short period of rest. Most patients with IC develop a serious walking impairment during daily life.

Barriers and misconceptions regarding supervised exercise therapy

Supervised exercise therapy (SET) is the first-line symptomatic treatment for IC as stated in several contemporary international guidelines.^{1,2} In clinical practice however, SET is largely underused³ and most IC patients do not receive SET at all.⁴ There are three categories of reasons why this cost-effective treatment is not widely adopted yet (**chapter 1**).^{5,6} First, SET places a considerable burden on patients in terms of effort and responsibility rather than offering a 'quick fix' for their discomfort, so patient reluctance is understandable. A second category of reasons for SET resistance involves clinicians. Self-interest of doctors performing interventions that involve fee-for-service is most likely a contributor. Moreover, there is also misinterpretation of potential SET indications, for instance with regard to the efficacy of SET for IC due to aortoiliac stenosis.⁷ A third and possibly most important factor precluding a wider implementation of SET is lack of access and inadequate reimbursement.⁸ Therefore, even clinicians who fully endorse SET as the initial treatment for IC may end up performing invasive interventions as their patients cannot find a nearby qualified SET practitioner. This is even more bitter when the absence of budgetary restrictions regarding invasive procedures is considered.

It is IC patients who lose out

These three different types of resistance severely frustrate a universal implementation of SET as the standard care for patients with IC. Based on a 2009 invoice data analysis of a large Dutch health insurer (3.4 million members) it was demonstrated that only 14% of the IC patients actually did receive SET.⁴ An unknown portion of the remaining IC patients likely underwent a primary invasive revascularization, while most others may

have possibly been provided with a single ‘go home and walk’ advice. Consequently, IC patients are either unnecessarily exposed to the risks of an invasive intervention or received a truly inferior IC treatment, since general and unstructured exercise recommendations as prescribed by a physician do not lead to sufficient clinical benefit.⁹⁻¹¹ Moreover, most physicians do not even recommend home-based walking exercise to patients with IC.¹²

In the Netherlands, the tide may slowly be turning now as increased numbers of IC patients were referred for SET in 2011 (to be published, based on similar invoice data analysis). Great effort has been put into the implementation of a nation-wide network of physiotherapists (PT) providing SET in a community-based setting.¹³ ClaudicationNet, founded in 2010, is a so-called open network which means that membership is attainable for every PT who fulfills a standard set of participation criteria. ClaudicationNet strives to provide a stepped-care approach where all IC patients are initially referred to a SET program whereas invasive revascularization is exclusively considered for individuals not responding sufficiently to SET.² This approach may be advantageous over a primary invasive intervention strategy as recent evidence indicated that a PTA is likely to be more cost-effective when combined with SET. These findings once again underscore the general benefits of any form of regular exercise.¹⁴

Blueprint for implementation of SET

To date, ClaudicationNet includes 1,552 fully trained PTs. These health care professionals provide information in a personalized portfolio on the network’s national website and attend mandatory educational courses. A web-based referral system is available to help patients find the ClaudicationNet PT nearest in their community. This referral system guarantees that SET is initiated within 5 working days after diagnosis as PTs are instructed to contact a patient within 3 days. If a first PT fails to do so, a second other PT is automatically invited to contact this patient.

While the scale of this Dutch network is comparatively small, this concept could provide a blueprint for the implementation of structured SET programs throughout Europe and the US. As for the health care budget as a whole, the financial benefits of SET are considerable. A recent calculation of this stepped care approach (assuming a 80% referral rate) showed savings of up to 32M euro a year in the Netherlands alone.⁴ Efforts to expand SET implementation outside the Netherlands is of importance for IC patients

in general, but also to anticipate to the current trend as observed in clinical trials which are mostly focusing on alternative IC exercising protocols (e.g., the value of home-based exercise programs). Unfortunately but not completely unexpected, large randomized controlled trials yielded mixed results on the efficacy of home-based protocols.^{15, 16} Moreover, the evidence that a conservative therapy is as effective as invasive alternatives is easily ignored.

Comparison of SET to alternative conservative exercise protocols

Further evidence for the efficacy of SET and its role as an alternative treatment tool was provided in a meta-analysis presented in **chapter 2**. The efficacy of four available conservative treatment options for IC (i.e. medical treatment, walking advice, home-based exercise, SET) was compared in the largest analysis to date (n=1,406 patients). A beneficial outcome of SET with significant effect sizes >0.8 was demonstrated at the 6 weeks, 3 and 6 months follow-up. SET resulted in superior walking distances compared to all other treatment options. A dose-response trend appeared present suggesting that grade of supervision was directly related to walking distances. Hence, supervision is necessary to optimally profit from the benefits of exercise in IC.

After 6 months of follow-up however, results following SET were not significantly different from a home-based protocol (HB). It therefore seems that the intensive supervision has its particular value during the first months of training. On the other hand, it may also be possible that ongoing improvement in maximal walking distance is not to be expected beyond the reported 50% to 200% increase.¹⁰ In addition, studies on the additional value of life-style interventions during SET have not been performed. These modifications probably make SET even more effective, both as reflected by an increased walking distance as in terms of altered morbidity and mortality as discussed later.

At the present time, a 3 months SET program is preferable, possibly followed by a combined 'SET-HB' program. Such a combined follow-up program may be more cost-effective due to the limited amount of supervision and use of training facilities. Moreover, these programs may be further optimized by future monitoring via novel eHealth and mHealth applications.^{8, 17}

Additional benefits of supervision

Intensive supervision at the start of an exercise program for IC may also have benefits when viewed from other perspectives. SET offers an opportunity for simultaneous motivational interviewing supporting IC patients in changing unhealthy habits including smoking, too high calorie of fat food intake and sedentary lifestyle. Evidence regarding the benefits of life style modification programs is growing.¹⁸ A lifelong habit of sedentary behavior due to reluctance to exercise aggravated by leg pain during walking or co-existing (multi-) morbidity can only be changed by simultaneous and prolonged efforts under professional supervision.¹⁹⁻²¹ A series of SET sessions evidently provide better opportunities for stimulating health-related behavioral changes than a single invasive intervention.²⁰ Unfortunately, large studies on the effect of these interventions during SET are currently lacking, as previously stated. The potential positive influence on lifestyle adjustments however is just another argument for advocating SET. Another plea would be the positive influence of SET on the entire vascular system rather than on a portion thereof. The contralateral leg, which may not appear to be affected by symptomatic PAD yet, may also be trained. SET trains the entire cardiorespiratory system and improves overall fitness levels²² and by the same token significantly reduces long-term cardiovascular morbidity and mortality.²³ Moreover, SET also allows to differentiate between (and further explore the influence of) comorbidities (e.g. osteoarthritis, chronic obstructive pulmonary disease). Last but not least, SET can be employed in a group setting, providing patients with a chance to share emotions and experiences. Such a group-based intervention also tends to increase the intrinsic motivation for exercise programs.²⁴

Concerns about safety of SET are unjust

Despite a nationwide coverage of community-based SET in the Netherlands and successful removal of some barriers (poor availability and limited access), there are still obstacles on the road to success. There is an ongoing uncertainty whether SET is sufficiently safe in IC populations as concomitant coronary artery disease is prevalent.²⁵ For example, a cross-sectional survey among Dutch vascular surgeons and fellows found that respondents were reluctant to refer for SET in the presence of significant cardiopulmonary comorbidity.⁷ This concern is also found among physiotherapists as reflected in their 2003 guideline of the Royal Dutch Society for Physical Therapy (KNGF) recommending screening by

a cardiologist or exercise-physiologist prior to the start of SET.²⁶ This guideline was only recently updated (2014).²⁷ Although the onset of a cardiovascular event during exercise is not inconceivable, cardio-pulmonary screening prior to the initiation of SET may raise an additional unnecessary barrier. The prediction of a future severe cardiac event during exercise is difficult, if not impossible.²⁸ Consequently, the use of cardiopulmonary exercise testing (CPET) as a screening tool for myocardial ischemia in people without known coronary artery disease is no longer recommended in the National Institute for Health and Care Excellence (NICE) guideline.²⁹ Surprisingly, the 2015 guideline of the Society for Vascular Surgery still advocates screening for cardiopulmonary reserves to allow safe participation.¹

In **chapter 3** of this thesis, evidence was provided regarding the safety of SET in patients with IC. SET related complications were systematically studied on the basis of 74 articles, representing 82,725 hours of SET in 2,876 IC patients. Six adverse events of cardiac and two of non-cardiac origin were identified resulting in a very low 1 to 10,340 patient-hours all-cause complication rate. SET can therefore safely be prescribed to patients with IC. In line with current evidence but contrary to the SVS 2015 guideline, routine cardiac screening prior to initiation of SET is therefore not advised.

Caution is only required if one wants to generalize these safety findings, as our systematic review excluded IC patients with known major exercise-limiting comorbidities (e.g. poorly controlled hypertension, severe congestive heart failure). However, other studies too demonstrated the safety and benefits of exercise in these subpopulations.³⁰ The risk of acute cardiovascular events was also low in patients with known coronary artery disease participating in a high-intensity exercise rehabilitation program.³¹ Moreover, exercise was superior compared to coronary angioplasty in improving exercise capacity and event-free survival in patients with coronary artery disease.³²

In conclusion, patients with (cardiac) comorbidity should not routinely be excluded from SET in daily practice. These patients obviously require careful monitoring whereas exercise intensity should always be tailored to the patient's condition by a well-educated PT. Unfortunately, the benefits of such personalized exercise programs are difficult to scientifically evaluate as some form of standardization is needed. Based on our study, the previous recommendation on a mandatory cardiac screening was removed from the recently updated KNGF guideline for PTs in the Netherlands.²⁷

Do women and men equally benefit from SET?

Gender-specific research on diagnostics and treatment in cardiology is very common but not in the field of peripheral arterial disease (PAD). This difference was also emphasized in a scientific statement of the American Heart Association.³³ From a cardiovascular pathophysiological perspective however, true gender differences likely exist.³⁴ For instance, smaller vessel size and dissimilar atherosclerotic plaque composition were demonstrated in females.³⁵ Women were also found to suffer more from the consequences of PAD as they perceive a lower physical function and greater impact on daily activities.³⁶ Moreover, women are less likely to receive antiplatelet and lipid-lowering therapy in the presence of cardiovascular diseases.³⁷ One study also reported inferior patency rates following surgical lower-extremity revascularization in women.³³

Data on gender-specific SET outcomes are limited and conflicting.³⁸⁻⁴⁰ In **chapter 4**, a follow-up analysis on gender-specific response following SET was reported. A population of 113 men and 56 women who initially participated in a 2010 multicenter randomized controlled trial named ExercIse Therapy in Peripheral Arterial Disease (EXITPAD) study were again studied. The SET program was supervised by PT's and included interval-based treadmill walking approximating maximal pain, combined with activities such as cycling and rowing. Patients usually started with three 30 minutes sessions a week, and training frequency was adapted during the following year on the basis of individual needs. At baseline, similar demographic characteristics (e.g. age, comorbidities, cardiovascular risk factors), maximal walking distances (men: 250 meters, women: 270 meters) and subjective walking impairment (expressed in terms of scored on a walking impairment questionnaire) were found. After 12 months of follow-up, both men and women demonstrated a significant increase in walking distance. However, men's maximal walking distances were significantly larger after 3 and 12 months of SET. A gender-difference of 95 meter (difference in median) after 12 months was found. Surprisingly, improvement in subjective walking impairment (as measured by the walking impairment questionnaire) was found to be similar in men and women.

It may be concluded that female IC patients certainly benefit from SET but demonstrate less improvement in walking distance after 12 months. The reasons for this difference may be related to pathophysiological dissimilarities (atherosclerotic plaques, vessel diameter), more common presence of atypical symptoms, different perception

of IC symptoms, more impaired lower extremity function and less leg strength in women.^{41, 42} However, if, how and to what extent these factors contribute to the gender-related difference in walking distance after SET is still unknown. Current results do not provide arguments for immediate initiation of gender-based exercise programs for IC. However, research on female aspects of cardiovascular care must be expanded as a previous study reported that IC women are more likely to present with further advanced disease, which is in line with the disparity in time-to-diagnosis and access-to-care between men and women with PAD.⁴²

Does diabetic status influence the efficacy of SET?

Diabetes mellitus (DM) is one of the strongest risk factors for the development of PAD⁴³, and a high prevalence of DM in IC is acknowledged.⁴⁴ IC patients with DM tend to experience worse lower-extremity function than patients with IC alone⁴⁵, and it has been suggested that patients with DM have a reduced exercise tolerance.⁴⁶ Others also advocated that IC patients with comorbidities might be less suitable for SET.⁴⁷ The exact influence of diabetes on the effect of SET in IC is under debate, and this lack of knowledge may raise unjust barriers against commencing SET.

In **chapter 5**, current evidence regarding the effect of DM on the response to SET in IC patients was summarized. A total of three studies representing a total of 845 IC patients met inclusion criteria. All reported maximal walking distance outcomes, one study also included functional walking distance whereas the two other studies described pain-free walking distance. In general, IC patients with DM did improve in walking distance following a SET program. Nevertheless, conflicting results were found when diabetic and non-diabetic IC patients were compared. The largest study found no differences⁴⁴, whereas significant and nearly significant differences on maximal and pain-free walking distance were demonstrated by the other two studies.^{40, 48} In a subanalysis on gender, female diabetic IC patients responded poorest to SET and were a most vulnerable group.⁴⁰ Similar results were found in a follow-up analysis as described in **chapter 4** of this thesis. Although future studies are warranted to precisely elucidate the role of DM on SET outcomes, no arguments have been found to deny diabetic IC patients a form of SET.

How to adequately interpret effects of SET?

Outcome of SET is often evaluated in terms of (changes in) walking distance. Whether to measure walking distance on a treadmill or in a corridor by means of a 6-minute walking test was recently discussed.^{49,50} Both methodologies have limitations considering that the optimal test should directly correlate with patient-reported physical limitations. An outdoor measurement by a community-based global positioning system (GPS) was recently found to be a promising alternative compared to both indoor walking tests.⁵¹ Outdoor measurements are expected to reflect a real life situation, and it must be appreciated that GPS assessment has been found to correlate better with patient-reported measures of walking limitation.⁵² On the other hand, GPS revealed larger short-term walking capacity variability thereby limiting its test-retest reliability.⁵³ Future studies are needed to determine the optimal functional outcome measure in IC.

Apart from the quest of the ideal method of measurement, adequate interpretation of currently applied outcome measures is important. To aid clinicians and researchers in determining what numerical change indicates a clinically meaningful change, the concept of a minimally important difference (MID) value was introduced as a means to define certain outcomes. In **chapter 6**, MID values were determined for treadmill-based walking distances in patients with IC. An anchor-based approach using longitudinal data of 103 IC patients who participated in a SET program was followed. Regarding the maximal walking distance after 3 months of SET, MIDs of 305 meters and 147 meters were found for improvement and deterioration, respectively. A positive value for deterioration implies that such a small increase in walking distance is apparently not satisfactory to the patient. This may not be surprising as SET demands a considerable patient's investment of time and effort (**chapter 1**). Although the largest effects of SET were reported after 3 months of SET (**chapter 2**)⁵⁴, it would be of interest to also determine MIDs for longer follow-up periods (i.e. 12 months). Inclusion of patient-reported outcome measures (PROMS, e.g. walking impairment questionnaire, vascular quality of life questionnaire) when evaluating treatment effects and patient satisfaction has been recommended.⁵⁵ However, the current quality of disease specific PROMs for IC is alarmingly low.⁵⁶

Physical activity in IC, a novel outcome measure?

There is an ongoing debate regarding the value of physical activity (PA) and its essential role in ensuring health and well-being.⁵⁷ A recent analysis found that acquiring the recommended minimum level of physical activity (from a level of ‘no activity’), led to an all-cause 19 percent mortality reduction.⁵⁸ A dose-response relationship between degree of PA and early death was reported⁵⁹ which is in line with the American Heart Association website’s statement saying that ‘Something is always better than nothing’. Moreover, an increase in daily activity was just as strongly associated with reduced mortality as quitting smoking.⁶⁰

Unsurprisingly, equal trends regarding the benefits of PA have also been reported in PAD patients. For instance, higher levels of PA were associated with less functional decline⁶¹ and a lower all-cause mortality risk.^{62, 63} Patients with IC exhibit lower daily PA levels compared to healthy controls^{64, 65} and several barriers (e.g. personal, environmental) to refrain from being physically active were described.⁶⁶ Therefore, benefits of increased PA are likely more substantial in IC. However, PA levels in IC populations are rarely questioned or objectively monitored in current clinical practice, in contrast to standardly used walking capacity tests. To explore whether commonly used physical exercise capacity (PEC) outcomes could serve as probably a surrogate marker for PA, a cross-sectional study was conducted in **chapter 7**. A total of 46 patients completed a set of PEC tests and wore a tri-axial accelerometer for seven consecutive days to determine actual PA levels. Overall, (very) weak to moderate correlations between PA and PEC indicate that the concepts PEC and PA, although overlapping, are distinct.

Achieving a higher level of PEC does therefore not necessarily mean that higher PA will follow. Notwithstanding, a higher exercise capacity that is often attained after prolonged training is permissive of greater physical activity (intensity and duration) in home and community environments. Previous assumptions are in line with a recent study which did not find an effect of SET on PA in patients with IC.⁶⁷ These results, and the established correlation between PA and all-cause mortality, provide compelling arguments for focusing on PA as a distinct novel outcome measure for PAD patients (and possibly other populations as well). As it has recently been recognized that prolonged sitting (i.e. sedentarism), independent of overall physical activity levels, may be even more important to the all-cause mortality risk⁶⁸, it seems most appropriate to measure both active and sedentary PA components.

Classification of IC patients

The currently proposed PA measurement is only clinically relevant when it has a conceivable effect on the patient's decisions and behavior. PA however is a complex endpoint that is influenced by a range of factors (e.g. personal; motivation, exercise-related, environment and policy). Current SET programs may be not specified (enough) for improving PA, as indicated by the lack of improvement in PA after SET.⁶⁷ Nevertheless, promising results were reported regarding the effect of a brief psychological intervention on walking behavior. Two 1-hour sessions, 1 week apart at the patients' homes, significantly improved the mean number of daily steps ($\Delta 1,567$ steps per day), as compared with a control group receiving standard care.²⁰ Interestingly, this effect was maintained for 2 years.²¹ Such a psychological intervention could perfectly be incorporated into SET as provided by specialized PT's trained in motivational interviewing, thereby probably extending the effectiveness and subsequent benefits of SET in regard to its effect on PA.

In the present thesis, measurements of both PEC and PA parameters are suggested, as this information allows for a novel classification of IC patients (*figure 1*). It is expected that a number of factors contribute to the category in which a patient actually belongs. For instance, an IC patient with a very good response to SET (high PEC) who leads a very sedentary life (low PA) fits into category C. A detailed characterization (e.g. demographics, motivation, health status, environment, etc.) of the patients in these four categories may facilitate an improved understanding of the underlying determinants for a certain type of PA behaviour. This may eventually aid in optimizing intervention strategies and employment of personalized medicine. Thus, the purpose is not to move patients from one category to the other, but to gain insight in the patients' characteristics in order to provide 'tailor-made' therapy.

Figure 1. Model to classify IC patients according to their physical exercise capacity (PEC) and daily physical activity (PA) status

Altered gait patterns in IC

Spatio-temporal changes of gait pattern were previously described in IC patients. IC patients were found to walk slower, have a lower cadence (i.e. steps per minute), and have a shorter step length.^{69, 70} Moreover, oxygen uptake during pain-free ambulation was higher when compared to age-matched controls indicating that IC patients exhibit a poorer walking economy.^{71, 72} Walking economy (i.e. cost of transport) progressively decreased following the onset of claudication pain. In addition, poorer walking economy correlated with diabetic status⁷³, probably explaining the poorer response to SET of diabetic IC patients (**chapter 5**). However, since oxygen uptake is already higher in pain-free ambulation, factors other than IC pain have to be responsible, and adaptations of the gait pattern might therefore be a contributor.⁷²

Previous research revealed that SET conferred no effect on altered gait pattern in patients with IC.⁷⁴ Lack of improvement in gait after SET may be due to insufficiently tailored SET programs to elicit significant improvement. Additional research into detailed muscle and biomechanical adaptations may provide new insights to improve the effects of SET.⁷⁴ Besides, previous research based their conclusions on just a couple of steps, while it has been recommended to include at least 20 to 30 strides.

In **chapter 8 and 9** of this thesis, different aspects of gait pattern of IC patients were studied using a treadmill-based protocol. Continuing analysis during treadmill walking allows for assessment of a large number of steps. In addition, this novel methodology permitted for data capturing immediately after the pain threshold was reached, thereby excluding confounding factors potentially due to recovery processes.

A first analysis of spatio-temporal parameters in 28 IC patients and 28 healthy age-matched controls was conducted (**chapter 8**). IC patients walked at a self-selected 3.3 km/h pace, whereas controls walked a significantly 1.2 km/h faster. Most evident differences between IC patients and controls were found in the foot contact phase and toe off (i.e. propulsion) phase. A 14% shorter propulsion and a 17% longer foot contact phase were demonstrated in IC patients. Moreover, the ankle-brachial index (a measure for disease severity and atherosclerotic occlusion) was correlated with both walking speed and decrease in propulsion during ischemic pain. IC patients seem to ‘discontinue’ walking for a longer period during every step. These adaptations might be intuitive as arterial blood inflow and supply of oxygen to the skeletal muscles takes place during this relaxation phase.^{75, 76} This may explain why IC patients take fewer rather than shorter steps when claudication pain develop as also suggested by a previous study.⁷⁷

Based on these spatio-temporal results (**chapter 8**) it was hypothesized that IC patients use a longer contact phase to enable muscle relaxation to occur for a prolonged period of time, as the relaxation phase is known to be the largest moment of arterial blood inflow. **Chapter 9** described the subsequent analyses to test this hypothesis. Lower limb joint kinematics and muscle activity by means of surface electromyography (EMG) were determined during similar self-selected comfortable walking speed. The study population consisted of 22 IC patients and 22 healthy age-matched controls. The kinematic analysis showed a significantly smaller ankle displacement (-28%) in IC patients, most evidently in the propulsion phase. Therefore, joint angle data supported the hypothesis. The

EMG data however demonstrated no differences in muscle activity duration of tibialis anterior and medial gastrocnemius muscles suggesting that IC patients use these muscles, considered main actuators of the ankle, for a similar amount of time during the gait cycle. Duration of muscle activity was expressed in percentages of the gait cycle in order to correct for the differences in walking speed between both groups.

In conclusion, IC patients demonstrate predictable spatio-temporal and kinematic changes during walking, even before the onset of claudication pain. This strategy however did not result into longer muscle relaxation periods, as duration of lower-limb muscle activity was similar in both groups. There are several ways to explain these results. Surface EMG solely measures muscle activity but not muscle force. It has been described that a minimal level of intensity (i.e. above 50% of the maximum voluntary contraction force) is needed to cause a reduction in calf muscle blood flow.⁷⁵ As a consequence, it might be the amount of muscle force rather than the duration of contraction which really determines arterial blood inflow. This idea is substantiated by previous research which demonstrated a reduced propulsion force and a decreased ability of the ankle plantar flexors in IC patients.^{78, 79} On the other hand, spatio-temporal and kinematic changes can also be due to a reduced muscle force, instead of an intended strategy to cope with the disease related arterial obstruction. This could also explain the unfavourable reduced metabolic efficiency in IC patients, which in fact adds to a reduced walking speed and walking capacity.

Implications for clinical practice and suggestions for future research

Serious effort should be put into effective measures overcoming the problem of a limited access of SET allowing its routine implementation in clinical practice. The success of the community-based ClaudicatioNet network proves that significant financial investments are not required.¹³ However, the mere availability of a nation-wide network of SET facilities is not enough, since it essentially only provides a sound infrastructure. After establishing a network, structural funding should be secured by incorporating SET in standard health care budgets. In addition, continuous education on IC related issues is required to motivate doctors, PT's as well as patients.

Further research should focus on identifying the optimal contents of a modular package of SET that is tailored to subgroups of IC patients. The possibility of incorporating

lifestyle-changing techniques into standard SET sessions requires exploring. Lifestyle-changing interventions fit perfectly into the suggested addition of PA measurement in daily clinical routines and its subsequent aim to improve PA in patients with IC. As it is very hard to change deep-rooted behavior of an IC patient, a second focus should be on gaining more insight into the type of factors determining this behavior. A classification as proposed in figure 1 may aid in categorizing IC patients and may allow for the identification of specific categories sharing certain characteristics.

Third, the effect of specific lower-limb muscle strength training on walking distance and gait patterns should be investigated. Limb muscle strength is an important contributor to both walking speed and balance (i.e. risk of falling)^{80, 81} and it seems therefore logical to add strength training to a SET program. This is in line with the current trend of providing a variety of exercises during SET. Longitudinal EMG registration (baseline measurement followed by an intervention and follow-up measurement) may be suggested to study the effect of muscle strength training on the gait pattern, as for paired EMG measures, amplitudes can be interpreted as muscle force.

The data in this thesis provide evidence for specific changes regarding contact time and propulsion phase during walking in IC. As these changes were related to walking speed, the fourth focus of future research should be on the effect of improving gait speed during SET.

Conclusions of this thesis

1. Supervised exercise therapy (SET) is a safe treatment in patients with intermittent claudication (IC).
2. SET leads to a longer walking distance when compared to other conservative treatment options.
3. Women with IC tend to benefit less from SET in terms of absolute walking distance.
4. Patients with IC and diabetes mellitus do profit from SET.
5. The 'minimally importance differences' (MID) of treadmill-based maximal walking distance for improvement and deterioration are 305 and 147 meters, respectively. The positive MID value for deterioration indicates that a minor improvement in walking distance apparently is not satisfactory in the patients' eyes.
6. Correlations between physical exercise capacity (PEC) and daily physical activity (PA) of patients with IC are weak to moderate indicating that the concepts PEC and PA, although overlapping, are distinct.
7. Patients with IC walk slower and present with less propulsion and ankle range of motion during walking compared to healthy controls. No difference in electromyographic muscle activity duration is present between IC patients and controls. However, painful walking in IC did result in significantly higher electromyographic muscle activity.

REFERENCES

1. Society for Vascular Surgery Lower Extremity Guidelines Writing G, Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JF, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg.* 2015;61(3 Suppl):2S-41S.
2. Layden J, Michaels J, Bermingham S, Higgins B, Guideline Development G. Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance. *BMJ.* 2012;345:e4947.
3. Shalhoub J, Hamish M, Davies AH. Supervised exercise for intermittent claudication - an under-utilised tool. *Ann R Coll Surg Engl.* 2009;91(6):473-6.
4. Fokkenrood HJ, Scheltinga MR, Koelemay MJ, Breek JC, Hasaart F, Vahl AC, et al. Significant savings with a stepped care model for treatment of patients with intermittent claudication. *Eur J Vasc Endovasc Surg.* 2014;48(4):423-9.
5. Popplewell MA, Bradbury AW. Why do health systems not fund supervised exercise programmes for intermittent claudication? *Eur J Vasc Endovasc Surg.* 2014;48(6):608-10.
6. Gommans LN, Teijink JA. Attitudes to supervised exercise therapy. *Br J Surg.* 2015.
7. Lauret GJ, van Dalen HC, Hendriks HJ, van Sterkenburg SM, Koelemay MJ, Zeebregts CJ, et al. When is supervised exercise therapy considered useful in peripheral arterial occlusive disease? A nationwide survey among vascular surgeons. *Eur J Vasc Endovasc Surg.* 2012;43(3):308-12.
8. Makris GC, Lattimer CR, Lavidia A, Geroulakos G. Availability of supervised exercise programs and the role of structured home-based exercise in peripheral arterial disease. *Eur J Vasc Endovasc Surg.* 2012;44(6):569-75; discussion 76.
9. Fokkenrood HJ, Bendermacher BL, Lauret GJ, Willigendael EM, Prins MH, Teijink JA. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev.* 2013;8:CD005263.
10. Fakhry F, van de Luijngaarden KM, Bax L, den Hoed PT, Hunink MG, Rouwet EV, et al. Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg.* 2012;56(4):1132-42.

11. Wind J, Koelemay MJ. Exercise therapy and the additional effect of supervision on exercise therapy in patients with intermittent claudication. Systematic review of randomised controlled trials. *Eur J Vasc Endovasc Surg.* 2007;34(1):1-9.
12. McDermott MM, Liu K, Guralnik JM, Criqui MH, Spring B, Tian L, et al. Home-based walking exercise intervention in peripheral artery disease: a randomized clinical trial. *JAMA.* 2013;310(1):57-65.
13. Lauret GJ, Gijsbers HJ, Hendriks EJ, Bartelink ML, de Bie RA, Teijink JA. The ClaudicatioNet concept: design of a national integrated care network providing active and healthy aging for patients with intermittent claudication. *Vasc Health Risk Manag.* 2012;8:495-503.
14. Mazari FA, Khan JA, Carradice D, Samuel N, Gohil R, McCollum PT, et al. Economic analysis of a randomized trial of percutaneous angioplasty, supervised exercise or combined treatment for intermittent claudication due to femoropopliteal arterial disease. *Br J Surg.* 2013;100(9):1172-9.
15. Collins TC, Lunos S, Carlson T, Henderson K, Lightbourne M, Nelson B, et al. Effects of a home-based walking intervention on mobility and quality of life in people with diabetes and peripheral arterial disease: a randomized controlled trial. *Diabetes Care.* 2011;34(10):2174-9.
16. Gardner AW, Parker DE, Montgomery PS, Scott KJ, Blevins SM. Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication: a randomized controlled trial. *Circulation.* 2011;123(5):491-8.
17. Fokkenrood HJ, Lauret GJ, Scheltinga MR, Spreeuwenberg C, de Bie RA, Teijink JA. Multidisciplinary treatment for peripheral arterial occlusive disease and the role of eHealth and mHealth. *J Multidiscip Healthc.* 2012;5:257-63.
18. Galea MN, Weinman JA, White C, Bearne LM. Do behaviour-change techniques contribute to the effectiveness of exercise therapy in patients with intermittent claudication? A systematic review. *Eur J Vasc Endovasc Surg.* 2013;46(1):132-41.
19. Cunningham MA, Swanson V, Pappas E, O'Carroll RE, Holdsworth RJ. Illness beliefs and walking behavior after revascularization for intermittent claudication: a qualitative study. *J Cardiopulm Rehabil Prev.* 2014;34(3):195-201.
20. Cunningham MA, Swanson V, O'Carroll RE, Holdsworth RJ. Randomized clinical trial of a brief psychological intervention to increase walking in patients with intermittent claudication. *Br J Surg.* 2012;99(1):49-56.

21. Cunningham MA, Swanson V, Holdsworth RJ, O'Carroll RE. Late effects of a brief psychological intervention in patients with intermittent claudication in a randomized clinical trial. *Br J Surg*. 2013;100(6):756-60.
22. Parmenter BJ, Raymond J, Fiatarone Singh MA. The effect of exercise on fitness and performance-based tests of function in intermittent claudication: a systematic review. *Sports Med*. 2013;43(6):513-24.
23. Sakamoto S, Yokoyama N, Tamori Y, Akutsu K, Hashimoto H, Takeshita S. Patients with peripheral artery disease who complete 12-week supervised exercise training program show reduced cardiovascular mortality and morbidity. *Circ J*. 2009;73(1):167-73.
24. Orth-Gomer K, Schneiderman N, Wang HX, Walldin C, Blom M, Jernberg T. Stress reduction prolongs life in women with coronary disease: the Stockholm Women's Intervention Trial for Coronary Heart Disease (SWITCHD). *Circ Cardiovasc Qual Outcomes*. 2009;2(1):25-32.
25. Tilloy E, Montaye M, Kee F, Bingham A, Arveiler D, Ruidavets JB, et al. Contribution of cardiovascular risk factors to coronary risk in patients with intermittent claudication in the PRIME Cohort Study of European men. *Atherosclerosis*. 2009;206(2):563-8.
26. Jongert MW, Hendriks HJ, van Hoek J, Klaasboer-Kogelman K, Robeer GG, Simens B, et al. [KNGF-Guideline Intermittent Claudication (author's translation)]. *Ned Tijdschr Fysiother*. 2003;113:3-50.
27. Merry AH, Teijink JA, Jongert MW, Poelgeest A, van der Voort SS, Bartelink ME, et al. [KNGF-guideline Symptomatic peripheral arterial disease (author's translation)]. 2014.
28. Pavy B, Iliou MC, Meurin P, Tabet JY, Corone S. Safety of exercise training for cardiac patients: results of the French registry of complications during cardiac rehabilitation. *Arch Intern Med*. 2006;166(21):2329-34.
29. Skinner JS, Smeeth L, Kendall JM, Adams PC, Timmis A. NICE guidance. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. *Heart*. 2010;96(12):974-8.
30. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301(14):1439-50.
31. Rognmo O, Moholdt T, Bakken H, Hole T, Molstad P, Myhr NE, et al. Cardiovascular risk of high- versus moderate-intensity aerobic exercise in coronary heart disease patients. *Circulation*. 2012;126(12):1436-40.

32. Hambrecht R, Walther C, Mobius-Winkler S, Gielen S, Linke A, Conradi K, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. *Circulation*. 2004;109(11):1371-8.
33. Hirsch AT, Allison MA, Gomes AS, Corriere MA, Duval S, Ershow AG, et al. A call to action: women and peripheral artery disease: a scientific statement from the American Heart Association. *Circulation*. 2012;125(11):1449-72.
34. Daniels LB, Maisel AS. Cardiovascular biomarkers and sex: the case for women. *Nat Rev Cardiol*. 2015.
35. Maas AH, van der Schouw YT, Regitz-Zagrosek V, Swahn E, Appelman YE, Pasterkamp G, et al. Red alert for women's heart: the urgent need for more research and knowledge on cardiovascular disease in women: proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010. *Eur Heart J*. 2011;32(11):1362-8.
36. Oka RK, Szuba A, Giacomini JC, Cooke JP. Gender differences in perception of PAD: a pilot study. *Vasc Med*. 2003;8(2):89-94.
37. Enriquez JR, Pratap P, Zbilut JP, Calvin JE, Volgman AS. Women tolerate drug therapy for coronary artery disease as well as men do, but are treated less frequently with aspirin, beta-blockers, or statins. *Gend Med*. 2008;5(1):53-61.
38. Lundgren F, Dahllof AG, Lundholm K, Schersten T, Volkmann R. Intermittent claudication-surgical reconstruction or physical training? A prospective randomized trial of treatment efficiency. *Ann Surg*. 1989;209(3):346-55.
39. Serracino-Inglott F, Owen G, Carter A, Dix F, Smyth JV, Mohan IV. All patients benefit equally from a supervised exercise program for claudication. *Vasc Endovascular Surg*. 2007;41(3):212-6.
40. Gardner AW, Parker DE, Montgomery PS, Blevins SM. Diabetic women are poor responders to exercise rehabilitation in the treatment of claudication. *J Vasc Surg*. 2014;59(4):1036-43.
41. Gardner AW, Parker DE, Montgomery PS, Blevins SM, Nael R, Afaq A. Sex differences in calf muscle hemoglobin oxygen saturation in patients with intermittent claudication. *J Vasc Surg*. 2009;50(1):77-82.
42. Vavra AK, Kibbe MR. Women and peripheral arterial disease. *Womens Health (Lond Engl)*. 2009;5(6):669-83.
43. Aronow WS. Peripheral arterial disease in women. *Maturitas*. 2009;64(4):204-11.

44. van Pul KM, Kruidenier LM, Nicolai SP, de Bie RA, Nieman FH, Prins MH, et al. Effect of supervised exercise therapy for intermittent claudication in patients with diabetes mellitus. *Ann Vasc Surg.* 2012;26(7):957-63.
45. Dolan NC, Liu K, Criqui MH, Greenland P, Guralnik JM, Chan C, et al. Peripheral artery disease, diabetes, and reduced lower extremity functioning. *Diabetes Care.* 2002;25(1):113-20.
46. Uçok K, Yalcinkaya H, Acay A, Coban NF, Aslanalp S, Akkan G, et al. Do patients with newly diagnosed type 2 diabetes have impaired physical fitness, and energy expenditures? *Neth J Med.* 2015;73(6):276-83.
47. Dos Anjos Souza Barbosa J, Henriques PM, De Barros MVG, Wolosker N, Ritti-Dias RM. Physical activity level in individuals with peripheral arterial disease: a systematic review. *J Vasc Bras.* 2012;11:1-7.
48. Allen JD, Stabler T, Kenjale AA, Ham KL, Robbins JL, Duscha BD, et al. Diabetes status differentiates endothelial function and plasma nitrite response to exercise stress in peripheral arterial disease following supervised training. *J Diabetes Complications.* 2014;28(2):219-25.
49. McDermott MM, Guralnik JM, Criqui MH, Liu K, Kibbe MR, Ferrucci L. Six-minute walk is a better outcome measure than treadmill walking tests in therapeutic trials of patients with peripheral artery disease. *Circulation.* 2014;130(1):61-8.
50. 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(1):69-78.
51. Le Faucheur A, Abraham P, Jaquinandi V, Bouye P, Saumet JL, Noury-Desvaux B. Measurement of walking distance and speed in patients with peripheral arterial disease: a novel method using a global positioning system. *Circulation.* 2008;117(7):897-904.
52. Tew G, Copeland R, Le Faucheur A, Gernigon M, Nawaz S, Abraham P. Feasibility and validity of self-reported walking capacity in patients with intermittent claudication. *J Vasc Surg.* 2013;57(5):1227-34.
53. Le Faucheur A, Noury-Desvaux B, Mahe G, Sauvaget T, Saumet JL, Leftheriotis G, et al. Variability and short-term determinants of walking capacity in patients with intermittent claudication. *J Vasc Surg.* 2010;51(4):886-92.
54. Gardner AW, Montgomery PS, Parker DE. Optimal exercise program length for patients with claudication. *J Vasc Surg.* 2012;55(5):1346-54.

55. Conijn AP, Jonkers W, Rouwet EV, Vahl AC, Reekers JA, Koelemay MJ. Introducing the Concept of the Minimally Important Difference to Determine a Clinically Relevant Change on Patient-Reported Outcome Measures in Patients with Intermittent Claudication. *Cardiovasc Intervent Radiol*. 2015.
56. Conijn AP, Jens S, Terwee CB, Breek JC, Koelemay MJ. Assessing the Quality of Available Patient Reported Outcome Measures for Intermittent Claudication: A Systematic Review Using the COSMIN Checklist. *Eur J Vasc Endovasc Surg*. 2015;49(3):316-34.
57. Holtermann A, Mortensen OS, Burr H, Sogaard K, Gyntelberg F, Suadican P. Fitness, work, and leisure-time physical activity and ischaemic heart disease and all-cause mortality among men with pre-existing cardiovascular disease. *Scand J Work Environ Health*. 2010;36(5):366-72.
58. Woodcock J, Franco OH, Orsini N, Roberts I. Non-vigorous physical activity and all-cause mortality: systematic review and meta-analysis of cohort studies. *Int J Epidemiol*. 2011;40(1):121-38.
59. Hupin D, Roche F, Gremeaux V, Chatard JC, Oriol M, Gaspoz JM, et al. Even a low-dose of moderate-to-vigorous physical activity reduces mortality by 22% in adults aged ≥ 60 years: a systematic review and meta-analysis. *Br J Sports Med*. 2015.
60. Holme I, Anderssen SA. [Physical activity, smoking and mortality among men who participated in the Oslo studies of 1972 and 2000]. *Tidsskr Nor Lægeforen*. 2014;134(18):1743-8. Fysisk aktivitet, royking og dodelighet hos menn som deltok i Oslo-undersokelsene i 1972 og 2000.
61. Garg PK, Liu K, Tian L, Guralnik JM, Ferrucci L, Criqui MH, et al. Physical activity during daily life and functional decline in peripheral arterial disease. *Circulation*. 2009;119(2):251-60.
62. Garg PK, Tian L, Criqui MH, Liu K, Ferrucci L, Guralnik JM, et al. Physical activity during daily life and mortality in patients with peripheral arterial disease. *Circulation*. 2006;114(3):242-8.
63. Gardner AW, Montgomery PS, Parker DE. Physical activity is a predictor of all-cause mortality in patients with intermittent claudication. *J Vasc Surg*. 2008;47(1):117-22.
64. Gardner AW, Killewich LA, Katzel LI, Womack CJ, Montgomery PS, Otis RB, et al. Relationship between free-living daily physical activity and peripheral circulation in patients with intermittent claudication. *Angiology*. 1999;50(4):289-97.

65. Lauret GJ, Fokkenrood HJ, Bendermacher BL, Scheltinga MR, Teijink JA. Physical activity monitoring in patients with intermittent claudication. *Eur J Vasc Endovasc Surg.* 2014;47(6):656-63.
66. Barbosa JP, Farah BQ, Chehuen M, Cucato GG, Farias Junior JC, Wolosker N, et al. Barriers to physical activity in patients with intermittent claudication. *Int J Behav Med.* 2015;22(1):70-6.
67. Fokkenrood HJ, Lauret GJ, Verhofstad N, Bendermacher BL, Scheltinga MR, Teijink JA. The effect of supervised exercise therapy on physical activity and ambulatory activities in patients with intermittent claudication. *Eur J Vasc Endovasc Surg.* 2015;49(2):184-91.
68. van der Ploeg HP, Chey T, Korda RJ, Banks E, Bauman A. Sitting time and all-cause mortality risk in 222 497 Australian adults. *Arch Intern Med.* 2012;172(6):494-500.
69. Gardner AW, Forrester L, Smith GV. Altered gait profile in subjects with peripheral arterial disease. *Vasc Med.* 2001;6(1):31-4.
70. Gardner AW, Montgomery PS, Ritti-Dias RM, Forrester L. The effect of claudication pain on temporal and spatial gait measures during self-paced ambulation. *Vasc Med.* 2010;15(1):21-6.
71. Womack CJ, Sieminski DJ, Katzel LI, Yataco A, Gardner AW. Oxygen uptake during constant-intensity exercise in patients with peripheral arterial occlusive disease. *Vasc Med.* 1997;2(3):174-8.
72. Marconi C, Ferretti G, Anchisi S, Catalano M, Scandale G, Antico A, et al. Energetics of walking in patients with peripheral arterial disease: a proposed functional evaluation protocol. *Clin Sci (Lond).* 2003;105(1):105-11.
73. Gardner AW, Ritti-Dias RM, Stoner JA, Montgomery PS, Scott KJ, Blevins SM. Walking economy before and after the onset of claudication pain in patients with peripheral arterial disease. *J Vasc Surg.* 2010;51(3):628-33.
74. King S, Vanicek N, Mockford KA, Coughlin PA. The effect of a 3-month supervised exercise programme on gait parameters of patients with peripheral arterial disease and intermittent claudication. *Clin Biomech (Bristol, Avon).* 2012;27(8):845-51.
75. Kagaya A. Relative contraction force producing a reduction in calf blood flow by superimposing forearm exercise on lower leg exercise. *Eur J Appl Physiol Occup Physiol.* 1993;66(4):309-14.
76. Pool J. The blood flow through the human calf during rhythmic exercise. *Pflugers Arch.* 1970;314(2):171-2.

77. Mockford KA, Vanicek N, Jordan A, Chetter IC, Coughlin PA. Kinematic adaptations to ischemic pain in claudicants during continuous walking. *Gait Posture*. 2010;32(3):395-9.
78. Scott-Pandorf MM, Stergiou N, Johanning JM, Robinson L, Lynch TG, Pipinos, II. Peripheral arterial disease affects ground reaction forces during walking. *J Vasc Surg*. 2007;46(3):491-9.
79. Koutakis P, Johanning JM, Haynatzki GR, Myers SA, Stergiou N, Longo GM, et al. Abnormal joint powers before and after the onset of claudication symptoms. *J Vasc Surg*. 2010;52(2):340-7.
80. Mockford KA, Mazari FA, Jordan AR, Vanicek N, Chetter IC, Coughlin PA. Computerized dynamic posturography in the objective assessment of balance in patients with intermittent claudication. *Ann Vasc Surg*. 2011;25(2):182-90.
81. Lane RA, Mazari F, Mockford KA, Vanicek N, Chetter IC, Coughlin PA. Fear of falling in claudicants and its relationship to physical ability, balance, and quality of life. *Vasc Endovascular Surg*. 2014;48(4):297-304.

CHAPTER 11

Samenvatting & algemene discussie

Valorisatie

SAMENVATTING & ALGEMENE DISCUSSIE

Perifeer arterieel vaatlijden

Perifeer arterieel vaatlijden, afgekort als PAV, is een uiting van atherosclerose (slagaderverkalking). Door afzetting van vetten en kalk verliezen de slagaderlijke bloedvaten van het been hun elasticiteit, kan de binnenkant van het bloedvat beschadigd raken, wordt de diameter kleiner en ontstaat een vernauwing.¹ Uiteindelijk leidt dit tot een belemmering van de bloeddoorstroming. PAV kenmerkt zich door een in ernst oplopend spectrum van klachten, beginnend bij ziekte zonder klachten (asymptotisch PAV) tot weefselversterf (gangreen) aan het einde van dit spectrum. Claudicatio intermittens (CI) is het meest voorkomende symptoom van PAV en betekent letterlijk ‘intermitterend hinken’.² Doordat de toevoer van bloed en daarmee zuurstof naar de spieren tekort schiet, ervaren patiënten met CI pijn en kramp in de benen tijdens inspanning, welke spontaan verdwijnt na een korte periode van rust. De loopafstand is veelal beperkt en bijkomend kan sprake zijn van een verminderd uithoudingsvermogen (conditie), beperkte spierkracht en angst voor pijn en/of inspanning.³⁻⁵

Nog vaak wordt vergeten dat atherosclerose een systeemziekte is. Dus ook de kransslagaders rond het hart en de slagaders naar en van de hersenen zijn per definitie aangedaan. Daardoor hebben patiënten met PAV (dus ook personen zonder merkbare symptomen) een aanzienlijk verhoogd risico op het krijgen van een hart- en/of herseninfarct en is de levensverwachting met ongeveer 10 jaar verkort.²

In een Nederlands populatieonderzoek onder 55-plussers werd de prevalentie van PAV geschat op 19,1%. Voor de Nederlandse situatie wordt uitgegaan van 800.000 tot één miljoen individuen.⁶ Per jaar krijgen ruim 25.000 nieuwe patiënten de diagnose CI te horen. Wereldwijd wordt het aantal patiënten met CI geschat op meer dan 200 miljoen.⁷ De verwachting is dat het aantal patiënten met deze ‘welvaartsziekte’ de komende jaren alleen maar verder zal toenemen. PAV wordt daarom terecht een pandemie genoemd welke met enorme kosten voor de gezondheidszorg gepaard gaat.

Behandeling van CI bestaat uit twee pijlers, het cardiovasculaire risicomanagement (CVRM) en de symptomatische behandeling. Het CVRM beoogt het voorkómen van toekomstige cardiovasculaire events (hart- en/of herseninfarct) en vroegtijdig overlijden en bestaat uit medicatie (plaatjesremmer en cholesterolverlager) en adequate regulering

van de eventueel aanwezige diabetes mellitus of hypertensie. Daarnaast wordt aangestuurd op leefstijlaanpassingen als stoppen met roken, gezonde(re) voeding en meer bewegen. De symptomatische behandeling is gericht op het verminderen van klachten, bij CI veelal de beperkte loopafstand. Als eerste keus behandeling wordt in (inter)nationale richtlijnen gesuperviseerde looptherapie (GLT) aanbevolen. GLT bestaat uit training onder begeleiding van een fysiotherapeut.^{2, 8} Meerdere malen per week wordt, veelal op de loopband, intervalsgewijs door de pijn heen gelopen. Daarnaast wordt een breed scala aan functionele en cardiopulmonale oefeningen aangeboden en worden patiënten gestimuleerd om ook in de thuisomgeving (meer) te gaan lopen en bewegen en een gezondere leefstijl na te streven.⁹

Idealiter wordt pas op het moment dat GLT tot onvoldoende resultaat leidt een invasieve behandeling (bijvoorbeeld een dotterbehandeling) overwogen.⁸ Helaas wordt nog te vaak primair voor een invasieve behandeling gekozen. Ondanks het feit dat uit onderzoek is gebleken dat een invasieve behandeling na meer dan een jaar tot vergelijkbare loopafstanden leidt als een traject GLT.¹⁰ Echter, invasieve behandelingen gaan gepaard met risico's voor de patiënt (kans op een hart- en/of herseninfarct peri-procedureel, (na-)bloedingen, infecties, trombo-embolische complicaties, valse aneurysmata, lokaal zenuwletsel) en substantieel hogere kosten.^{11, 12}

Barrières en misconcepties ten aanzien van GLT

Ondanks dat GLT de eerste keus behandeling is, ontvangt slechts een minderheid van de patiënten deze veilige en aangetoond doelmatige behandeling in de dagelijkse praktijk. Uit een analyse op basis van verzekeringsgegevens (2009; 3,4 miljoen verzekerden), bleek dat slechts 14% van de patiënten in Nederland daadwerkelijk werd doorverwezen voor GLT.⁶

Drie categorieën van oorzaken kunnen worden onderscheiden waarom deze behandeling voor CI nog geen landelijke (en zeker geen wereldwijde) implementatie heeft gevonden (**hoofdstuk 1**).^{13, 14} Ten eerste de weerstand van patiënten. GLT vraagt de nodige inzet, inspanning en tijd van een patiënt, terwijl een invasieve behandeling als een 'quick-fix' uitkomst voor het ongemak biedt. De tweede categorie betreft weerstand bij de behandelde (of verwijzende) artsen die zijn opgeleid om, al dan niet invasief, in te grijpen. Gebrek aan kennis over de mogelijkheden van GLT of de wijze waarop

patiënten verwezen kunnen worden voor GLT liggen hier aan ten grondslag.¹⁵ Daarnaast bestaan vermeende categorieën van patiënten die primair voor een invasieve behandeling in aanmerking zouden moeten komen. Patiënten met CI veroorzaakt door een aorto-iliacale stenose of occlusie bijvoorbeeld.¹⁶ Wetenschappelijk bewijs ontbreekt echter. Tot slot dragen ook financiële prikkels, onderhouden door de invloedrijke industrie, hieraan bij. De belangrijkste categorie die verdere implementatie van GLT belemmert, is het ontbreken van een gedegen financiële vergoeding (GLT in Nederland moet voor de eerste 20 behandelingen worden vergoed uit een aanvullend verzekeringspakket). Hierdoor raken zelfs huisartsen en vaatchirurgen die GLT volledig onderschrijven ontmoedigd en zijn daardoor te vaak genoodzaakt om naar de tweede lijn te verwijzen respectievelijk invasief te behandelen. Dit staat in schril contrast met de vergoeding voor invasieve behandelingen die wel worden vergoed vanuit de basiszorg.

ClaudicationNet

In de rest van de wereld wordt het beperkte aanbod van geschoolde therapeuten als een ernstig belemmerende factor gezien voor het niet slagen van GLT.^{16, 17} Het landelijk netwerk voor gesuperviseerde looptherapie; ClaudicationNet (CNet), heeft dit probleem in Nederland reeds opgelost.¹⁸ ClaudicationNet werd in 2010 opgericht als netwerk van gespecialiseerde fysiotherapeuten. Iedere fysiotherapeut die aan de vooraf gestelde set van eisen voldoet (d.w.z. scholing, praktijkisen), kan lid worden van dit open netwerk. CNet streeft naar een 'stepped-care' aanpak waarbij iedere patiënt met CI als eerste wordt verwezen voor GLT. Deelnemende fysiotherapeuten zijn zichtbaar op de website (www.claudicationet.nl) met een persoonlijk portfolio en het hieraan gekoppeld digitaal verwijssysteem staat garant voor een snelle verwijzing van patiënten naar desbetreffende fysiotherapeut in de nabije omgeving. Sinds 2014 bestaat in Nederland een landelijk dekkend netwerk van ruim 1.400 aangesloten fysiotherapeuten.

Uit een nog te publiceren analyse met verzekeringsgegevens uit 2011 blijkt dat het aantal patiënten doorverwezen voor GLT ten opzichte van 2009 is toegenomen. Het tij lijkt zich dus (heel) langzaam te keren. CNet heeft laten zien dat met minimale investeringen het aanbod van GLT in de nabije omgeving van de patiënt geoptimaliseerd kan worden. Hoewel Nederland relatief klein is en daarmee een hoge populatiedichtheid

kent, kan CNet prima dienen als blauwdruk voor de implementatie van gestructureerde GLT programma's binnen Europa, de Verenigde Staten en elders in de wereld.

Vergelijking van GLT met andere conservatieve behandelingen

Aanvullend bewijs dat GLT superieur is ten opzichte van andere conservatieve behandelingen (d.w.z. medicamenteus, eenmalig loopadvies, 'home-based' oefentherapie) werd geleverd in **hoofdstuk 2** van dit proefschrift.¹⁹ In de grootste meta-analyse (1,406 patiënten met CI) tot op heden werden deze vier verschillende behandelvormen met elkaar vergeleken. GLT bleek het meest effectief na respectievelijk 6 weken, 3 maanden en 6 maanden in vergelijking met de alternatieve conservatieve behandelingen. Tevens werd een dosis-respons trend gezien waarbij meer supervisie leidde tot een grotere loopafstand. Opvallende bevinding was dat de 'home-based' en GLT groep na 6 maanden niet significant van elkaar verschilden. Het zou kunnen dat de meest intensieve supervisie vooral zijn vruchten afwerpt in de eerste maanden van behandeling. Overigens hebben eerdere studies laten zien dat patiënten maximaal 50% tot 200% in loopafstand vooruit gaan.²⁰ Een andere verklaring voor het uiteindelijke vergelijkbare resultaat tussen home-based oefentherapie en GLT is dat de GLT groep dit plafond mogelijk in kortere tijd reeds heeft bereikt.

Wat wij ons daarnaast moeten realiseren is dat de mogelijkheden van GLT en leefstijlinterventies nog in de kinderschoenen staan. De mogelijke (meer)waarde van leefstijlinterventies tijdens de GLT sessies is tot nu toe nauwelijks onderzocht. Toevoeging van dergelijke interventies kan GLT mogelijk nog effectiever maken. Niet door een vergrote loopafstand, maar ook door mogelijke reductie in mortaliteit en morbiditeit wanneer patiënten een gezondere leefstijl aannemen.

Op basis van het huidige bewijs en in overeenstemming met eerdere onderzoeken lijkt GLT voor ten minste 3 maanden het meest effectief.²¹ Mogelijk zou GLT vervolgens gecontinueerd kunnen worden binnen een gecombineerd 'GLT/home-based' programma. Met de mogelijkheden van innovatieve M-health en E-health applicaties, die op dit moment binnen CNet worden onderzocht, kan een dergelijk programma in de toekomst gerealiseerd worden.²²

Vermeende onzekerheid over veiligheid van GLT blijkt ongegrond

Ondanks een landelijk dekkend netwerk van GLT programma's zijn er in Nederland nog tal van barrières te beslechten. Zo blijkt een voortdurende onzekerheid over de veiligheid van GLT te bestaan onder zowel artsen als fysiotherapeuten.¹⁵ In de richtlijn van het Koninklijk Nederlands Genootschap voor Fysiotherapie (KNGF, 2003) werd bijvoorbeeld voor aanvang van GLT cardiale screening door een cardioloog of inspanningsfysioloog geadviseerd.²³ Hoewel bewijs voor dit advies ontbrak, bleek dit een diepgewortelde angst bij veel fysiotherapeuten die (sub)maximale belasting tijdens trainingen in de weg stond. Gezien de kwetsbare patiëntengroep met een verhoogd risico op cardiovasculaire incidenten en de reële kans dat tijdens training een incident plaatsvindt, is de angst wel begrijpelijk. Echter, voorspellen van toekomstige cardiale incidenten is lastig, zo niet onmogelijk.²⁴ Mede daardoor wordt screening van patiënten met onbekend coronair lijden door vigerende internationale richtlijnen en in de herziende KNGF richtlijn (2014), niet meer geadviseerd.^{9, 25} Het is dan ook opvallend dat de zeer recente richtlijn van de Society for Vascular Surgery (2015) cardio-pulmonale screening nog steeds aanbeveeld.²

In **hoofdstuk 3** van dit proefschrift werd de veiligheid van GLT bij patiënten met CI bestudeerd. GLT-gerelateerde incidenten werden systematisch beoordeeld op basis van een review van 74 studies, met 2.876 claudicanten. Zes cardiale en twee niet-cardiale incidenten werden gerapporteerd hetgeen op een ratio van 1 complicatie per 10.340 patiënt-trainingsuren neer komt. GLT blijkt dus een veilige behandeling, en cardiale screening voorafgaand aan GLT wordt, mede gezien het feit dat het dit eigenlijk niet goed mogelijk is, niet geadviseerd.

Enige voorzichtigheid is natuurlijk geboden bij patiënten met een uitgebreide cardiopulmonale comorbiditeit (bijv. ernstig hartfalen), omdat de helft van de studies zoals opgenomen in deze review patiënten met deze problematiek uitsloot van studie deelname. Echter, andere studies met deze patiëntencategorieën hebben eerder aangetoond dat zelfs tijdens een hoog-intensief programma zich niet tot nauwelijks (cardiale) incidenten voordoen.²⁶ Bovendien bleek een oefenprogramma bij patiënten met coronair lijden een beter effect te hebben op de mortaliteit en morbiditeit dan een dotterbehandeling.²⁷ Daarmee zijn de gunstige effecten van inspanning op het gehele hart- en vaatstelsel nogmaals bevestigd.

Kortom, ook CI patiënten met cardiopulmonale comorbiditeit dienen een traject GLT aangeboden te krijgen en hoeven in de dagelijkse praktijk zeker niet routinematige geëxcludeerd te worden. Vanzelfsprekend dient zorgvuldige begeleiding en een individueel programma te worden aangeboden door goedgeschoolde fysiotherapeuten die alarmsymptomen tijdig herkennen, basic life support volledig beheersen en bij voorkeur een AED (automatische externe defibrillator) in de praktijk hebben.

Profiteren mannen en vrouwen met CI in dezelfde mate van GLT?

In de cardiologie is al geruime tijd aandacht voor geslachts-specifiek wetenschappelijk onderzoek.²⁸ Bij PAV daarentegen is nog nauwelijks iets bekend over eventuele man-vrouw verschillen met betrekking tot diagnostiek en therapie. Dit verschil werd ook benadrukt in een recente oproep van de American Heart Association waarin werd gepleit voor meer geslachts-specifiek onderzoek bij patiënten met PAV.²⁹ Vanuit pathofysiologisch vasculair oogpunt zijn namelijk duidelijke verschillen tussen mannen en vrouwen beschreven. Zo zijn bij vrouwen de bloedvaten kleiner en de atherosclerotische plaques vaak diffuser van aard.³⁰ Bovendien is bekend dat vrouwen meer fysieke beperkingen ervaren en heeft PAV een grotere impact op de dagelijkse activiteiten.³¹ Daarnaast lijken vrouwen minder vaak adequate medicatie te krijgen in de aanwezigheid van cardiovasculaire aandoeningen.³² Een studie beschreef ook dat chirurgische revascularisatie bij vrouwen vaker minder succesvol is. Met betrekking tot geslachts-specifieke uitkomsten van GLT bij patiënten met CI is weinig bekend en van beschikbaar onderzoek zijn de resultaten tegenstrijdig.^{33,34}

Hoofdstuk 4 beschrijft een analyse waarin gekeken is naar de geslachts-specifieke uitkomsten van GLT bij patiënten met CI. De gegevens van 113 mannen en 56 vrouwen die eerder deelnamen aan de Exercise Therapy in Peripheral Arterial Disease (EXITPAD) studie, een multicenter gerandomiseerde klinische studie, zijn opnieuw onderzocht. Alle patiënten ontvingen een standaard GLT programma, zoals beschreven in de KNGF richtlijn.²³ Het programma startte met een frequentie van 3 trainingen van 30 minuten per week, waarna op individuele behoefte het aantal door een fysiotherapeut begeleidde trainingen werd gereduceerd. Aan het begin van de studie waren de twee onderzoeksgroepen (d.w.z. mannen en vrouwen) vergelijkbaar wat betreft demografische kenmerken, maximale loopafstand (mannen: 250 meter, vrouwen: 270 meter) en subjectief

ervaren loopbeperking (zoals gerapporteerd op de ‘walking impairment vragenlijst’). Zowel mannen als vrouwen lieten een significante verbetering zien in loopafstand na 12 maanden. Echter, zowel na 3 als 12 maanden was de maximale loopafstand bij mannen significant groter dan bij vrouwen. Er bestond een mediaan geslacht-specifiek verschil van 95 meter na 12 maanden. Opmerkelijk genoeg werden geen verschillen gevonden in subjectieve wandelbeperking tussen de beide groepen.

Hoewel vrouwen dus minder progressie lieten zien, mag geconcludeerd worden dat zowel mannen als vrouwen met CI baat hebben bij GLT. De eerder genoemde pathofysiologische verschillen kunnen een rol spelen bij het gevonden man-vrouw verschil in loopafstand na GLT, maar ook de vaak atypische symptoompresentatie van vrouwen, het verschil in klachtenperceptie en de vaak meer beperkte functie van de onderste extremiteiten en spierkracht dragen hier mogelijk aan bij.³⁵ Het is echter nog onbekend in welke mate de individuele factoren een rol spelen.

Hoe dan ook geeft het huidige onderzoek niet direct aanleiding tot het ontwikkelen van geslachts-specifieke GLT programma's, maar aanvullend onderzoek om de kennis naar man-vrouw verschillen binnen de cardiovasculaire zorg verder uit te breiden is noodzakelijk. Zeker gezien het feit dat er nog steeds ongelijkheid bestaat tussen mannen en vrouwen met PAV voor wat betreft de tijd tot diagnose en de toegang tot zorg.³⁶

Heeft diabetes mellitus invloed op de effectiviteit van GLT?

Diabetes mellitus (DM) is een van de sterkste risicofactoren voor het ontwikkelen van PAV.³⁷ De hoge prevalentie van DM onder patiënten met CI is welbekend.³⁸ CI patiënten met DM lijken een slechtere functie van de onderste extremiteiten te hebben in vergelijking met CI patiënten zonder DM.³⁹ Bovendien heeft DM een negatieve invloed op de inspanningstolerantie.⁴⁰ Anderen suggereren dat IC patiënten met comorbiditeiten ongeschikt zouden zijn voor GLT.⁴¹ De exacte invloed van DM op het effect van GLT bij patiënten met IC is echter nog onbekend. Het gebrek aan kennis lijkt daardoor met name een barrière te vormen voor het starten van GLT.

In **hoofdstuk 5** is het beschikbare bewijs ten aanzien van de rol van DM op het effect van GLT onderzocht. Een drietal studies waarin 845 patiënten met CI voldeed aan de inclusiecriteria van deze review.^{34, 38, 42} Alle studies rapporteerden maximale loopafstand na GLT, twee rapporteerden daarnaast ook de pijnvrije loopafstand, terwijl één studie

tevens de functionele loopafstand heeft gemeten. In zijn algemeenheid lieten patiënten met zowel CI als DM duidelijke vooruitgang in loopafstand zien. De vergelijking tussen CI patiënten met en zonder DM liet echter tegenstrijdige resultaten zien. Terwijl de grootste studie geen verschillen in verbeterde loopafstand liet zien³⁸, vonden de andere twee studies een trend richting significantie in maximale en pijnvrije loopafstand na GLT.^{34, 42} In een subanalyse betreffende de rol van het geslacht kwam bovendien naar voren dat met name vrouwen met CI en DM een slechte respons hebben op GLT. Dit komt overeen met het verschil tussen mannen en vrouwen zoals gevonden in hoofdstuk 4 van dit proefschrift. Hoewel nieuwe studies ter verder verduidelijking nodig zijn, heeft het huidige review geen argumenten gevonden om patiënten met CI en DM een traject GLT te onthouden.

Hoe kunnen we de effecten van GLT juist interpreteren?

Uitkomsten van GLT worden vaak geëvalueerd in termen van (veranderingen in) loopafstand. Of het beter is om deze loopafstand te meten op een loopband of door middel van een 6-minuten wandeltest werd onlangs bediscussieerd.^{43, 44} De meest optimale test moet direct te correleren zijn aan de zogenaamde patiënt-gerapporteerde fysieke beperkingen. Vanuit dit perspectief kennen beide methoden hun beperkingen. Een meting in de dagelijkse omgeving door middel van een global positioning system (GPS) met een mobiele applicatie werd onlangs beschreven en lijkt een veelbelovend alternatief voor de eerder genoemde methode die worden afgenomen in een gecontroleerde situatie.⁴⁵ Op basis van eerder onderzoek wordt aangenomen dat een meting in de dagelijkse omgeving meer overeenkomt met de werkelijke praktijk. Anderzijds lijken deze metingen wel een grotere variabiliteit in de wandelcapaciteit op te leveren, ten nadelen van de test-hertest betrouwbaarheid.⁴⁶ Aanvullende studies zijn nodig om de meest optimale uitkomstmaat voor het bestuderen van het effect van GLT te bepalen bij patiënten met CI.

Naast deze aanvullende studies is correcte interpretatie van de huidige meetinstrumenten van even groot belang. Om klinici en onderzoekers te helpen bij het bepalen welke numerieke verandering overeenkomt met een aanzienlijke verandering vanuit het perspectief van de patiënt, is het begrip ‘minimaal relevant verschil’ (Engels: minimally important difference, MID) geïntroduceerd.⁴⁷ Met andere woorden: bij welke verandering is sprake van een verandering die er in de ogen van de patiënt toe doet. In

hoofdstuk 6 zijn de MID's voor de loopafstand zoals gemeten op een loopbandtest geschat voor patiënten met CI. Met behulp van een ankermethode en longitudinale gegevens van 103 CI patiënten die eerder hebben deelgenomen aan een GLT programma in het kader van de EXITPAD studie, werden de MID's bepaald. Voor de maximale loopafstand na 3 maanden GLT werden MID's van +305 meter en +147 meter gevonden voor respectievelijk een verbetering en verslechtering van de loopafstand. De positieve waarde voor verslechtering is hierbij met name een interessante bevinding. Blijkbaar wordt een kleine vooruitgang in loopafstand door de patiënt niet als een relevante vooruitgang gevoeld. Dit is misschien niet geheel onverwacht want GLT vraagt om een aanzienlijke inzet, inspanning en tijdsinvestering van de patiënt (hoofdstuk 1). Hoewel de grootste effecten van GLT zijn beschreven na 3 maanden (hoofdstuk 2), zou het interessant zijn om ook MID's te bepalen na een langere follow-up periode (d.w.z. na 12 maanden GLT). Daarnaast is het zinvol om ook zogenaamde patient-reported outcome measures (PROMS) te analyseren in de evaluatie van GLT. Echter, de kwaliteit van de huidige ziekte-specifieke PROMS (walking impairment questionnaire (WIQ), vascular quality of life questionnaire (VasQol)) laat nog te wensen over, zo blijkt uit recent onderzoek.⁴⁸

Fysieke activiteit van patiënten met CI als nieuwe uitkomstmaat?

Er is momenteel discussie over de waarde van de fysieke activiteit (FA) en de essentiële rol in het behouden van een goede gezondheid en algemeen welzijn.^{49,50} Uit een recente analyse bleek dat het voldoen aan de aanbevolen minimale hoeveelheid lichaamsbeweging per dag (vergeleken met het niveau van 'geen enkele lichamelijke activiteit'), leidt tot een vermindering in 'sterfte door alle oorzaken' van 19 procent.⁵⁰ Een dosis-respons relatie tussen de mate van FA en vroegtijdig overlijden werd beschreven.⁵¹ Deze resultaten zijn in overeenstemming met een verklaring op de website van de 'American Heart Association' die zegt dat 'Something is always better than nothing'.⁵² Opmerkelijk genoeg is een toename in dagelijkse fysieke activiteit net zo sterk gerelateerd aan een reductie in sterfte als het stoppen met roken.⁵²

Zoals te verwachten gelden de gunstige effecten van FA ook voor patiënten met PAV. Een hogere FA is geassocieerd met een kleinere functionele achteruitgang⁵³ en een lagere mortaliteit.⁵⁴ Het is bekend dat patiënten met CI minder frequent fysiek actief zijn in vergelijking met gezonde controles.⁵⁵ Er zijn diverse barrières (zoals

persoonsgebonden en omgevingsfactoren) beschreven die patiënten met CI weerhouden om te gaan bewegen.⁵⁶ Tot op heden wordt FA echter nauwelijks uitgevraagd, laat staan objectief gemeten tijdens een bezoek aan een arts (vaatchirurg) in tegenstelling tot de wandelcapaciteit die standaard wordt bepaald met behulp van een loopbandtest. De maximale wandelcapaciteit maakt onderdeel uit van de fysieke inspanningscapaciteit (FIC). Om te onderzoeken of de FIC als surrogaatmarker kan dienen voor FA werd een cross-sectionele studie verricht in **hoofdstuk 7**. Een totaal van 46 patiënten onderging een reeks van testen om de FIC te bepalen en droeg daarnaast gedurende zeven dagen een versnellingsmeter om de FA vast te stellen. Over het algemeen werden (zeer) zwakke tot matige correlaties gevonden tussen FIC en FA. Dit betekent dat deze deels overlappende uitkomstmaten als twee afzonderlijke entiteiten beschouwd kunnen worden.

Het bereiken van een betere FIC leidt dus niet per definitie tot een toename van de dagelijkse FA. Desalniettemin, een zekere toename in FIC, veelal bereikt door training, blijft noodzakelijk voor een toename van FA in de thuisomgeving. De eerder geformuleerde conclusies komen overeen met studies die geen effect van GLT beschreven op de dagelijkse fysieke activiteit bij patiënten met CI.⁵⁷ De huidige resultaten en de aangetoonde associaties tussen fysieke activiteit en mortaliteit vormen duidelijke argumenten om FA te introduceren als nieuwe uitkomstmaat voor patiënten met PAV (en mogelijk ook andere groepen van chronische patiënten). Recente studies lieten daarnaast zien dat ook langdurige inactiviteit (d.w.z. zitten en liggen), onafhankelijk van de mate van activiteit, een belangrijke risicofactor is voor vroegtijdig overlijden.⁵⁸ Het lijkt daarom zinvol om zowel activiteit als sedentaire gedrag te meten.

Classificatie van CI patiënten

De voorgestelde meting van het fysieke activiteitsniveau is alleen zinvol (klinisch relevant) wanneer dit een aanmerkelijk effect heeft op beslissingen en gedrag van een patiënt. FA is echter een complex eindpunt dat beïnvloedt wordt door tal van factoren als motivatie, training en omgeving maar ook politieke beslissingen in het kader van vergoedingen bijvoorbeeld. Daarnaast zijn de huidige GLT programma's mogelijk niet specifiek (genoeg) om daadwerkelijk effect te hebben op FA, zoals werd aangetoond door uitblijven van verbetering op de FA na 3 maanden GLT.⁵⁷ Daarentegen zijn er wel gunstige resultaten beschreven van een kortdurende psychologische interventie op het loopgedrag

van patiënten met CI.⁵⁹ De interventiegroep die twee behandelingen van één uur ontvingen liet een significante verschil in het dagelijks aantal stappen ($\Delta 1.567$ stappen per dag) zien in vergelijking met de controlegroep die standaardzorg ontving. Dit effect hield tot 2 jaar na de interventie aan.⁶⁰ Dergelijke psychologische interventies (gespreksvoering) zouden uitstekend ingebouwd kunnen worden in een GLT programma, zoals uitgevoerd door fysiotherapeuten die getraind zijn in 'motivational interviewing' technieken. Op die manier wordt de effectiviteit van GLT op de verbetering van FA mogelijk extra verbeterd.

In het huidige proefschrift worden metingen van zowel FIC als FA geadviseerd, want informatie over beide uitkomstmaten is behulpzaam bij het classificeren van IC patiënten (*figuur 1*). Naar verwachting draagt een aantal (nog onbekende) factoren bij aan de categorie waartoe een patiënt behoort. Bijvoorbeeld, een CI patiënt met een goede reactie op GLT (hoge FIC) die een sedentair leven leidt (lage FA) behoort tot categorie C. Een gedetailleerde karakterisatie (bijv. demografische kenmerken, motivatie, gezondheidstoestand, omgeving, etc.) van patiënten uit deze vier categorieën kan bijdragen tot het begrip van de onderliggende determinanten die het beweeggedrag van patiënten bepalen. Dit zou uiteindelijk kunnen leiden tot geoptimaliseerde en meer geïndividualiseerde zorg. Dus het doel is niet om patiënten van een 'ongezonde' categorie te verplaatsen naar een meer gezonde categorie, maar juist inzicht te verwerven waarom patiënten in een bepaalde categorie terechtkomen om zodoende een passende behandeling te kunnen geven.

Figuur 1. Schematische weergave om patiënten in te delen op basis van het fysieke activiteitsniveau en de inspanningscapaciteit

Aanpassingen van het looppatroon door claudicatio intermittens

Spatio-temporele veranderingen van looppatroon werden eerder beschreven in patiënten met CI.^{61, 62} Ze lopen langzamer, hebben een lagere cadans (d.w.z. minder stappen per minuut) en een kortere staplengte. Bovendien is de zuurstofopname tijdens pijnvrij lopen hoger in vergelijking met controles van dezelfde leeftijd.^{63, 64} CI patiënten nemen blijkbaar een slechtere loopefficiëntie ('cost of transport') aan, welke nog verder afneemt op het moment dat de claudicatio klachten ontstaan. Cost of transport lijkt verder onder andere beïnvloed te worden door het hebben van diabetes.⁶⁵ Deze bevinding kan in ieder geval ten dele verklaren waarom CI patiënten met diabetes slechter reageren op GLT dan CI patiënten zonder diabetes (hoofdstuk 5). Aangezien de zuurstofopname reeds verhoogd is tijdens pijnvrij lopen, moeten er andere factoren zijn die ook een rol spelen hierin. Aanpassingen van het looppatroon dragen hier mogelijk ook aan bij.

Uit eerder onderzoek bleek dat GLT geen effect had op het veranderde looppatroon bij patiënten met CI.⁶⁶ Het uitblijven van verbetering kan samenhangen met onvoldoende afstemming van de GLT oefeningen om daadwerkelijk evidente verbeteringen te kunnen bewerkstelligen. Aanvullend onderzoek naar aanpassingen op bijvoorbeeld spierniveau zouden mogelijk nieuwe inzichten kunnen opleveren die GLT programma's kunnen optimaliseren. Opmerkelijk genoeg zijn bevindingen uit voorgaand onderzoek gebaseerd op analyses van slechts enkele stappen terwijl het natuurlijk veel logischer is om minstens 30 of 40 stappen te bestuderen.

In **hoofdstuk 8 en 9** van dit proefschrift werden de verschillende aspecten van het looppatroon van CI patiënten onderzocht met behulp van een loopbandprotocol. Gecontinueerde analyse tijdens het lopen op een loopband maakt beoordeling van een oneindig aantal stappen mogelijk. Daarnaast kan deze methodologie het looppatroon op het moment dat de pijndrempel bereikt is nauwkeurig analyseren.

Allereerst werd een analyse van spatio-temporale parameters in 28 CI patiënten en 28 gezonde voor leeftijd gematchte controles (hoofdstuk 8) verricht. CI patiënten liepen met een zelf gekozen snelheid van 3,3 km/uur, terwijl controles 1,2 km/uur harder liepen. Het duidelijkste verschil werden gevonden in contact- en afzetfase (zie *figuur 2*, pagina 170). CI patiënten lieten een 14% kortere afzetfase en een 17% langere contactfase zien. Daarnaast bleek de enkel-arm index (een maat voor de ernst van de ziekte en atherosclerotische occlusie) gecorreleerd te zijn aan zowel de loopsnelheid als de afname in afzet tijdens het optreden van claudicatio pijn. CI patiënten blijken dus tijdens iedere stap net iets langer stil te staan. Deze aanpassingen kunnen intuïtief verklaard worden wanneer men bedenkt dat de arteriële bloedinstroom en daarmee zuurstoftoevoer naar de skeletspieren plaatsvindt tijdens deze relaxatiefase.^{67, 68} Dit kan ook verklaren waarom CI patiënten niet kleinere stappen gaan zetten als de pijn optreedt, maar juist minder, zoals ook in eerder onderzoek beschreven werd.⁶⁹

Op basis van deze spatio-temporele resultaten (hoofdstuk 8) werd gedacht dat CI patiënten misschien wel gebruik maken van een langere contactfase om zodoende een maximale spierontspanning te bewerkstelligen. Immers, hoe langer de ontspanning des te meer tijd voor instroom van bloed. **Hoofdstuk 9** beschrijft de verschillende analyses met behulp van kinematica en oppervlakte elektromyografie (EMG) om deze hypothese te toetsen. De onderzoekspopulatie bestond uit 22 CI patiënten en 22 gezonde gematchte

controles. De kinematische (d.w.z. knie- en enkelgewrichtshoeken) analyse toonde een significant kleinere enkelbeweging (-28%) bij CI patiënten en ondersteunt daarmee de eerder geformuleerde hypothese. Echter, de EMG data toonden geen verschillen aan in duur van spieractiviteit van de tibialis anterior en de mediale gastrocnemius (m.a.w. kuitspier) spieren. Patiënten met CI gebruiken de belangrijkste onderbeenspieren voor het lopen dus voor een vergelijkbare duur als gezonden. De duur van de spieractiviteit werd uitgedrukt als percentage van de complete gangcyclus om te corrigeren voor de verschillen in loopsnelheid tussen beide groepen en kunnen dus onderling met elkaar vergeleken worden ondanks het verschil in loopsnelheid.

Concluderend, CI patiënten vertonen duidelijke spatio-temporele en kinematische veranderingen van het looppatroon, zelfs al voordat de claudicatiopijn optreedt. Het is echter niet aangetoond dat deze strategie ook leidt tot een kortere aanspanning van de kuitspier aangezien de duur van spieractiviteit gelijk was in gezonde controlepersonen. Er zijn verschillende manieren om deze resultaten te verklaren. Oppervlakte EMG meet uitsluitend spieractiviteit en geen spierkracht. Het is eerder beschreven dat een minimale intensiteit (d.w.z. boven 50% van de maximale vrijwillige contractiekracht) vereist is om een verlaging van de arteriële bloeddoorstroming van de kuitspier te veroorzaken. Het is dus mogelijk dat niet de duur, maar de mate van aanspanning verschillend is tussen CI patiënten en gezonde controles. Dit idee wordt ondersteund door onderzoek waarin een verminderde afzetkracht en een afgenomen vermogen van de kuitspieren bij claudicanten werden beschreven.^{70, 71} Anderzijds zijn de gevonden spatio-temporele en kinematische veranderingen mogelijk niet een (on)bewuste strategie om met de aan CI gerelateerde arteriële obstructie te gaan, maar juist het gevolg van een, deels door ischemie veroorzaakte, vermindering van spierkracht. Dit zou namelijk ook de ongunstige metabole efficiëntie (cost of transport) van CI patiënten kunnen verklaren, aangezien een verminderde spierkracht bijdraagt aan een verminderde loopsnelheid en een beperkte wandelcapaciteit.

Implicaties voor de praktijk en suggesties voor nieuw onderzoek

Beleidsmatig dienen serieuze inspanningen geleverd te worden om de beperkte beschikbaarheid en toegang tot GLT te slechten zodat deze voorkeursbehandeling routinematig en wereldwijd in de klinische praktijk kan worden toegepast. Het succes

van het ClaudicationNet netwerk bewijst dat aanzienlijke financiële investeringen niet per se nodig zijn. Maar louter beschikbaarheid van een landelijk netwerk van GLT is niet genoeg, omdat dit systeem feitelijk alleen een goede infrastructuur biedt. Na de oprichting van een netwerk, is structurele financiering noodzakelijk voor waarborging van de faciliteiten. Dit zou in de Nederlandse situatie bijvoorbeeld bewerkstelligd kunnen worden door opname van GLT in het basispakket van de zorgverzekering. Daarnaast is permanente scholing van CI gerelateerde onderwerpen noodzakelijk om artsen, fysiotherapeuten alsmede patiënten te motiveren.

Toekomstig wetenschappelijk onderzoek zou zich idealiter dienen te richten op inhoudelijke verbetering van GLT. Het meest optimale en effectieve GLT programma alsook de ontwikkeling van aangepaste programma's voor subgroepen van CI patiënten moet worden vastgesteld. Daarnaast lijkt met name het verwerken van voorstellen tot leefstijlverandering in het GLT programma veelbelovend. Advies en interventies rondom de (ongezonde) leefstijl passen uitstekend bij de voorgenomen toevoeging van fysieke activiteit als uitkomstmaat voor patiënten met CI. Immers, verbetering van de fysieke activiteit maakt vanzelfsprekend onderdeel uit van de leefstijl. Aangezien het erg lastig is om diepgeworteld gedrag te veranderen, moet een andere onderzoeksfocus zich richten op het verkrijgen van inzicht in de factoren die het beweeggedrag van CI patiënten bepalen. Het voorgestelde model in figuur 1 kan ondersteunen in het vergaren van inzicht en het identificeren van determinanten die bepaald gedrag kan verklaren.

Ten derde kan het effect van specifieke spierkrachttraining van de onderste extremiteiten op loopafstand en looppatroon verder worden onderzocht. Spierkracht levert een belangrijke bijdrage aan zowel de loopsnelheid als balans (en daarmee het valrisico),⁷² en het lijkt dan ook logisch om spierkrachttraining toe te voegen aan een GLT programma. Echter, eenduidig wetenschappelijk bewijs hiervoor ontbreekt. Voorgestelde suggesties zijn wel in lijn van de huidige trend waarop GLT ingevuld wordt, namelijk in de vorm van een gevarieerd aanbod aan oefenvormen.⁷³ Longitudinale EMG registratie (d.w.z. een nulmeting gevolgd door een interventie en follow-up meting) kan behulpzaam zijn bij het bepalen van het effect van GLT op de spierkracht en het looppatroon, aangezien tijdens gepaarde metingen EMG amplitudes wel geïnterpreteerd mogen worden als zijde spierkracht.

De resultaten van dit proefschrift leverden bewijs voor specifieke veranderingen in het looppatroon bij claudicanten, met name op het niveau van de contact- en afzetfase. Aangezien deze veranderingen duidelijk verband hielden met de loopsnelheid, dient een vierde onderzoeksfocus te liggen op studies naar de mogelijkheden om de loopsnelheid te verbeteren. Dit zou vervolgens kunnen leiden tot een verbetering van het looppatroon.

Conclusies van dit proefschrift

1. Gesuperviseerde looptherapie (GLT) is een veilige behandeling bij patiënten met claudicatio intermittens (CI).
2. GLT leidt tot een grotere loopafstand in vergelijking met andere conservatieve behandelopties.
3. Vrouwen met CI hebben de neiging om minder te profiteren van GLT als het gaat om een verbeterde maximale loopafstand.
4. Diabetespatiënten met CI hebben ook baat bij GLT.
5. De ‘minimaal relevante verschillen’ van de loopband bepaalde maximale loopafstand voor verbetering en verslechtering, zijn respectievelijk +305 en +147 meter. De positieve waarde van het relevant verschil voor een verslechtering van de loopafstand geeft aan dat zelfs een kleine verbetering blijkbaar niet afdoende is in de ogen van de patiënt.
6. De correlaties tussen de fysieke inspanningscapaciteit (FIC) en dagelijkse fysieke activiteit (FA) bij patiënten met CI zijn zwak tot matig. Dit betekent dat FIC en FA, hoewel enigszins met elkaar overeenkomend, beschouwd moeten worden als verschillende entiteiten.
7. Patiënten met CI lopen langzamer en vertonen een korte afzetfase en afgenomen enkelbewegingen in vergelijking met gezonde controles. Daarentegen zijn er geen verschillen in aanspanningsduur van de tibialis anterior en mediale gastocnemiusspieren. Echter, tijdens lopen met door ischemie geïnduceerde pijn, zijn de elektromyografische amplitudes wel significant hoger dan tijdens pijnvrij lopen.

REFERENTIES

1. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res.* 2015;116(9):1509-26.
2. Society for Vascular Surgery Lower Extremity Guidelines Writing G, Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JE, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg.* 2015;61(3 Suppl):2S-41S.
3. Mays RJ, Casserly IP, Kohrt WM, Ho PM, Hiatt WR, Nehler MR, et al. Assessment of functional status and quality of life in claudication. *J Vasc Surg.* 2011;53(5):1410-21.
4. Lane RA, Mazari F, Mockford KA, Vanicek N, Chetter IC, Coughlin PA. Fear of falling in claudicants and its relationship to physical ability, balance, and quality of life. *Vasc Endovascular Surg.* 2014;48(4):297-304.
5. Crowther RG, Spinks WL, Leicht AS, Quigley F, Golledge J. Relationship between temporal-spatial gait parameters, gait kinematics, walking performance, exercise capacity, and physical activity level in peripheral arterial disease. *J Vasc Surg.* 2007;45(6):1172-8.
6. Fokkenrood HJ, Scheltinga MR, Koelemay MJ, Breek JC, Hasaart F, Vahl AC, et al. Significant savings with a stepped care model for treatment of patients with intermittent claudication. *Eur J Vasc Endovasc Surg.* 2014;48(4):423-9.
7. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet.* 2013;382(9901):1329-40.
8. Layden J, Michaels J, Bermingham S, Higgins B, Guideline Development G. Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance. *BMJ.* 2012;345:e4947.
9. Merry AH, Teijink JA, Jongert MW, Poelgeest A, van der Voort SS, Bartelink ME, et al. [KNGF-guideline Symptomatic peripheral arterial disease (author's translation)]. 2014.
10. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, 3rd, Cohen DJ, Reynolds MR, et al. Supervised Exercise, Stent Revascularization, or Medical Therapy for Claudication Due to Aortoiliac Peripheral Artery Disease: The CLEVER Study. *J Am Coll Cardiol.* 2015;65(10):999-1009.

11. Egorova NN, Guillerme S, Gelijns A, Morrissey N, Dayal R, McKinsey JF, et al. An analysis of the outcomes of a decade of experience with lower extremity revascularization including limb salvage, lengths of stay, and safety. *J Vasc Surg.* 2010;51(4):878-85, 85 e1.
12. Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Cost-effectiveness of endovascular revascularization compared to supervised hospital-based exercise training in patients with intermittent claudication: a randomized controlled trial. *J Vasc Surg.* 2008;48(6):1472-80.
13. Gommans LN, Teijink JA. Attitudes to supervised exercise therapy. *Br J Surg.* 2015.
14. Popplewell MA, Bradbury AW. Why do health systems not fund supervised exercise programmes for intermittent claudication? *Eur J Vasc Endovasc Surg.* 2014;48(6):608-10.
15. Lauret GJ, van Dalen HC, Hendriks HJ, van Sterkenburg SM, Koelemay MJ, Zeebregts CJ, et al. When is supervised exercise therapy considered useful in peripheral arterial occlusive disease? A nationwide survey among vascular surgeons. *Eur J Vasc Endovasc Surg.* 2012;43(3):308-12.
16. Makris GC, Lattimer CR, Lavidia A, Geroulakos G. Availability of supervised exercise programs and the role of structured home-based exercise in peripheral arterial disease. *Eur J Vasc Endovasc Surg.* 2012;44(6):569-75; discussion 76.
17. Stewart AH, Lamont PM. Exercise for intermittent claudication. Supervised programmes should be universally available. *BMJ.* 2001;323(7315):703-4.
18. Lauret GJ, Gijssbers HJ, Hendriks EJ, Bartelink ML, de Bie RA, Teijink JA. The ClaudicationNet concept: design of a national integrated care network providing active and healthy aging for patients with intermittent claudication. *Vasc Health Risk Manag.* 2012;8:495-503.
19. Gommans LN, Saarloos R, Scheltinga MR, Houterman S, de Bie RA, Fokkenrood HJ, et al. Editor's choice--The effect of supervision on walking distance in patients with intermittent claudication: a meta-analysis. *Eur J Vasc Endovasc Surg.* 2014;48(2):169-84.
20. Fakhry F, van de Luijngaarden KM, Bax L, den Hoed PT, Hunink MG, Rouwet EV, et al. Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg.* 2012;56(4):1132-42.
21. Gardner AW, Montgomery PS, Parker DE. Optimal exercise program length for patients with claudication. *J Vasc Surg.* 2012;55(5):1346-54.
22. Fokkenrood HJ, Lauret GJ, Scheltinga MR, Spreeuwenberg C, de Bie RA, Teijink JA. Multidisciplinary treatment for peripheral arterial occlusive disease and the role of eHealth and mHealth. *J Multidiscip Healthc.* 2012;5:257-63.

23. Jongert MW, Hendriks HJ, van Hoek J, Klaasboer-Kogelman K, Robeer GG, Simens B, et al. [KNGF-Guideline Intermittent Claudication (author's translation)]. *Ned Tijdschr Fysiother.* 2003;113:3-50.
24. Pavy B, Iliou MC, Meurin P, Tabet JY, Corone S. Safety of exercise training for cardiac patients: results of the French registry of complications during cardiac rehabilitation. *Arch Intern Med.* 2006;166(21):2329-34.
25. Skinner JS, Smeeth L, Kendall JM, Adams PC, Timmis A. NICE guidance. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. *Heart.* 2010;96(12):974-8.
26. Rognmo O, Hetland E, Helgerud J, Hoff J, Slordahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil.* 2004;11(3):216-22.
27. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA.* 2009;301(14):1439-50.
28. Maas AH, van der Schouw YT, Regitz-Zagrosek V, Swahn E, Appelman YE, Pasterkamp G, et al. Red alert for women's heart: the urgent need for more research and knowledge on cardiovascular disease in women: proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010. *Eur Heart J.* 2011;32(11):1362-8.
29. Hirsch AT, Allison MA, Gomes AS, Corriere MA, Duval S, Ershow AG, et al. A call to action: women and peripheral artery disease: a scientific statement from the American Heart Association. *Circulation.* 2012;125(11):1449-72.
30. Lozano FS, Gonzalez-Porras JR, March JR, Carrasco E, Lobos JM, Investigators V. Differences between women and men with intermittent claudication: a cross-sectional study. *J Womens Health (Larchmt).* 2014;23(10):834-41.
31. Oka RK, Szuba A, Giacomini JC, Cooke JP. Gender differences in perception of PAD: a pilot study. *Vasc Med.* 2003;8(2):89-94.
32. Enriquez JR, Pratap P, Zbilut JP, Calvin JE, Volgman AS. Women tolerate drug therapy for coronary artery disease as well as men do, but are treated less frequently with aspirin, beta-blockers, or statins. *Gend Med.* 2008;5(1):53-61.
33. Serracino-Inglott F, Owen G, Carter A, Dix F, Smyth JV, Mohan IV. All patients benefit equally from a supervised exercise program for claudication. *Vasc Endovascular Surg.* 2007;41(3):212-6.

34. Gardner AW, Parker DE, Montgomery PS, Blevins SM. Diabetic women are poor responders to exercise rehabilitation in the treatment of claudication. *J Vasc Surg.* 2014;59(4):1036-43.
35. Gardner AW. Sex differences in claudication pain in subjects with peripheral arterial disease. *Med Sci Sports Exerc.* 2002;34(11):1695-8.
36. Vavra AK, Kibbe MR. Women and peripheral arterial disease. *Womens Health (Lond Engl).* 2009;5(6):669-83.
37. Aronow WS. Peripheral arterial disease in women. *Maturitas.* 2009;64(4):204-11.
38. van Pul KM, Kruidenier LM, Nicolai SP, de Bie RA, Nieman FH, Prins MH, et al. Effect of supervised exercise therapy for intermittent claudication in patients with diabetes mellitus. *Ann Vasc Surg.* 2012;26(7):957-63.
39. Dolan NC, Liu K, Criqui MH, Greenland P, Guralnik JM, Chan C, et al. Peripheral artery disease, diabetes, and reduced lower extremity functioning. *Diabetes Care.* 2002;25(1):113-20.
40. Uçok K, Yalcinkaya H, Acay A, Coban NF, Aslanalp S, Akkan G, et al. Do patients with newly diagnosed type 2 diabetes have impaired physical fitness, and energy expenditures? *Neth J Med.* 2015;73(6):276-83.
41. Dos Anjos Souza Barbosa J, Henriques PM, De Barros MVG, Wolosker N, Ritti-Dias RM. Physical activity level in individuals with peripheral arterial disease: a systematic review. *J Vasc Bras.* 2012;11:1-7.
42. Allen JD, Stabler T, Kenjale AA, Ham KL, Robbins JL, Duscha BD, et al. Diabetes status differentiates endothelial function and plasma nitrite response to exercise stress in peripheral arterial disease following supervised training. *J Diabetes Complications.* 2014;28(2):219-25.
43. McDermott MM, Guralnik JM, Criqui MH, Liu K, Kibbe MR, Ferrucci L. Six-minute walk is a better outcome measure than treadmill walking tests in therapeutic trials of patients with peripheral artery disease. *Circulation.* 2014;130(1):61-8.
44. 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(1):69-78.
45. Le Faucheur A, Abraham P, Jaquinandi V, Bouye P, Saumet JL, Noury-Desvaux B. Measurement of walking distance and speed in patients with peripheral arterial disease: a novel method using a global positioning system. *Circulation.* 2008;117(7):897-904.

46. Le Faucheur A, Noury-Desvaux B, Mahe G, Sauvaget T, Saumet JL, Leftheriotis G, et al. Variability and short-term determinants of walking capacity in patients with intermittent claudication. *J Vasc Surg.* 2010;51(4):886-92.
47. Conijn AP, Jonkers W, Rouwet EV, Vahl AC, Reekers JA, Koelemay MJ. Introducing the Concept of the Minimally Important Difference to Determine a Clinically Relevant Change on Patient-Reported Outcome Measures in Patients with Intermittent Claudication. *Cardiovasc Intervent Radiol.* 2015.
48. Conijn AP, Jens S, Terwee CB, Breek JC, Koelemay MJ. Assessing the Quality of Available Patient Reported Outcome Measures for Intermittent Claudication: A Systematic Review Using the COSMIN Checklist. *Eur J Vasc Endovasc Surg.* 2015;49(3):316-34.
49. Holtermann A, Mortensen OS, Burr H, Sogaard K, Gyntelberg F, Suadcani P. Fitness, work, and leisure-time physical activity and ischaemic heart disease and all-cause mortality among men with pre-existing cardiovascular disease. *Scand J Work Environ Health.* 2010;36(5):366-72.
50. Woodcock J, Franco OH, Orsini N, Roberts I. Non-vigorous physical activity and all-cause mortality: systematic review and meta-analysis of cohort studies. *Int J Epidemiol.* 2011;40(1):121-38.
51. Hupin D, Roche F, Gremeaux V, Chatard JC, Oriol M, Gaspoz JM, et al. Even a low-dose of moderate-to-vigorous physical activity reduces mortality by 22% in adults aged ≥ 60 years: a systematic review and meta-analysis. *Br J Sports Med.* 2015.
52. Holme I, Anderssen SA. [Physical activity, smoking and mortality among men who participated in the Oslo studies of 1972 and 2000]. *Tidsskr Nor Laegeforen.* 2014;134(18):1743-8. Fysisk aktivitet, royking og dodelighet hos menn som deltok i Oslo-undersokelsene i 1972 og 2000.
53. Garg PK, Liu K, Tian L, Guralnik JM, Ferrucci L, Criqui MH, et al. Physical activity during daily life and functional decline in peripheral arterial disease. *Circulation.* 2009;119(2):251-60.
54. Garg PK, Tian L, Criqui MH, Liu K, Ferrucci L, Guralnik JM, et al. Physical activity during daily life and mortality in patients with peripheral arterial disease. *Circulation.* 2006;114(3):242-8.
55. Lauret GJ, Fokkenrood HJ, Bendermacher BL, Scheltinga MR, Teijink JA. Physical activity monitoring in patients with intermittent claudication. *Eur J Vasc Endovasc Surg.* 2014;47(6):656-63.

56. Barbosa JP, Farah BQ, Chehuen M, Cucato GG, Farias Junior JC, Wolosker N, et al. Barriers to physical activity in patients with intermittent claudication. *Int J Behav Med.* 2015;22(1):70-6.
57. Fokkenrood HJ, Lauret GJ, Verhofstad N, Bendermacher BL, Scheltinga MR, Teijink JA. The effect of supervised exercise therapy on physical activity and ambulatory activities in patients with intermittent claudication. *Eur J Vasc Endovasc Surg.* 2015;49(2):184-91.
58. van der Ploeg HP, Chey T, Korda RJ, Banks E, Bauman A. Sitting time and all-cause mortality risk in 222 497 Australian adults. *Arch Intern Med.* 2012;172(6):494-500.
59. Cunningham MA, Swanson V, Pappas E, O'Carroll RE, Holdsworth RJ. Illness beliefs and walking behavior after revascularization for intermittent claudication: a qualitative study. *J Cardiopulm Rehabil Prev.* 2014;34(3):195-201.
60. Cunningham MA, Swanson V, Holdsworth RJ, O'Carroll RE. Late effects of a brief psychological intervention in patients with intermittent claudication in a randomized clinical trial. *Br J Surg.* 2013;100(6):756-60.
61. Gardner AW, Forrester L, Smith GV. Altered gait profile in subjects with peripheral arterial disease. *Vasc Med.* 2001;6(1):31-4.
62. Gardner AW, Montgomery PS, Ritti-Dias RM, Forrester L. The effect of claudication pain on temporal and spatial gait measures during self-paced ambulation. *Vasc Med.* 2010;15(1):21-6.
63. Womack CJ, Sieminski DJ, Katzel LI, Yataco A, Gardner AW. Improved walking economy in patients with peripheral arterial occlusive disease. *Med Sci Sports Exerc.* 1997;29(10):1286-90.
64. Marconi C, Ferretti G, Anchisi S, Catalano M, Scandale G, Antico A, et al. Energetics of walking in patients with peripheral arterial disease: a proposed functional evaluation protocol. *Clin Sci (Lond).* 2003;105(1):105-11.
65. Gardner AW, Ritti-Dias RM, Stoner JA, Montgomery PS, Scott KJ, Blevins SM. Walking economy before and after the onset of claudication pain in patients with peripheral arterial disease. *J Vasc Surg.* 2010;51(3):628-33.
66. King S, Vanicek N, Mockford KA, Coughlin PA. The effect of a 3-month supervised exercise programme on gait parameters of patients with peripheral arterial disease and intermittent claudication. *Clin Biomech (Bristol, Avon).* 2012;27(8):845-51.
67. Kagaya A. Relative contraction force producing a reduction in calf blood flow by superimposing forearm exercise on lower leg exercise. *Eur J Appl Physiol Occup Physiol.* 1993;66(4):309-14.

68. Pool J. The blood flow through the human calf during rhythmic exercise. *Pflugers Arch.* 1970;314(2):171-2.
69. Mockford KA, Vanicek N, Jordan A, Chetter IC, Coughlin PA. Kinematic adaptations to ischemic pain in claudicants during continuous walking. *Gait Posture.* 2010;32(3):395-9.
70. Scott-Pandorf MM, Stergiou N, Johanning JM, Robinson L, Lynch TG, Pipinos, II. Peripheral arterial disease affects ground reaction forces during walking. *J Vasc Surg.* 2007;46(3):491-9.
71. Koutakis P, Johanning JM, Haynatzki GR, Myers SA, Stergiou N, Longo GM, et al. Abnormal joint powers before and after the onset of claudication symptoms. *J Vasc Surg.* 2010;52(2):340-7.
72. Mockford KA, Mazari FA, Jordan AR, Vanicek N, Chetter IC, Coughlin PA. Computerized dynamic posturography in the objective assessment of balance in patients with intermittent claudication. *Ann Vasc Surg.* 2011;25(2):182-90.
73. Lauret GJ, Fakhry F, Fokkenrood HJ, Hunink MG, Teijink JA, Spronk S. Modes of exercise training for intermittent claudication. *Cochrane Database Syst Rev.* 2014;7:CD009638.

VALORISATIE

Introductie

Claudicatio intermittens (CI) is de meest voorkomende uitingsvorm van perifeer arterieel vaatlijden (PAV) en wordt gekenmerkt door inspanning gebonden pijn in de benen, welke verdwijnt na een periode van rust.¹ De loopafstand is daardoor beperkt en bijkomend kan sprake zijn van een verminderd uithoudingsvermogen, verlies van spierkracht, verhoogd valrisico en angst voor pijn en/of inspanning.²⁻⁴ Uit onderzoek blijkt verder dat patiënten met PAV een verminderde kwaliteit van leven rapporteren en slechter scoren op functionele testen.⁵ Om klachten te maskeren gaan patiënten tijdens de noodzakelijke rustpauzes soms voor een winkeletalage staan. CI wordt daarom ook wel ‘etalagebenen’ genoemd.

PAV is vrijwel altijd het gevolg van atherosclerose (slagaderverkalking).⁶ De bloedvaten van en naar de benen raken vernauwd en/of verstopt, waardoor de toevoer van bloed en daarmee zuurstof naar de spieren (bij inspanning), tekort schiet. Nog vaak wordt vergeten dat atherosclerose een systeemziekte is. Niet alleen de bloedvaten in de benen zijn aangedaan, maar ook de kransslagaders rond het hart en de slagaders naar en van de hersenen. Daardoor hebben patiënten met PAV een aanzienlijk verhoogd risico op een hart- en/of herseninfarct, ten opzichte van mensen zonder PAV. Dit gaat gepaard met een aanzienlijke morbiditeit. Bovendien is de levensverwachting verkort met ongeveer 10 jaar.⁷

Veelvoorkomend gezondheidsprobleem

In Nederland krijgen jaarlijks ruim 25.000 mensen de diagnose CI te horen. Wereldwijd ligt het aantal mensen met PAV net boven de 200 miljoen.⁸ In het afgelopen decennium is het aantal patiënten met bijna een kwart gestegen. De grootste toename wordt gezien in de laag- en middeninkomenslanden, waar onder invloed van de toenemende welvaart geassocieerde ziekten als obesitas en diabetes mellitus steeds vaker voorkomen.⁸

Voor de gezondheidszorg als geheel heeft de behandeling van PAV een groot aandeel in de totale zorgkosten, welke naar verwachting de komende jaren alleen verder zullen stijgen. Terecht werd recent een oproep gedaan aan overheden, relevante organisaties

en de private sector om met een oplossing te komen voor de maatschappelijke en economische consequenties van PAV.⁸

Gesuperviseerde looptherapie als *totaalbehandeling* voor CI

Gesuperviseerde LoopTherapie (GLT), dat wil zeggen onder begeleiding van een fysiotherapeut trainen, is de eerste keus behandeling voor patiënten met CI en wordt in (inter)nationale richtlijnen van zowel de eerste als tweede lijn geadviseerd.^{7,9} Studies die GLT vergeleken met een loopadvies en/of een vasculaire interventie (zoals: een dotter, stent of bypass operatie) hebben overtuigend bewijs geleverd dat GLT de meest kosteneffectieve behandeling is.¹⁰⁻¹³ Recent werd de toegevoegde waarde van GLT ten opzichte van een vasculaire interventie ook aangetoond door haar positieve effecten op balans en het valrisico.¹⁴ Daarnaast heeft GLT invloed op het gehele cardiovasculaire systeem, waaronder het contralaterale been welke ten tijde van de therapie mogelijk nog asymptomatische is.^{15,16} Een GLT programma van (slechts) 12 weken reduceert de mortaliteit en morbiditeit door cardiovasculaire oorzaken daardoor aanzienlijk.¹⁷

Op dit moment wordt slechts een minderheid van de patiënten met CI verwezen voor GLT, zo bleek uit een analyse van Nederlandse verzekeringsgegevens.¹⁸ Deze analyse liet ook zien dat wanneer 80% van de patiënten met CI wordt verwezen voor GLT en deze GLT wordt vergoed, een kostenbesparing van 33 miljoen gerealiseerd kan worden.¹⁸ Met het oog op noodzakelijk besparingen in de zorg en het toenemend aantal patiënten met CI, zou GLT toch een aantrekkelijke behandeling moeten zijn.

Onterechte barrière door onzekerheid rondom veiligheid

Er bestaat onzekerheid onder zowel fysiotherapeuten als verwijzend artsen over de veiligheid van GLT voor (bepaalde) CI patiënten (bijvoorbeeld bij patiënten met cardiale comorbiditeit). Deze onzekerheid wordt gevoed door adviezen uit (inter)nationale richtlijnen om CI patiënten voor aanvang van de behandeling cardiopulmonaal te screenen.^{7,19} Vanzelfsprekend is veiligheid van therapie een belangrijk thema en dient het risico op complicaties in verhouding te staan tot de noodzaak van behandeling. Daarnaast moeten alternatieve behandelvormen overwogen worden.

Gedegen wetenschappelijk bewijs ten aanzien van de veiligheid van GLT ontbrak echter en vormde een duidelijke barrière om patiënten te verwijzen voor GLT. In dit proefschrift (hoofdstuk 3) werd aangetoond dat GLT een veilige behandeling is, zonder een noemenswaardig aantal complicaties.²⁰ Daarentegen gaat de alternatieve invasieve behandeling (dotter, stent, bypassoperatie) gepaard met door literatuur ondergeschreven complicaties als bloedingen, trombo-embolische events en infecties.²¹ Ingegeven door de resultaten uit dit proefschrift werd het advies tot cardiale screening voor aanvang van GLT geschrapt uit de herziene richtlijn van het Koninklijk Nederlands Genootschap voor Fysiotherapie (KNGF, 2014).²²

‘Claudicatiotherapeut’

GLT is eigenlijk geen goede benaming meer voor wat een daartoe getrainde fysiotherapeut onder deze noemer moet gaan leveren. Want naast intervaltraining op de loopband, bestaat behandeling van CI uit oefeningen ter verbetering van het algehele uithoudingsvermogen, spierkracht, coördinatie, balans en meer specifiek het looppatroon. In de hoofdstukken 8 en 9 van dit proefschrift werden naar aanleiding van de gevonden verschillen in het looppatroon van patiënten met claudicatio intermittens, concrete adviezen geformuleerd voor fysiotherapeuten. Er werd gesuggereerd dat verbetering van het looppatroon een positief effect kan hebben op de efficiëntie van lopen, waardoor de actieradius vervolgens positief wordt beïnvloed. Op deze manier draagt dit proefschrift bij aan de inhoudelijke verbetering van GLT.

De behandeling dient zich daarnaast te richten op aanwezige cardiovasculaire risicofactoren, als stoppen met roken, meer bewegen, stimuleren van een verantwoord dieet en een gezond gewicht. In de komende jaren dient het accent nog meer op beïnvloeding van leefstijl te worden gericht, want uiteindelijk bepaalt leefstijl (en in het bijzonder de fysieke activiteit) de prognose (risico op vroegtijdig overlijden) van patiënten met CI.²³ De claudicatiotherapeut wordt daarmee een gespecialiseerde leefstijlcoach, die als onderdeel van de totaalbehandeling ook medicatie compliance controleert en waar nodig non-compliance rapporteert aan de verwijzende arts. Idealiter de huisarts, want CI is een eerstelijns aandoening die op dit moment nog teveel door vaatchirurgen wordt gezien.

Wetenschappelijk bewijs voor de meerwaarde van leefstijl coaching tijdens GLT is nog niet beschikbaar. Maar dat lijkt een kwestie van tijd. Recent onderzoek bij patiënten met CI toonde aan dat een kortdurende interventie met motiverende gespreksvoering, een positief effect had op het dagelijks loopgedrag.²⁴ Bovendien lijkt met name herhaalde gespreksvoering effectief en hield het effect tot twee jaar na de interventie stand.²⁵ Laat juist een GLT traject met bijna 50 contactmomenten gedurende een jaar de perfecte gelegenheid zijn om motiverende gesprekvoering toe te passen.

ClaudicationNet

In 2011 werd het landelijk netwerk van fysiotherapeuten voor de behandeling van patiënten met CI opgericht. Op dit moment bestaat landelijke dekking van regionale netwerken en zijn ruim 1.400 therapeuten aangesloten.²⁶ Naast de scholingseisen volgen deelnemers tijdens het specialisatietraject tot claudicationtherapeut onder andere een driedaagse cursus motiverende gespreksvoering. Hierin wordt geleerd om patiënten te stimuleren tot verandering (van leefstijl) door te praten over verandering. Waar hulp van de huisarts gewenst is, kan dat via een verzoek aan de huisarts met toelichting, aan de patiënt worden meegegeven. Stoppen met roken, een gezond dieet, verantwoord gewicht, maar ook medicatie compliance worden zo een gezamenlijke actie van patiënt, claudicationtherapeut én de huisarts. Met voortdurende scholing wordt getracht deze kwaliteit van zorg te waarborgen.

Uit oogpunt van transparantie zijn deelnemende therapeuten zichtbaar op de landelijke website via een persoonlijk portfolio en wordt vanaf 1 januari 2016 via het elektronisch patiëntendossier geanonimiseerde data verzameld over therapieresultaten. Met deze gegevens kan GLT verder verbeterd worden door te leren van fysiotherapeuten die bovengemiddelde resultaten behalen. Met behulp van intervisie kan deze kennis en kunde worden overgedragen.

Geïndividualiseerde behandeling

Vanwege de sterke associatie tussen leefstijlfactoren en mortaliteit is verandering van leefstijl een belangrijke pijler van de behandeling van CI. Verandering van gedrag en diepgewortelde gewoontes (verslaving) is echter bijzonder moeilijk.²⁷ Daarnaast is

matige motivatie voor GLT onder patiënten niet onvoorstelbaar, gezien de alternatieve behandeling die geen inspanning van de patiënt vraagt en wel een snelle en effectieve oplossing verzorgt.

Het is bekend dat mensen verschillende coping strategieën gebruiken om problemen op te lossen. Het is voor te stellen dat mensen voor gedragsverandering ook verschillende stijlen hanteren. Voortbordurend op de resultaten van hoofdstuk 7 uit dit proefschrift werd in de algemene discussie (hoofdstuk 10) een model geïntroduceerd waarmee patiënten op basis van twee uitkomstmaten geclassificeerd kunnen worden. Door vervolgens, bij voorkeur prospectief, gegevens te verzamelen van deze patiënten kan aanvullend inzicht verworven worden van de kenmerken (demografie, motivatie, ziektegeschiedenis) die mogelijk een rol spelen bij bepaald gedrag. Een vervolgstap van dit onderzoek zou een studie kunnen zijn naar geïndividualiseerde zorg die past bij de kenmerken van een bepaalde categorie van patiënten. Op deze manier kan GLT wellicht verder geoptimaliseerd worden.

Hoe nu verder?

Structurele bekostiging is essentieel voor het slagen van GLT. Financiering zou bijvoorbeeld gerealiseerd kunnen worden vanuit het basispakket van de zorgverzekering. Volgens het stepped-care principe worden alle patiënten met CI in eerste instantie verwezen voor GLT en pas wanneer onvoldoende resultaat wordt geboekt, kan een invasieve behandeling overwogen worden.

REFERENTIES

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-society consensus for the management of peripheral arterial disease. *Int Angiol.* 2007;26(2):81-157.
2. Crowther RG, Spinks WL, Leicht AS, Quigley F, Golledge J. Relationship between temporal-spatial gait parameters, gait kinematics, walking performance, exercise capacity, and physical activity level in peripheral arterial disease. *J Vasc Surg.* 2007;45(6):1172-8.
3. Mays RJ, Casserly IP, Kohrt WM, Ho PM, Hiatt WR, Nehler MR, et al. Assessment of functional status and quality of life in claudication. *J Vasc Surg.* 2011;53(5):1410-21.
4. Lane RA, Mazari F, Mockford KA, Vanicek N, Chetter IC, Coughlin PA. Fear of falling in claudicants and its relationship to physical ability, balance, and quality of life. *Vasc Endovascular Surg.* 2014;48(4):297-304.
5. McDermott MM, Greenland P, Ferrucci L, Criqui MH, Liu K, Sharma L, et al. Lower extremity performance is associated with daily life physical activity in individuals with and without peripheral arterial disease. *J Am Geriatr Soc.* 2002;50(2):247-55.
6. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res.* 2015;116(9):1509-26.
7. Society for Vascular Surgery Lower Extremity Guidelines Writing G, Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JE, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg.* 2015;61(3 Suppl):2S-41S.
8. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet.* 2013;382(9901):1329-40.
9. Layden J, Michaels J, Bermingham S, Higgins B, Guideline Development G. Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance. *BMJ.* 2012;345:e4947.
10. Fokkenrood HJ, Bendermacher BL, Lauret GJ, Willigendael EM, Prins MH, Teijink JA. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev.* 2013;8:CD005263.

11. Gommans LN, Saarloos R, Scheltinga MR, Houterman S, de Bie RA, Fokkenrood HJ, et al. Editor's choice--The effect of supervision on walking distance in patients with intermittent claudication: a meta-analysis. *Eur J Vasc Endovasc Surg.* 2014;48(2):169-84.
12. van Asselt AD, Nicolai SP, Joore MA, Prins MH, Teijink JA, Exercise Therapy in Peripheral Arterial Disease Study G. Cost-effectiveness of exercise therapy in patients with intermittent claudication: supervised exercise therapy versus a 'go home and walk' advice. *Eur J Vasc Endovasc Surg.* 2011;41(1):97-103.
13. Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Cost-effectiveness of endovascular revascularization compared to supervised hospital-based exercise training in patients with intermittent claudication: a randomized controlled trial. *J Vasc Surg.* 2008;48(6):1472-80.
14. Mockford KA, Mazari FA, Jordan AR, Vanicek N, Chetter IC, Coughlin PA. Computerized dynamic posturography in the objective assessment of balance in patients with intermittent claudication. *Ann Vasc Surg.* 2011;25(2):182-90.
15. Januszek R, Mika P, Konik A, Petriczek T, Nowobilski R, Nizankowski R. Effect of treadmill training on endothelial function and walking abilities in patients with peripheral arterial disease. *J Cardiol.* 2014;64(2):145-51.
16. Parmenter BJ, Raymond J, Fiatarone Singh MA. The effect of exercise on fitness and performance-based tests of function in intermittent claudication: a systematic review. *Sports Med.* 2013;43(6):513-24.
17. Sakamoto S, Yokoyama N, Tamori Y, Akutsu K, Hashimoto H, Takeshita S. Patients with peripheral artery disease who complete 12-week supervised exercise training program show reduced cardiovascular mortality and morbidity. *Circ J.* 2009;73(1):167-73.
18. Fokkenrood HJ, Scheltinga MR, Koelemay MJ, Breek JC, Hasaart F, Vahl AC, et al. Significant savings with a stepped care model for treatment of patients with intermittent claudication. *Eur J Vasc Endovasc Surg.* 2014;48(4):423-9.
19. Jongert MW, Hendriks HJ, van Hoek J, Klaasboer-Kogelman K, Robeer GG, Simens B, et al. [KNGF-Guideline Intermittent Claudication (author's translation)]. *Ned Tijdschr Fysiother.* 2003;113:3-50.
20. Gommans LN, Fokkenrood HJ, van Dalen HC, Scheltinga MR, Teijink JA, Peters RJ. Safety of supervised exercise therapy in patients with intermittent claudication. *J Vasc Surg.* 2015;61(2):512-8 e2.

21. Egorova NN, Guillerme S, Gelijns A, Morrissey N, Dayal R, McKinsey JF, et al. An analysis of the outcomes of a decade of experience with lower extremity revascularization including limb salvage, lengths of stay, and safety. *J Vasc Surg.* 2010;51(4):878-85, 85 e1.
22. Merry AH, Teijink JA, Jongert MW, Poelgeest A, van der Voort SS, Bartelink ME, et al. [KNGF-guideline Symptomatic peripheral arterial disease (author's translation)]. 2014.
23. Garg PK, Tian L, Criqui MH, Liu K, Ferrucci L, Guralnik JM, et al. Physical activity during daily life and mortality in patients with peripheral arterial disease. *Circulation.* 2006;114(3):242-8.
24. Cunningham MA, Swanson V, O'Carroll RE, Holdsworth RJ. Randomized clinical trial of a brief psychological intervention to increase walking in patients with intermittent claudication. *Br J Surg.* 2012;99(1):49-56.
25. Cunningham MA, Swanson V, Holdsworth RJ, O'Carroll RE. Late effects of a brief psychological intervention in patients with intermittent claudication in a randomized clinical trial. *Br J Surg.* 2013;100(6):756-60.
26. Lauret GJ, Gijsbers HJ, Hendriks EJ, Bartelink ML, de Bie RA, Teijink JA. The ClaudicatioNet concept: design of a national integrated care network providing active and healthy aging for patients with intermittent claudication. *Vasc Health Risk Manag.* 2012;8:495-503.
27. Bauman AE, Reis RS, Sallis JF, Wells JC, Loos RJ, Martin BW, et al. Correlates of physical activity: why are some people physically active and others not? *Lancet.* 2012;380(9838):258-71.

CHAPTER 12

Dankwoord

List of publications

Curriculum vitae

DANKWOORD

Graag wil ik een aantal personen bedanken voor de directe of indirecte bijdrage aan het tot stand komen van dit proefschrift.

Allereerst de deelnemers aan mijn onderzoeken, zowel de patiënten met claudicatio intermittens als gezonde proefpersonen. Zonder uw belangeloze inzet in naam van de wetenschap was dit proefschrift er niet geweest. Hartelijk dank hiervoor!

Professor dr. J.A.W. Teijink, beste Joep. ‘Ambitieuze studenten met interesse in onderzoek’, zo luidde de oproep op het studentenprikbord waar ik ruim drie jaar geleden op reageerde. Twee dagen na het versturen van mijn brief zat ik al aan jouw bureau en weer een uur verder was mijn promotieonderzoek beklonken. Jij grapte toen al over de flikflak die ik door de gang zou maken na de afronding van mijn proefschrift. Onze kennismaking was illustratief voor jouw werkwijze en de rest van mijn promotietraject. Je grenzeloze energie, enthousiasme en daadkracht inspireren mij enorm. Ik prijs mijzelf gelukkig met de kansen en het vertrouwen dat ik heb gekregen om in alle vrijheid onderzoek te doen en mijn eigen plannen uit te kunnen werken. Maar ook je adviezen en support toen duidelijk werd dat ik mijn carrière wilde vervolgen binnen de Kindergeneeskunde heb ik enorm gewaardeerd. Joep, dank voor alles! *Zullen we die flikflak nu maar eens gaan doen?*

Dr. M.R.M. Scheltinga, beste Marc. Ik ken weinig mensen die in jouw ongekende tempo artikelen lezen en van kritische opmerkingen voorzien. Een perfecte match met de strakke planning zoals ik die voor ogen had. Naast scherpe inhoudelijke opmerkingen, heb je met recht een ‘taalbult’, zoals je dat zelf weleens treffend omschreef. Artikelen liepen na jouw aanvullingen als een trein en taal-technisch heb ik enorm veel van je geleerd. Ik heb bewondering voor de passie waarmee je onderzoek doet en hoop in de toekomst jonge onderzoekers op dezelfde manier enthousiast te kunnen maken.

Dr. K. Meijer, beste Kenneth. Ik was op zoek naar een inhoudelijk expert op het gebied van gangbeeldanalyse. Via Frans Brooijmans kwam ik bij jou terecht en zonder twijfel besloot je om als copromotor in dit project te stappen. Ik heb onze bijeenkomsten in

Maastricht als zeer leerzaam ervaren en wil je bedanken voor de inhoudelijke bijdrage aan mijn onderzoek naar het looppatroon van patiënten met claudicatio intermittens.

Medeauteurs van diverse artikelen, dank voor jullie bijdrage aan het tot stand brengen van een aantal mooie publicaties.

Leden van de beoordelingscommissie, hartelijk dank voor de beoordeling van mijn manuscript.

Paranimfen:

Lieve Ilse, er zijn weinig mensen die mij zo goed kennen als jij. Vanaf de dag dat we elkaar leerden kennen als studiegenoten aan de opleiding Fysiotherapie zijn we onafscheidelijk. Tegenwoordig helaas wat meer in de figuurlijke zin van het woord. Ik heb geen enkel moment getwijfeld om jou te vragen, mij tijdens de verdediging van dit proefschrift bij te staan. Bedankt voor je interesse in mijn onderzoek, maar vooral ook voor je wijze raad, lieve woorden, altijd attente appjes en bijzondere momenten die wij samen hebben beleefd.

Lieve Daniëlle, ik weet nog dat jij tijdens mijn sollicitatiegesprek per ongeluk binnen liep. Als vanzelfsprekend werd ik aan jou voorgesteld als nieuwe collega en twee dagen later maakte jij mij wegwijs in de website van ClaudicatioNet. Daarna volgde een tijd van coschappen waardoor ik slechts af en toe in het ziekenhuis was en wij elkaar vooral zagen bij de basiscursussen die we door het hele land gaven. Maar jij was en bent altijd geïnteresseerd gebleven in zowel mijn onderzoek als sociale leven daarbuiten. Binnen de vaatclub zijn we 'partners in crime' en met recht ben jij dan ook mijn vaatmaatje! Fijn dat jij op dit bijzondere moment naast me wil staan.

Collega onderzoekers (uit de kelder): Geert, Emmeline, Martin, Thijs, Maikel, Gijs en Boudewijn. Vaak werd er hard gewerkt, soms ook goed ontspannen. Tijdens de eerste promovendiborrel van het Catharina Ziekenhuis, een paar dagen vóór mijn vertrek uit het Catharina Ziekenhuis, werd ik mij er pas echt van bewust hoe uniek, fijn en effectief onze (veel besproken) kelder is. Ik wens een ieder veel succes met het afronden van zijn/haar promotieonderzoek.

Vaatclub: Marc, Philippe, Eva, Olga, Anja, Yvonne, Jolien, Edith, Bianca, Saskia, Lotte, Bart-Jeroen, Gert-Jan, Hugo, Rutger, Pieter, Yannick, David, Emiel, Marijn, Regine, Nicole en Sjaak. Heerlijk om bij zo'n leuke club te mogen horen! De tripjes naar Budapest en Porto, de vaatdagen in Noordwijkerhout en de jaarlijkse vaatuitjes waren onvergetelijk en ga ik zeker missen. Het gaat jullie allemaal goed!

Nicole, bedankt voor je adviezen bij het opstellen van mijn onderzoeksprotocollen en dank ook voor alle hulp bij het afronden van mijn proefschrift.

David en Marijn, mijn opvolgers in de perifere onderzoekslijn. Heel veel succes!

ClaudicationNet: Loes, Yvonne, Robert, Steven, Tobias, Ben, Simon, Frans, Harm en alle fysiotherapeuten aangesloten bij ClaudicationNet. Ik vind het een eer om mee te mogen denken en doen in dit unieke landelijke netwerk. Met veel plezier heb ik vele cursussen gegeven aan altijd enthousiaste deelnemers. Voor alle patiënten met claudication intermittens hoop ik dat de ClaudicationNet plannen uiteindelijk werkelijkheid mogen worden.

Maatschap Chirurgie Catharina Ziekenhuis, dank voor de mogelijkheid om in dit prachtige ziekenhuis onderzoek te mogen doen. Medewerkers Polikliniek Chirurgie, bedankt voor de ondersteuning tijdens het includeren van potentiële studiepatiënten. Arts-assistenten en semi-artsen Chirurgie, alle geluk met jullie carrières.

Frans, zonder twijfel wil ik ook jou persoonlijk bedanken. Toen ik je belde om te praten over mijn onderzoeksplannen was jij meteen bereid om je praktijk, inclusief meetopstelling, 24/7 voor mij open te stellen zodat ik mijn metingen kon doen. Het was een voorrecht om in jouw gezellige praktijk, waar we op vrijdagmiddag regelmatig een glas wijn dronken, te gast te zijn. Ik bewonder je sportiviteit, je energie en de manier waarop je op geheel eigen wijze je praktijk runt. Ook heb ik genoten van onze gezamenlijke 'optredens' tijdens ClaudicationNet cursussen en op het jaarcongres. Gelukkig mogen we in maart nog een keer. Veel geluk met het afronden van jouw eigen promotieonderzoek.

Beste Roel, toen ik belde met een vraag over de synchronisatie van mijn meetopstelling was je meteen bereid om mee te denken. Sterker nog, om half 2 's nachts mailde jij met

een mogelijke oplossing nadat je de complete handleiding van een veel te ingewikkelde synchronisatiebox had doorgenomen. Jij knutselde de befaamde kabel waarmee uiteindelijk metingen bij zo'n 100 personen zijn verricht. Zonder jouw technische kennis en hulp was dat niet gelukt. Enorm bedankt!

Studenten:

Annemieke, wat heb ik het met jou getroffen. In het kader van de LoopPad studie voerden we samen meer dan 70 metingen uit om het looppatroon van patiënten met claudicatio intermittens in kaart te brengen. 's Ochtends, 's avonds en in het weekend, jij was altijd bereid om te komen. Van dichtbij maakte je de frustraties mee toen het meetsysteem maar niet leek te functioneren en samen sprongen we een gat in de lucht toen het uiteindelijk was gelukt. Ik kijk met veel plezier terug op alle serieuze metingen, maar ook op de gezellige en hilarische momenten daar omheen. De kers op de taart was het congres in Maastricht waar we beiden een presentatie mochten geven. Wat een topweekend was dat! Ik bewonder je inzet en motivatie en wil je nogmaals bedanken voor al je hulp.

Ingeborg en Robbin, jullie beiden wil ik bedanken voor de bijdrage aan de MovePAD studie. Zonder jullie hulp was het zeker niet gelukt om in zo'n korte tijd een uitgebreid pakket aan metingen te verrichten bij meer dan 50 patiënten. De vlotte publicatie die daarop volgde komt jullie meer dan toe.

Dierbare vriendinnen: Patricia, Kyra en Roos. Als we elkaar zien, vragen jullie altijd met oprechte interesse naar mijn promotieonderzoek. Als we elkaar niet zien, omdat ik weer eens te druk ben met onderzoek en werk, is ook dat altijd goed. Wat fijn om zulke vriendinnen te hebben! Met het afronden van dit proefschrift is er hopelijk weer wat meer tijd om samen door te brengen.

BMW-chicks: Sanne K, Sanne F, Marjan, Loes, Karin en Noortje. Samen begonnen we aan de studie Biomedische Wetenschappen en woonden we allemaal op kamers in Nijmegen. Vele etentjes, stapavonden, feestjes, kroegentochten en volleybaltoernooien volgden. Ruim acht jaar later wonen we verspreid over het land, hebben we uiteenlopend werk, is de eerste promotie voltrokken, de eerste bruiloft gevierd en de eerste puppy

aangeschaft! Het aantal etentjes, feestjes en borrels is helaas wat minder geworden, maar als we elkaar zien, is het onveranderd gezellig en wordt er onverminderd veel over onze favoriete onderwerpen gesproken. Maar wat is het fijn om elkaar ook zo goed te begrijpen wanneer het tijdens mijn onderzoek soms wat minder ging. Ik hoop dat er nog meer promoties, bruiloften en baby's mogen volgen.

Team 'A': Loes, Esther, Evelien en Suzanne. Met elkaar begonnen we als coassistenten en wat was het leuk om de eerste ervaringen en verhalen uit het ziekenhuis met elkaar te delen. Samen begonnen we daarna als dokters aan hele verschillende, stuk voor stuk ambitieuze trajecten. We hebben eindeloos over elkaars keuzes gesproken en sollicitatiegesprekken samen voorbereid. Dank voor al jullie adviezen, interesse en onze fijne vriendschap. Ik hoop dat we onze succesreeks nog lang mogen voortzetten.

Feestcommissie ('4, 5, 6 feest'): Joyce en Kathelijn! Na onze succesvolle organisatie van het vriendenweekend in de Ardennen, was er geen twijfel over mogelijk dat de organisatie van mijn promotiefeestje bij jullie in goede handen zou zijn. Ik waardeer jullie oprechte interesse in al mijn bezigheden. Samen gaan wij er een mooie avond van maken.

Vrienden uit Eindhoven. Gelukkig zijn er genoeg feestjes om af en toe te ontspannen. Nu dit proefschrift is afgerond, ga ik proberen weer wat vaker van de partij te zijn.

Lieve pap en mam, broer Kay, schoonzus Nadine, oma's, opa en schoonouders Ad en Lenie. In zowel aandacht als tijd doe ik jullie allen soms te kort. De onvoorwaardelijke steun bij alle keuzes die ik maak, waardeer ik daarom des te meer. Het is fijn om in alle drukte en hectiek te weten dat ik bij mijn familie altijd terecht kan.

Liefste Niels, onbeschrijfelijk dankbaar ben ik voor je liefde, het vertrouwen en de vrijheid die je mij geeft om al mijn dromen waar te maken. Ik houd van ons leven en kijk uit naar onze droom samen!

LIST OF PUBLICATIONS

Gommans LNM, Saarloos R, Scheltinga MRM, Houterman S, De Bie RA, Fokkenrood HJP, Teijink JAW. Editor's choice - The influence of supervision on walking distance in patients with intermittent claudication: a meta-analysis. *Eur J Vasc Endovasc Surg* 2014; 48:169-84.

Gommans LNM, Fokkenrood HJP, Van Dalen HCW, Scheltinga MRM, Teijink JAW, Peters RJG. Safety of supervised exercise therapy in patients with intermittent claudication. *J Vasc Surg* 2015; 61:512-18.

Gommans LNM, Scheltinga MRM, Van Sambeek MRHM, Maas AHEM, Bendermacher BLW, Teijink JAW. Gender differences following supervised exercise therapy in patients with intermittent claudication. *J Vasc Surg* 2015; 62:681-8.

Gommans LNM, Fasseart YAH, Jenniskens WM. Vitamine D-suppletie bij kinderen neemt toe. *JGZ Tijdschrift voor Jeugdgezondheidszorg* 2015; 47: 2-5.

Gommans LNM, Teijink JAW. Attitudes to Supervised Exercise Therapy. *Br J Surg* 2015; 102:1153-5.

Gommans LNM, Spring in 't Veld LG, Van der Putten ME, Wijnen MHWA. Het infantiel myofibroom: een neonaat met een zwelling van de onderarm. *Ned Tijdschr Geneesk*. 2015;159:A8685

Hageman D, **Gommans LNM**, Fokkenrood HJP, Koelemay MJW, Teijink JAW. Commentary on "Supervised versus Unsupervised Exercise for Intermittent Claudication: A Systematic Review and Meta-analysis. *Am H J* 2015; 170:e1-3, online May 28.

Gijsbers HJH, Van Hofwegen A, **Gommans LNM**. De fysiotherapeutische behandeling van patiënten met symptomatisch perifere arterieel vaatlijden. *Physios* 2015; 7:21-26.

Gommans LNM. Behandeling voor claudicatio intermittens: looptherapie en leefstijl-interventies. *Fysiopraxis* 2015; 24:47.

Hellegers LM, **Gommans LNM**, Spierings YAF, Teijink JAW. Doelmatige behandeling van claudicatio intermittens. *Fysiopraxis* 2015; 24:24-25.

Gommans LNM, Smid AT, Scheltinga MRM, Brooijmans FAM, Van Disseldorp EMJ, Van der Linden FThPM, Meijer K, Teijink JAW. Altered joint kinematics and increased electromyographic muscle activity during walking in patients with intermittent claudication. *Accepted, J Vasc Surg.*

Gommans LNM, Hageman D, Jansen I, de Gee R, Van Lummel RC, Scheltinga MRM, Teijink JAW. Minimal correlation between physical exercise capacity and daily activity in patients with intermittent claudication. *Accepted, J Vasc Surg.*

Van den Houten MML, **Gommans LNM**, Van der Wees PJ, Teijink JAW The Minimally Important Difference of the Absolute and Functional Claudication Distance in Patients with Intermittent Claudication. *Accepted, Eur J Vasc Endovasc Surg.*

CURRICULUM VITAE

Lindy Gommans werd geboren op 18 september 1985 in Venlo. Van jongs af aan stond haar leven in het teken van turnen. In 1999 werd zij Nederlands Kampioen. Van 2000 tot 2002 trainde ze onder leiding van Boris Orlov (voormalig coach van Wereldkampioene Olga Bitsjerova, 1981) bij de Hazenkamp in Nijmegen en maakte ze deel uit van de nationale turnselectie.

Na het afronden van de middelbare school startte ze in 2003 met de studie Fysiotherapie aan de Fontys Paramedische Hogeschool te Eindhoven. In 2007 behaalde ze voor deze opleiding het diploma (*cum laude*) en begon ze met de studie Biomedische Wetenschappen aan de Radboud Universiteit Nijmegen. In haar masterprogramma combineerde ze twee afstudeerrichtingen; Bewegingswetenschappen en Epidemiologie. Na het behalen van dit diploma (*cum laude*) in 2010 volgde registratie als epidemioloog en was ze onder andere werkzaam op de afdeling Epidemiologie, Biostatistiek en Health Technology Assessment van de Radboud Universiteit Nijmegen.

Tijdens de studie Biomedische Wetenschappen kwam zij voor het eerst in aanraking met de geneeskunde en raakte bijzonder geïnteresseerd in dit vakgebied. Dit deed haar besluiten om in 2010 via een verkort programma de opleiding Geneeskunde (Radboud Universiteit Nijmegen) te volgen. Vervolgens kwam zij in 2012 in contact met professor dr. J.A.W. Teijink (vaatchirurg in het Catharina Ziekenhuis Eindhoven) en werden de eerste stappen gezet voor dit proefschrift. Vanaf die tijd combineerde ze promotieonderzoek met de coschappen. Het afsluitend coschap liep ze op de afdeling Neonatologie van het Radboud Universitair Medisch Centrum Nijmegen. In augustus 2014 behaalde ze het artsexamen (*cum laude*) en begon ze fulltime aan haar promotieonderzoek in het Catharina Ziekenhuis Eindhoven, afdeling Vaatchirurgie. De belangrijkste projecten binnen dit onderzoek waren twee prospectieve studies naar het looppatroon en het beweeggedrag van patiënten met claudicatio intermittens. Daarnaast was zij actief als medisch coördinator van ClaudicatioNet en gaf tientallen cursussen aan fysiotherapeuten over de behandeling van perifere arterieel vaatlijden.

Tijdens de coschappen stal de Kindergeneeskunde haar hart en sinds oktober 2015 is Lindy werkzaam als ANIOS Kindergeneeskunde in het Rijnstate Ziekenhuis Arnhem. Ze hoopt in de toekomst met de opleiding tot kinderarts te mogen starten.