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LOWER EXTREMITY ARTERY DISEASE: INTEREST, FEASIBILITY AND EFFECT OF EXERCISE TRAINING

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“The real cycle you're working on is a cycle called yourself”

Robert M. Pirsig

Summary

Lower extremity artery disease or LEAD is a disease caused by a narrowing of lower leg arteries mostly due to atherosclerosis. Atherosclerosis is a non-communicable disease which is characterized by progressive build-up of lipid particles in the inner arterial layer. This progressive disease is typically the result of an unhealthy lifestyle, including smoking, an unhealthy diet and a sedentary lifestyle. It is estimated that approximately 237 million people worldwide have LEAD. Due to aging and global rising trends in important underlying risk factors a further increase in prevalence is to be expected. Despite this high prevalence there remains a lack in awareness among healthcare workers and the general public.

Similar to a heart attack or stroke, narrowed arteries in the lower limbs can cause problems with blood flow. In patients with LEAD, this lack of blood reaching the muscles distal from the occlusion, can cause pain in the (lower) limbs, but can also result in pain at rest or in trophic wounds. The first symptoms typically present during physical activities (e.g. walking) in which case the blood supply has to match the metabolic needs from the working muscle. Therefore, complaints depend on the mode and intensity of the activity, and typically disappear after a period of rest. This symptom is called intermittent claudication, or shop window legs in laymen terms, the cardinal symptom of LEAD and will be the main focus of this PhD work. Intermittent claudication is bothersome, yet not immediately life threatening at first sight. However, the condition triggers a progressive decline in mobility, physical activity, and daily life functionality. Not surprisingly, this vicious cycle will negatively impact quality of life, but will also contribute to an already high cardiovascular risk profile. As could be expected from the underlying pathophysiology and vicious cycle of decline, LEAD is often the harbinger of future cardiovascular complications.

To breach this vicious cycle, early treatment of intermittent claudication is warranted. Next to symptomatic relief, the identification and treatment of the underlying cardiovascular risk profile is primordial to avoid further progression of atherosclerotic plaque formation. Here, the importance of walking therapy and lifestyle changes are internationally acknowledged as a cornerstone in first line treatment of intermittent claudication. Exercise as a treatment was already introduced in 1966 and is now considered a class IA recommendation. However, only one out of three vascular surgeons in Europe can count on the availability of supervised exercise programs in their centers to refer their patients to. Also, when programs are available, uptake and adherence by patients is limited. Therefore, there is an emerging need for alternative exercise programs that are feasible, more accessible, and at least equally effective as the fully supervised exercise programs.

In **chapter two** of this PhD thesis I investigated whether technology could be used as a tool to support patients to take up and adhere to their exercise prescription. First, a survey was performed among 99 patients with LEAD to investigate their current use of technology and interest to use technology in an exercise program (**chapter 2.1**). Our results showed that a large group of patients were already using technology such as mobile phones and e-mail, and were in favor of using technology, including wearables, in an exercise program. Further elaborating on these results we performed an observational pilot project among 20 patients with LEAD to pragmatically test a home-based exercise program (**chapter 2.2**). After the 4-week intervention, patients were satisfied and accepted the proposed intervention, including the use of sports watches and uploads to an online platform. In contrast, exercises with elastic resistance bands were not preferred over prescribed walking exercise. Subsequently, these results led to the development of a 12-week hybrid walking program, the PROSECO-IC study, combining on site sessions and remotely guided home-based walks. Results on effectiveness, feasibility and adherence are described in **chapter 2.3**.

Although the benefits of exercise are undeniable in the group at large, significant heterogeneity is noted among subjects. Reasons behind this variability in training response are largely unknown, as are the mechanisms that explain progression in ambulatory performance following exercise therapy. Moreover, large vessel blood supply is typically unaltered after exercise therapy. In this regard, the muscle is not to be overlooked. Near-Infrared Spectroscopy (NIRS) is a method that allows us to observe both muscle function and local microcirculation during exercise. In **chapter three** we showed that NIRS-measurements showed a slower decline in muscle oxygen concentration (deoxygenation) and more rapid increase in muscle oxygen concentration (reoxygenation) after an exercise program in patients with intermittent claudication. This observation was made based on a systematic review with meta-analysis of current literature. Though, we also highlighted the lack of reproducibility measures and transparency in the description of NIRS methods. Following this, we explored the NIRS-data of our PROSECO-patients, obtained before and after the hybrid walking intervention (**chapter 3.2**). Here, we confirmed the observations on slowed deoxygenation after exercise, especially in high responders after the intervention. These results underscore the presence of a local response, yet, future research should investigate whether an increased oxygen extraction or improved metabolic efficiency are explaining this finding.

Finally, I aimed to investigate the effect of exercise therapy on the cardiovascular risk profile in patients with LEAD in **chapter four**. In a systematic review with meta-analysis we found only little effect of currently applied exercise programs on the traditional cardiovascular risk factors (**chapter 4.1**). I.e. we observed only a lowered systolic blood pressure after exercise, whereas all other risk factors (e.g. lipids and weight measures) were unaltered. Using

propensity matching, I compared peak oxygen consumption (Peak VO_2), an independent predictor for future morbidity and mortality, in 50 patients with LEAD to a matched group of 50 patients initiating cardiac rehabilitation after an elective intervention. In LEAD, we showed that cardiorespiratory fitness is moderately impaired and inferior compared to peers in cardiac rehabilitation (**chapter 4.2**). As recent guidelines highlight the importance of improved secondary prevention in LEAD, this observation once again emphasized the need for a multidisciplinary rehabilitation approach. Exercise is an important component of suchlike intervention, having the unique ability to be a leading approach in symptom reduction for some, yet can serve as an important preventive measure to improve longevity in all patients.

Samenvatting

Perifeer arterieel vaatlijden in de onderste ledematen wordt ingeleid in **hoofdstuk één**. Arterieel lijden in de onderste ledematen is een aandoening ten gevolge van slagadervernauwing of atherosclerose. Atherosclerose is een niet overdraagbare aandoening die wordt gekenmerkt door progressieve opbouw van vetpartikels in de slagaderwand. Deze progressieve vernauwingen zijn grotendeels het gevolg van een ongezonde levensstijl, waarbij roken, een ongezond dieet en fysieke inactiviteit kenmerkend zijn. Arterieel lijden in de onderste ledematen zou wereldwijd bij maar liefst 237 miljoen mensen aanwezig zijn. Door de vergrijzing en toename in risicofactoren wereldwijd, lijkt een verdere stijging onafwendbaar. Hoewel de aandoening bij ongeveer 10% van de 65-plussers aanwezig is, blijft arterieel lijden in de onderste ledematen vaak onder de radar van zowel gezondheidswerkers als de algemene bevolking.

Net zoals bij een hartaanval of beroerte kunnen deze vernauwingen ook in de benen voor doorbloedingsproblemen zorgen. Door een tekort aan bloed dat de spieren bereikt, ontstaan er pijnlijke klachten ter hoogte van de (onder)benen. Deze klachten zijn hoofdzakelijk aanwezig tijdens inspanning, waarbij de bloedtoevoer snel stijgt om aan de metabole noden van onze spieren te voldoen. Bijgevolg zijn de klachten sterk afhankelijk van het type activiteit en de intensiteit van de inspanning, en verdwijnen ze ook na een periode van rust. Deze klacht wordt intermittente claudicatio, of in de volksmond etalagebenen, genoemd en is kenmerkend voor arterieel lijden in de benen. Etalagebenen zijn vervelend, doch niet levensbedreigend op het eerste zicht. Echter, de aandoening zorgt voor een progressieve achteruitgang in mobiliteit, fysieke activiteit, en functioneren in het dagelijks leven. Deze vicieuze cirkel heeft op termijn dan ook een negatieve impact op de kwaliteit van leven, en zorgt tevens voor het in standhouden (of toenemen) van een erg hoog risico op cardiovasculaire aandoeningen. Bijgevolg is het niet te verwonderen dat perifeer vaatlijden vaak een voorbode is voor cardiovasculaire verwikkelingen in de toekomst.

Om dergelijke vicieuze cirkel te doorbreken is een behandeling van intermittente claudicatio noodzakelijk. Daarnaast is het aanpakken van het cardiovasculair risicoprofiel primordiaal om verdere progressie van atherosclerose vorming te voorkomen. Hier is het belang van wandeltraining en levensstijlaanpassing internationaal erkend als een belangrijke pijler in het conservatief beleid van patiënten met klachten van intermittente claudicatio. De introductie van training onder de vorm van wandelen gebeurde reeds in 1966, met op heden de hoogste wetenschappelijke onderbouwing (IA richtlijn) samengevat in grote literatuuronderzoeken. Echter, de beschikbaarheid van gesuperviseerde trainingsprogramma's is beperkt tot ongeveer één op drie vasculaire chirurgen in Europa.

Sterker nog, bij bestaande programma's is de rekrutering en therapietrouw van patiënten met arterieel lijden vaak gelimiteerd tot één derde van de beschikbare patiënten. Bijgevolg is er dus dringend nood aan alternatieve trainingsvoorzieningen die rekening houden met de noden van patiënten, maar ook even effectief zijn als gesuperviseerde programma's.

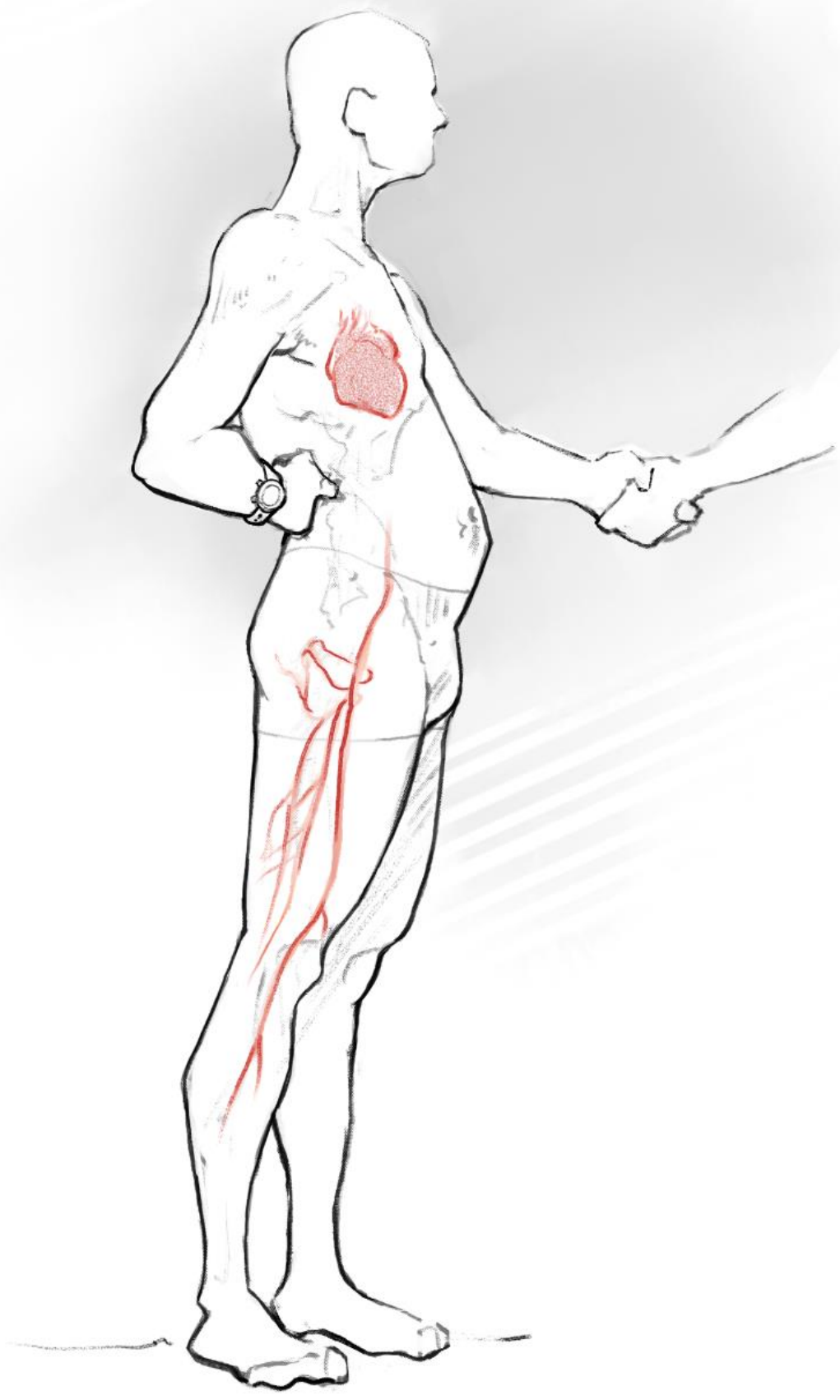
In **hoofdstuk twee** van dit doctoraatswerk ging ik na in hoeverre technologie ons kan helpen om een effectief programma op te bouwen. Dit onderzoek was een cross-sectionele peiling naar het gebruik van technologie en de interesse om deze te gebruiken in een trainingsprogramma van thuis uit (**hoofdstuk 2.1**). Uit de peiling bleek dat een grote groep van patiënten technologie ter beschikking heeft en deze wenst te gebruiken als hulpmiddel bij een trainingsprogramma. Verder bouwend op deze resultaten werd een observationeel proefproject opgezet om een thuisprogramma in de praktijk te testen (**hoofdstuk 2.2**). Na het doorlopen van een 4-weken programma waren patiënten tevreden met de interventie en het gebruik van sporthorloges in combinatie met een online platform. Echter, krachttraining met elastieken banden werd niet beschouwd als een meerwaarde. De resultaten van dit pilootproject hebben finaal geleid tot het ontwikkelen en opstarten van een 12-weken wandelprogramma voor patiënten met klachten van intermittente claudicatio, de PROSECO-IC interventie. Hiervan beschrijf ik de effectiviteit, haalbaarheid en therapietrouw in **hoofdstuk 2.3** van dit doctoraatswerk.

Hoewel de voordelen van training onmiskenbaar zijn in een grote groep, is er steeds sprake van een grote variabiliteit in respons. De redenen hiervoor zijn echter onbekend, daar de mechanismen achter de toename in wandelcapaciteit onvoldoende onderzocht zijn. Bloedvoorziening door de grote slagaders lijkt alvast onveranderd na training. Echter, recente inzichten duiden op de belangrijke rol van de spier. Om zowel de spier als de lokale voorziening van bloed in kaart te brengen tijdens inspanning gebruiken we Near-Infrared Spectroscopy (NIRS). In **hoofdstuk drie** concludeerde ik samen met collega P. Chatzinickolaou, na een systematische review van de huidige literatuur rond NIRS (**hoofdstuk 3.1**), dat NIRS-metingen ter hoogte van de kuitspier een vertraagde afname in zuurstofconcentratie (deoxygenatie) tijdens inspanning en een versnelde toename in zuurstofconcentratie (reoxygenatie) na training vertonen. Daarnaast bespreken we ook het gebrek aan methodologische duiding en transparantie in huidige NIRS-methoden, met een exploratie van de NIRS-resultaten van onze eigen PROSECO-IC interventie (**hoofdstuk 3.2**). Hier bevestigen onze bevindingen dat deoxygenatie tijdens inspanning duidelijk vertraagt bij de groep van patiënten met het grootste trainingseffect. Hoewel deze resultaten een lokale respons tonen zou toekomstig onderzoek moeten nagaan of een toename in zuurstofextractie, dan wel metabole efficiëntie aan de grondslag ligt van deze bevindingen.

Tenslotte onderzocht ik in **hoofdstuk vier** de gekende cardiovasculaire risicofactoren en hoe training deze kan beïnvloeden. In een systematische review met meta-analyse werd slechts

een beperkt effect gevonden van verschillende trainingsregimes op cardiovasculaire risicofactoren, waarvan slechts systole bloeddruk gunstig evolueerde (**hoofdstuk 4.1**). Verder ging ik de cardiorespiratoire fitheid (piek zuurstofopname (Piek VO_2)), een belangrijke voorspeller voor toekomstige morbiditeit en mortaliteit, na bij patiënten actief in de PROSECO-IC interventie. Na correctie voor de rol van intermittente claudicatio en pijnklachten tijdens inspanning vond ik een duidelijke afname in cardiorespiratoire fitheid in vergelijking met leeftijdsgenoten in de cardiale revalidatie (**hoofdstuk 4.2**). Deze bevindingen wijzen nog maar eens op het belang van een multidisciplinaire benadering bij patiënten met arterieel lijden in de onderste ledematen. Training is hier een belangrijke component, voor symptoomreductie, maar ook op de lange termijn ter bevordering van het globale risicoprofiel.

Chapter one: General introduction



1.1 LEAD, what's in a name?

Peripheral vascular disease, peripheral obliterative arteriopathy, peripheral artery occlusive disease, artery occlusive disease or peripheral artery disease (PAD), are all different terms referring to the same underlying disease, i.e. narrowing of arteries not including the coronary arteries or aorta. This narrowing of an artery results in a heterogenous clinical symptomatology, depending on the affected vascular bed and respective organ. In short, arterial narrowing will lead to an insufficient blood flow towards the distal organ. Since arterial blood flow is essential for the delivery of oxygen and nutrients to support normal physiology, obstruction will impede optimal organ functioning. The impact of narrowing or complete occlusion on flow was first described in the 19th century by the French physicist Poiseuille and German engineer Hagen resulting in the Hagen-Poiseuille-law:

$$F\ (flow) = \frac{P\ (Pressure\ gradient) \times r\ (Radius)^4}{8 \times V\ (Viscosity) \times L(Length)}$$

This law of fluid dynamics highlights the impact of a narrowed artery. Namely, a small change in arterial radius will significantly reduce blood flow to the organs in the absence of major changes in blood pressure (1,2). For instance, when vessel diameter is reduced to half of the original diameter, blood flow will only be 6% of the normal supply (2). Depending on the location of the lesion, different symptoms can develop as a result of this local oxygen deficit. For example, angor abdominalis, uncontrolled hypertension due to renal insufficiency or even neurological symptoms develop when either the mesenteric, renal, carotid or cerebral arteries are narrowed. Yet, the term peripheral vascular diseases - or related synonyms - are mostly used in the context of lower limb arterial narrowing. Therefore the European Society of Cardiology in collaboration with the European Society of Vascular and Endovascular Surgery recently proposed to use the term *Lower extremity artery disease (LEAD)*, to avoid any confusion (3). Similar to other peripheral vascular diseases, the cause of the underlying obstruction can vary and include amongst others remote trauma, arteritis or artery inflammation, entrapment due to muscular tension or cyst formation, a peripheral embolus or endofibrosis.[1] Yet, all of the

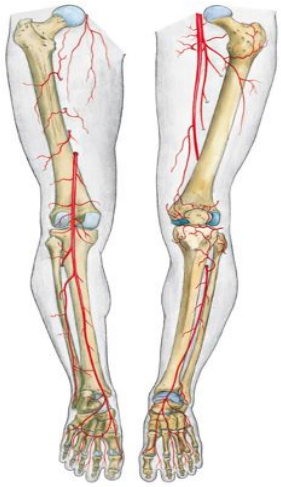


Figure 1. *Lower limb arteries.* ***Left side****: posterior view on the popliteal artery and tibialis posterior.* ***Right side****: anterior view on femoral artery (profunda and superficialis), peroneal artery, tibialis anterior and dorsalis pedis. Permission to use from Sobotta: Atlas of Human Anatomy (15th edition). Copyright Elsevier (2013).*

[1] The latter is typically seen in elite amateurs or professional cyclists younger than 40 years old, spending in between 14 500 and 20 000 km/year on their bike, stretching the external iliac artery in hip flexion, which may ultimately lead to subendothelial proliferation of fibrous

aforementioned causes of LEAD are quite rare and can be categorized as non-atherosclerotic LEAD. The typical patient with LEAD is older (>50 years old) and suffers from several well-known cardiovascular risk factors. As such, the main cause of LEAD is atherosclerosis. It is this category of LEAD which will be the main focus of my PhD-research.

1.2. Atherosclerotic LEAD

1.2.1 Prevalence and risk factors

Atherosclerosis involves the formation of intraluminal fatty plaques, which ultimately leads to arterial stenosis or occlusion (4). Different cardiovascular risk factors are related to the complex pathophysiologic etiology of atherosclerosis; initially low-density lipid infiltration

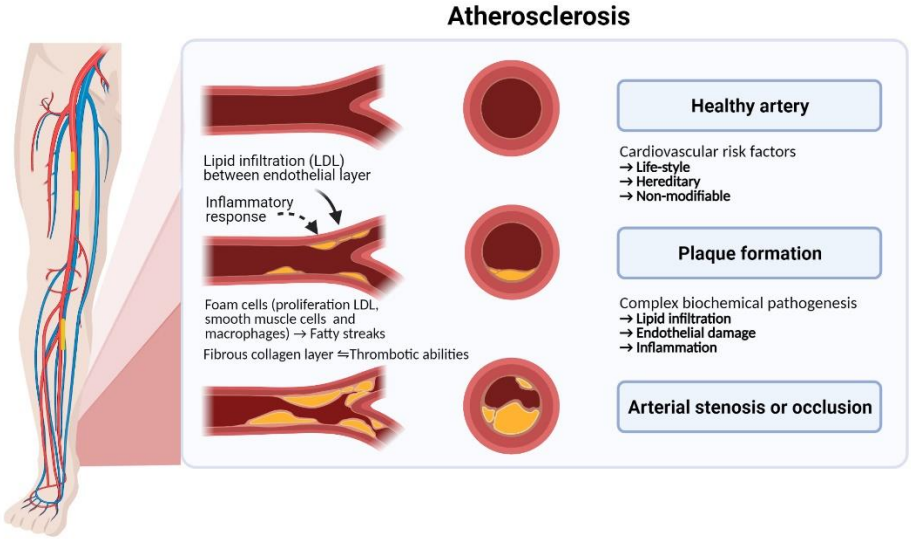


Figure 2. *Atherosclerotic process (Created using Biorender).*

diffuses through the endothelial layer, causing a local inflammatory reaction through oxidation. As a result of local oxidation, nitric oxide diffusion is diminished causing endothelial dysfunction to develop. Moreover, oxidation of infiltrated lipids will stimulate chemokines to trigger local inflammation. A so called "foam cell" will form, a combination of oxidized lipids, smooth muscle cells, and infiltrated macrophages. Being visible as a fatty streak, a combination of fibromatous collagen and small vessel growth will further stimulate this inflammatory cascade, resulting in a detectable atherosclerotic plaque (4). In short, this process is dynamic, where atherosclerotic plaques can either stabilize or cause atherothrombotic complications in the long run (4) (**Figure 2**).

The relation between cardiovascular risk factors, atherosclerosis and lower leg symptoms was first discovered approximately 100 years ago by the German scientist Wilhelm Erb. He defined the condition as "dysbasia intermittens ateriosclerotica". Erb was also the first to

tissue. However not seldom in this specific population (estimated to be 10-20%), endofibrotic narrowing of the external iliac artery is rather uncommon in the general population (129).

show that narrowing of the lower leg artery was not only observed in a handful of reports in Parisian horses (5), but was also present in humans. Nowadays, atherosclerotic LEAD is a significant burden on healthy aging with an estimated 237 million cases worldwide, 5.6% of the adult population aged 25 or more (6). With a sharply increasing prevalence rate of 9.2 to 24.6% from those older than 65 years, growing LEAD numbers are largely driven by demographic aging (6) (**Figure 3**). As such, age is considered an important non-modifiable risk factor regarding the prevalence of LEAD. With regards to gender, methodological differences seem to limit the possibility to draw firm conclusions. However, it seems that the ratio of both sexes suffering from LEAD is equal, yet males are more prone to suffer from classic claudication symptoms (7). In addition, the projected rise in the prevalence of cardiovascular risk factors further adds to the growing public health burden of LEAD (6). This observation is especially true in low-to-middle income countries, where the relative increase is almost fivefold compared to high income countries (22.6% and 4.5% respectively) (6).

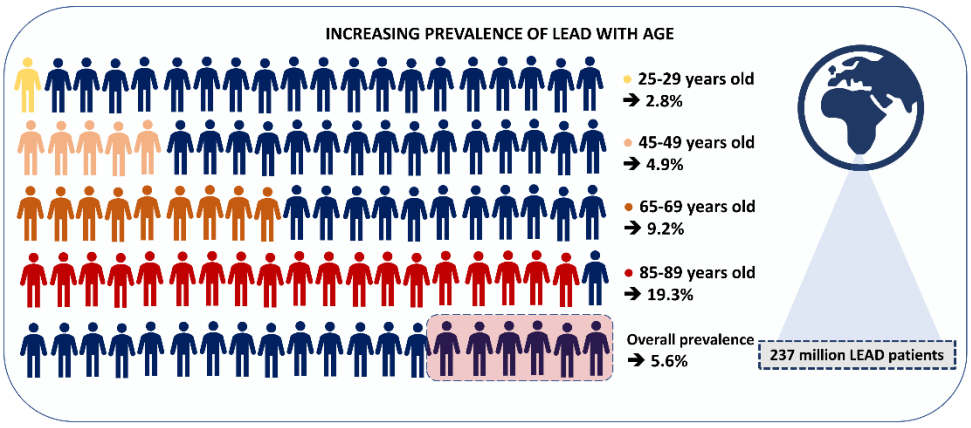


Figure 3. *Global prevalence of LEAD following data from Song et al. 2019* (6).

Among modifiable cardiovascular risk factors (CVRF), Erb identified smoking as the most important risk factor for LEAD (5). One centennial later, smoking has remained the leading risk factor for LEAD (8). Further, as atherosclerosis is a systemic disease, other well-known risk factors for atherosclerotic burden in other vascular territories are shared as a precursor of LEAD. However, the level of risk associated with atherosclerotic plaque formation in a vessel territory will vary for each risk factor. An overview of the important risk factors for LEAD is presented in **Figure 4**. After smoking, diabetes is the risk factor most commonly associated with LEAD (6), with the imposed risk being proportional to the severity of diabetes and glycemic control (8). In addition, dyslipidemia or abnormal serum lipid levels (including high-density, low-density lipids and triglycerides) are typical risk factors and noted in patients suffering from LEAD. Hypertension as a categorical outcome is also a risk factor in most studies (8). Weighted for its high prevalence, the influence of hypertension is gauged to be the second most important risk factor after current smoking (8). Interestingly, when considered in combination with other risk factors, overweight is

inversely correlated with the presence of LEAD. Somewhat counterintuitive, this observation is probably an artefact of risk factor interaction, with body mass index (BMI) being confounded by smoking status and chronic illnesses (8). Central adiposity markers such as waist-hip ratio, body fat percentage or visceral fat measures could improve future insights on atherosclerotic development in LEAD. In line, peak oxygen consumption (peak VO_2) is well-recognized as an independent predictor of all-cause mortality in different populations (9), including patients with LEAD (10). As peak VO_2 is a potentially stronger predictor of mortality than smoking, hypertension, hypercholesterolemia and type 2 diabetes, the American Heart Association now promotes routine assessment of cardiorespiratory fitness as a clinical vital sign (9). However, current reports in LEAD patients do not consider the peripheral nature of exercise limitation (i.e. treadmill tests) when evaluating cardiorespiratory fitness, resulting in reported peak VO_2-values that might not represent a true physiological peak effort.

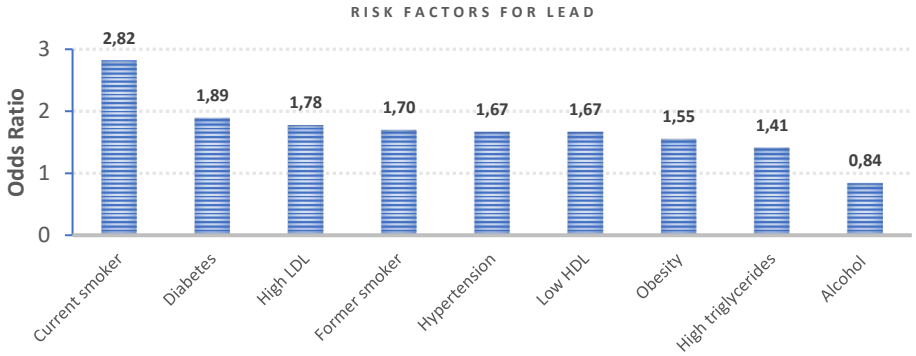


Figure 4. *Risk factors for LEAD adapted from Song et al. (2019)* (6).

As visualized in **Figure 1**, these atherosclerotic lesions can occur at different anatomical positions in the lower limbs, which seems to be influenced by the presence of specific cardiovascular risk factors (11). For instance, increasing age and diabetes were more associated with infra-genicular lesions, whereas proximal lesions (iliac artery) are more common in current smokers and people with dyslipidemia. These findings underscore the complexity of underlying mechanisms involved (11). In summary, atherosclerosis will cause insufficient blood flow, and thus insufficient oxygen and nutrients supply to active tissues located after the apparent stenosis or occlusion. In coronary arteries, atherosclerosis will cause the symptom angina pectoris or the incident myocardial infarction. An obstruction in lower extremity arteries will cause the symptom intermittent claudication.

1.2.2 Intermittent claudication

The cardinal symptom of LEAD is intermittent claudication, sometimes referred to as vascular claudication. Derived from the Latin words ‘intermittent’ and ‘claudicare’,

intermittent claudication literally translates as periodic limping. Whereas at rest, blood supply is most of the time sufficient to meet the metabolic demands, a blood flow mismatch occurs during exercise, causing ischemia-induced muscle pain. The resulting sensation is often described as burning, cramping-like pain in the calf region which warrants the patient to stop his activity, and typically resolves within 10 minutes of rest. This typical symptom was first described by Dr. Rose, a London epidemiologist. Today, the Rose Claudication Questionnaire is still being used to characterize and differentiate LEAD symptoms (8). Although intermittent claudication is the key symptom, the presence of intermittent claudication is often atypical or even absent in patients with LEAD. That is, only one out of three patients with LEAD will complain of typical symptoms on initial presentation (12). Consequently, the variable degree of sensations, pain, locations, and recovery time represent a triad of mechanisms involved, as will be discussed in the following paragraph.

1.2.3 What is happening in the leg as a result of this narrowing?

Interestingly, the functional impairment observed in patients with LEAD is not only explained by arterial insufficiency. Indeed, LEAD is considered a supply-demand disease where supply is limited following arterial narrowing. Yet, demand on its turn is depending on local tissue health and intensity of the performed activities. Though intermittent claudication can be experienced in a variety of ways, the sensation of pain is dysfunctional and leads to physical inactivity. Moreover, patient's belief that intermittent claudication is an indication that walking or being physically active is causing instantaneous damage (13) enhances the adoption of sedentary behavior. As such, better understanding of underlying disease seems primordial to induce long-term behavior change, which is important in all chronic diseases (14). A short sequence on the underlying mechanism of intermittent claudication follows:

I. In patients categorized as having symptomatic LEAD during activities, resting blood supply is sufficient at rest, through a compensatory lower vascular and/or muscular resistance (2,15). However, in patients with an ankle pressure lower than 40 mmHg, chances of ischemic rest pain are plausible according to the Rutherford classification (16). Ischemic rest pain will develop when blood supply is inadequate to even sustain rest metabolism and will cause painful limbs at rest or trophic wounds when left untreated.
II. During exercise however, redistribution of blood towards active organs (e.g. calf muscles) can increase up to 4 times the values at rest (40 $ml.min^{-1}$ to 160 $ml.min^{-1}$) when walking at 4 $km.h^{-1}$ (2) in healthy persons. As introduced, in patients with LEAD, atherosclerotic narrowing will impair the blood supply and cause a supply-demand mismatch, which is further pronounced by ineffective vasorelaxation and endothelial dysfunction, leading to an ischemic cascade resulting from dominant anaerobic energy production.

III. Spillover of local metabolites such as ATP, H+ and lactate formation will trigger group III/IV somatosensory (both metabolic and mechanic) afferents signaling the thalamus and cerebral cortex (17), the respective areas included in pain perception. In this way, theoretically, intermittent claudication is not different from high intensity exercise, considering the supply demand mismatch that occurs during the final meters of a 100-meter all-out sprint (18,19).

IV. In the need of homeostasis our bodies' attempt to compensate insufficient blood flow is well-known as the exercise pressor reflex[2]. Noted in heavy-weight lifting, but also present in conditions such as heart-failure and LEAD, sympathetic drive causes vasoconstriction in non-active regions (increasing vascular resistance throughout the body). Additionally, parasympathetic influence on the heart is decreased. Consequently, a disproportional rise in blood pressure and heart rate is noted to accommodate supply in response to afferent signaling of both metabolic and muscular origin (20).

However, compared to athletes, the supply-demand mismatch in LEAD is of chronic nature due to the underlying atherosclerosis. For this reason, repeated cycles of ischemic insult, perfusion-reperfusion injury, will result in local tissue adaptations. As such, LEAD progressively evolves to a complex pathophysiological state, with skeletal muscle damage, arterial dysfunction and resulting metabolic inertia beyond the initial circulatory deficit (21–25). Therefore, muscle tissue characteristics and local microcirculation are expected to provide more insights into LEAD physiology, functional deficits and possible treatment modalities.

1.2.4 More than just a disease of the leg

As shown in **Figure 5**, intermittent claudication is a relatively stable condition in most patients, with 70-80% of patients with ambulatory symptoms having stable claudication after 5-year of follow-up (12). Yet, the real threat is to be expected from the underlying disease. Given that most risk factors for atherosclerosis are overlapping, it is not surprising that 61% of patients with LEAD also present with atherosclerosis in other organ regions (8). In contrary, "only" 25% of coronary artery disease patients suffer from concomitant cerebrovascular disease or LEAD (8). From this perspective, the presence of LEAD is an exclusive marker of more advanced, widespread atherosclerosis (26). As a result, only a minority (20-30%) of LEAD patients will die from a non-cardiovascular disease (12), with a high future cardiovascular mortality, estimated to be 1.3 to 6.3 times the risk in peers after

[2] The exercise pressor reflex is typically increased in patients with LEAD and associated with functional capacity, with a higher exercise pressor reflex being associated with a lower peak walking distance (130). Interestingly, the reflex is immediately lowered by revascularization of a stenotic of occluded artery in LEAD patients. In addition, the exercise pressor reflex is not diminished in upper-body exercise, highlighting the specificity of the working muscle group and the supply-demand mismatch responsible for this reflex (131). In short, the exercise pressor reflex can be considered a central response, mirroring the local (muscular) inability to perform a given activity.

adjustment for conventional risk factors (8) and increasing with LEAD severity (27). Therefore, LEAD is considered a coronary artery equivalent, justified by the (at least) equally high presence of cardiovascular morbidity and mortality caused by underlying atherosclerosis (7,28). In a nationwide study in Denmark, a greater long-term risk was observed in patients with peripheral artery disease compared to patients after a myocardial infarction (28), The authors predominantly attributed this observation to a lack of secondary prevention measures (see **paragraph 1.3.1**) (29). However, no differences in long-term mortality rates are noted after two decades, highlighting the emerging need for LEAD awareness and enhanced secondary prevention in this vulnerable group of patients (27). As the cardiovascular mortality risk is even twofold in asymptomatic LEAD patients, a diagnosis of LEAD can be considered equally important in determining future cardiovascular risk (8,27).

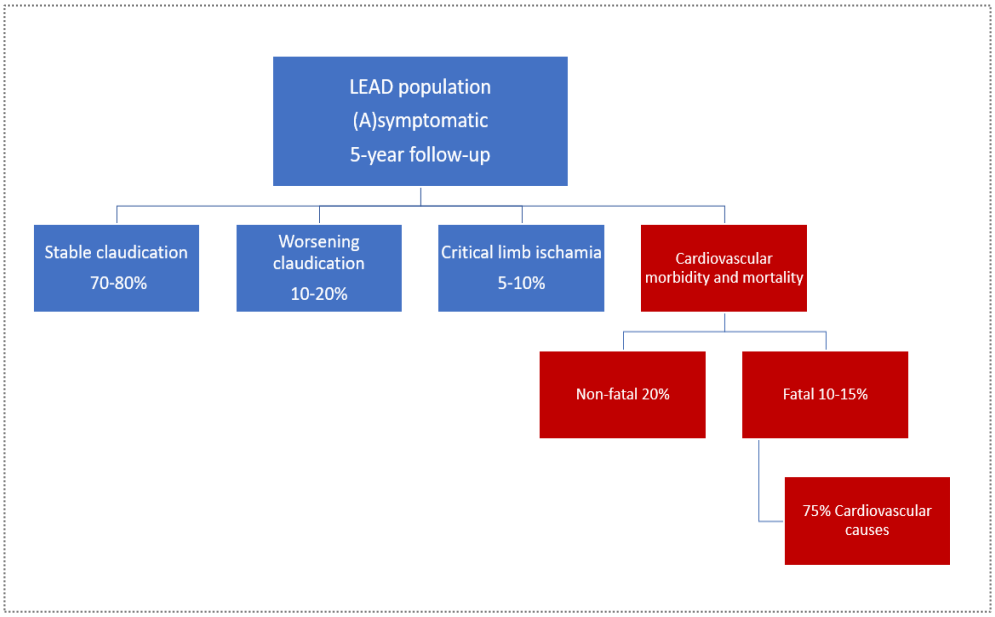


Figure 5. *Fate of the claudicant, adapted from Norgen et al. (2007)* (12)*, originally described by Hirsch and colleagues* (30)*.*

1.2.5 How is the diagnosis of LEAD established?

The diagnosis of LEAD follows the basic principles of medicine, i.e. a thorough anamnesis and clinical examination. To quote Robert Rutherford: "There are few areas in medicine in which the conditions encountered lend themselves so readily to diagnosis solely on the basis of thoughtful history and careful physical examination as do vascular diseases" (4). Namely, a proper evaluation of the symptoms, an assessment of the patients' cardiovascular risk profile, and clinical testing including inspection, palpation and auscultation are the basis to diagnose LEAD. Following this, the diagnosis is confirmed by the measurement of the ankle-brachial index, referred to as the ABI. The ABI is the ratio of systolic blood pressures measured at the level of the ankle and brachial artery, providing

non-invasive information on leg blood flow. Namely, evolutionary changes to an upright position and the distal reflection of blood flow waves cause ankle pressures to be higher in normal physiology (31). Therefore, a normal ABI ranges between 1.0 and 1.4. An ABI exceeding these normal values (>1.4) signalize the inability to compress distal vessels, which is often associated with diabetes and resulting arterial stiffness. ABI values below or equal to 0.9 indicate the presence of stenotic or occlusive lesions above the ankle, with high sensitivity (95%) and high specificity[3] (100%) compared to arteriographic objectified LEAD in symptomatic individuals (12). However, given the dynamic nature of blood flow disturbances during exercise, post exercise evaluation is ideally added to the resting ABI assessment. A 20% drop in ABI after exercise is suggestive for LEAD, which is especially useful in patients with borderline diagnostic values at rest. Summarized, LEAD diagnosis is objectified by:

Diagnosis LEAD: ABI ≤ 0.9 and/or a ≥ 20% drop in ABI after exercise

Hence, LEAD is characterized as a dynamic condition, in which first symptoms will develop during exercise or increased activities. Therefore, exercise testing is not only valuable to confirm diagnosis, but also yield important information on the impact and functional consequences of lower limb ischemia. In this regard, the evaluation of functional capacity is an important aspect of LEAD evaluation following primary diagnosis.

1.2.5.1 Impact of disease on functional performance

Functional evaluation is generally performed during a formal exercise test on a treadmill. Here, pain-free and maximal walking distances are recorded to assess ambulatory capacity. Considered to be a direct surrogate of the patients' ability to perform activities of daily life, treadmill tests are important to diagnose, evaluate treatment or serve as an independent risk factor for future mortality in LEAD (10). In addition, functional performance is directly reflecting the complex pathophysiology underlying LEAD (**paragraph 1.2.3**), as objectified blood flow (e.g. ABI) not necessarily translates into measures of functional performance (32). The interpretation of functional performance is also dependent on the selected protocol, where progressive test protocols have several advantages in terms of reliability compared to constant speed treadmill tests (33). In short, constant work rate tests (in general 3.0 $km.h^{-1}$, 10-12% inclination) have a limited metabolic range to evaluate functional performance. In other words, test intensity far exceeds or does not trigger symptoms, limiting the ability to evaluate most patients adequately (32). Here, a graded

[3] Bernoulli has shown that disturbance of laminar flow and higher flow rates cause reduced pressures distal to the lesion. A mild decrease in ABI (±5%) is within expectations after lower leg exercise (e.g. walking or cycling) due to local vasodilation, increasing the vessel diameter and thus reducing local pressure. In patients with LEAD a more pronounced decrease in ABI is witnessed due to the enhanced flow disturbance at the level of the lesion (31).

treadmill test (Most often the Gardner-Skinner protocol; typically 3.2 $km.h^{-1}$ with increasing inclination every 2 minutes (34)) is considered to be more reproducible, metabolically flexible, clinically relevant to evaluate functional performance and able to provide insights in quality of life (32). In the opposite, treadmill walking is not always representative of daily walking, given its learning curve, the need for balance (or handrail support) and unfamiliarity (35). Therefore, the six-minute walk test (6MWT) has been suggested as an alternative outcome. Here patients are asked to walk as far as possible within six minutes, where selected pace and breaks are allowed to accurately reflect ambulatory capacity. The 6MWT is easy to perform as no equipment is required, more sensitive to natural decline in walking performance and predictive of mortality and future mobility loss in LEAD (35). In addition, the 6MWT offers the opportunity for a clinician to evaluate specific symptomatology in patients with LEAD. These symptoms are typically referred to as intermittent claudication (**paragraph 1.2.2**), yet, LEAD can result in different clinical presentations.

1.2.6 Clinical presentation

As introduced, the main focus throughout this PhD thesis will be LEAD with concomitant intermittent claudication complaints. However, overall symptomatology of LEAD can be divided in three broad categories: *asymptomatic, symptomatic during physical activities and symptomatic at rest*. Here, clinical presentation of patients depends on supply-demand balance in local tissue oxygenation and is further defined by the Rutherford and Fontaine classifications as shown in **Table 1**[4]**.** The 2007 TASC II group inter-society consensus on LEAD management reported that 97-99% of patients are classified as either asymptomatic (Fontaine I or Rutherford 0) or symptomatic during activities (Fontaine IIa-IIb or Rutherford I-III), with only 1-3% of patients clinically presenting with chronic limb threatening ischemia (Fontaine III-IV or Rutherford IV-VI) (12). Chronic limb threatening ischemia is typically associated with highly obstructed blood supply to the lower limb (e.g. ABI < 0.40 and ankle pressure < 50 mmHg (3)). Moreover, chronic limb threatening ischemia troubles wound healing with formation of trophic lesions (Fontaine IV or Rutherford V-VI) and both localized and systemic inflammation. Next to wound care, revascularization is the primary treatment modality in chronic limb threatening ischemia, to restore blood flow and salvage the limb. In comparison, exercise as a treatment option is mainly considered in patients being asymptomatic (Fontaine I or Rutherford 0) or those with symptoms during activity (Fontaine

[4]Emerging from the need to classify symptoms in patients with LEAD Fontaine and colleagues developed a LEAD classification in 1952. Providing more objective values for each classification (e.g. ankle pressures or pulsation volume recordings), Rutherford did adapt the use of classification models in LEAD in 1986 (132).

IIa-IIb or Rutherford I-III). As such, I will consider these subclasses more closely, given that their clinical presentation is more heterogenous than typically described (**Paragraph 1.2.2, intermittent claudication**).

***Table 1**. Classification of LEAD using the Fontaine or Rutherford categories* (3).

Fontaine Classification		Rutherford Classification		
Asymptomatic	I	Asymptomatic	0	Grade 0
Non-disabling intermittent claudication	IIa	Mild claudication	I	Grade 1
Disabling intermittent claudication	IIb	Moderate claudication	II	Grade 1
		Severe claudication	III	Grade 1
Ischemic rest pain	III	Ischemic rest pain	IV	Grade 2
Ulceration or gangrene	IV	Minor tissue loss	V	Grade 3
		Major tissue loss	VI	Grade 3

1.2.6.1 Asymptomatic: no symptoms?

A significant proportion of LEAD patients (20-50%) is classified as asymptomatic, having "masked" LEAD. Indeed, autopsy studies by Nakamura found highly stenotic lesions in asymptomatic patients without a reported history of claudication (36), suggesting that the underlying disease progress is independent of the experienced symptoms (12). In addition, using oxygen pressure measures the presence of ischemia was observed in the non-symptomatic limb in patients with unilateral disease (37). One possible explanation for the asymptomatic presentation of LEAD is low levels of physical activity of these patients in their daily life. Patients often limit physical activity to avoid leg symptoms (12,38), or they are inactive and therefore do not experience the symptoms. Typically, these asymptomatic patients tend to be older, women, have reduced pain sensitivity or suffer from different comorbidities limiting physical activities (3). The fact almost half of asymptomatic patients presents with leg pain during a walking test is illustrative, given the higher exertion compared to usual daily activities (39,40). Moreover, research by McDermott et al underscored that asymptomatic LEAD is not a benign condition. They found adverse muscle histologic changes, lower functional performance, decreased nerve functioning, slower walking speeds and an increased risk of mobility decline compared to patients with symptoms of intermittent claudication (39,41).

1.2.6.2 Symptoms: typically, atypical

Intermittent claudication as defined by Dr. Rose has been historically defined as the cardinal symptom of LEAD (**paragraph 1.2.2**). However, only 10-35% of initial consults with LEAD is characterized by traditional symptoms of pain in the calf region (12). Another 30-40% of LEAD patients present with atypical claudication symptoms such as the presence of varying rest pain (distinct from ischemic rest pain), being able to continue walking without need for a rest period or conversely, needing breaks exceeding 10 minutes (12,40). In addition, claudication pain can occur in both distal and proximal muscle groups, with rare cases describing foot claudication. One reason to explain the diversity of symptoms regarding location can be done through the anatomical structure of lower leg arteries, where different branches, twigs, can be affected by atherosclerosis. This has been shared by a British Association of Sport and Exercise Sciences (BASES) expert statement, suggesting that the site of pain is indicative of the lesion location (42). As such, local ischemia can cause pain in different muscle groups at the level of the buttock, lower back, hip, thigh or knee region (43). In this regard, LEAD is still underdiagnosed in a large group of patients (40), especially in those with internal iliac artery stenosis or proximally induced ischemia (44), where the golden standard ABI evaluation (measured at the ankle) is suboptimal (37). Next to differences in location, actual symptom description is highly heterogenous as well. For example, in 83 exercise tests a tight (33.7%) symptom description at maximal discomfort was most prevalent, compared to classic descriptors such as ache (21.7%), cramp (21.7%) or pain (8.4%) (45). Secondly, different co-existing comorbidities not only trouble diagnostic reasoning, but also superimpose vascular pain patterns. For example, prevalence of spinal stenosis (reported to be 75.7% in a group of 107 LEAD patients (46)), peripheral (diabetic) neuropathy or other comorbidities blur the diagnosis of LEAD (40). In summary, the systemic nature of atherosclerosis and underlying comorbidities add to complex pain patterns in patients with LEAD. However, the impact on physical activity levels and functional capacity is equally detrimental, independent of symptomatology (47,48).

1.2.7 Awareness

Given the direct impact of LEAD on everyday functioning and the future risk to experience a serious cardiovascular event (**paragraph 1.2.4**), the lack of public and patient awareness is striking. As highlighted in the latest European guidelines (3), absence of medical and public awareness is at the roots of this discrepancy in atherosclerotic disease management (**paragraph 1.3.1, treatment**). Based on the GBD (Global Burden of Disease)-study, peripheral artery diseases tend to represent 25.4% of the global cardiovascular burden (*in comparison: coronary artery disease: 32.7%*) (26). Yet, prevalence of peripheral vascular diseases approaches or exceeds those of ischemic heart disease in Europe (49). In summary,

minor differences exist in overall burden, with a higher financial impact due to pan vascular disease in LEAD (26). However, the large discrepancy in published literature on coronary and peripheral artery disease over time is mirroring a lack of public awareness regarding the latter (**Figure 6**). This partition is mainly based on the ischemic organ tissue involved, which is calling for a more unified approach of atherosclerosis as such (50). In addition, this division is also noted at the level of healthcare workers and patients, with almost three out of four US adults not recognizing LEAD and its major risk factors in a 2006 questionnaire (7). More than a decade later, Bridgwood and colleagues found that insufficient understanding of the disease and its underlying causes and risk factors were still present in the public, but also in patients suffering from LEAD (51). Patients thought that exercise was the cause of claudication symptoms and physical activity would worsen their status (52). Moreover, this lack of health literacy, causing uncertainty, stops patients to engage in active self-management (51).

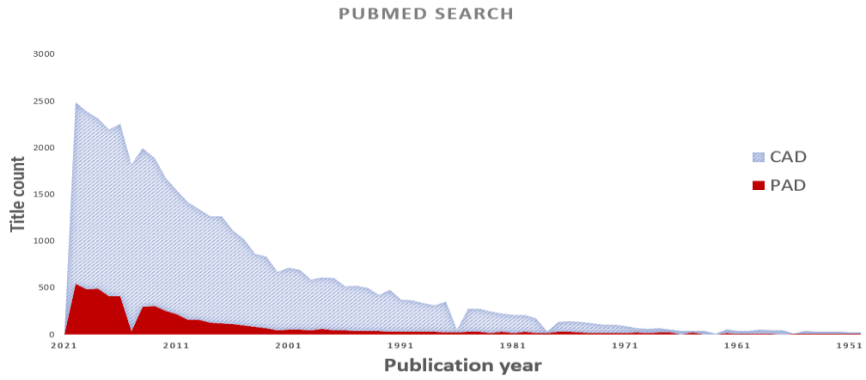


Figure 6. *Cumulative area chart including counts on title appearance of the term "Coronary artery disease" or "CAD" compared to "Peripheral artery disease" or "PAD" in a PubMed query search.*

1.2.8 Vicious cycle

The debilitating symptomatology of intermittent claudication, the lack of awareness and pre-existing atherosclerotic risk profile partially explain the unfavorable prognosis of patients with LEAD. A vicious cycle aggravating the risk for cardiovascular morbidity and mortality develops. In line with the dynamic nature of intermittent claudication, walking capacity is limited. Yet, the consequences of (a)symptomatic LEAD go well beyond a person's functional capacity in daily life, impacting health-related quality of life, reducing physical activity levels (53) and therefore also decreasing functional capacity in terms of cardiorespiratory fitness and muscular strength. Decrements in physical activity are confirmed in studies (54), with an estimated mean of 3550 steps.day^{-1} in LEAD when combining data from six studies published in between 2007 and 2019 (55). Regarding physical fitness, baseline analysis of peak VO_2 data from a 2015 systematic review reported a mean value of 15.3 ml.kg^{-1}.min^{-1}, which is sufficient to only perform moderately intense

activities (56). This was confirmed by Hernandez and colleagues, showing that LEAD patients' physical activity patterns rarely exceed low intensities (55). Importantly, both physical activity, functional performance and physical fitness levels not only contribute to quality of life, but are independent risk factors for future morbidity and mortality. These findings are also replicated in patients with LEAD (10,41,57–60), highlighting the importance of symptom improvement, but more importantly emphasize the importance of long-term behavioral change battling a chronic disease. This was underscored by two recent publications, where invasive treatment approaches failed to induce changes in physical activity levels (61,62). On top of functional limitation, depressive symptoms (19.2% in LEAD vs 12.9% in non-LEAD), anxiety and decreased quality of life are more often reported in patients with LEAD (63–65). Moreover, patients developing depression present a higher risk of mortality (64) and are likely to avoid physical activity participation (63) causing sedentary behavior. Sedentary behavior on its turn was associated with increased levels of inflammation and worse cardiovascular risk factors in a cross-sectional sample of 297 patients reporting intermittent claudication (66). The crux of the matter is that a vicious cycle of physical and mental deterioration is invigorated by symptoms of LEAD, which causes worsening of an already existing cardiovascular risk profile. However, improving the fate of the leg is a first step, to improve patient outcomes in the long run a more systemic approach seems mandatory.

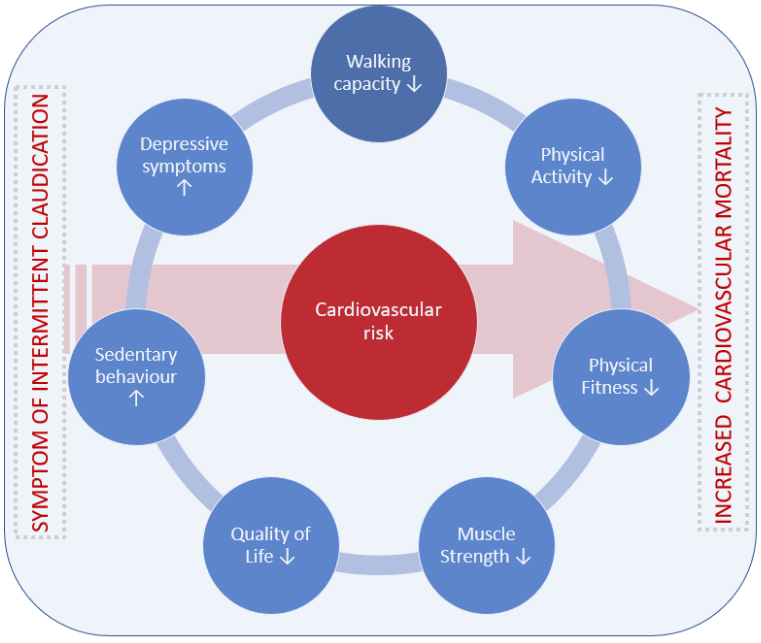


Figure 7. *Vicious cycle in LEAD.*

1.3 Treatment of patients with intermittent claudication

The overlapping treatment of patients with LEAD aims to improve the underlying cardiovascular risk profile and prevent further progression of the atherosclerotic disease. In patients presenting with LEAD, the initial conservative approach (Phase I in **Figure 8**) to alleviate the deteriorating nature of intermittent claudication symptoms (3,67,68) consists of:

- The identification of cardiovascular risk factors contributing to the underlying disease
- Life-style changes and pharmacotherapy addressing the underlying risk factors

In patient presenting with LEAD and intermittent claudication (supervised) exercise programs to improve walking capacity and quality of life is added as a cornerstone therapy.

If the effect of this initial conservative approach is insufficient for the individual patient, revascularization through endovascular treatment or surgery is considered (Phase II in **Figure 8**). Depending on the anatomical lesion location and patient status, endovascular or by-pass surgery will be the preferred treatment option (3). In practice, deviations from this stepped-care model were highly prevalent, with Dutch insurance-data analysis from 2009 showing that 28% percent received primary revascularization as the first treatment (69). Yet, practices are changing and nowadays early invasive interventions are being more and more avoided (70,71).

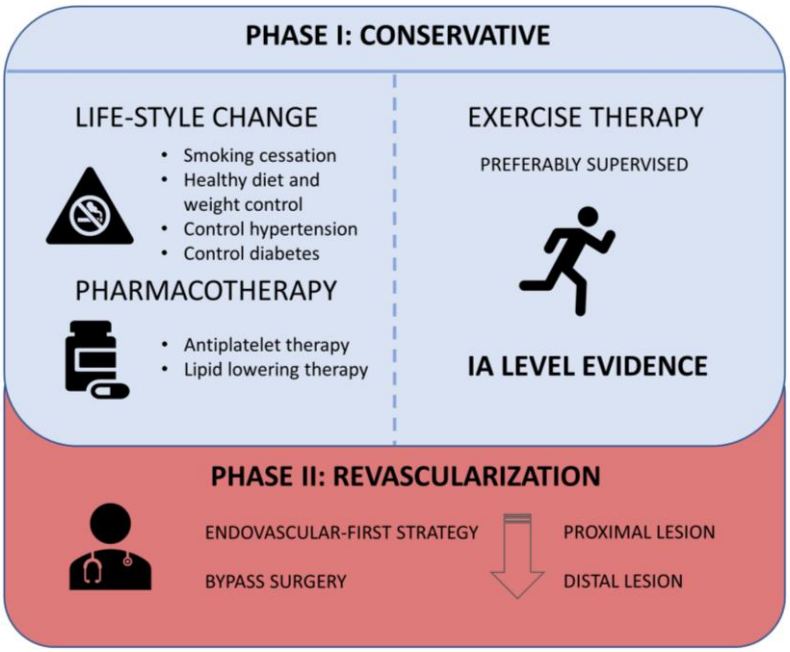


Figure 8. *Treatment phases in LEAD patients with concomitant complaints of intermittent claudication.*

1.3.1 Cardiovascular risk assessment, life style & optimal pharmacological treatment

Life-style changes and pharmacological treatment are mandatory to tackle further progression of atherosclerotic disease in this population, with the level of LEAD risk factors being predictive of LEAD progression and outcomes (8). Introduced as the most important risk factor, smoking cessation (even passive smoking) is crucial to avoid excess morbidity and mortality (3,68,72). More precisely, repeated advice to quit smoking is important, with counselling and pharmacological guidance further improving success (73). In addition, promoting physical activity and a healthy diet to improve cholesterol levels, blood pressure and glycemic control are well-known preventive measures for cardiovascular diseases, advised by the ESC (3,74). These life-style changes are accompanied by pharmacological treatment with single antiplatelet therapy and the prescription of statins (3), both endorsed by the highest level of evidence (IA) for symptomatic patients.

The benefits in terms of cardiovascular and limb-specific outcomes are undisputed (72). Yet, adoption and adherence to adequate preventative measures is disappointingly low. Although improving from 2010 to 2017, lipid control was found to be according to guidelines in only 45% of symptomatic patients referred for revascularization, reaching an LDL < 70 $mg.dl^{-1}$ in 2017 (75). In addition, medical therapy and lifestyle counseling was often poorly managed (e.g. only 20% of LEAD patients receive exercise or diet counseling) (76,77). In comparison, the presence of concomitant cardiovascular disease in LEAD increases the likelihood for patients to receive optimal secondary prevention (26,29,76,77). Considering the high cardiovascular burden on patients with LEAD, new initiatives to improve secondary prevention (e.g. quality indicators (78)) are warranted with regards to personal, societal and financial burdens (76).

1.3.2 Exercise therapy

The father of modern medicine, Hippocrates (460-370 BC) already promoted the importance of a healthy life-style and regular physical activity to improve well-being (79). His famous quote “Walking is man’s best medicine” is even more applicable to patients with LEAD and intermittent claudication. Intriguingly, Hippocrates was also the first to dose and prescribe physical activity similar to the prescription of medicines (79). A seemingly trivial act which is still important considering the nuance in terminology regarding physical activity and exercise. Nowadays, physical activity is defined as “any bodily movement produced by skeletal muscles that result in energy expenditure” (80). Hence physical activity covers a range of activities such as household, transport, occupational or leisure time activities. However, when physical activity is applied in “a planned, structured, and repetitive manner to improve or maintain physical fitness”, the term exercise is used (80). Exercise, which is

predominantly prescribed as walking, is a cornerstone therapy in patients with LEAD and intermittent claudication. Being part of the overall treatment plan, exercise will be referred to as exercise therapy in the following chapters to improve walking capacity, a measure of individual physical fitness or capacity. Evidence has grown substantially throughout decades, supporting the cost-effective implementation of exercise therapy to improve functional status and quality of life in patients with LEAD, with effects being comparable to primary revascularization (15,81).

1.3.2.1 Supervised exercise therapy – evidence in the 21st Century

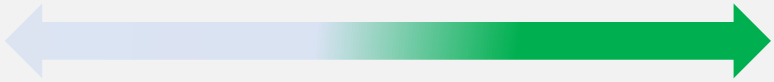
The first study on exercise therapy for intermittent claudication was published in 1966 by Larsen and Lassen in *the Lancet*: "Effect of daily muscular exercise in patients with Intermittent Claudication" (82). In their paired-controlled study including fourteen patients with intermittent claudication the authors reported a trifold increase in maximum walking distances on a treadmill (2.9 to 8.2 minutes) after daily walking, without changes observed in the control group. Moreover, patients in the exercise group reported "general well-being during the training period".

Larsen and Lassen applied a home-based intervention, using a pedometer with fading feedback during six months (82). Though effective, the authors concluded that supervised sessions are to be preferred (82). Following this recommendation, research has focused on evaluating the effect of center-based supervised exercise programs, in which treadmill walking was the preferred modality. Evidence emerged and systematic reviews have established the benefits of center-based walking therapy to improve functional capacity (e.g. pain-free and maximal walking capacity) and measures of quality of life (56,83–86) as shown in **Table 2**. These effects were also observed in the latest Cochrane systematic review, when comparing supervised exercise to the widespread Go-Home-and-Walk advice. Here, a 210 and 140 meter increase in maximal and pain-free walking distance was observed (84). In line, quality of life improved in terms of physical and mental well-being compared to controls (83). Interestingly, it was shown that there is a dose-response relation between supervision and progression in walking capacity (87). Whether exercise in LEAD has potential benefit in terms of morbidity, cardiovascular health or total mortality, as seen in cardiac rehabilitation, is not clear. However, a most recent publication on Dutch claims data, including 54 504 patients with 5-year follow-up, analyzed the number of secondary interventions and mortality in exercise and primary revascularization groups. The authors concluded that patients receiving exercise as an initial treatment had a lower risk for future revascularization or mortality, compared to patients receiving primary revascularization

(71). However limitations to their model are present[5], these results strengthen findings from the IRONIC trial, where the rate of revascularization after 5-years was 3.5 fold lower in patients receiving a noninvasive first approach compared to primary revascularization (88).

Table 2. *Effects of supervised, center-based exercise therapy.*

EXERCISE vs CONTROL		N	MWD or MWT	N	PFWD or PFWT	LOE
Supervised exercise program	Placebo or usual care	5	6.05 (5.47-6.62)†	3	4.95 (4.38-5.53) †	Not available
Supervised exercise program	Walking advice	7	0.80 (0.53-1.07)	4	0.74 (0.56-0.93)	High quality evidence
Supervised exercise program	Home-based exercise program	8	0.37 (0.12-0.62)	7	0.51 (0.21-0.81)	Moderate quality evidence
Home-based exercise program	Walking advice	4	0.30 (-0.45-1.05)	3	0.65 (-0.51-1.82)	Moderate to low quality evidence



Small: 0.2 **Medium: 0.5** **Large: 0.8**

Standardized mean difference, effect size

Note. *All results are (standardized) mean differences (95% confidence intervals) for 12-week interventions. Abbreviations: MWD or MWT = maximal walking distance/time, PFWD or PFWT = pain-free walking distance/time, LOE = level of evidence.* ***†From Lane et al. 2017*** (83)*, presenting mean differences (minutes) for maximal and pain-free walking time.*

1.3.2.1.1 Barriers towards high uptake of supervised exercise therapy

One of the biggest hurdles preventing patients from receiving exercise therapy is the lack of available supervised programs. An international survey showed that underutilization of supervised exercise therapy as a treatment option is undeniable, with a minority (30%) of vascular surgeons having the opportunity to refer patients to a specific supervised program (89). It is well anticipated that these numbers are an overestimation, especially since the number of respondents from some countries (e.g. France) were low (89). In addition, only one out of five vascular surgeons would provide specific exercise prescription (e.g. using activity logs) (89). As such, supervised exercise implementation is not seldom replaced by a less efficient Go-Home-and-Walk advice. Fortunately, availability of programs has improved throughout the years with improved access reported in the UK (41.6%) and initiation of

[5] These findings are in contrast with earlier reports on mortality comparing exercise therapy and revascularization (133). The main strength of the claims study is the use of real-word data in a large group of patients with LEAD undergoing routine care. Yet, given the nature of the data retrieved, authors were limited to correct their analyses for confounding variables such as ABI, walking distances and cigarette smoking.

insurance reimbursements in the USA from 2017 (90,91). Next to the availability of programs, referral itself also impacts total uptake in supervised programs. For example, in the Netherlands (100% accessibility), a remarkable gap is noted in the referral rates from primary care (10%) compared to vascular surgeons (i.e. 97% referring 3 out of 4 eligible patients) (90,92). In contrast to the high level of evidence to support exercise, a dearth of

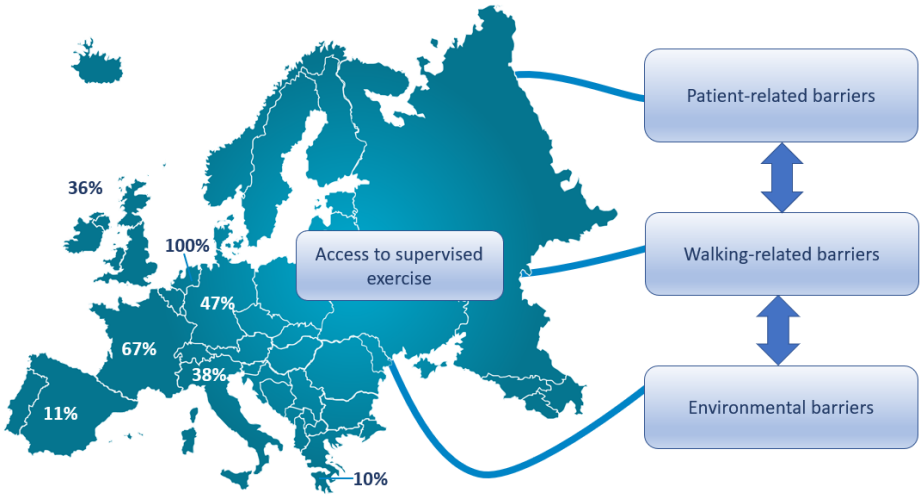


Figure 9. *Accessibility of supervised exercise programs following Makris et al (88).*

research is available about the actual implementation, possibly reflecting the lack of application in national healthcare (e.g. Belgium) (90).

Although the lack of facilities and insurance coverage are limiting supervised exercise implementation, patient adherence to exercise programs is often cited as an important reason for inferior referral as well (90). Therefore, another challenge lies in activating patients to improve participation rates (90,93). In a clinical trial setting it was estimated that only one out of three patients were found eligible and willing to initiate supervised exercise training (93). Similar numbers were reported in routine management were Dutch and German supervised programs report that only about one third of eligible patients participate (90). These numbers are somewhat coinciding with uptake in cardiac rehabilitation programs (30% projected uptake) (94). Several barriers from a patient point of view have been summarized in a systematic review from Abaraogu and colleagues, exploring these low levels of enthusiasm to engage in exercise (93,95). Person related barriers such as comorbidities (e.g. diabetes or obesity) were limiting physical activity uptake, walking capacity and engagement in walking exercise (95). Time constraint and transportation, perceived absence of improvement and the lack of disease understanding were cited as barriers as well (95). More specifically, the lack of health literacy with regards to walking exercise and underlying risk factors (i.e. atherosclerosis as a systemic disease) limits the uptake of exercise as a therapy, especially when no specific walking advice is given (95). Not surprisingly, walking induced pain was a barrier in almost all of the referenced

studies (95). This finding emphasizes the importance of personalized exercise prescription in order to provide mild to moderate pain levels, especially as suchlike programs were equally effective and associated with improved adherence (91,96). Moreover, since most improvements are anticipated to occur after 8 weeks (97), it seems mandatory to facilitate patient adherence throughout the program. The importance of pre-exercise patient education cannot be underestimated as initial illness perceptions and illness beliefs are correlated with walking intention (98), and overall adherence to a supervised program was found to be directly associated with symptom improvement (99).

1.3.2.2 Home-based exercise programs as an alternative for center-based programs?

To bridge the gap between the recognized effects of supervised exercise programs and the less effective Go-Home-and-Walk advice, home-based exercise programs are appealing and recommended when supervised programs are unavailable. Especially in these unprecedented times of global pandemic, home-based exercise programs become increasingly attractive. Interestingly, patients would even prefer to follow an exercise program in their home environment (100). Although promising, optimization of suchlike programs are paramount to attain the same quality and evidence as in supervised exercise programs (101). To illustrate, European Society of Cardiology (ESC) and American Heart Association (AHA) highly recommend the use of home-based exercise programs, based on expert opinion and small (retrospective) studies (Level C) (3,68). Initial attempts to summarize findings were confounded by the use of inappropriate terminology, where unsupervised exercise programs and structured home-based exercise programs differ significantly with regards to clinical effectiveness (102–104). Therefore, structured home-based exercise programs were later defined in the AHA/ACC Guidelines (68) as having to include the following:

I. Exercise program in the personal setting of the patient
II. Self-directed with guidance from healthcare providers
III. Prescription of an exercise program which is similar to supervised exercise regimens
IV. Patient counseling with an explanation on basic principles how to adjust training and maintain the program
V. Behavioral change techniques and the use of activity monitors are optional

Combining these different components, structured home-based exercise programs are characterized by monitoring, feedback and personalized exercise prescription to optimize

Figure 10. *Different components of home-based exercise programs.*

effectiveness. In this regard, a more recent review on the topic highlighted the potential of suchlike programs to improve ambulatory performance and levels of physical activity compared to non-exercise controls (104). Interestingly, all outcomes had a considerable degree of variability (e.g. standardized mean differences for maximal walking distance ranging from -0.09 (105) to 1.38 (82) in the included studies) (104). These findings are not surprising, given the large discrepancy in implementation of the aforementioned components of a structured home-based exercise program (illustrated in **Figure 10**). In essence, the type and underlying behavioral construct (e.g. self-monitoring) of the intervention seems to be the most important aspect of an effective home-based exercise program, translating essential components from a supervised exercise program (104). In line, the presence of a coach, who is monitoring, reviewing and adjusting the exercise prescription with regular feedback seems important in a successful home-based exercise program (91).

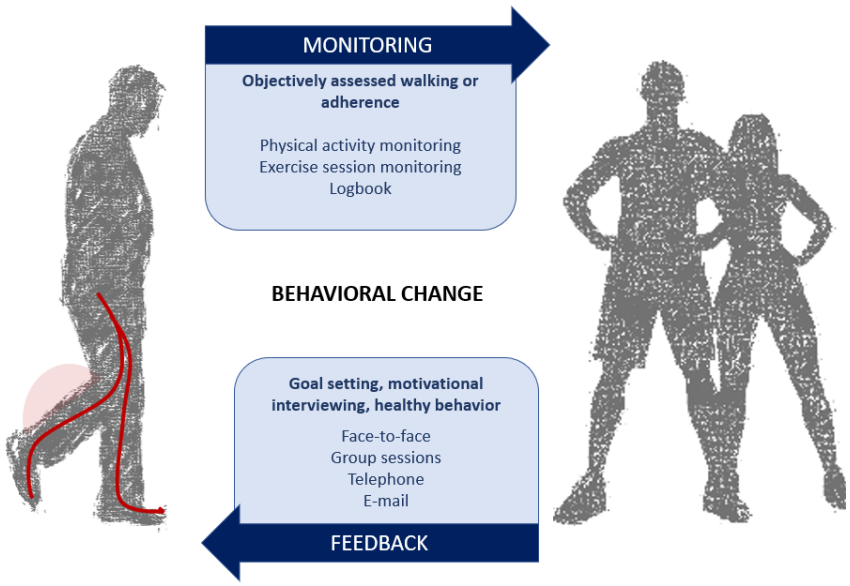


Figure 11. *The role of the coach in a structured home-based exercise program.*

The increasing possibilities of commercial wearables or sports watches and eHealth tools, might further drive the full potential of home-based exercise programs as they can overcome several of the cited barriers (106). In addition, wearables can serve as a catalyst to support healthy lifestyle changes, objectify physical activity and adherence, prescribe and monitor intensity levels, and drive lifestyle change in a varied population of patients (107). Therefore, it is not surprising that the wide array of consumer wearables is still growing (286% increase from 2016-2021) (108), which is also reflected in the high number of new publications and grants including commercial wearables (107). In this regard, wearables could be the metaphorical bridge to preserve the patient-provider relationship in a home-based exercise program for patients with LEAD. In cardiac rehabilitation, the inclusion of digital health systems in rehabilitation are commonly defined as telerehabilitation (109). Here, telerehabilitation has been widely investigated and shown to be accepted and effective in the secondary prevention of different cardiac pathologies (110,111). In accordance, Haveman and colleagues explored digital health systems in care for LEAD patients. They concluded that the area of research is still underexplored, yet, possess high potential to have added value (112). This added value is also acknowledged by Dutch physiotherapists, of which 89% endorsed the use of GPS-tracking (113). However, the needs, interest and acceptability need to be evaluated across all stakeholders when implementing technology. Patients with LEAD are generally older, have different comorbidities and are generally limited by symptoms of pain. Whether the merit of technology is also supported by LEAD patients is not clear. In summary, technology offers new opportunities in designing structured home-based exercise programs and aid to implement important components of successful supervised programs. Yet, finding the right

balance between patient preferences, technology usage and program effectiveness in a home-based environment remains to be elucidated in LEAD.

1.3.2.3 Overall effective does not mean always effective

The clinical benefit in terms of improvement in functional capacity in patients with LEAD is undisputed, yet the heterogeneity of responses to exercise is at least equally important when we aim to provide best possible care. In the era of personalized medicine, early identification of patients that respond less to a specific intervention could inform future and better treatment. The latest Cochrane review from Lane and colleagues found a 95% effect size confidence interval varying from 51 to 190 meters regarding improvement in maximal walking distance (83). Within individual trials, similar variability in ambulatory outcomes can be observed. For example, exercise results from the CLEVER trial in patients (n=38) with aorto-iliac LEAD show results ranging from -0.4 to 16.9 minutes in maximal walking capacity (114). A more recent publication from Patel et al, combining data from two RCT's, found a lack of improvement in 6MWT in 36% of their participants after 12-weeks of supervised exercise (115). This study replicated similar findings in a smaller sample of patients, emphasizing the variability of response using different functional outcomes (116). Also in daily practice, one fourth of exercisers was found to improve ≤40% and another fourth ≥169% after 12-weeks of supervised exercise (117). In this context, knowledge on the underlying mechanisms and determinants explaining improvements observed after exercise therapy is important, yet remains to be explored (15,118).

1.3.2.4 Exercise prescription in LEAD: should they only be walking?

Exercise is most often prescribed as walking exercise (treadmill, track walking or Nordic walking (119)) Emerging evidence in the last three decades regarding supervised treadmill programs also improved prescription (i.e. frequency, intensity of exercise, time needed and type or mode of exercise) of walking programs. To illustrate, intensity has shifted considerably as the first instructions were to "walk until the pain was unbearable" to a moderate-strong pain limitation using a guiding pain scale. Most recent guidelines for walking programs are highlighted in a scientific statement from the AHA and can be consulted in **Figure 12** (15,91). For example, low-intensity treadmill training has been shown to elicit similar responses compared to more severe claudication throughout training (120). In this regard, a mild-to-moderate approach in pain intensity would be preferred in order to obtain improved adherence to the exercise regimen (15,96). In contrast, a recent RCT found that walking without ischemic symptoms was less effective compared to moderate-severe pain instructions (121).

Despite being most effective, walking may not be the indicated mode of exercise in some patients (e.g. fall risk or foot wound) (91). Only a small number of studies have focused on alternative exercise modes of which arm ergometry (122,123), cycling (124) and resistance training (125) are most reported (126,127). Although limited by the available evidence, these exercise modes have shown to be effective and should be considered when walking is either not preferred or contra-indicated (91,126,127). Moreover, the Australian guideline included resistance training as part of the exercise prescription, beyond traditional walking exercise (67). A recent meta-analysis has shown the potential of resistance training to improve walking capacity (125). Resistance training is particularly indicated to improve muscular function, muscle mass and measures of strength which are related to future morbidity and mortality in LEAD, and by extension in the overall population (41). In a small pilot trial, resistance training has been shown to balance the muscular burden associated with repeated ischemia when performing claudication interval walking (128).

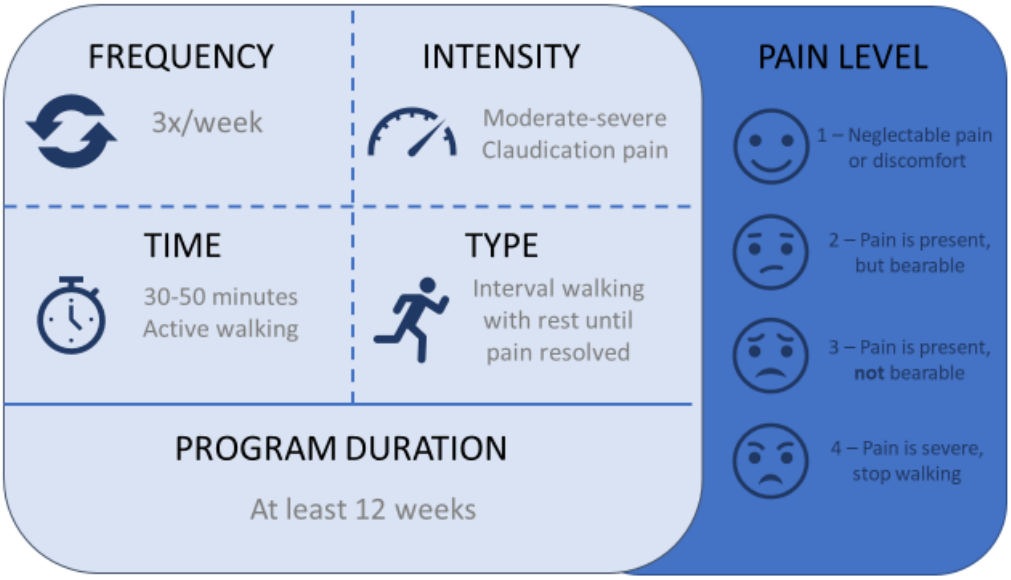


Figure 12. *Guidelines on exercise therapy in patients with LEAD.*

1.4. PhD objectives

The first objective of this PhD was the development of a structured home-based exercise program supported by technology. Given the potential of structured home-based exercise programs, we first wanted to explore interest, need and barriers towards physical activity in the specific population of LEAD patients having intermittent claudication symptoms (**chapter 2.1**). Thereafter, pilot testing of an exploratory home-based exercise program, combining resistance and walking training, was done. Here, training prescription and monitoring was tested using commercial wearables and the acceptability and feasibility of this program was explored (**chapter 2.2**). Finally, within this first objective we explored the

feasibility and efficacy of a 12-week home-based intervention, build upon the findings from chapter 2.1 and chapter 2.2 (**chapter 2.3**).

The second objective of this PhD was to explore the underlying mechanisms and determinants of improvement. Here we addressed local muscle oxygenation more in detail and explored the added value of Near Infrared Spectroscopy (NIRS). NIRS is considered an interesting method to non-invasively evaluate oxygenation of a target muscle group during dynamic measures. As such, we investigated whether NIRS has additional value in the exploration of local metabolic changes and exercise improvement in LEAD and intermittent claudication after exercise (**chapter 3.1 and 3.2**).

Finally, **the third objective in this PhD work** was to explore the impact of exercise on the underlying cardiovascular risk factor profile in LEAD and intermittent claudication (**chapter 4.1**). In addition, we explored the rationale for a multidisciplinary approach (e.g. cardiac rehabilitation) to impact measures of physical fitness (peak VO_2) and improve overall secondary prevention. In order to provide an effort-independent measure of physical fitness, we closely matched LEAD patients with peers starting cardiac rehabilitation. As such, intensity-matched measures of peak VO_2 were investigated along with an exploration of alternative outcomes in order to guide the potential need for future rehabilitation programs in LEAD **(chapter 4.2)**.

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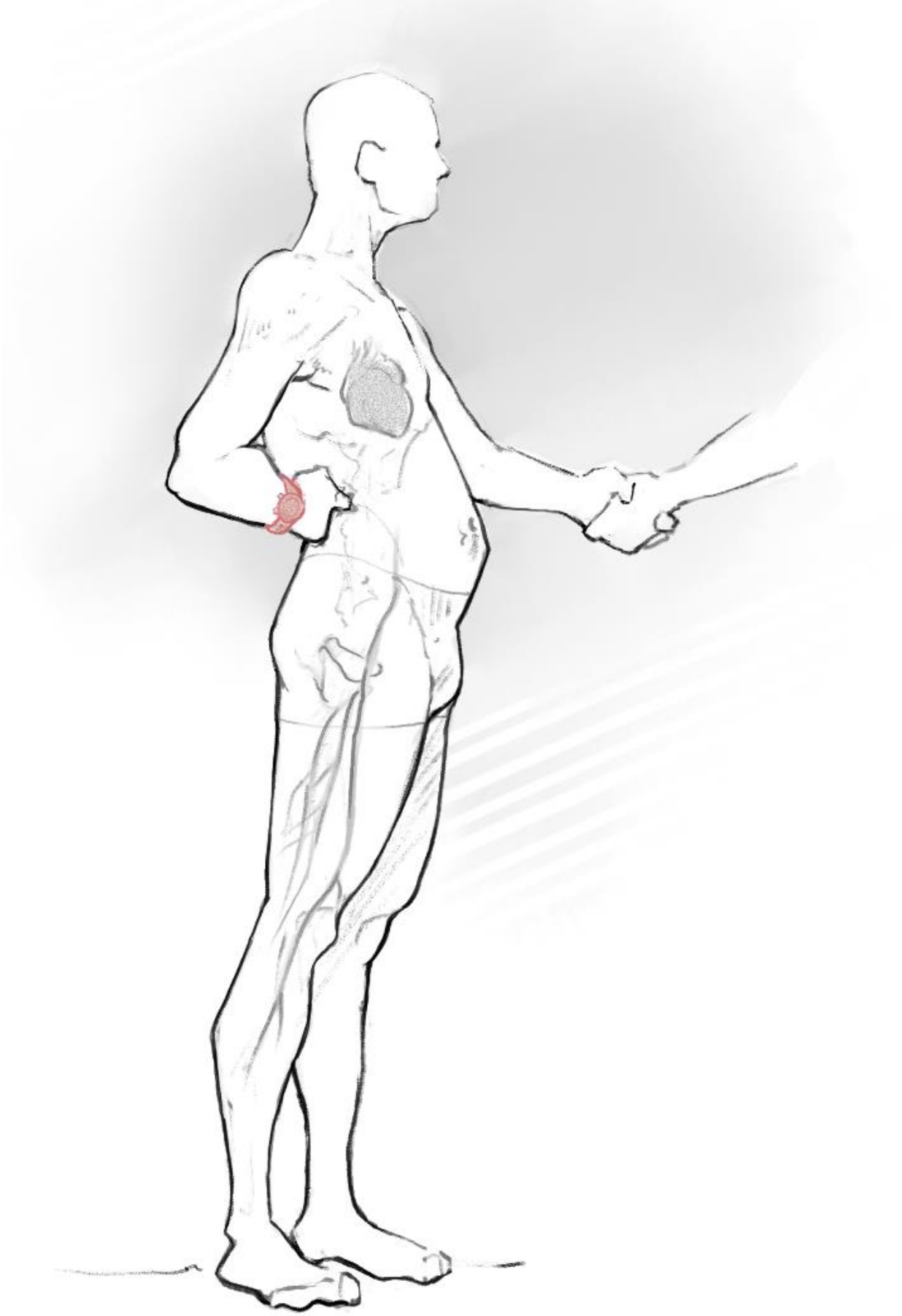
Chapter two: Home-based exercise program development and evaluation



Chapter 2.1: Exploring physical activity behaviour - needs for and interest in a technology-delivered, home-based exercise program among patients with intermittent claudication

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Abstract

Background: Supervised walking is a first line therapy in peripheral arterial disease (PAD) with complaints of intermittent claudication. However, uptake of supervised programmes is low. Home-based exercise seems an appealing alternative; especially since technological advances, such as tele-coaching and tele-monitoring, may facilitate the process and support patients when adopting a physically active lifestyle. To guide the development of such an intervention, it is important to identify barriers of physical activity and the needs and interests for technology-enabled exercise in this patient group.

Patients and methods: PAD patients were recruited at the vascular centre of UZ Leuven (Belgium). A questionnaire assessing PA (SF-International Physical Activity Questionnaire), barriers to PA, and interest in technology-supported exercise (Technology Usage Questionnaire) was completed. Descriptive and correlation analyses were performed.

Results: Ninety-nine patients (76 men; mean age 69 years) completed the survey. Physical activity levels were low in 48%, moderate in 29%, and high in 23%. Intermittent claudication itself is the most important barrier for enhanced PA, with most patients reporting pain (93%), need for rest (92%), and obstacles worsening their pain (74%) as barriers. A total of 93% participants owned a mobile phone; 76% had Internet access. Eighty-seven reported the need for an exercise programme, with 67% showing interest in tele-coaching to support exercise. If technology was available, three-quarter stated they would be interested in home-based tele-coaching using the Internet (preferably e-mails, 86%); 50% via mobile phone, 87% preferred text messages. Both were inversely related to age (r_{pb} = 0.363 and r_{pb} = 0.255, $p < 0.05$). Acquaintance with elastic bands or gaming platforms was moderate (55 and 49%, respectively), but patients were interested in using them as alternatives (84 and 42%). Interest in platforms was age-dependent ($r_s = –0.508$, $p < 0.01$).

Conclusions: PAD patients show significant interest in technology-delivered exercise, offering opportunities to develop a guided home-based exercise programme.

Introduction

Physical activity and regular exercise are key in the management of chronic diseases, including peripheral arterial disease (PAD). In this subgroup of vascular diseases, intermittent claudication or atypical leg symptoms are the most common complaints (1). Although not immediately life threatening, this debilitating symptom often leads to reduced physical activity levels, profoundly impacting walking capacity, functionality, and quality of life (2, 3). Moreover, limited physical activity in PAD patients has been linked to a higher mortality rate (4). Not surprisingly, concomitant coronary or cerebrovascular disease is estimated to be as high as 61% in PAD patients (5). Today, supervised exercise training is a class IA recommendation for patients with IC (6). Supervised exercise therapy can increase maximum and pain-free walking distance by 120 and 180%, respectively (7). As such, this clinical benefit from exercise training is not different from the use of endovascular treatments (8). Despite these results, the implementation of supervised exercise therapy in clinical practice is scant, with only 30% of European vascular surgeons having access to structured walking programmes (9). In addition, a systematic review by Harewood et al. showed that only one out of three patients initiates some type of exercise training or physical activity programme (10). Lack of interest (30.6%) and logistical problems (transportation, access to facilities) (11.7%) are listed as major perceived barriers to participation. Since these numbers are derived from clinical trials, underestimation in the general PAD population seems plausible (10). In addition, the lack of reimbursement and awareness adds to the current underuse of supervised exercise therapy, regardless of the suggested favourable cost-effectiveness of supervised exercise therapy in comparison with more invasive approaches (11). Since barriers associated with supervised exercise are ubiquitous, the “Go-Home-And-Walk”-advice is a widely used alternative for conservative management. However, it is not surprising that just giving advice is not as effective as supervised training (12). Structured home-based exercise programmes (HEP) serve as a bridge between the gap of supervised exercise and the less effective “Go-Home-And-Walk”-advice, and therefore become increasingly interesting in PAD patients (9, 13). Although HEP might offer a solution when supervised training is not feasible, strong evidence supporting HEP is still lacking. This is due to a low number of high quality randomized controlled trials and the significant heterogeneity among HEP trials with regard to communication, exercise prescription, follow-up, and adopted behavioural change models (13, 14). There is growing interest in the implementation of eHealth as an alternative or adjunct to face-to-face contact. eHealth involves the incorporation of information technology into health care, connecting patient and healthcare specialists to achieve health objectives through technology (15). Therefore, technology-enabled HEP, which offers tele-monitoring to enhance guidance and supervision of exercise and tele-coaching to enhance patients’ motivation, might become a valuable alternative to supervised exercise therapy. A current

European project, PATHway, has initiated the development of a home-based training intervention using an interactive platform for cardiac rehabilitation (16). A population of patients with cardiac diseases showed high interest in such online exercise programmes (17). Although this information might be indicative, no objective data are available for PAD patients suffering from intermittent claudication. Specifically, the more advanced age and explicit symptoms in this population differ substantially from cardiac patients and justify further research, examining their needs. Therefore, the main objective of this study was to evaluate access, utilization, interests, and needs of PAD patients with regard to eHealth exercise programmes. Secondary objectives included the investigation of physical activity levels, personal and environmental barriers to exercise, and to explore the association between physical activity behaviour and interest in e-health platforms to exercise.

Patients and methods

Study design and participants

A prospective study was conducted between November 2016 and May 2017 at the vascular centre of the University Hospital Leuven (Belgium). Patients were eligible if the vascular surgeon during the consultation diagnosed them with complaints of claudication due to underlying PAD. No specific exclusion criteria were set. The study received ethical approval by the UZ/KU Leuven biomedical ethical committee. After providing written informed consent, participants were asked to complete a 37-item questionnaire on paper or as an online survey on a laptop or tablet.

Questionnaire

The 37-item questionnaire was composed of four parts: 1) demographics, 2) physical activity, 3) barriers to physical activity, and 4) current access to and use of technology as well as interest in, need for and willingness to use an eHealth application for exercise training. The *demographics* section collected data on age, gender, level of education, and current profession. Data on medical history and current disease state were extracted from the hospitals' electronic database. *Physical activity* was assessed by means of the Dutch Short-Form International Physical Activity Questionnaire (SF-IPAQ). This questionnaire quantifies physical activity performed during the last seven days in four different categories: vigorous intensity, moderate intensity, walking activities, and sitting. Within each category, frequency (number of days) and duration of physical activity performed for at least 10 Minutes at a time (number of minutes per day) are assessed. Vigorous intensity was defined as experiencing a significant increase in breathing rate and requiring a lot of effort, whereas moderate intensity was defined as experiencing a slight increase in breathing rate with some effort. In addition, examples were provided for each of the categories. The "Guidelines for data processing and analysis of the IPAQ" were used to clean and analyse

the data. Based on these guidelines, the total weekly volume of physical activity was calculated by multiplying the number of days by the amount of time and the assigned metabolic equivalent (MET) value for the intensity of that activity, ranging from 3.0 to 8.0 METs. After exclusion of one patient that reported more than 960 Minutes/day and termination of activities exceeding 180 Minutes, the remaining 98 participants' physical activity was categorized as *low, moderate or high* (18) (see **Table 1**). Next, we included two comprehensive items, based on the study of Barbosa et al. (19), addressing the *personal and environmental barriers* of physical activity in patients with PAD. A five-point ordinal scale *(never, seldom, sometimes, frequently, always)* was used to assess the limiting character of each of these 14 barriers (see **Table 2**). Finally, 15 questions assessing *current access to technology, their usage of technology, and their interest in a technology-enabled home-based exercise programme* were taken and/or adapted from the Technology Usage Questionnaire (TUQ) (17). Current technology usage was covered by questions asking for access to and use of Internet, mobile phones, heart rate monitors, and physical activity devices. A subsequent question enquired about the interest or disinterest of patients in a home-based exercise programme specifically designed to counter the aforementioned barriers. Exercising with elastic bands and video game devices were presented as specific home-based exercise modalities. An additional seven questions covered the acquaintance of patients with these exercise modalities, the interest in a training programme involving these specific modalities, and further specifications. The last question asked patients to gauge the usefulness of and need for different health advices (e. g. motivation to exercise, healthy dietary advice, smoking cessation, etc.), provided via Internet or mobile phone (not useful, somewhat useful, rather useful, useful, and very useful).

Table 1. *SF-IPAQ categories regarding physical activity.*

Low	Not meeting criteria for moderate or high activity
Moderate	• 3 ≥ days of vigorous-intensity of at least 20 minutes per day • 5 ≥ days of moderate-intensity activity and/or walking of at least 30 minutes per day • 5 ≥ days of any combination of walking, moderate- or vigorous intensity activities achieving a minimum total PA of ≥ 600 MET-minutes/week
High	• Vigorous-intensity activity ≥ 3 days achieving a minimum total PA of at least 1500 MET-minutes/week • ≥ 7 days of any combination of walking, moderate intensity or vigorous-intensity activities achieving a minimum total PA of ≥ 3000 MET-minutes/week

Statistical analyses

Database management was performed by means of the Google Forms online questionnaire utility, which allowed export to Excel spreadsheets (Microsoft Excel) for subsequent coding. SF-IPAQ analysis was done separately with an algorithm designed to categorize and calculate outcomes based on the aforementioned presumptions regarding physical activity

(20). All data were analysed using the statistical software package IBM SPSS Statistics Version 20. Data processing of survey responses was largely descriptive. When analysing relations between variables, point-biserial correlations (r_{pb}) were used when dealing with one continuous and one dichotomous variable. In addition, spearman-rank correlations (r_s) were used for ordinal and continuous data, chi-square statistics (X^2) were performed for categorical data. A Mann-Whitney U test was performed when analyzing gender differences in physical activity. Statistical significance was set two-sided at a p-value of .05.

Table 2. *Personal and environmental barriers.*

Personal	i) Pain, ii) Need for rest, iii) Fear of falling, iv) Lack of knowledge regarding exercise-benefits, v) Need for supervision/control, vi) Lack of time, vii) Other health issues, viii) Financial reasons
Environmental	i) Obstacles aggravating pain, ii) Unfavorable weather, iii) Poor quality or dangerous sidewalks, iv) No place to rest when experiencing pain, v) Shortness of space to exercise or be physically active, vi) Hilly terrain

Results

Patient characteristics, physical activity levels, and barriers towards physical activity

Ninety-nine patients (76 men) with a mean age of 69.4 years completed the questionnaire. As can be seen in **Table 3**, 24 patients presented at the vascular centre for a follow-up of their conservative management, consisting of "Go-Home-And-Walk"-advice (GHWA), 21 had residual or recurrent symptoms post-revascularization, and the majority (n = 54) presented with new-onset claudication symptoms. Prevalence of cardiovascular risk factors was high; most patients (89%) were current smokers or used to smoke, 85 % were hypertensive, 92% had hyperlipidaemia, and one third of the patients had diabetes. According to the SF-IPAQ, almost half (48%) of the participants' physical activity was classified as being only low. Twenty-nine per cent of patients were classified as being moderately active and 23% were in the highly active group. The median volume of physical activity was 1,221 METs min/week, which was not significantly related to the patients' Rutherford category ($r_s = –0.074$, $p = 0.470$). Although total volume of physical activity was not significantly different among men and women (1,059 MET min/week vs. 1,638 MET min/week, $p = 0.21$), more women were moderately active compared to men (720 MET min/week vs. 240 MET min/week, $p < 0.05$). Further exploration of the data showed that less than half (46 %) of the study sample reported a total activity of ≥ 1,500 METs min/week and one third ≤ 600 METs min/week. Sixty-four patients reported no vigorous activity in daily life and 32 of them reported no moderate physical activity. A small number of patients reported more than two days of vigorous (12%) or ≥ 5 days of moderate (17%) activity.

Combined, one out of four patients completing the survey reported no moderate or high physical activity during the past week. When focusing specifically on walking, approximately 55% of PAD patients reported walking on three or more days of at least 10 Minutes each. **Figure 1** shows an overview of the personal and environmental barriers to physical activity and exercise in 99 PAD patients. Pain (n = 92) and the need for rest when being physically active (n = 91) were the most reported personal barriers. Their combined value was just under the threshold of being significantly associated with the Rutherford class (r_s = 0.183, p = 0.070) or weekly volume of physical activity (r_s = –0.165, p = 0.105). One third of patients reported to avoid exercise due to fear of falling. This was significantly associated with the presence of comorbidities and symptoms such as dyspnoea, lower back pain, etc. (r_s = 0.256, p < 0.05). In addition, the presence of other comorbidities and/or lack of knowledge about the benefits of exercise were related to an increased need for supervision (r_s = 0.251, p <. 05 and r_s = 0.493, p < 0.01). Most important environmental barriers were the presence of obstacles aggravating the pain in the limbs (n = 73), hilly terrain (n = 70) or unfavourable weather (n = 83).

Table 3. *Patient Characteristics (n = 99).*

Age *(years)*	69.4 (40-90)
Gender *(♂/♀)*	76 / 23
Employment status	
Employee	10
Unemployed	1
Unable to work	8
Retired	80
Highest qualification	
Elementary and lower grade	35
Secondary higher grade	44
Higher education	15
University	5
Bilateral symptoms *(n)*	52
Rutherford classification *(n)*	
Rutherford 1	23
Rutherford 2	29
Rutherford 3	45
Rutherford 4	1
Rutherford 5	1
Reason of consultation *(n)*	
FU conservative management of ICU	24
FU post-revascularization	21
New onset IC	54
History*(n)*	
Vascular	80
Cardiovascular	54
Respiratory	9
Cardiovascular Risk* (*%)*	
Smokers	27%
History smokers	62%
Hyperlipidemia	92%
Hypertension	85%
Diabetes Mellitus	30%
Physical activity	
Vigorous (MET min/week)	0 (0 – 960)
Moderate (MET min/week)	240 (0 – 1260)
Walking (MET min/week)	247.5 (99 – 717.8)
Total activity (MET min/week)	1221 (360.3 – 3379.8)
PA time (min/week)	275 (97.5-687.5)
Sitting time (min/day)	360 (240 – 540)

Note. FU: *Follow-up;* ***IC:*** *intermittent claudication;* ****Missing data*** *for smoking n = 2, hyperlipidemia n = 4, hypertension = 3 and diabetes mellitus n = 7. Age is reported as* ***mean*** *and range. Physical activity (PA) data is reported as* ***median*** *and 1st and 3th quartile.*

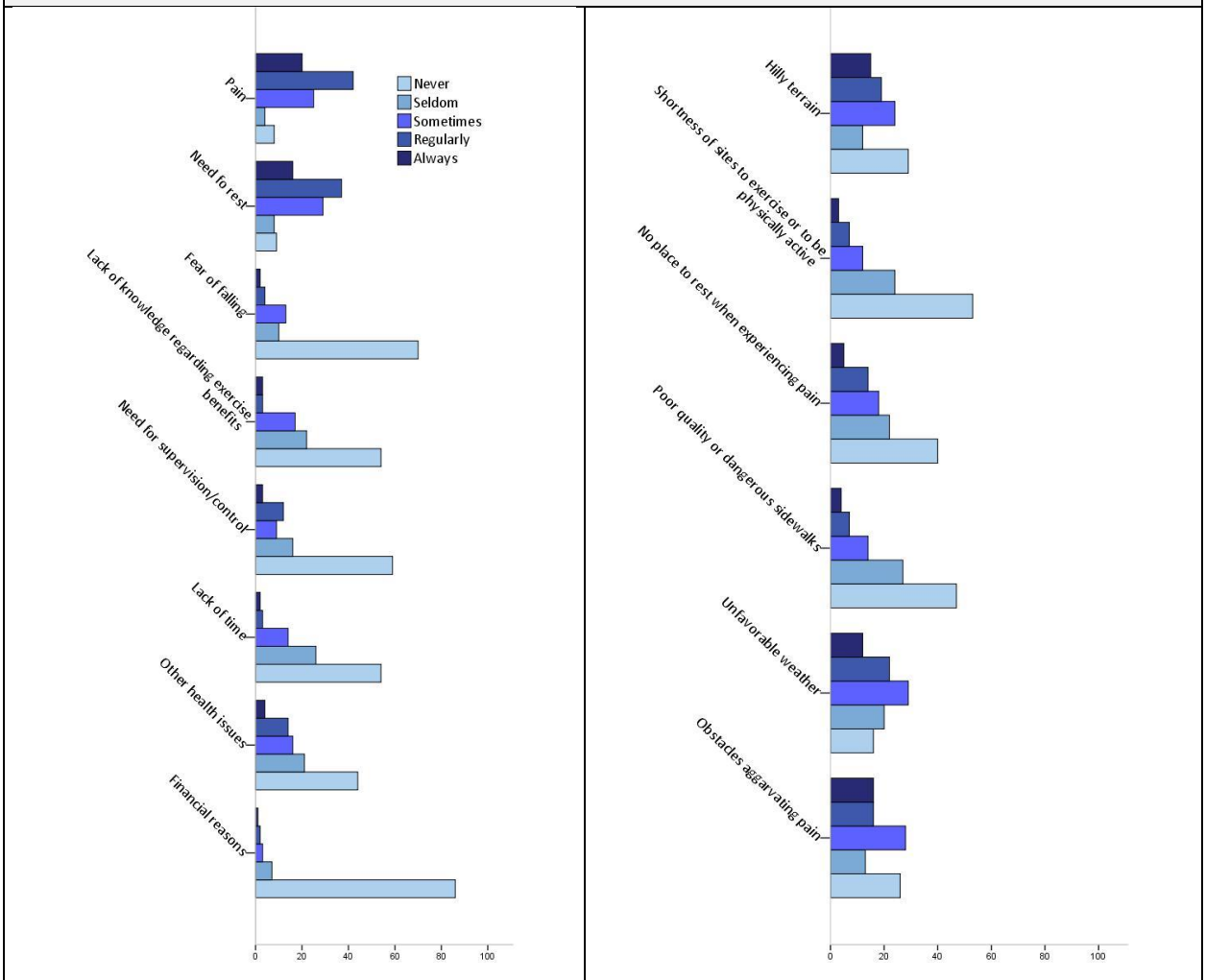
Tele-coaching and tele-monitoring

The majority of the patients (n = 87) reported to be interested in participating in an exercise programme designed for patients with PAD. Reasons for lack of interest were: dislike of

exercise (n = 5), preference to exercise on their own (n = 3), already being sufficiently physically active (n = 2) or the conviction that exercise will not affect their current situation (n = 2). Ninety-two participants owned a mobile phone. The most commonly used features were phone calls (99%) followed by texting (74%). Less common were browsing the internet (37%), using apps (26%), sending or receiving videos or photos (25%), social networking (24%), instant messaging services (16%), and playing mobile games (9%). Mobile phone usage in general was not related to age, gender or education level. However, a significantly negative correlation was observed between age and the use of social networks (r_{pb} = –0.415), apps (r_{pb} = –0.384), instant messaging services (r_{pb} = –0.340), browsing the Internet (r_{pb} = –0.338), sending text messages (r_{pb}= –0.286), and playing mobile games (r_{pb} = –0.250) ($p < 0.05$ for all). Seventy-five patients reported to have regular Internet access, of which 59 (79%) reported using the Internet daily and only 3% accessed the Internet less than once a week. A negative correlation regarding Internet access and age was present (r_{pb} = –0.274, $p < 0.01$). Most participants accessed the Internet via personal computer (91%), followed by tablets (39%) or smartphones (36%). Overall, 67% showed interest in tele-coaching. Three quarters (57 out of 75) of patients with Internet access were interested in a home-based exercise programme with telecoaching over the Internet, whereas 46 (50%) participants owning a mobile phone were interested. Most patients preferred text messages as a communication medium (87%). Half of them (49%), preferred one or two texts each week, 24% three to four texts each week, 18% liked to receive one message a day, and 8% less than one or two a week. Forty-three per cent showed interest in receiving e-mails and one fifth desired a specific smartphone application or learning videos. With regard to communication via the Internet, patients were most interested in e-mails (86%), followed by videos (51%) or a specific website (26%). Qualitative research revealed that a lack of knowledge regarding mobile phone usage or preference for the Internet were the main reasons to decline mobile phone support in this patient population. In addition, violation of privacy (n = 1) and fear of becoming dependent on technology (n = 1) were other reasons to decline support through mobile phone. As displayed in **Figure 2**, 33 respondents revealed no interest in any of the possibilities. Although, when considering the group owning a mobile phone and having Internet access, only 19% (14/72) declined both options. The entire cohort's age was significantly correlated with both interest in mobile phone and Internet support (r_{pb} = –0.363 and r_{pb} = –0.255, $p < 0.05$), whereas the participants' age, of those owning both a mobile phone and having access to the Internet, was only related to mobile phone support (r_{pb} = –0.378, $p < 0.01$ and r_{pb} = –0.108, $p = 0.366$). Interest in mobile phone or Internet support involving an exercise programme was not related to gender or educational level. Patients using apps or searching the web with their phone were more interested in mobile phone support (X^2 = 8.118 and X^2 = 9.144, $p < 0.01$). Finally, patients with a physical activity categorized as low, reported significantly less interest in mobile

phone support ($X^2 = 10.726$, $p < 0.01$). Interests in separate rehabilitation aspects are shown in **Figure 3**. Advice on exercise ideas and local exercise opportunities, stress-management, support and encouragement, as well as healthy meals and recipes for healthy eating were considered as rather useful by at least 60% of respondents. Advice to control the urge of smoking was popular with smokers, with 69% reporting this option to be (very) useful ($X^2 = 39.216$, $p < 0.01$). Patients were least interested in advice with regard to medication intake. Age was negatively correlated with almost all health advices ($p < 0.05$), except regarding medication intake and the possibility to contact peers. Strikingly, women were more interested in getting in contact with peers ($X^2 = 18.985$, $p < 0.01$) compared to men. Only eight patients used a heart rate monitor to measure their heart rate during physical activity and a similar number used physical activity devices like pedometers, mobile phone apps or tracking wristbands to register their physical activity. Of the 91 patients that were not using a heart rate monitor, 44 (48%) were interested in continuous heart rate tele-monitoring when exercising at home.

Figure 1. *Personal and environmental barriers to physical activity in PAD patients.*

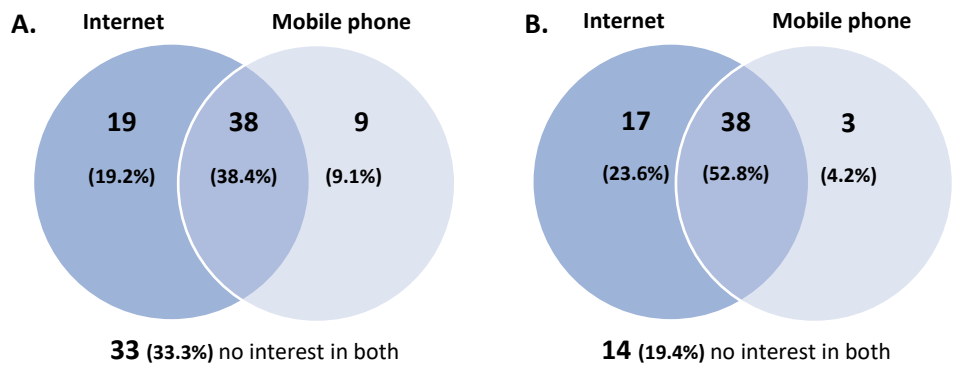


Note. *Bar charts on the left represent **personal** barriers to physical activity or exercise in the population of PAD patients. Bar charts on the right are **environmental** related barriers. X-axis represents the number of patients reporting this variable as a barrier to exercise.*

Interest in specific home-based programmes

Slightly more than half of the patients (54/99) knew about elastic bands to exercise with. When asked about their interest in an exercise programme using these elastic bands as an alternative to walking, 83 responded positively. Half of the patients (49/99) was familiar with video game platforms or interactive computer games; but only 14% had experience with computer-based physical activity games. Patients showed a moderate interest in an exercise-based online rehabilitation programme, with younger patients having more interest in computer-based exercise platforms (r_s = –0.508, p < 0.01). One third of the interested patients preferred only a minimum of interaction when using the platform, whereas another third (31%) wanted a full option menu. Finally, the implementation of a virtual trainer sounded appealing to half of the participants, with 52% showing interest in such a platform.

Figure 2. *Venn-diagram of interest in tele-coaching using mobile phone or internet.*



Note. *Diagram **A** represents the whole population finishing the questionnaire (n = 99). Diagram **B** represents the interest in tele-coaching in the sub-population having a mobile phone and internet access (n = 72).*

Discussion

Nowadays, technology has become an integral part of our daily life. As such, the rise of eHealth applications offers possibilities to implement structured rehabilitation programmes in the patients' home environment in an attempt to improve management of PAD patients. This study was performed to document patients' needs and expectations in the preparation of a home-based rehabilitation programmes/platforms for patients with PAD. The results of this study revealed a significant interest in home-based guided exercise programmes by these insufficiently active patients, specifically by means of the Internet and, to a lesser extent, by mobile technology. In addition, a significant group of patients was interested in trying new exercise modalities, like the use of elastic bands or online exercise platforms, although most of them had never used it before.

Physical activity and its barriers

Our data confirm the high prevalence of cardiovascular risk factors in PAD patients, indicating the need for effective secondary prevention. Exercise and physical activity are widely recognized as key in both the treatment of PAD symptoms but also its underlying risk factors. Unfortunately, half of our study sample's physical activity was categorized as being only low. This is in line with Lauret et al. who showed, using tri-axial accelerometers, that 55% of PAD patients did not reach the ACSM/AHA lower limit recommendation (2). Earlier, Wassink-Vossen et al. used the SF-IPAQ to document physical activity behaviour in 128 healthy adults of similar age (21). Compared to these healthy elderlies, the weekly volume of PA is significantly lower in our cohort (2,560 MET min/week vs. 1,221 METmin/week). This is fully in line with Barbosa et al. who showed that physical activity levels in PAD patients are consistently lower compared to healthy controls (22). Another study by Gomes and colleagues, using the SF-IPAQ, showed an even lower weekly activity (670 MET min/week) in PAD patients (23). Yet, the tendency for higher physical activity in women contrasts with the findings of a population study in Spain who showed that 61–75-year-old men have a higher total activity compared to women (24). Though, one possible explanation for this contrasting finding could be the broad interpretation of the SF-IPAQ, with women reporting to do more house chores, leading to higher physical activity levels. Walking is the most recommended and studied mode of exercise for patients with PAD. Compared to elderly men (≥ 75 years) our PAD patients walk four times less (24). It is of note that one fourth of patients was specifically advised to take up walking as they were conservatively managed. To accommodate future barriers regarding exercise and physical activity, we aimed to identify main barriers to physical activity in our PAD patients. In agreement with Barbosa et al., we found that claudication-related symptoms (pain and the need for rest) were most limiting (19). In addition, factors which could induce pain, like stairs and hilly terrains, were found, both in our population and in a Brazilian population, to be important environmental barriers (19). As such, if we aim for maximizing uptake and adherence to an exercise intervention, it is important that we try to overcome these barriers by offering alternative exercise modes.

Patterns and needs regarding technology use in PAD patients

It was interesting that patients did not express the need for supervision of exercise as a barrier, which makes home-based exercise therapy an interesting alternative to supervised exercise therapy. Since technology use is known to be influenced by age, our study was highly needed to document mobile phone and internet use in the generally older PAD population. As compared to the study from Buys and colleagues, our participants were approximately ten years older (17). This advanced age is reflected in lower access to Internet (76% vs. 91%) in PAD patients compared to cardiac patients. With regards to mobile

phone use, only a slight difference is noted (93 vs. 97%). However, smartphone use was high in the study of Buys, with 64% of mobile phone users owning one. Therefore, the lower interest in mobile phone tele-coaching (50 vs. 69%) observed in our study might be explained by less experience in smartphone use. In contrast, a Canadian population study reported only 41% interest in text messaging as an eHealth tool in 65 to 74-year-old patients suffering from at least one noncommunicable disease (25). It has been confirmed that web-based interventions are considered more appealing (17, 25) and, when Internet access is available, no age-related effect was noticed in PAD patients. In short, mobile phone, and especially smartphone use, seem a viable option to support exercise in younger generations, whereas Internet use seems more useful in all ages. Following this, most patients reported interest in receiving health advice (e.g. healthy eating, exercise or stress), demonstrating their willingness to enhance their ability of self-managing their disease. As disease understanding is considered crucial in conservative treatment and necessary to breach the quick-fix thinking, shared among a vast number of patients, tele-coaching and e-learning are attractive tools in promoting self-efficacy. In addition, when healthcare contact to a vascular surgeon is scarce and limited, the concomitant use of eHealth in PAD seems to pose an interesting option to strengthen orally provided health advices received during consultation. As a secondary preventive strategy, support through technology is an effective means to improve cardiovascular disease outcomes (26), although no distinct effect on cardiovascular risk factors was noted in this review. In contrast, an earlier review, combining telehealth interventions, with at least 50% communication via mobile phone or Internet, presented considerable reductions in lipid profile, blood pressure, and smoking status (27). Increased physical activity was noted in five out of seven studies (27).

eHealth in home-based rehabilitation: future perspectives

To sum up, eHealth applications might offer the possibility to guide and monitor exercise and lifestyle changes in PAD patients, whilst accounting for important barriers. Whereas unsupervised exercise is less efficient and known to have low adherence, transition to a home-based programme supported by an interactive platform could bridge this gap. Importantly, promotion of eHealth should be according to both patient and professional needs and expectations, since the booming eHealth solutions are often mostly technically driven (28). An example of such an integrated model is ClaudicatioNET, where healthcare providers and patients interact and share information to obtain the best results in supervised exercise (15). Extensions of such a programme to the home-based setting is challenging. Yet, it could offer an important incentive to a more active lifestyle in PAD patients complementary to timely follow-ups, as the therapeutic relationship should not be overlooked when implementing technology (29).

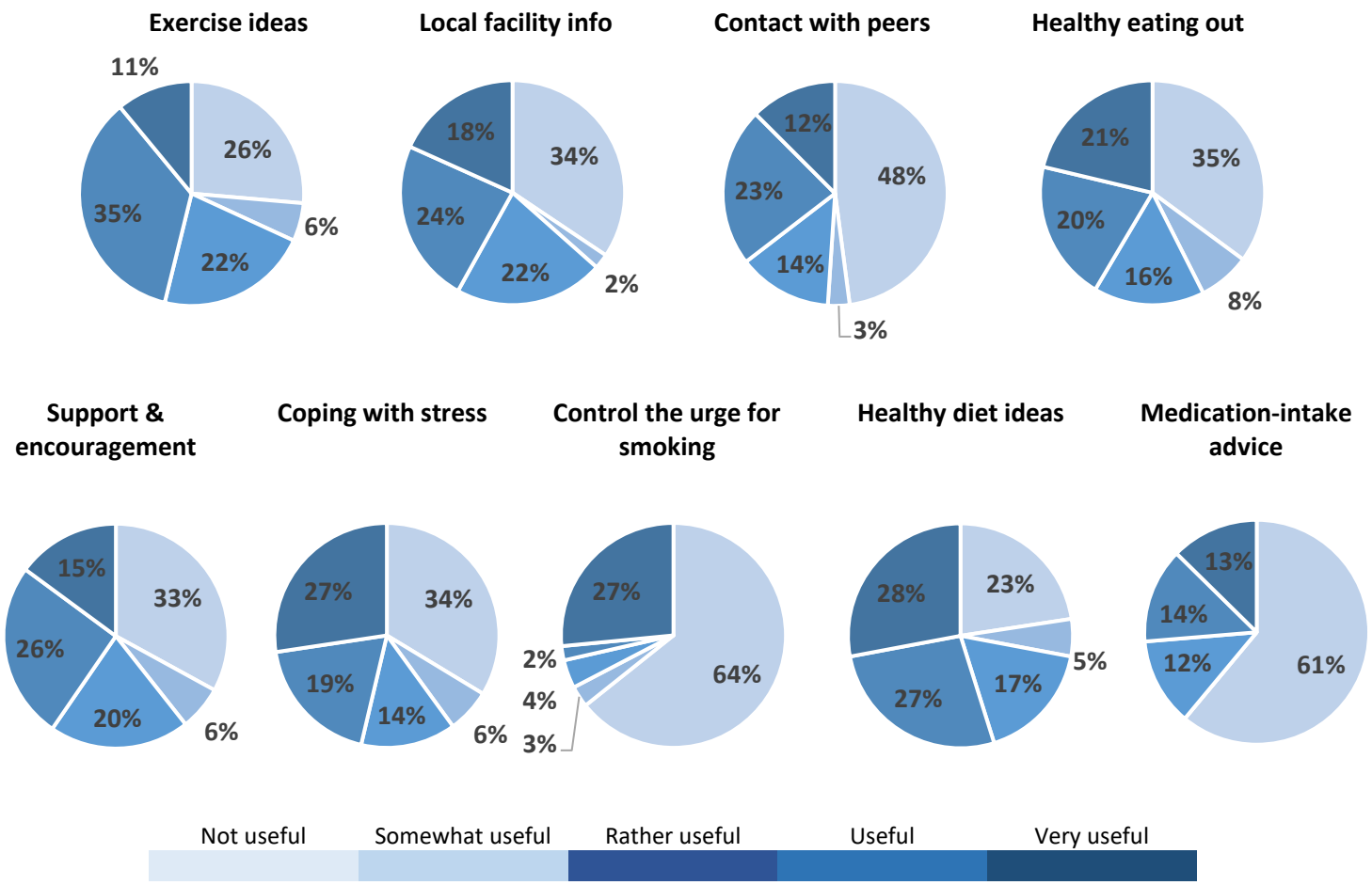
Limitations

First, the cross-sectional and single centre design limits causal interpretation of the results as well as generalizability to other countries. Second, we used the SF-IPAQ, which is a subjective tool to assess physical activity. Although the SF-IPAQ has been shown to be valid and reliable to assess physical activity, more recent studies highlight that overestimation of PA is highly frequent (30). In addition, Finger et al. underlined the potential difficulties in regard to reporting of asked behaviour among participants when there are underlying cognitive problems. This was especially true in participants older than 60 years, having an irregular or no physical activity pattern (31). It is highly likely that this also occurred in our study sample. Third, it should be noted that the TUQ was created to gather the interest and needs of a heterogeneous sample of PAD patients. Consequently, further exploration of these needs and expectations should be complemented with qualitative research (17).

Conclusions

This study documents the need for, but also the interest in, a specific exercise programme for the population of PAD patients with low physical activity. The introduced concept of technology-enabled exercise provision was well received in a large group of patients, offering further possibilities to explore and develop eHealth applications in first line PAD patient care.

Figure 3. Interest in specific health advices through tele-coaching services by mobile phone or internet services.



Note. *The question of which tele-health-advices were considered useful or not was responded irrespective of interest in mobile phone or internet tele-coaching.* ***Missing values:*** *exercise ideas; 8, local facility info; 6, contact with peers; 3, healthy eating out; 5, support & encouragement to exercise; 5, coping with stress; 4, control the urge for smoking; 1; healthy food ideas; 6, medication-intake advice; 4.*

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Chapter 2.2: Satisfaction and acceptability of telemonitored home-based exercise in patients with intermittent claudication: pragmatic observational pilot study

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Abstract

Background: Current guidelines recommend supervised exercise training (SET) as a first-line treatment in patients with intermittent claudication (IC). SET has been shown to be more effective than home-based exercise therapy (HBET). However, the lack of available SET programs hampers broad SET implementation in clinical practice.

Objective: The aim of this study is to assess patient satisfaction and acceptability of a structured HBET program using wearable technology and elastic band resistance exercises.

Methods: A total of 20 patients with IC (Rutherford 1-3) with internet access and currently not engaged in structured exercise training were recruited in a pragmatic observational pilot study. Participants were instructed to complete 3 walking sessions and 2 elastic band resistance exercise sessions per week in their home environment during a 4-week period. Patient satisfaction and acceptability were assessed using a 5-point Likert scale questionnaire (1-2 = very unsatisfied, 3 = neutral, and 4-5 = very satisfied) evaluating the materials and intervention content. Secondary outcomes were evaluated at baseline and at completion of the 4-week intervention and included maximal walking distance (MWD) and pain-free walking distance (PFWD), physical fitness, and patient-reported outcomes on quality of life, walking capacity, levels of kinesiophobia, and self-efficacy. Statistically significant changes were tested using paired t tests or Wilcoxon signed-rank tests.

Results: All patients (15 men, 5 women; mean age 64.6, SD 10.6 years; range 41-81 years) completed the 4-week intervention and were highly satisfied with the program (mean overall score 4.5, SD 0.5). Patients' questionnaire responses documented willingness to recommend the exercise program to other patients (mean 4.5, SD 0.5; median 4.5) and preference for continuing the intervention (mean 4.3, SD 0.5; median 4). Furthermore, participants endorsed the use of the sports watches to track walking sessions (mean 4.25, SD 0.6; median 4), felt safe (mean 4.4, SD 0.6; median 4), and appreciated personal feedback (mean 4.55, SD 0.5; median 5) and flexibility of training (mean 4.1, SD 0.7; median 4). Resistance training was not preferred over walking training (mean 2.65, SD 0.8; median 3). In addition, PFWD (+89 m; P = .001), MWD (+58 m; P = .03), Walking Impairment Questionnaire distance score (+0.18; P = .01), activity-related scores (+0.54; P < .001), and total quality of life (+0.36; P = .009) improved following the intervention. Other patient-related outcomes, physical fitness, and physical activity remained to be statistically unaltered.

Conclusions: Patients with IC were satisfied and accepted technology to monitor and guide HBET, with observed short-term effectiveness regarding walking capacity and quality of life. However, elastic band resistance exercises as a part of HBET were not preferred over progressive walking.

Introduction

Background

Lower extremity artery disease (LEAD) is a chronic disease characterized by progressive atherosclerotic narrowing of the lower limb arteries. As such, insufficient blood flow to active muscles during exercise may result in complaints of intermittent claudication (IC), which often presents as cramping or burning-like pain during physical activities. Although not immediately life-threatening, LEAD and IC have a great impact on patients' functional status and quality of life (1) through long-term pathophysiological changes (e.g. atrophy, muscle weakness, reduced cardiorespiratory fitness) (2-4). Furthermore, IC limits the ability to be physically active, enhancing the risk of serious cerebral and cardiovascular events (5).

Recent guidelines emphasize the importance of a first-line lifestyle-oriented approach when consulting with IC (6). In this context, supervised exercise and walking in particular are cornerstone therapies that result in clinically significant improvements in pain-free walking distance (PFWD) and maximal walking distance (MWD) (7). Meta-analytic research has shown that direct supervision of exercise training (SET) is a major contributor to progression in walking capacity (8). However, SET is not readily available in most European countries, with only 30% of vascular surgeons having direct access (9,10). Furthermore, even when SET is available, patients' participation is low, mainly because of a lack of transportation and time (11,12). In addition, reimbursement issues and lack of uptake in health policy plans further hamper the widespread use of SET (13). As a result, next to optimal pharmacological treatment, first-line IC management is often limited to a less-effective Go-Home-And-Walk advice. Structured home-based exercise therapy (HBET) seems promising to bridge the gap between Go-Home-And-Walk advice and the underuse of SET programs (9,10). Although recommended as the best available therapy when SET is unavailable (6), evidence supporting HBET programs is considerably scarce (7,14). However, it is noteworthy that the first HBET studies included only general advice to exercise, relied on patient recall, and did not incorporate behavioral change techniques (15,16). A more recent meta-analysis by Golledge et al (17) showed that when HBET was more structured (and monitored), the effectiveness of HBET in improving walking performance and physical activity was increased. Furthermore, the importance of regular contacts empowering behavioral change and a therapeutic relationship is crucial for success (16,18,19).

At present, eHealth technologies offer valuable tools to elicit the full potential of HBET (20). Currently, eHealth, referred to as telerehabilitation in cardiac rehabilitation, includes exercise supervision (telemonitoring), guidance of exercise (telecoaching), and promotion of a healthy lifestyle (21). Telerehabilitation interventions, such as telephone or internet-based coaching, designed to increase physical activity behavior and compliance to exercise

therapy, have already proven to be feasible and effective in cardiac patients (22,23). Moreover, recent advancements in commercial wearables offer a unique opportunity to monitor physical activity and exercise and support behavioral changes toward an active lifestyle (24). As such, wearable technology might help to bridge the gap by preserving the patient-provider relationship and offering home-based structured exercise therapy of adequate intensity in a health care system under pressure (14). However, one needs to address the needs and interests of all stakeholders, including patients (21). In this line, a previous cohort study from our group showed that 81% of patients owning a computer and telephone were interested in telecoaching (25). In addition, most patients preferred home-based exercise (26), and physiotherapists showed utmost interest (89%) in GPS tracking to monitor these sessions (27). With regard to the mode of exercise, most guidelines highlight the use of walking intervals until experiencing moderate-to-severe IC pain to improve walking distance (16). However, resistance training is also considered to be an effective exercise mode and offers the potential to induce a pain-free exercise stimulus (28). Furthermore, in addition to offering general health-related benefits, the addition of resistance exercises seems promising in terms of disease-specific measures (29) in patients with IC. However, the most recent review did not include any home-based resistance training alternatives, although elastic band exercises might be an effective home-based solution (28).

Objectives

In this exploratory, pragmatic observational pilot study, we primarily aimed to evaluate patient satisfaction and acceptability of a structured model of HBET using wearable technology during walking, in combination with home-based resistance exercises. In addition, we aimed to report on the adherence and potential effectiveness of this combined intervention on walking capacity, physical fitness, physical activity levels, and quality of life in the development of an HBET program for patients with IC.

Methods

Study Design

We conducted a 4-week exploratory observational cohort study to assess patient satisfaction and acceptability of an experimental HBET program combining walking therapy with elastic band exercises. The study was approved by the Ethical Committee of UZ (ethics approval number: S59686; Belgian registration: B322201630074) Leuven/KU Leuven (Leuven, Belgium) and registered on ClinicalTrials.gov (NCT04043546).

Participants

Patients consulting the ambulatory vascular center of the University Hospitals Leuven (Leuven) between October 2017 and July 2018 were recruited by vascular surgeons. Using convenience sampling, we aimed to recruit 20 patients. Eligibility criteria included patients presenting with LEAD (Ankle-Brachial Index (ABI) ≤0.9 and/or a 15% decrease in ABI after a maximal treadmill test) and new-onset or conservatively treated IC (Rutherford I-III). Patients were excluded if they (1) had already participated in a structured, regular exercise program (e.g. weekly physiotherapy); (2) showed exercise-induced signs of myocardial ischemia or complex ventricular arrhythmias during maximal treadmill exercise; (3) did not receive medical clearance for exercise; or (4) did not have access to a computer or the internet.

Intervention

The flow of this study is schematically depicted in **Figure 1**. To guide the 4-week home-based exercise program, participants were offered an informative booklet, a self-developed DVD with demonstration of the resistance band exercises (Supplementary file 1), and a Garmin Forerunner 210. The booklet provided background information about the symptoms of IC, a person-tailored walking prescription with a logbook, and images to illustrate the resistance exercises.

Walking and Resistance Program

The exercise intervention consisted of 3 walking days and 2 resistance training days each week. Walking was prescribed according to the Dutch activity guidelines for IC (30) and person tailored (e.g. adjustment of walking speed, hilly terrain, duration of rest period, unsteady surface) to elicit only moderate claudication pain during 2- to 10-minute intervals. Interval breaks were generally 1.5 to 2 minutes depending on pain recovery. Walking sessions were monitored and evaluated using GPS-derived data from the web-based Garmin Connect platform. Resistance training consisted of 4 elastic band exercises: plantar flexion, hip flexion, hip extension, and hip abduction. The appropriate resistance was selected during a single familiarization session at baseline to successfully complete the prescribed 2 sets of 12 repetitions for each leg. According to their individual preferences, participants received feedback twice weekly to only once during the 4-week intervention period via telephone or email. Exercise therapy was monitored and guided by a physiotherapist (NC) who progressively adjusted the volume and intensity over the 4-week period. This was personalized during contact moments using subjective reflection from the patients, baseline treadmill tests, and GPS-derived data. As such, participants had the possibility to self-monitor their walking sessions, received timely feedback on their

performance, and were provided with information on how to adapt their walking program (31).

Outcome Measures

After a consultation at the vascular center, participants were invited for baseline and 4-week follow-up measurements at our research laboratory (University Hospitals Leuven), as shown in **Figure 1**. Doppler measurements from the latest clinical evaluation at the ambulatory vascular center were used to report the ABI of the most affected leg. Similarly, sociodemographic and clinical characteristics (e.g. Rutherford classification) were derived from the electronic patient records of the last clinical consultation. In addition, the feasibility of physical activity assessment was evaluated at baseline and after 3 months.

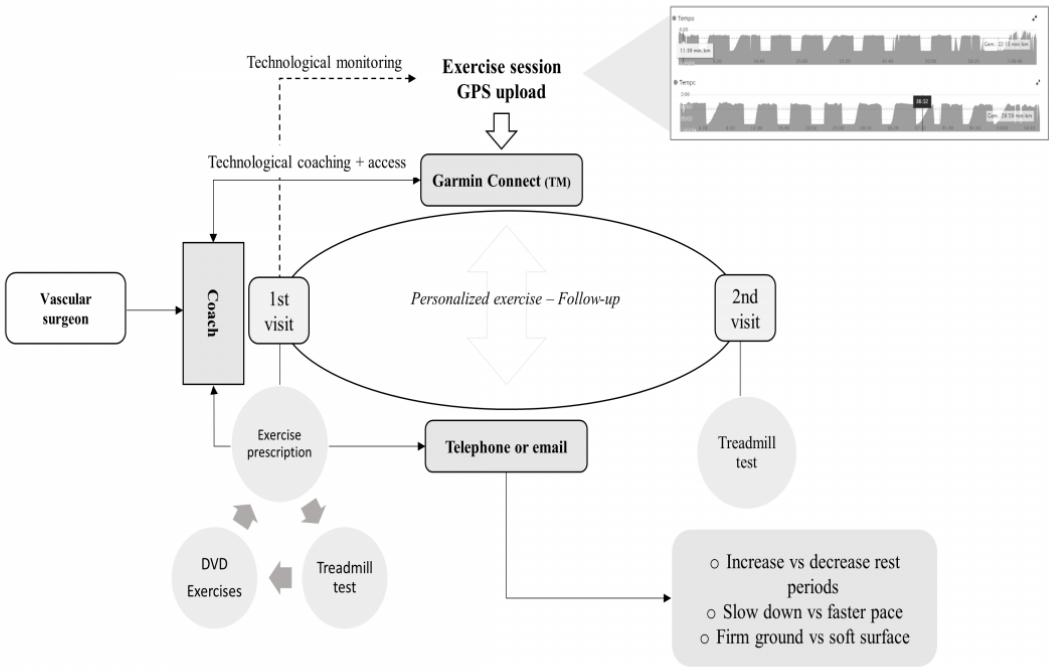

Figure 1. *Pilot 4-week exercise intervention flow: baseline testing was done to provide a personal exercise program. The exercise program was monitored through GPS-derived data, uploaded by the participant. Telecoaching was provided through telephone or email.*

Primary Outcome Measures: Patient Satisfaction and Acceptability

Patient satisfaction and acceptability of HBET were evaluated using a feedback survey adapted from Learmonth et al (32). Patients were asked to rate the HBET, offered materials, coaching, and exercise prescription on a 5-point Likert scale (i.e. very unsatisfied, unsatisfied, neutral, satisfied, and very satisfied). In addition, the participants were asked to provide written feedback on the received intervention and to provide suggestions for improvement. Furthermore, all communication logs (telephone calls and emails) were registered and adherence to exercise was assessed using walking uploads and self-reported

walking or resistance logs provided by the participant. Adherence was defined as the ratio of the number of exercise sessions to the number of prescribed exercise sessions.

Secondary Outcomes

Walking Capacity

Participants performed a progressive treadmill test using the Gardner protocol (33). The walking speed was set at 3.2 km/h and adjusted (±1 km/h) if needed. Every 2 minutes, we increased the inclination by 2% to a maximum of 10%. Participants were asked to report the onset and maximally tolerated claudication pain. Patients without IC symptoms who limited their walking capacity on the treadmill were excluded from this analysis. In addition, we used the Walking Impairment Questionnaire (WIQ) (34) to evaluate the walking distance, walking speed, and stair climbing capacity, with lower scores indicating greater impairment.

Quality of Life, Exercise Self-Efficacy, and Kinesiophobia

Patients were asked to fill in VascuQoL, a disease-specific questionnaire to assess quality of life. VascuQoL contains 25 seven-point Likert statements to measure the activity, symptom burden, pain, emotions, and social consequences related to LEAD (35). Total scores and subscores for the VascuQoL questionnaire ranged from 1 to 7, with higher scores indicating a better quality of life. In addition, the Exercise Self-Efficacy Scale (ESES) was used to evaluate participants' confidence in overcoming personal and environmental barriers to be physically active (36). The ESES has a total score of 40 (highest level of exercise self-efficacy), combining 10 statements scored with a 4-point ordinal outcome. Finally, kinesiophobia, or movement-related fear of pain, was evaluated using the Tampa Scale of Kinesiophobia (TSK) (37), which assists in identifying participants avoiding physical activity because of unjustified pain beliefs. The TSK is scored on a 17-item questionnaire, with higher scores (4-point Likert scale) indicating elevated levels of kinesiophobia. A cut-off score of ≥37 was used to diagnose kinesiophobia (37).

Physical Fitness

Physical performance was assessed using the Short Physical Performance Battery (SPPB) and the Timed-Up-and-Go (TUG) test, with patients wearing their shoes. The SPPB evaluates the standing balance, 4-m gait speed, and lower extremity strength (38). Each category of SPPB is scored from 0 to 4, resulting in a maximum score of 12 points, with higher scores indicating better performance. The TUG test is a functional test that evaluates functional chair stand and walking flexibility (39). Participants were instructed to stand up from a chair, walk fluently around a 3-m separated cone, and sit down again. We used the fastest time for the 2 attempts in the analysis.

Physical Activity

Participants were instructed to wear a Sensewear (R) Mini device (Bodymedia) on the right upper arm for 7 days to measure the daily physical activity levels. An assessment was considered valid if the patient had worn it for at least 3 weeks and 2 weekend days with 90% daily (24-hour measurement) wear time (40). Physical activity intensity was categorized as light (1.5-2.9 metabolic equivalents (METs)), moderate (3.0-5.9 METs), and (very) vigorous (≥6 METs). Sedentary behavior included all activities below a threshold of 1.5 METs. In addition, steps were registered to assess walking activities in daily life.

Statistics

All data were presented as median and IQR or mean and SD. Normality of data was evaluated using the Shapiro-Wilk test. Statistical analyses were performed using JASP 0.11.1 (University of Amsterdam), with pre-post parametric (paired two-tailed t test) and nonparametric equivalent (Wilcoxon signed-rank) tests. An alpha level of 5% (two-sided) was used for statistical significance. No power calculations were performed on the study outcomes.

Results

Participants and Data Collection

Out of 41 eligible patients, 21 (50% recruitment success) volunteered to participate (15 men and 6 women). A total of 3 patients were referred for additional cardiologic screening after baseline measurements because of presumed cardiac ischemia, complaints, or arrhythmias. Consequently, for 1 participant (P1), the intervention start was postponed, resulting in a 75-day interval period between measurements. One patient was excluded after recruitment. Our participants' average age was 64.6 years (SD 10.6; range 41-81 years) and heterogeneous with regard to comorbidities, walking capacity, claudication location, duration of symptoms, and severity of disease (ABI; mean 0.65, SD 0.20; Rutherford classification (3 in 50%)). Moreover, all participants had dyslipidemia, 70% were hypertensive, 25% had diabetes, and 85% were ex-smokers or were still smoking. Individual demographic characteristics are detailed in Supplementary file 2, and the study flow is presented in **Figure 2**. Baseline and follow-up measurements were completed within a median time period of 36 days (IQR 6), which corresponds to a median intervention time of 32 days (IQR 5).

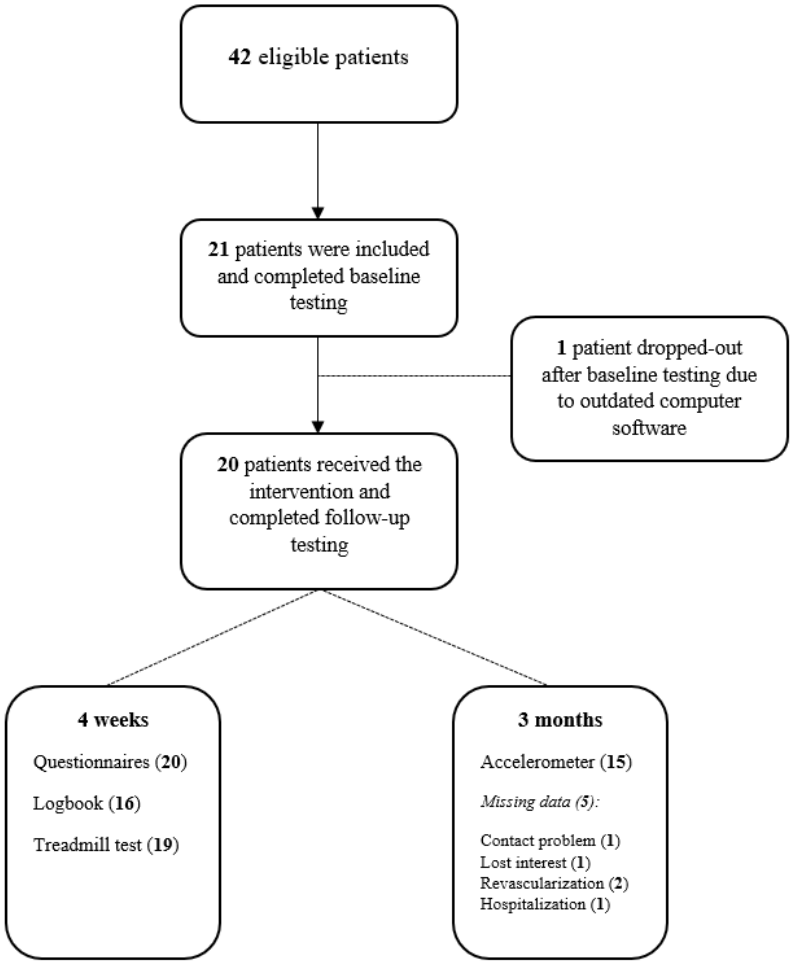

Figure 2. *Flowchart with study inclusion and final analysis.*

Primary Outcomes

All users were very satisfied (mean overall score 4.5, SD 0.5; median 4.5, range 4-5) with the HBET program. These results were reflected in high adherence to the prescribed walking sessions (GPS and logbook combined = mean 89%, SD 25; GPS only = mean 86%, SD 28), with 75% (15/20) of the patients completing all prescribed walking sessions. In contrast, patients were less compliant with resistance training (mean 85%, SD 22; 56% (9/16) completed all prescribed sessions and 20% (4/20) of patients did not return their logbook) and did not prefer this exercise alternative over conventional walking therapy (mean 2.65, SD 0.8; median 3, range: 1-5). Intervention satisfaction scores regarding materials, feedback, personalization, and content of the intervention are depicted in **Figure 3**. Furthermore, it is important to note that participants perceived the home-based program as safe (mean 4.4, SD 0.6; median 4, range 3-5). Most participants also stated that they would re-enroll in the exercise program (mean 4.4, SD 0.5; median 4, range 4-5) and would recommend it to their peers (mean 4.5, SD 0.5; median 4.5, range 4-5). Qualitative reporting revealed that participants were positive about the option to visualize progression using the recorded training logs (n = 2) or trigger to improve (n = 2), personal guidance (n = 2), and

flexibility (n = 2). However, resistance training (n = 7) and pain during sessions (n = 2) were perceived as less enjoyable.

In addition, we registered the number of telephone and/or email contacts. A median of 5 contacts during the 4-week intervention was provided for each patient: 3 follow-up contacts, 1 contact moment to provide technical assistance, and 1 contact combining the aforementioned. In addition, most contacts were provided through email (median 3) as compared with telephone calls (median 2).

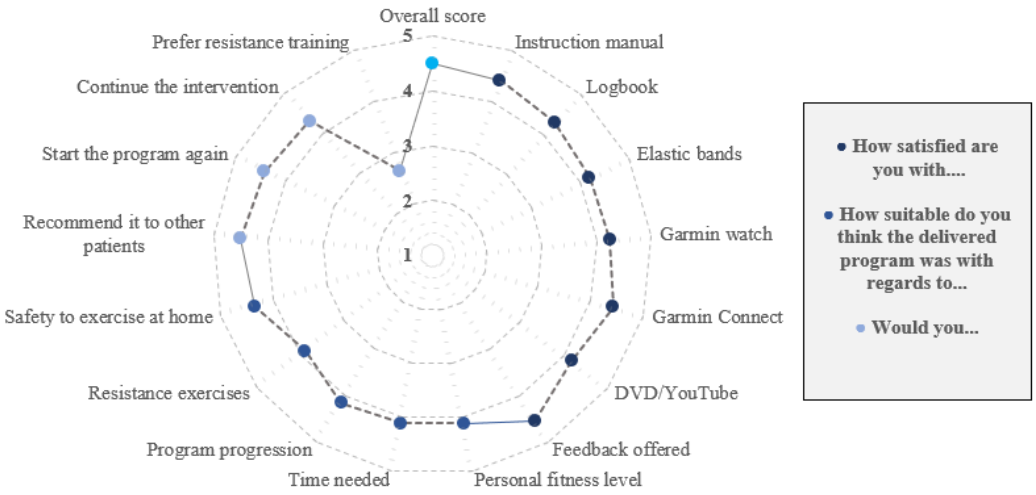

Figure 3. *Feasibility of the intervention as scored by a 5-point Likert scale (mean scores). Range of scores: 1 (very dissatisfied or unsuitable), 2 (dissatisfied or unsuitable), 3 (neutral), 4 (satisfied or suitable), and 5 (very satisfied or suitable). Missing values: instruction manual (1), logbook (3), Garmin Connect (1), DVD/YouTube-link (3), personal fitness level (2), time needed (1), program progression (1), resistance exercises (1), safety to exercise at home (1), starting the program again (1), and continuing the intervention (1).*

Secondary Outcomes

Walking Capacity

At baseline, MWD ranged between 141 and 828 m (median 414 m, IQR 253 m), with 2 patients being stopped by the investigator as claudication symptoms were not limiting the exercise test. In addition, 1 patient (P2) experienced claudication symptoms but stopped both tests because of gastric problems. Patients (n = 3) were excluded from MWD analysis. Participants improved their PFWD and MWD compared with baseline, with a mean progression of +89 (SD 95) and +58 m (SD 97), respectively ($P < .001$ and $P = .03$; Supplementary file 2). Similarly, the WIQ distance score (+0.18; $P = .01$) was significantly higher after the intervention. As no statistically significant change was established in WIQ speed (+0.03; $P = .53$) and WIQ stair climbing score (+0.02; $P = .55$), the overall WIQ score remained to be statistically unaltered (+0.08; $P = .06$; Supplementary file 2).

Quality of Life, Exercise Self-Efficacy, and Kinesiophobia

Quality of life was better after the intervention (+0.36 on total VascuQoL; P = .009). The main areas of improvement were pain (+0.41; P = .04), physical activity (+0.54; P < .001), and emotions (+0.33; P = .06). No changes were noted in the social (+0.08; P = .56) and symptom (+0.15; P = .30) subscores. Kinesiophobia was elevated at baseline, with a median score of 38 (IQR 8.50). Self-efficacy (ESES) and kinesiophobia did not change (P = .18 and P = .17, respectively; Supplementary file 2).

Physical Activity and Physical Fitness

At baseline, physical activity values for valid days were averaged for each participant, resulting in a median of 59 minutes of moderate to vigorous physical activity (IQR 63 minutes) per day. Moderate physical activity was the main contributor to daily physical activity in our sample, as 80% (16/20) of our sample did not reach 5 minutes of vigorous physical activity (median 2 minutes, IQR 4.3 minutes). In addition, our participants completed a median of 5297 (IQR 3118) steps per day. Follow-up data did not show any significant changes after 3 months. With regard to physical activity data acquisition, 95% (19/20) of participants fulfilled the targeted 90% daily Sensewear on-body time for at least 3 weeks and 2 weekend days at baseline. In contrast, 25% (5/20) of the patients did not complete the physical activity assessment after 3 months. Furthermore, the 4 follow-up measurements did not fulfill our strict validity criteria. Consequently, only 55% (11/20) of the participants had follow-up physical activity data. More information is provided in Supplementary file 2, with elaboration on the encountered methodological issues. Physical performance (SPPB total score) was not significantly different (P = .06) after the intervention (Supplementary file 2).

Discussion

Principal Findings

This study evaluated the satisfaction, acceptability, adherence, and potential effectiveness of a novel home-based exercise intervention that combines resistance training and walking therapy using wearables to monitor and guide patients with IC. Although our sample of 20 conservatively treated patients was heterogeneous in nature, participants generally perceived the exercise program with personalized feedback and monitoring as (very) positive. However, contrary to our hypothesis, elastic band exercises were not preferred over traditional walking sessions. Furthermore, we also found beneficial effects on quality of life (VascuQoL), subjective walking distance (WIQ), and objective walking distances (PFWD and MWD). Despite the short intervention duration, a clinically relevant improvement was found in the WIQ distance score (41). As this study was designed to

primarily evaluate patients' satisfaction and acceptance, our results complement contemporary pilot studies in the field of eHealth solutions in patients with IC (20,42-45).

We used commercially available wearables supported by GPS tracking to guide and monitor walking training. The exercise uploads showed additional value to evaluate adherence and guide personalized exercise prescription in our study. Researchers have already explored the advantages of GPS-derived walking information to evaluate community-based walking in patients with IC (46,47). They found an acceptable 0.81 correlation comparing free-living PFWD and results from a standardized treadmill test documenting its usefulness for the evaluation of walking distances (46). As such, wearables offer possibilities to assess physical activity levels and monitor (48), guide, and evaluate progress in future structured home-based exercise programs (46) (**Figure 1**). Recently, Dusha et al (44) reported on their 12-week pilot study in 10 patients in which they used commercial step counters with adapted coaching that resulted in improved walking capacity in patients with IC. Conversely, the largest trial to date—Home-Based Monitored Exercise for the PAD (HONOR) study (43)—did not provide feedback based on the uploaded exercise information. Patients only received monthly feedback for the last 4.5 months during the 9-month HONOR intervention, which might explain the unchanged walking frequency compared with usual care after 9 months. Our participants asked for and received weekly feedback. Therefore, incongruity between the use of activity trackers to increase the overall physical activity (e.g. daily steps) and specific exercise recommendations with appropriate, direct feedback might explain the lack of improvement (43). In summary, the appropriate use of technology seems mandatory to provide a symbiosis between the wearable (tool) and the intervention (goal), which is generally acceptable to patients with IC.

The novelty of this study was the incorporation of home-based resistance training. Although more than 80% stated that they were interested in using elastic bands as an alternative to walking therapy (25), patients now rated the addition of elastic band exercises as neutral or negative compared with walking. This was somewhat surprising, as pain is the most cited barrier to exercise (25), and resistance exercises were anticipated to result in less pain in terms of oxygen demand in the lower legs (28). However, similar results were noted in geriatric inpatients, where objective measures of elastic band use contrasted with positive attitudes of staff and patients regarding the benefits (49). Although no specific reasons were provided, we hypothesize that highly prevalent musculoskeletal comorbidities in patients with IC (e.g. lumbar spine disease in 75.7% (50)) and lack of direct supervision might have hampered the correct execution of the elastic band exercises. Quality of execution has been proposed as an important driver of improved adaptation after supervised resistance programs compared with non-supervised programs in older adults (51). Therefore, direct supervision appears to be essential when prescribing technically challenging exercises.

Moreover, it is interesting to note that 60% (12/20) of our sample experienced some degree of kinesiophobia (i.e. TSK ≥ 37) at baseline. Compared with the significant changes observed in terms of walking outcomes, no change occurred at the level of fear avoidance. This discrepancy might be evoked by the short intervention period or the lack of patient education to explain the pain and induce behavioral change. These findings once again emphasize the importance of addressing these beliefs when designing an exercise intervention, as they might interfere with exercise therapy perception and adoption (52,53). In addition, the importance of the patient-provider alliance using in-person visits may not be overlooked when designing telemonitored exercise programs (18,43). Therefore, the development of so-called hybrid interventions (44) might bridge this gap, which has been shown in an earlier successful trial using step monitors (54). Therefore, future studies should investigate the add-on effect of direct supervision in home-based interventions to 1) evaluate patient perception and methods to implement resistance exercises and 2) reduce activity-related fear using behavioral change or educational interventions.

Furthermore, this study also included a feasibility evaluation of the different assessments. Our findings were in line with earlier publications, that is, 2 recent studies also reported difficulties (55% and 50% baseline and follow-up data, respectively (43,45)) in collecting physical activity data using a triaxial pedometer or accelerometer on the hip. A possible explanation for these missing values might be the instruction to wear the monitor during waking hours compared with a more compliant 24-hour protocol (55). In addition, one has to consider the trade-off between the study power and validity of the collected physical activity data (55). However, missing follow-up data were mainly because of early revascularization or hospitalization (3 participants) and lack of valid combinations of at least three weekdays, Saturday, and Sunday (4 participants). Thus, missing follow-up data in our pilot study were considered to be the result of the selected analysis protocol (40) and patient hospitalization at follow-up.

Limitations

Further limitations include the generalizability of this pilot intervention, which was part of developing a larger trial and should be interpreted as such. Only one researcher provided feedback and evaluated all outcomes. With regard to monitoring and feedback, calls or emails were structured to discuss walking training, elastic band training, and progression toward the new week. Although we incorporated some behavioral change techniques through the addition of sports watch technology (e.g. self-monitoring), we did not assess and evaluate the underlying psychosocial constructs or the distinct effect of each behavioral change technique on effectiveness (31). However, our evaluation of satisfaction and acceptance of technology could drive future research to evaluate and design technology to support long-term behavioral changes in a home-based environment. We did not assess the

similarity between the uploaded exercise sessions and the actual walking prescription, which limits the interpretation of quantity and quality of exercise prescription (19). One barrier to this approach was the presence of uninterpretable GPS signals (e.g. because of a lack of satellite connections or an obstructed environment high buildings or trees) (46). Similarly, although technology was well accepted, patients often reported the need for technical assistance during setup and interpretation (56). In addition, it is well known that self-reported adherence rates from walking sessions and resistance training might result in overreporting (19). However, our pilot did show good adherence to the walking sessions in comparison with other physiotherapy-led home-based exercise programs (67%) (19). Moreover, our sample was generally fit in terms of activities of daily life measured by the SPPB and TUG total scores, which resulted in a ceiling effect (57). Although both SPPB and TUG possess prognostic (e.g. mortality (58)) information in patients with IC, high baseline scores impose an important risk for type II errors in clinical trials (57). Therefore, physical fitness levels can be overestimated, as can be seen from the comparison of our measured time data with normative values (57). As such, future studies are encouraged to report the measured time for both chair-stand and 4-m gait speed tests (57).

Conclusions

This observational pilot study has shown that patients with IC are satisfied and accept technology to monitor and guide a home-based combined exercise program through remote feedback. Participants did not prefer resistance training over walking exercise; however, a general positivity toward the combined intervention was reflected in clinically relevant improvements in subjectively reported walking distances and quality of life.

Appendices

Supplementary file 1

DVD or YouTube-link:
https://youtube.com/playlist?list=PLQ0UsklrRgdfXdTEcr6JaEs_ZNGPYO_Je

Supplementary file 2

Table S2.1. *Characteristics of the studied sample (n = 20) at baseline.*

Demographics			*Cardiovascular Risk*					*Symptoms*				*Walking distance and questionnaires*					
Participants	Gender	Age	BMI	DM	DYSL	HTN	SMO	RF	LOC	TIME	ABI	PFWD	MWD	VascuQOL	TSK	WIQ	ESES
P1	♀	64	21.2		●	●	●	3	LC	7.5	0.75	598	828	5.52	30	0.55	32
P2	♀	75	29.6		●	●		1	RC	2	0.70	126	-	5.96	31	0.62	34
P3	♀	58	27.8		●		●	3	LC	48	0.60	73	561	5.52	39	0.72	35
P4	♂	62	34.1	●	●	●	○	3	BH	30	0.35	123	306	3.96	41	0.32	30
P5	♂	69	21.7	●	●	●	○	1	LC	18	0.70	-*	-*	5.56	37	0.87	36
P6	♂	71	19.4		●	●	○	3	BC	120	0.45	158	300	4.64	47	0.59	38
P7	♂	50	29.3		●		○	3	BCH	15	0.45	138	227	4.52	38	0.78	33
P8	♂	66	36.2		●		○	3	BC	36	0.60	343	448	4.36	45	0.33	29
P9	♂	71	29	●	●	●	○	3	BC	228	0.80	95	141	5.32	43	0.40	38
P10	♂	79	26.8		●	●	○	3	BC	12	0.85	84	142	6.20	29	0.58	37
P11	♂	69	31.5		●	●	○	2	RC	22	-	284	414	5.36	34	0.64	40
P12	♂	67	30.5	●	●	●	○	2	LC	12	0.70	196	611	5.76	27	0.79	37
P13	♂	71	26.4		●	●	○	2	RC	6	0.55	334	559	5.32	35	0.70	32
P14	♂	77	30.6		●	●	○	2	BC	90	0.60	210	507	4.96	38	0.44	37
P15	♀	50	34.8	●	●	●	○	2	BC	11	0.70	226	322	3.32	41	0.68	32
P16	♂	56	29.7		●	●	○	1	BC	7.5	0.60	142	347	6.16	32	0.58	38
P17	♂	61	32.7		●	●	○	1	BC	12	0.85	562	600	5.44	38	0.58	40
P18	♀	41	27.2		●		●	3	BT	36	0.60	97	441	3.36	40	0.44	33
P19	♂	54	23.9		●			3	RFC	21	0.30	165	365	5.28	29	0.63	35
P20	♂	81	25.1		●			2	RC	6	1.15	183	-	6.28	39	0.83	39
Overall	15♂ 5♀	64.6	29.0	25%	100%	70%	15%	-	18C	37	0.65	218	418	5.14	36.7	0.60	35.3

Note. *Abbreviations: Cardiovascular risk factors; BMI = body mass index (kg/m²). DM = diabetes mellitus. DYS = dyslipidemia. HTN = hypertension. SMO = smoking (○ ex-smoker. ● current smoker (including e-cigarette)); RF= Rutherford- class. LOC = location of symptoms (L = left. R = right and B = bilateral; F = foot. C = calf. T= thigh and H = hip). TIME = duration of symptoms (in months). ABI = ankle-brachial index (Doppler data most affected limb); PFWD = pain-free walking distance (meter). MWD = maximal walking distance (meter). TSK = Tampa scale for kinesiophobia. WIQ = Walking impairment questionnaire and ESES = Exercise self-efficacy scale. Overall data are either counts (n. %) or mean values. P5*: did not experience any IC symptoms during baseline and follow-up treadmill testing although anamnesis reported complaints were typical of IC.*

Table S2.2. *Questionnaires.*				
	Baseline	*Follow-up*	*Difference*	*P-value*
VascuQOL	N = 20	N = 20		
Pain	4.76 (0.86)	5.18 (0.74)	+0.41 (0.84)	*0.040*
Symptoms	4.84 (1.17)	4.99 (1.18)	+0.15 (0.63)	0.301
Activities	5.10 (0.81)	5.64 (0.87)	+0.54 (0.59)	*<0.001*
Emotions	5.43 (IQR: 1.00)	6.14 (IQR: 1.29)	+0.36 (IQR: 0.86)	0.064
Social*	6.50 (IQR: 2.00)	7.00 (IQR: 2.50)	0.00 (IQR: 0.50)	0.556
Total	5.14 (0.87)	5.50 (0.91)	+0.36 (0.55)	*0.009*
WIQ	N = 20	N = 20		
Distance	0.45 (0.24)	0.63 (0.27)	+0.18 (0.29)	*0.013*
Speed	0.60 (0.21)	0.63 (0.21)	+0.03 (0.21)	0.528
Stairs	0.77 (IQR: 0.27)	0.80 (IQR: 0.32)	+0.03 (IQR: 0.14)	0.552
Total	0.60 (0.16)	0.68 (0.19)	+0.08 (0.17)	0.056
TSK	N = 20	N = 20		
Total*	38.0 (IQR: 8.50)	35.5 (IQR: 10.25)	-1.0 (IQR: 4.25)	0.169
ESES	N = 20	N = 20		
Total	35.50 (IQR: 5.25)	37.50 (IQR: 5.50)	+1.00 (IQR: 2.50)	0.178

Note. *Data mean (SD) or median (IQR)*. Non-parametric testing (Wilcoxon-Signed Rank) is performed when the difference scores are not normally distributed (*)*

Table S2.3*. Physical fitness & physical activity.*					
	Baseline		*Follow-up*	*Difference*	*P-value*
SPPB	N = 20		N = 20		
Balance*	4 (IQR: 1)		4 (IQR: 0)	0 (IQR: 1)	0.066
4-m gait speed *	4 (IQR: 0)		4 (IQR: 0)	0 (IQR: 0)	1.000
4-m gait speed (sec)	4.14 (0.54)		4.02 (0.61)	-0.11 (0.44)	0.263
chair stand* (n = 19)	3 (IQR: 1)		4 (IQR: 1)	0 (IQR: 1)	0.565
chair stand (sec) (n = 19)	11.33 (2.50)		10.93 (2.14)	-0.40 (1.55)	0.275
*Total** (n = 19)	11 (IQR: 2)		11 (IQR: 1)	0 (IQR: 1)	0.060
TUG	N = 20		N = 20		
TUG (t)	8.26 (1.32)		8.06 (1.35)	-0.20 (0.86)	0.305
Physical activity	N = 19	N = 11	N = 11	N = 11	
Light PA (min/day)	185 (IQR: 72)	185 (IQR: 89)	209 (IQR: 127)	5.0 (64)	0.800
Moderate PA (min/day)	59 (IQR: 59)	64 (IQR: 69)	67 (IQR: 48)	-13.8 (42)	0.299
Vigorous PA (min/day)*	2.0 (IQR: 4.3)	2.1 (IQR: 4.3)	1.3 (IQR: 15)	-0.0 (IQR: 2.8)	0.673
Steps (number/day)	5297 (IQR: 3118)	4507 (IQR: 3876)	4537 (IQR: 1736)	-443 (1452)	0.335
Sedentary time (min/day)	1181 (IQR: 130)	1181 (IQR: 164)	1147 (IQR: 128)	-0.9 (92)	0.975

Note*. Data mean (SD) or median (IQR) based on distribution. Non-parametric testing (Wilcoxon-Signed Rank) is performed when the difference scores are not normally distributed or data is ordinal scaled (*).*

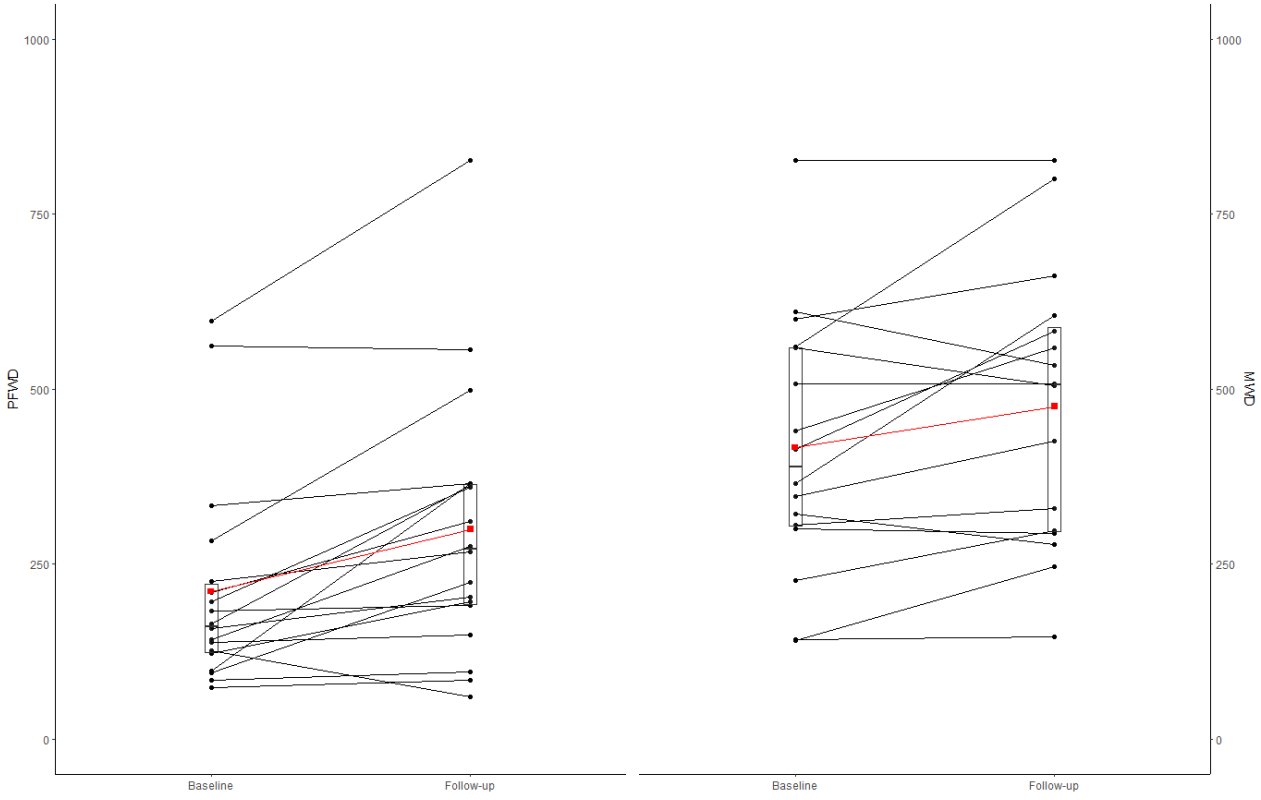

Figure S2.4. *Pain-free (n = 18; left side) and maximal walking distances (n = 16; right side) displayed as connected scatters at baseline and follow-up. Boxplots are overlapping and mean scores are indicated red.*

Table S2.5. *Sensewear: Physical Activity.*		
Sensewear PA	*95% criterion*	*90% criterion*
Baseline		
Weekdays (>= 3 days)	18 (90%)	19 (95%)
Weekend (>= 2 days)	15 (75%)	19 (95%)
Total	15 (75%)	19 (95%)
Follow-up		
Weekdays (>= 3 days)	14 (70%)	14 (70%)
Weekend (>= 2 days)	9 (45%)	12 (60%)
Total	8 (40%)	11 (55%)

Note. *Analysis of PA data using different wear-time (95% and 90%) cut-offs.*

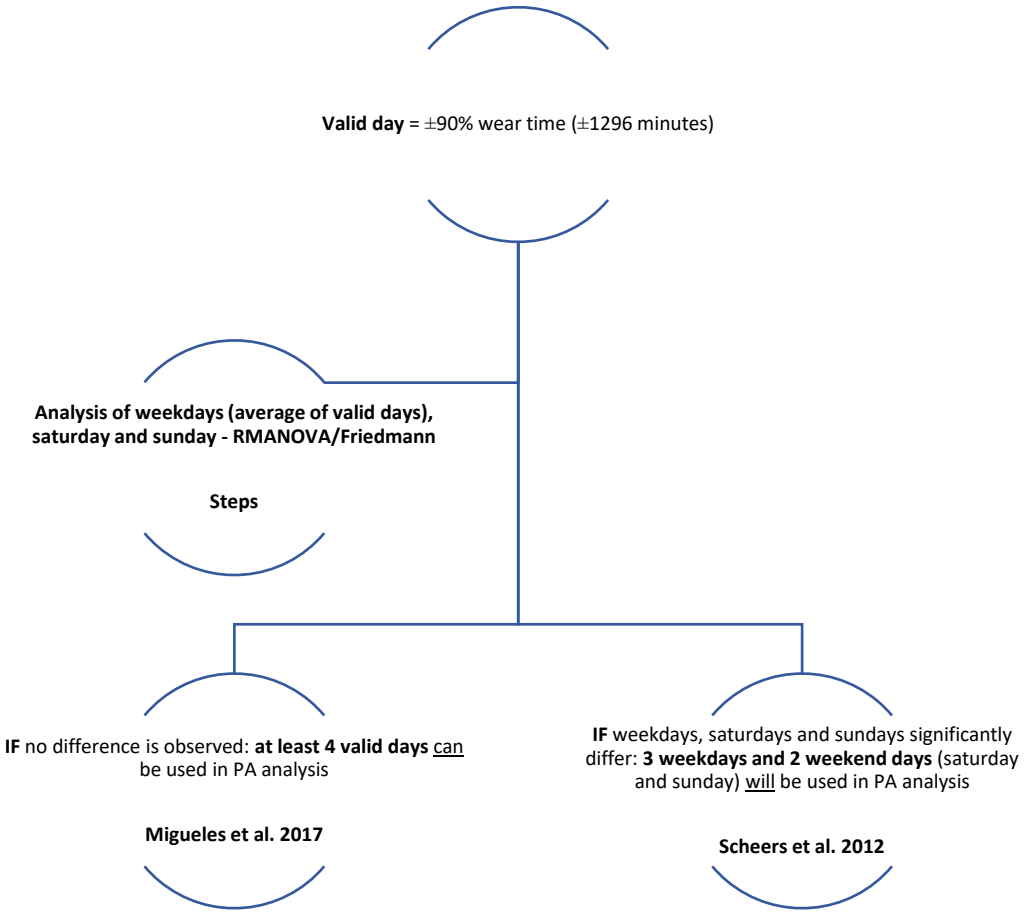

Figure S2.6. Physical activity data analysis.

Plantar flexion 	**Hip flexion** 
Hip extension 	**Hip abduction** 

Figure S2.7. *Resistance exercises.*

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Chapter 2.3: Acceptability, adherence and efficacy of a hybrid walking program in patients with intermittent claudication: an evaluation of the PROSECO-IC intervention

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To be submitted

Abstract

Background: Supervised exercise therapy is recommended as a first line therapy in patients with lower extremity artery disease (LEAD) suffering of intermittent claudication (IC). However, supervised, center-based programs are often unavailable for patients. To provide patients with LEAD with an effective alternative, structured home-based exercise programs can offer a solution. Moreover, modern technology such as wearables can be used to monitor exercise sessions and facilitate progressive exercise prescription in a home-based environment.

Methodology: A prospective cohort study was conducted to evaluate the 12-week PROSECO-IC intervention in patients with LEAD (Ankle-Brachial Index (ABI) ≤ 0.9 or 20% decrease in ABI after a maximal treadmill test) suffering from IC (Rutherford I-III). A hybrid intervention was developed, combining two home-based exercise sessions, guided by a wearable, and one in-person, center-based visit each week. To evaluate acceptability and adherence, a 5-point Likert scale questionnaire was used to evaluate materials, coaching and overall content. In addition, an objective evaluation of exercise adherence was performed using recorded logs from the wearable. Ambulatory capacity, defined as pain-free (PFWD) and maximal walking distance (MWD) was evaluated using a progressive treadmill test, six-minute walk test (6MWT) and patient-reported using the Walking Impairment Questionnaire (WIQ). Disease-specific quality of life was assessed using the VascuQOL questionnaire, in addition to an evaluation of overall cardiovascular risk profile including physical activity (PA) levels, cardiorespiratory fitness (CRF) and traditional cardiovascular risk factors.

Results: Forty-one out of 52 participants (30 men, 69.4 years old (range 43-84 years old)) completed the intervention. Overall, adherence to the intervention was high (85%) with general positivity regarding the intervention, materials and offered feedback. Ambulatory capacity was significantly improved after the intervention, objectively during progressive treadmill exercise (+161 ± 176 m MWD, +124 ± 137 m PFWD, both $p < 0.001$) and 6MWT (+18 ± 28 m, $p < 0.001$), subjectively on the WIQ. In line, total disease-specific quality of life was significantly improved (4.4 ± 0.8 to 4.9 ± 1.0, $p < 0.001$) with significant amelioration of the symptoms, activities and social subdomain. With regards to PA levels, no changes were observed in weekly steps, yet, participants significantly increased their daily time being moderate-to-vigorously active (+14.6 ± 39.6 minutes, $p = 0.029$). Both CRF and traditional cardiovascular risk factor were statistically unaltered.

Conclusion: A hybrid intervention combining home-based exercise sessions using a wearable and center visits was found to be acceptable, with high adherence and satisfaction, and effective to improve ambulatory outcomes and quality of life in a single cohort of patients with LEAD and IC.

Introduction

Exercise therapy is a cornerstone of conservative treatment in patients with lower extremity artery disease (LEAD) and intermittent claudication (IC) (1). Nowadays, the implementation of supervised exercise therapy (SET) is recommended (IA-recommendation) as a means to improve patients' ambulatory capacity, leg symptoms and quality of life (1,2). Additionally, breaching the vicious cycle of inactivity in which many of these patients end up, is of major importance to avoid further deterioration of functional, social and cardiovascular health in patients already at high risk for future cardiovascular morbidity (1). Still, a substantial difference exists between the acknowledgement of clinical benefit by clinicians, research findings and the routine implementation of exercise therapy (3). This treatment gap is mainly caused by several barriers both on the patient as well as the care provider level, resulting in only one third of vascular surgeons having access and approximately one third of patients actually participating in SET (3–5). And even then, when supervised programs (e.g. cardiac rehabilitation) are available, referral rates are low and programs remain underused (4,6,7). A possible reason for this lowered referral is that patient engagement and adherence to existing exercise programs was reported to be disappointingly low (3). Although some of the barriers to uptake and adherence of exercise therapy are shared among multiple patient populations (e.g. transport, time constraints), the pain-related concerns of a patient with IC typically withhold patients to participate. Walking is still the most specific exercise mode to improve ambulatory capacity in patients with LEAD suffering from IC. However, simple Go-Home-And-Walk advice, is generally not helpful. From this perspective, research has increasingly focused on the delivery of effective exercise programs in the home environment.

Home-based exercise therapy (HBET) seems to be an appealing alternative to supervised exercise programs. However, scientific evidence to support unsupervised HBET is poor (8–10). Two reasons might explain the lower effectiveness of HBET: 1) early HBET trials were generally unsupervised and 2) ambulatory capacity was most of the time evaluated by treadmill tests, with direct bias related to the specificity of training in SET compared to HBET. Therefore a six-minute walk test (6MWT) is considered more responsive to HBET and is a better reflection of walking in daily life (11). Moreover, in recent years HBET is evolving, with an enhanced focus on structured HBET. Structured HBET incorporates different components of SET to optimize efficacy: an individualized exercise regimen with coaching and monitoring from healthcare providers, patient counseling and the addition of behavioral change techniques to sustain walking and physical activity (PA) (2). In this perspective, the availability of a coach, monitoring and timely visits seem primordial for the effectiveness of structured HBET (11). This has been confirmed by a recent meta-analysis were structured HBET including monitoring was equally effective to SET (12).

Current technology might bridge the gap between feasible HBET and effective SET, providing monitoring in a home-based environment to improve accessibility and adherence. For example, new wearables show potential to serve as useful tools in providing direct feedback and allow monitoring to personalize an exercise regimen (13,14). In addition, caregivers (physiotherapists (89%) and vascular surgeons (67%)) as well as patients support the idea to include telemonitoring and telecoaching in HBET (4,15–17). However, one cannot overlook the value of the caregiver-patient relationship (18). With regards to feedback mode, HBET programs including in-person visits were found to be successful (11). Therefore, hybrid exercise programs seem to be the intersect of HBET and SET, where wearables are interesting supportive tools. Indeed, GPS walks or PA data can provide direct self-monitoring, can be used to offer specific feedback and allow to define future goals more specifically (19). The combination with timely visits to directly supervise exercise and address barriers, or to provide education on symptoms or technology use, seems appealing to improve both adherence, cost-effectiveness and clinical benefits.

In this prospective study we evaluated a hybrid walking program, combining in-person and home-based exercise training sessions during 12 weeks, in patients with LEAD suffering from IC. Our aim was to report on efficacy in terms of ambulatory capacity, quality of life and cardiovascular risk factors. In addition, we further studied patient experience and program and wearable adherence.

Methods

Design and study protocol

We conducted a prospective study with a 12-week hybrid intervention, including one in-hospital supervised exercise session and at least two home-based exercise sessions per week. Home-based sessions were recorded using a GPS wearable (Forerunner 30, Garmin). Hence, all sessions were monitored and personalized feedback was provided during in-patient visits. This intervention was part of a more comprehensive research project (PROSECO-IC: Determinants of **PRO**gression after **S**upervised **E**xer**C**ise training through techn**O**logy in patients with Intermittent Claudication) where the initial goal was to study heterogeneity of training response and underlying determinants of change. All participants provided written informed consent before participation. The study was approved by the local Ethical Committee of University Hospitals Leuven (s62125) and was registered on clinicaltrials.gov: NCT03995589.

Participants

Patients were contacted after a consultation and referred by a vascular surgeon at the vascular center of the University Hospitals of Leuven. Patients (≥18 years) were included

when they: 1) presented with new complaints of IC (Rutherford I-III), 2) had an ABI ≤ 0.9 and/or 20% decrease in ABI after a maximal treadmill test, 3) had a conservative treatment plan for three months, and 4) were able to read and understand Dutch questionnaires. Patients were excluded when: 1) patients presented with signs of complex arrhythmias or significant ischemia during a screening cardiopulmonary exercise test, or 2) had a mental or physical comorbidity which limited participation in an exercise program.

Intervention

The PROSECO-IC intervention was designed following current exercise recommendations for LEAD patients with IC (11). All participants were asked to perform three walking sessions per week, of which one was center-based, performed on a treadmill and directly supervised by a member of the research team and two were performed in the home environment. The 12-week program was designed as a 6-week endurance build-up, followed by 6 weeks with increasing (IC pain) intensity. All sessions were interval based (e.g. alternating walking and rest). During the first 6 weeks, the total duration of exercise session was progressively increased from 28 to 48 minutes, by increasing the duration of the walking bouts (e.g. 4 to 6 minutes) and alternating the number of intervals (7 to 8 bouts). Here, intensity of IC complaints was monitored and was aimed to be moderate at the end of each interval (2/4 on the claudication pain scale (CPS)). Active bouts were interspersed with passive rest periods of 2 minutes during the first week, with shorter (or longer) periods of rest or active recovery introduced on a personal basis aiming to achieve complete symptom resolution during recovery. During the last 6 weeks, duration was generally fixed at 50 minutes, yet intensity was gradually increased by adding short intervals (e.g. 2 to 3 minutes) at a higher pain intensity of 3/4 on the CPS. As such, exercise prescription in week 12 typically consisted of endurance-based intervals (5 blocks of 6 minutes at 2/4 CPS) interspersed by intense short intervals with moderate-severe IC (8 blocks of 2-3 minutes at 3/4 CPS). An overview of the walking intervention is depicted in **Figure 1**.

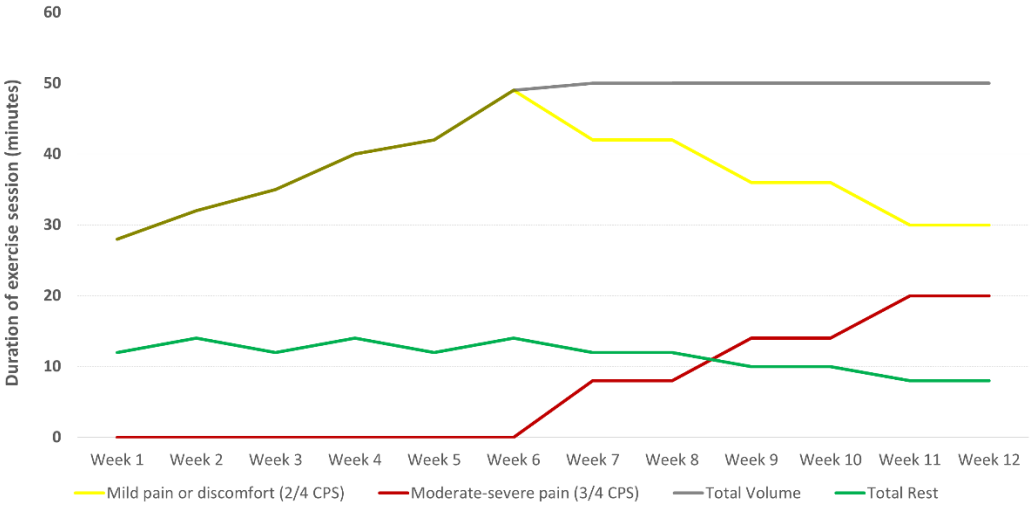

Figure 1. *Summary of the PROSECO-IC intervention training characteristics. CPS = Claudication Pain Scale.*

Center-based supervised sessions

Center-based sessions were performed one-on-one to maintain in person contact, to provide personalized feedback, and to discuss adjustments and safe progression of the program. Supervised sessions included a short (5-10 minutes) warm-up of the major muscle groups, and ended with a cool-down during which all lower limb muscle groups were statically stretched for 15 seconds and 3 repetitions.

Home-based sessions

Participants were asked to log all home-based exercise sessions using their Forerunner 30 wearable (Garmin) which were reviewed and discussed during the weekly in-patient visit. Uploading of data was done using anonymized profiles with unique coding on the online Garmin Connect (Garmin, connect.garmin.com) platform, either at home or during SET. As such, participants could self-monitor their progression and set goals, but also received direct feedback from a member of the research team during in-hospital visits (19). This feedback was based on the development of supervised exercise sessions and online logs, and consisted of advice to adjust pace or resting periods and to change terrain or walking surface to reach appropriate intensity. To provide detailed feedback, beyond evaluating adherence, participants were instructed to use the GPS function to track their activities. In addition, participants were allowed to increase their exercise frequency above the prescribed 3 times per week and log these extra sessions as well.

Outcomes

At enrollment, participants' medical history was summarized using the hospital records of the vascular center and concomitant blood sampling was done in order to evaluate the cardiovascular risk profile (lipid profile: high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG) and total cholesterol (TC)). The latter was repeated at the follow-up consultation 12 weeks later. After inclusion, participants were invited at our exercise lab (KU Leuven, Leuven) before and after the 12-week intervention. Patients were asked to fast and to avoid smoking, alcohol, caffeine and vigorous exercise at least 12-hours before lab testing. Weight (electronic scale), waist circumference at the level of the umbilicus and body fat estimated using bio-impedance (Omron BF306, Omron) were measured. Resting office blood pressure (Omron M3, Omron) was evaluated according to current standards (20) and fasting blood glucose was measured. Hereafter, participants could eat and drink and prepare for a cardiopulmonary exercise test (CPET). In terms of patient reported outcome measures, participants completed the Walking Impairment Questionnaire (WIQ), the Vascular Quality of Life Questionnaire (VascuQOL) and the RAND-36 Questionnaire (SF-36) in Dutch. Feasibility was assessed using adherence, acceptability and satisfaction.

Ambulatory capacity

Ambulatory capacity was evaluated objectively by means of a progressive treadmill test and six-minute walk test (6MWT). First, pain free (PFWD) and maximal walking distance (MWD) were established during the progressive treadmill test, applying the Gardner-Skinner protocol (21). In short, speed was set at 3.2 $km.h^{-1}$ starting from a level surface. Every 2-minutes, inclination was increased with 2% until the patients was maximally limited by IC or other symptom. Maximal inclination was reached at 14%, at which the test continued to reach a maximal duration of 20 minutes. Electrocardiogram and blood pressure were monitored continuously during the test and walking speed was adjusted at the start (± 1 $km.h^{-1}$) when needed. For the 6MWT, participants walked up and down along a 30-meter hospital corridor (22). They were instructed to cover as much distance as possible in six minutes (six-minute walking distance (6MWD)) and report the onset of IC symptoms (pain free walking time (PFWT)). All patients received similar standardized instructions allowing them to adapt their walking speed or take a short break if needed. The total distance covered after 6 minutes was recorded. Minimal clinically important difference (ES = 0.50) for PFWD and MWD is 81 and 95 seconds (72 and 84 meters with a constant speed of 3.2 $km.h^{-1}$) by distribution-based approach in HBET (23). For 6MWD, improvement of 8 to 20 meters has been deemed meaningful in LEAD (24).

WIQ

Subjectively, ambulatory capacity was evaluated using the WIQ, a validated LEAD-specific questionnaire (25). WIQ scores assess the degree of impairment due to IC on walking distance (7 items), walking speed (4 items) and stair climbing (3 items) (25). All items are scored using a 5-point ordinal scale and are multiplied by a constant according to overall weight of the item. Three subscores and a total score are derived and present a percentage of impairment (0% complete impairment, 100% no impairment). Minimal clinically important difference (ES = 0.50) for distance, speed and stair climbing is 14%, 12% and 13% by distribution-based approach in HBET (23).

Quality of life

VascuQOL

Disease-specific quality of life was evaluated using the VascuQOL (26). This 25-item questionnaire evaluates the impact of vascular disease on activity-levels (8 items), symptomatic burden (4 items), pain (4 items), emotions (7 items) and social consequences (2 items). All items are scored using a 7-point ordinal scale and are reported as mean scores for each subcategory and the total questionnaire (1 complete impairment, 7 no impairment).

SF-36

In addition, a more generic quality of life questionnaire (SF-36) was used as well. Here, different components are addressed: physical functioning (10 items), limitation due to physical health (4 items) or emotional problems (3 items), energy and fatigue (4 items), emotional well-being (5 items), social functioning (2 items), pain (2 items), general health (5 items) and perceived change in general health (1 item). All items are scored on a nominal or ordinal scale and transformed to percentage of impairment (0% complete impairment, 100% no impairment) (27). Minimal clinically important difference (ES = 0.50) for physical functioning is 8% by distribution-based approach in HBET (23).

Adherence, acceptability and remote monitoring

Adherence SET and HBET

Adherence was analyzed using wearable derived logs and compared with the expected exercise program for each participant (*performed sessions/expected sessions*100*), also including participants not completing the trial. To anticipate recording problems and avoid overestimation of activities, log processing was done as follows: 1) all activities shorter than 10 minutes, and 2) all activities exceeding 180 minutes (without clear activity recorded)

were excluded from analysis; 3) activities on the same day were labelled as a single activity, 4) a breakdown in home-based exercise and extra activities was performed to quantify sessions outside the program, with separate analysis for walking. Here, all participants were informed to only record activities such as planned walking, cycling or swimming exceeding 10 minutes of activity. In addition, all exercise logs were converted to active time in seconds.

Acceptability

Acceptability was evaluated using a questionnaire previously used in a pilot study (16). This survey was based on work from Learmonth and colleagues (28) and evaluated different components of the intervention using a 5-point ordinal scale range from 1 (not acceptable, very unsatisfied) to 5 (completely acceptable, very satisfied).

Physical activity and cardiorespiratory fitness

Physical activity

Before and after the intervention, participants were asked to wear a multisensory armband (SenseWear Mini device, Bodymedia) on the back of the upper right arm continuously for 7-days. The device could only be removed for taking a shower, bath or during swimming. The device had to be worn at least 90% of the time during at least 3 week- and 2 weekend-days to be considered valid. Data analyzed from the device using SenseWear Professional 8.1 software (Bodymedia) included daily active energy expenditure (kJ), number of daily steps and moderate-vigorous PA (MVPA) (≥3 METs) time in minutes.

Cardiorespiratory fitness

Peak oxygen uptake (Peak VO_2) was evaluated by means of a CPET on a cycle ergometer applying a 10W +10W/minute or 20W + 20W/min protocol. Breath-by-breath analysis of respiratory gases and ventilation (Oxycon Pro Jaeger, CareFusion) were registered continuously as well as electrocardiogram monitoring. Blood pressure recordings were performed every two minutes (Suntech Tango+, SunTech Medical). Respiratory data was analyzed using 30-second averages. To correct for the submaximal character of CPET due to IC symptoms, the oxygen uptake efficiency slope (OUES) was calculated to provide a submaximal index of cardiorespiratory fitness (29). In short, OUES is the loglinear slope (a) in the equation: VO_2 = a log10 VE + intercept (29).

Statistics

All data was described as either mean and standard deviation or median and interquartile range based on the underlying distribution. Normality was evaluated using the Shapiro-Wilk test. Paired comparisons were performed using a two-tailed paired t test or Wilcoxon signed rank test. Similarly, correlation statistics were either Spearman's rho (r_s) or Pearson's r (r_p)

after consideration of bivariate normality. All analyses were performed using JASP (Version 0.14.1, University of Amsterdam). Statistical significance was set at $P < 0.05$.

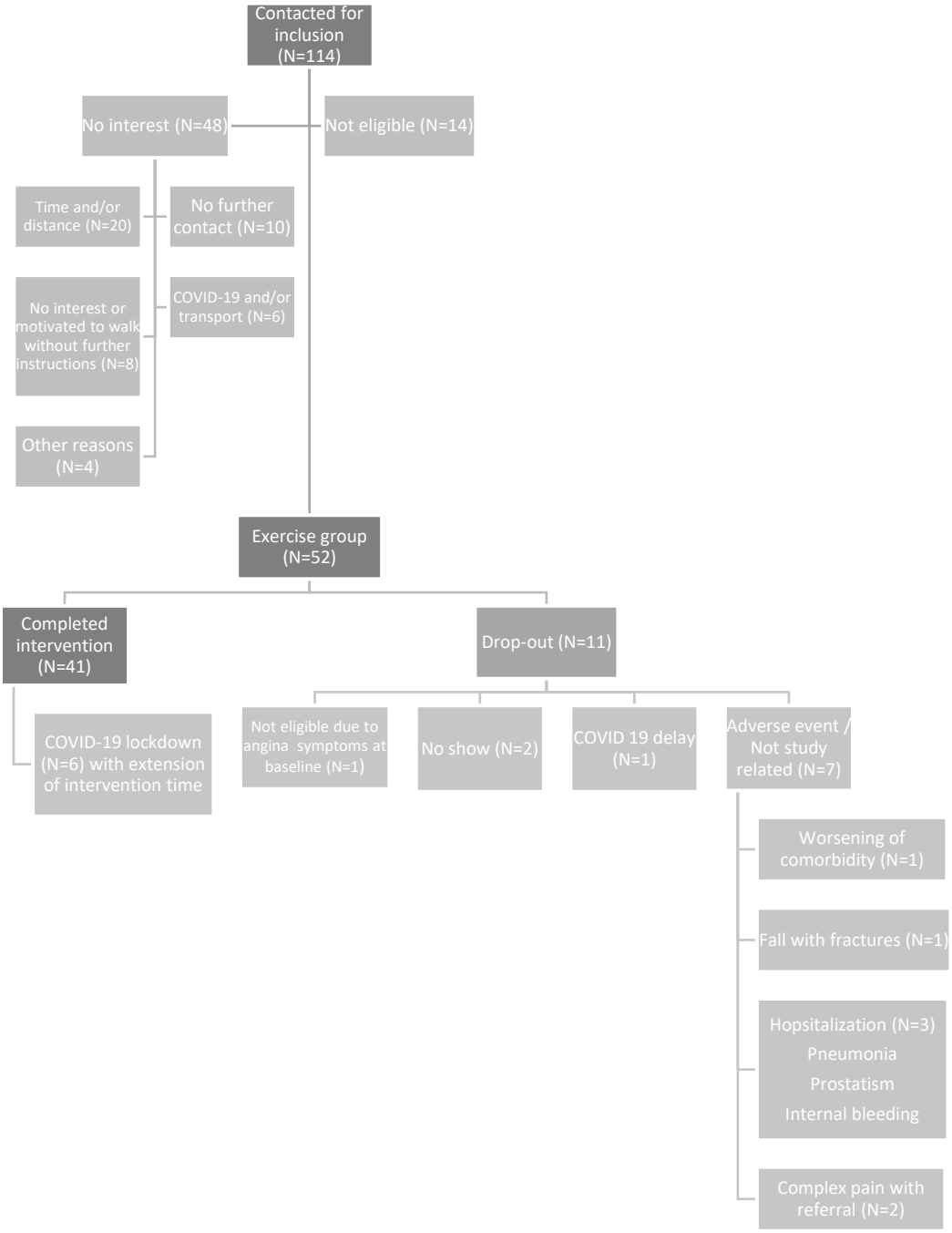

***Figure 2**. Flow chart on PROSECO-IC inclusion and completion. Patients without interest were predominantly male (38/48, 79%) and aged 69.0 ± 9.2 years (**4 missing values**).*

Results

Participants

A total of 114 eligible patients were contacted between 25th of February 2019 and 20th of January 2021 by a member of the research team. Study flow is presented in **Figure 2**. Forty-two percent (48/114) declined participation at the moment of recruitment, with more than half (54%, 26/48) declining due to transport, time-management issues or anxiety in the COVID-19 pandemic. Patients declining to participate did not differ from participants with regard to age (P = 0.892) or sex (P = 0.476). In total, 52 patients agreed to participate, with baseline characteristics presented in **Table 1**. Participants were on average 69.4 years old (range 43-84 years) and predominantly male (73%). Half of the cohort (26/52) presented with bilateral complaints and claudication pain was typically reported to be in the calf-region (46/52, 88%). Eleven patients dropped out, with underlying comorbidities (e.g. hospitalization due to pneumonia, internal bleeding or prostatism) interfering with continuation of the program being the main cause of drop out (8 out of 11 (73%) patients). In drop-outs, diabetes mellitus was more prevalent (12% vs 64%, P < 0.001). Forty-one participants completed the intervention. Six patients exceeded the planned 12-week duration due to COVID-19 lockdown regulations. As a result, intervention was continued in the home environment until follow-up measurements that have been postponed for an average of 54 days (range 28 to 81 days) in these 6 participants.

Ambulatory outcomes

At 12 weeks of follow-up, both subjective and objective ambulatory outcomes were significantly higher. As shown in **Figure 3**, an improvement in PFWD (174 ± 93 to 297 ± 93 meter, P < 0.001) and MWD (409 ± 215 to 569 ± 271 meter, P < 0.001) was observed after 12 weeks. In accordance, PFWT and 6MWD were higher (132 ± 54 to 157 ± 63 seconds, P = 0.044 and 403 ± 88 to 420 ± 96 meter, P < 0.001) after the intervention. These improvements in objectively measured walking capacity were also confirmed in subjective reporting on WIQ: increased distance (+21%), walking pace (+13%), staircase ascending (+8%). As such, a total improvement of 14% (Range -34 and 58%) on the WIQ was reported (P < 0.001) (**Table 2**).

Quality of life

Disease-specific scores (VascuQOL) indicate significant improvement in symptoms and activity domains associated with LEAD (**Table 2**). In combination with improved social functioning (P = 0.012), total VascuQOL scores improved from 4.4 ± 0.8 to 4.9 ± 1.0 (P < 0.001). In line, participants improved significantly on SF-36 physical functioning with an average 11% (49 ± 17 to 60 ± 20, p < 0.001). Emotional well-being, social functioning and

general health significantly improved on the SF-36. All components are reported in Supplementary file 1.

Table 1. *Baseline characteristics.*

	Baseline (N=52)	Completed (N=41)	Drop-outs (N=11)	P-Value
Age (years)	69.4 ± 8.8	70.3 ± 9.2	66.0 ± 6.7	0.157
Height (cm)	167.9 ± 7.8	167.9 ± 8.1	167.9 ± 7.0	0.992
Weight (kg)	75.3 ± 14.3	74.9 ± 14.0	77.0 ± 16.1	0.683
BMI ($kg.m^{-2}$)	26.6 ± 4.4	26.5 ± 4.2	27.3 ± 5.5	0.618
Gender				
Male	38 (73%)	32 (78%)	6 (55%)	0.119
Female	14 (27%)	9 (22%)	5 (45%)	
Disease-specific				
Ankle-Brachial Index	0.65 ± 0.25	0.66 ± 0.26	0.60 ± 0.21	0.467
IC symptoms				
Bilateral symptoms	26 (50%)	22 (54%)	4 (36%)	0.471*
Foot	3 (6%)	2 (5%)	1 (9%)	0.595
Calf	46 (88%)	37 (90%)	9 (82%)	0.437
Thigh	9 (17%)	5 (12%)	4 (36%)	0.060
Hip	11 (21%)	7 (17%)	4 (36%)	0.164
Cardiovascular risk factor				
Obesity	10 (19%)	8 (20%)	2 (18%)	0.921
Dyslipidemia	46 (88%)	35 (85%)	11 (100%)	0.177
Hypertension	46 (88%)	36 (88%)	10 (91%)	0.775
Diabetes Mellitus	12 (23%)	5 (12%)	7 (64%)	**<0.001**
Smoker				
Active smoker	15 (29%)	12 (29%)	3 (27%)	0.737
Past smoker	35 (67%)	27 (66%)	8 (73%)	
Never smoked	2 (4%)	2 (5%)	0 (0%)	
Comorbidities				
Cardiovascular	40 (77%)	30 (73%)	10 (91%)	0.215
CABG / PCI	22 (42%)	16 (39%)	6 (55%)	0.355
Arrhythmias	10 (19%)	9 (22%)	1 (9%)	0.337
COPD	7 (13%)	4 (10%)	3 (27%)	0.131
Low-back pain	21 (40%)	17 (41%)	4 (36%)	0.760
LEAD intervention				
By-pass	7 (13%)	6 (15%)	1 (9%)	0.632
PTA/Stent	22 (42%)	17 (41%)	5 (45%)	0.812
Atherectomy	7 (13%)	5 (12%)	4 (10%)	0.605
Medication				
B-blocker	31 (60%)	24 (59%)	7 (64%)	0.760
Anti-platelet	39 (75%)	30 (73%)	9 (82%)	0.556
Anti-coagulants	11 (21%)	10 (24%)	1 (9%)	0.270
Cholesterol lowering medication	48 (92%)	38 (93%)	10 (91%)	0.845

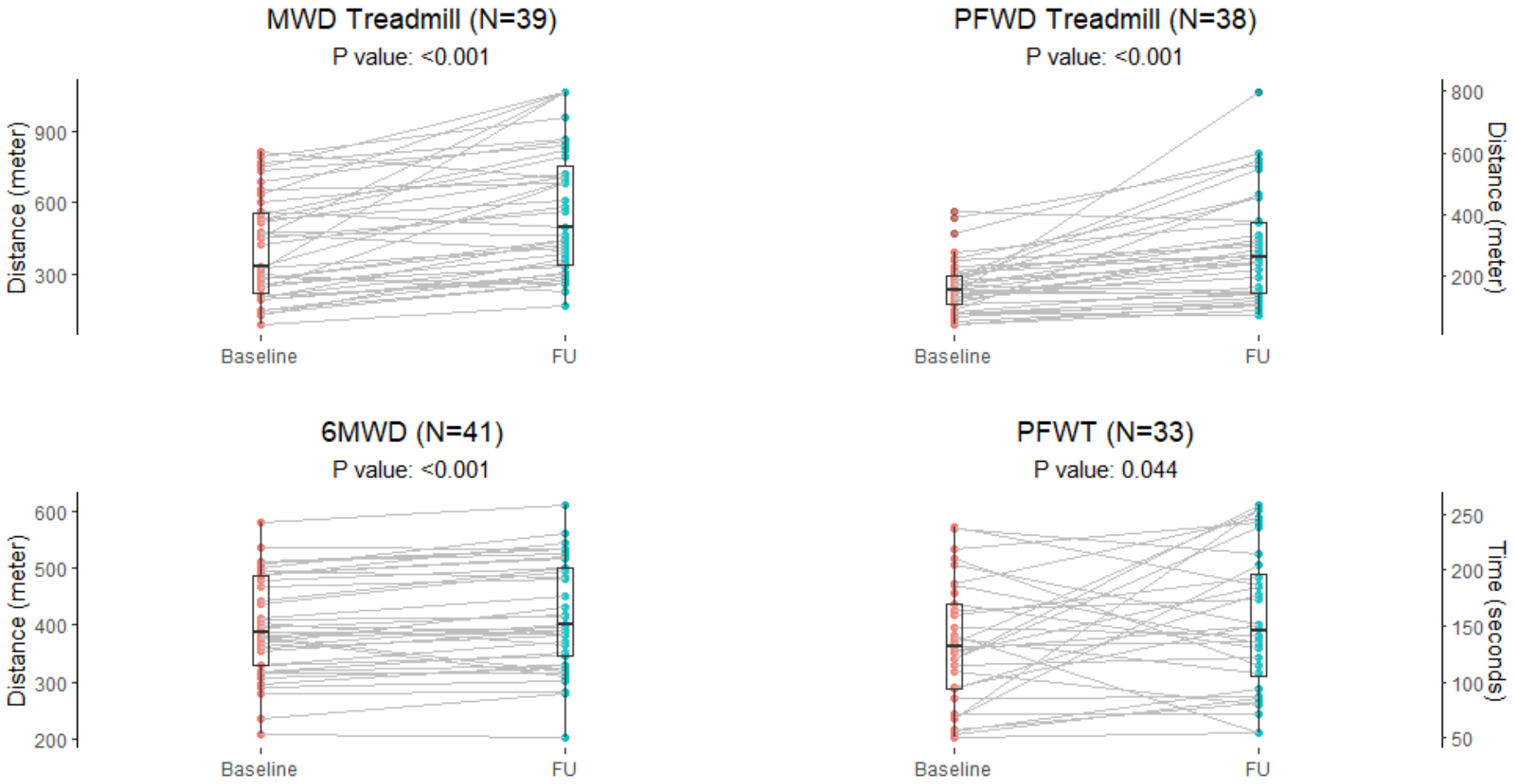

Figure 3. *Ambulatory outcomes after 12-weeks of PROSECO-IC intervention.*

Table 2. *Intervention effect.*

Walking Impairment Questionnaire	**(N=41)**	**(N=41)**	
WIQ Distance (%)*	37 ± 26	58 ± 28	**< 0.001**
WIQ Speed (%)	40 (IQR 40)	53 (IQR 33)	**< 0.001**
WIQ Stairs (%)	79 (IQR 37)	88 (IQR 33)	0.050
WIQ Total (%)*	51 ± 21	64 ± 20	**< 0.001**
Physical activity (PA)	**(N=38)**	**(N=38)**	
Total daily energy (kJ)	9805 ± 2030	10057 ± 2019	0.055
Active daily energy (kJ)	1553 ± 1377	1890 ± 1614	**0.040**
Daily steps	4720 ± 2505	5146 ± 3201	0.190
Moderate-vigorous PA ($min.day^{-1}$)	69.1 ± 60.3	83.7 ± 68.8	**0.029**
Physical fitness (PF)	**(N=39)**	**(N=39)**	
Peak VO_2 ($ml.min^{-1}$)	1205 ± 404	1170 ± 411	**0.035**
Peak VO_2 ($ml.min^{-1}.kg^{-1}$)	16.2 ± 4.4	15.8 ± 4.9	0.056
Wasserman (%)	73.6 ± 23.0	71.4 ± 22.1	0.067
Test duration (seconds)	410 ± 118	405 ± 105	0.437
Borg-score*	15 (IQR 2)	17 (IQR 2)	0.217
Peak HR (bpm)	115 ± 23	109 ± 22	**< 0.001**
Peak SBP (mmHg)†	189 ± 36	182 ± 36	0.082
RER	1.12 ± 0.10	1.12 ± 0.09	0.611
VascuQOL – Specific quality of life	**(N=41)**	**(N=41)**	
Pain	4.7 ± 1.0	4.9 ± 1.1	0.114
Symptoms	4.1 ± 0.9	4.7 ± 1.1	**0.002**
Activities	4.2 ± 0.9	4.9 ± 1.0	**< 0.001**
Emotional	4.7 ± 1.1	5.0 ± 1.3	0.063
Social	4.8 ± 1.5	5.4 ± 1.5	**0.012**
Total	4.4 ± 0.8	4.9 ± 1.0	**< 0.001**

Note. Missing values: **WIQ Distance and total score, 40 participants; Gas exchange variables, 38 participants; †Peak SBP, 37 participants; *Borg, 36 participants*

Adherence, acceptability and remote monitoring

As can be noted in **Figure 4**, the overall adherence rate for the whole intervention was 85% of prescribed exercise sessions (1433/1687): adherence rate to SET sessions (99 ± 4% or 493/499) and adherence to HBET sessions (79 ± 23% or 940/1188). GPS was used in a total of 73% HBET sessions. No difference was observed in adherence to HBET between completers and drop-outs (P = 0.174). HBET sessions were of median duration of 56 (IQR 11) minutes, including active and recovery phases. Eighty-seven percent of participants (42/49) uploaded at least one extra exercise session with a median of 11 sessions per participant (Range 0 to 53, median session time 42 (IQR 21) minutes). As a consequence of COVID-19, seven participants could not attend the defined 12 center-based, supervised sessions (4 (IQR 3) vs 11 (IQR 1.8), P < 0.001). Adherence to HBET sessions exceeding the 12-week intervention during governmental lockdown was 56% on average (Range 0 to 97%). Adherence to the exercise program, in terms of percentage attendance or logs, was not found to correlate with functional ambulatory outcomes (Supplementary file 2). A weak correlation was found between total HBET logged minutes and change in MWD (r_s = 0.316, p = 0.050). Interestingly, a correlation of total logged time (including minutes spent on extra sessions) and change in MWD (r_s = 0.365 with P = 0.023) was more pronounced (Supplementary file 2). In terms of satisfaction and acceptability, overall median score was 10 out of 10 (Range 3 to 10), highlighting the postive experience of the majority of participants. This was reflected in general agreement to recommend the program to peers (82.5% or 33/40), continue training like this (77.5% or 31/40) or start over the program again (75% or 30/40). In addition, the home-based exercise provision was considered to be safe and in line with personal fitness levels (both 90% or 36/40). Separate scoring on material, content and statements regarding the intervention are summarized in **Figure 5**. Here as well, general positivity can be observed, although SET sessions were not prefered over HBET sessions in 58% (24/40) participants.

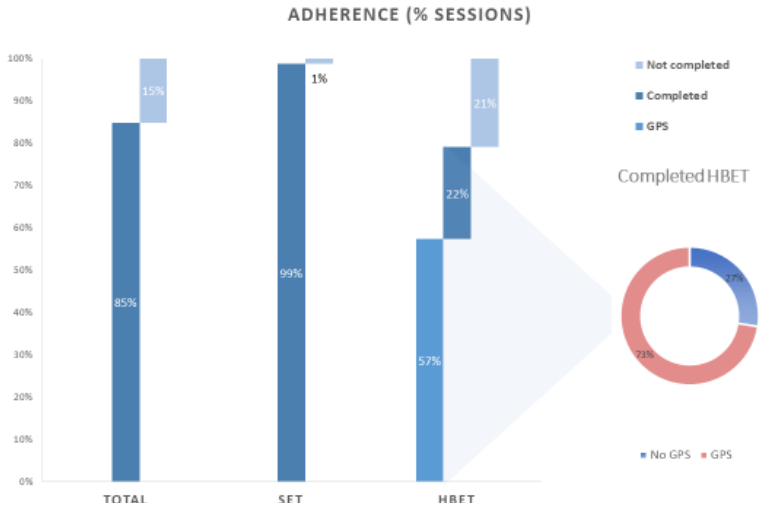

Figure 4. *Adherence during the PROSECO-IC (12-week) intervention for total exercise sessions, supervised (SET) and home-based (HBET) exercise sessions.*

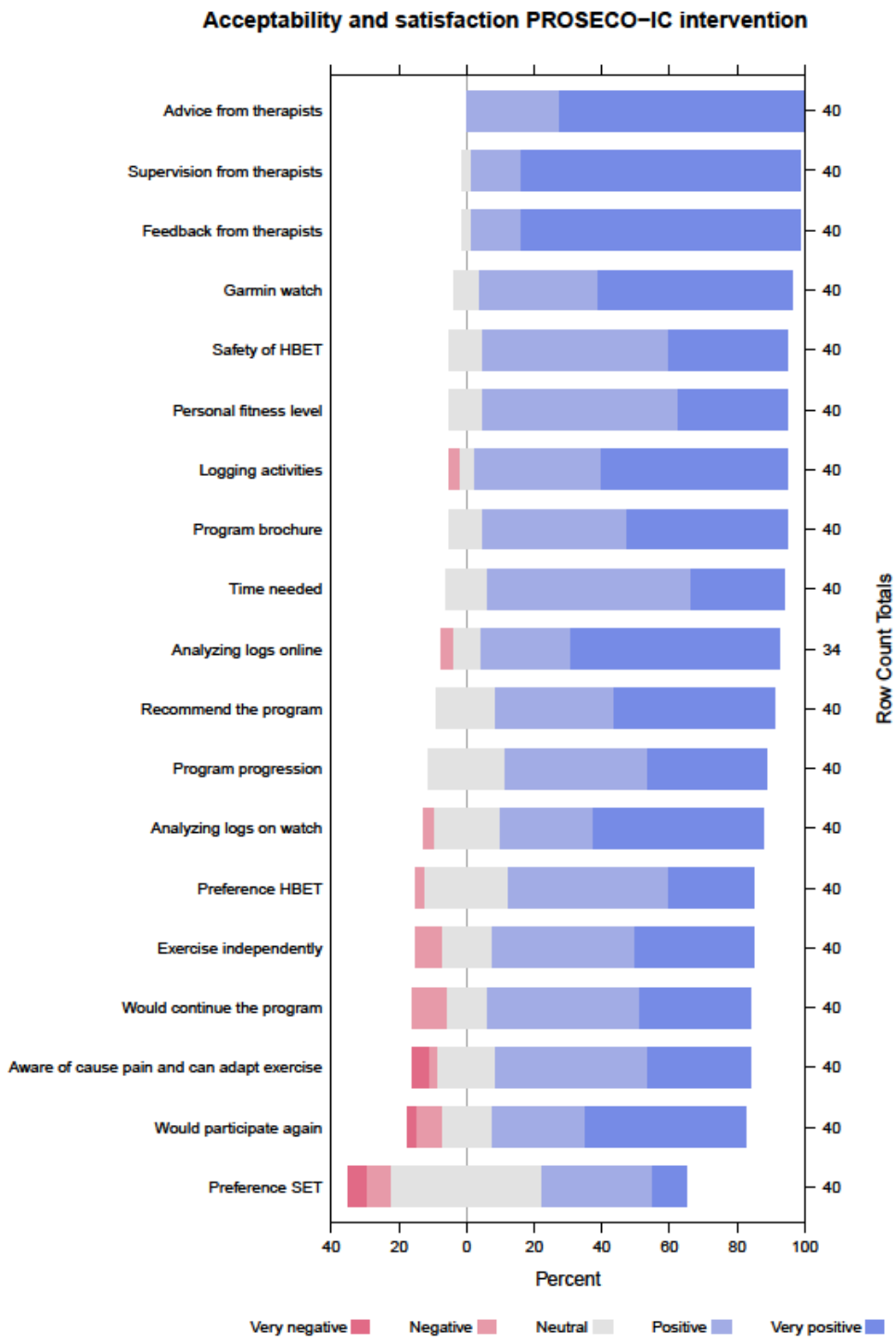

Figure 5. *Acceptability and satisfaction score on a 5-point Likert scale (N=40). Participants valued the intervention materials and content, exercise program and scored different statements. Here "negative" and "positive" are interchangeable with acceptable or suitable. No responses (Analyzing logs online, N = 6) were omitted from analysis.*

Physical activity, cardiorespiratory fitness and cardiovascular risk factors

Three participants did not reach sufficient valid days, consequently PA monitoring was available in 38 (93%) participants. As shown in **Table 2**, participants spent more time doing moderate-vigorous PA with a mean of 14.6 minutes.day^{-1} and active daily energy expenditure of 337 kJ (P = 0.029 and P = 0.040) after the intervention. Yet, no significantly higher value in number of daily steps was noted (p > 0.05). Further, measures of CRF (Peak VO_2, test duration and OUES) remained stable after the 12-week walking intervention (p > 0.05). Despite similar levels of exertion as shown by unaltered RER and BORG scores during CPET, peak heart rate was on average 6 beats lower after the 12-week intervention (P < 0.001). A lower heart rate was also noted during seated rest (P = 0.014). Cardiovascular risk profile remained unaltered after the intervention (Supplementary file 1).

Discussion

In this prospective trial we report on the acceptability, adherence and efficacy of a 12-week hybrid intervention. In general, participants were positive about the hybrid approach in which SET and HBET were combined, both in terms of technology usage, HBET prescription and SET sessions. Concordant, acceptability was good. Namely, we found a high adherence to both SET and HBET, with successful use of the Garmin watch to log and upload almost three out of four sessions with GPS-derived data. On a group-level a better ambulatory capacity and improved quality of life was found after the intervention. Time spent in activities of moderate-to-vigorous intensity was higher, though daily number of steps was unchanged at follow-up. Finally, CRF and traditional cardiovascular risk factors remained stable over the 12-week period.

In the search for an effective, but also feasible alternative to unavailable SET programs, structured HBET programs are appealing (30). Here, exercise programs combining in-center visits, accountability to a coach and home-based exercise prescription were already reported to be effective (31). Individually tailored exercise prescription, supervision on adherence and log-based feedback can be provided using wearable technology (32–34). Although being used to evaluate ambulatory capacity, this is the first intervention using a GPS wearable to guide HBET in patients with IC (35). The latter combination was perceived as acceptable and patients were generally satisfied by this hybrid approach, in terms of time needed, safety and interaction with a coach. Moreover, our hybrid program was effective in improving ambulatory capacity and physical functioning, with improvements being comparable to previous reports on structured HBET (14,31). Improvement in MWD on the treadmill was associated with total logged time. This finding replicates results from a recent study where an association of change in maximal walking time and the amount of algorithm-detected exercise sessions (r = 0.28) was found (34). Interestingly, recent reports emphasize

the importance of intensity beyond frequency and duration when prescribing exercise (34,36). The addition of intensity as a parameter (e.g. step count or pace) was available in 73% of GPS logged HBET sessions.

Besides ambulatory capacity, SET and HBET show potential to improve PA levels in patients with IC (37). However, a recent systematic review found a lack of evidence of improved daily step count in technology-guided HBET (14). This is line with our data, yet, a significant improvement in daily minutes of MVPA was noted. As MVPA is a measure of both intensity and time, previously objectified faster walking pace or improved cadence could underlie this observation (14,31). These outcomes highlight improved functionality as reported in the WIQ, VascuQOL and SF-36. Moreover, higher levels of MVPA are primordial to improve CRF and overall risk profile. In comparison to other studies we did not observe any change in CRF after the intervention (14,38,39). In fact, a downward trend was noted in peak VO_2. However, observed changes (-2.9 ± 8.8%) are within CPET measurement error or day-to-day variability (i.e. 5.6%) (40) and not clinically meaningful (23). In addition, test duration, peak load and OUES were unchanged after the intervention, highlighting an equal metabolic load and CRF. The addition of a ventilatory filter (i.e. increasing dead space ventilation) in seven participants tested before and after the first COVID-19 governmental lockdown might explain this discrepancy. Furthermore, a cycling test is less sensitive to training adaptations after a walking-based exercise program. Whether increased levels of MVPA can improve CRF levels in the long term has to be elucidated. With regards to the cardiovascular risk profile, no changes were noted in our cohort. This is in line with the results from our systematic review indicating that exercise programs only resulted in significantly reduced systolic blood pressure (41). However, in terms of diminished returns, baseline values in our cohort already indicate well-managed risk factors.

Limitations

Our findings of preferred HBET are in line with Harwood et al (42) and highlight the importance of tailoring SET and HBET sessions on an individual level to balance time and transport issues (i.e. most prevalent barrier for non-participation (42%)) and the need for in-person supervision and feedback. This was not considered in the present study as all patients were expected to attend a weekly SET session, yet, would be interesting to evaluate in future research. Moreover, current findings are reflecting short-term results, with possible wearable fatigue (43) and lack of benefit using wearables alone or with remote feedback on the long-term (44). In contrast, a recent study from McDermott and colleagues was efficient to improve 6MWD after 12-months, with initial in-person visits followed by weekly telephone contact (36). As such, technology to support sustainable exercise adherence with concomitant weaning of personal feedback seems plausible (14). As not all sessions (73% HBET logs) were GPS recorded, we could not quantify session intensity or

frequency and duration of recovery phases. Possible reasons are the lack of signal reception in urban or wooded areas. Moreover, digital illiteracy may also trouble accurate use of log recording and GPS data acquisition. In addition, we had to deviate from our initial study protocol as intended sample sizes were not reached and data in our intended control group was only available in five patients. Therefore, this prospective study is an extension of our previous pilot (16) study and further studies should compare effectiveness in a randomized-clinical trial. Moreover, we only recruited patients in a tertiary university hospital, limiting generalizability of our results.

Conclusion

This study shows that patients with LEAD suffering from IC can improve ambulatory capacity and quality of life after a structured 12-week hybrid program using wearable technology. Technology was accepted and patients were satisfied with this hybrid approach combining SET and HBET, with high adherence to SET and HBET sessions.

Appendix

Supplementary file 1: *Cardiovascular risk factors & generic quality of life.*

Table S1.1. *Cardiovascular risk factors.*

	Baseline	Follow-up	P-value
Blood sampling	**(N=41)**	**(N=41)**	
Total cholesterol (mg.dl^{-1})	150 ± 34	147 ± 41	0.459
LDL-C (mg.dl^{-1})	69 ± 29	65 ± 30	0.277
HDL-C (mg.dl^{-1})	51 ± 19	54 ± 20	0.244
Triglycerides (mg.dl^{-1})	154 ± 96	149 ± 104	0.655
Fasting Blood Glucose (mg.dl^{-1})	101 ± 17	100 ± 14	0.371
Blood pressure and heart rate			
SBP (mmHg)	122 ± 16	121 ± 17	0.563
DBP (mmHg)	70 ± 9	69 ± 10	0.600
Resting HR (bpm)	62.1 ± 11.7	59.7 ± 10.3	**0.014**
Anthropometrics			
Weight (kg)	74.9 ± 14.0	74.8 ± 13.4	0.298

Intervention effects. ***Missing values:*** *Total cholesterol, 40 participants; LDL-C, 38 participants; HDL-C, 40 participants; Triglycerides, 40 participants*

Table S1.2. *Generic - Quality of life.*

	Baseline	Follow-up	P-value
SF-36 - General	**(N=41)**	**(N=41)**	
Physical functioning (%)	49 ± 17	60 ± 20	**< 0.001**
Role physical (%)	50 (IQR 100)	50 (IQR 100)	0.455
Role emotional (%)	67 (IQR 67)	100 (IQR 67)	0.599
Energy and fatigue levels (%)	57 ± 17	61 ± 17	0.082
Emotional well-being (%)	69 ± 19	73 ± 17	**0.010**
Social functioning (%)	75 (IQR 50)	88 (IQR 38)	**0.027**
Pain (%)	55 ± 24	63 ± 20	0.061
General health (%)	51 ± 18	56 ± 18	**0.005**

Intervention effects.

Supplementary file 2: *Correlations.*

Table S2.1. *Spearman's Correlations (**N=39**, exclusion of two participants reaching maximal protocol time).*

Variable		SET% Adherence	HBET% Adherence	HBET Minutes/session	HBET+Extra Total minutes	ΔPFWD	ΔMWD	Δ6MWD
1. SET% Adherence	Spearman's rho	—						
	p-value	—						
2. HBET% Adherence	Spearman's rho	**0.382 ***	—					
	p-value	**0.016**	—					
3. HBET Minutes/session	Spearman's rho	0.004	0.239	—				
	p-value	0.980	0.143	—				
4. HBET+Extra Total minutes	Spearman's rho	0.203	**0.731 *** **	**0.406 ***	—			
	p-value	0.215	**< .001**	**0.010**	—			
5. ΔPFWD	Spearman's rho	0.289	0.046	0.301	0.046	—		
	p-value	0.087	0.791	0.075	0.788	—		
6. ΔMWD	Spearman's rho	0.257	0.268	**0.316**	**0.365** *	**0.619 *** **	—	
	p-value	0.115	0.099	**0.050**	**0.023**	**< .001**	—	
7. Δ6MWD	Spearman's rho	0.082	-0.037	0.123	-0.087	**0.335 ***	**0.346 ***	—
	p-value	0.621	0.825	0.454	0.599	**0.046**	**0.031**	—

* p < .05, ** p < .01, *** p < .001

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Chapter three: Underlying mechanism and determinants of improved walking

Chapter 3.1: The use of near infrared spectroscopy to evaluate the effect of exercise on peripheral muscle oxygenation in patients with lower extremity artery disease: a systematic review

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Abstract

Objective: Near infrared spectroscopy (NIRS) has been suggested as a new diagnostic tool in patients with lower extremity artery disease (LEAD). The aim of this systematic review was to summarise the impact of exercise therapy on lower limb muscle oxygenation, evaluated by NIRS, in patients with LEAD, and to give an overview on NIRS instruments and methodology.

Data Sources: MEDLINE and Embase.

Review Methods: A systematic search was conducted in MEDLINE and Embase, from the earliest date available until 16 March 2020, to identify peer reviewed studies involving the use of NIRS in the evaluation of exercise training on muscle oxygenation in patients with LEAD. Primary outcomes were NIRS derived variables during treadmill exercise. Effect sizes were calculated as standardised mean differences. Assessment of methodological quality was done using a combined checklist from the Cochrane bias and the quality assessment tool for before and after studies without a control group.

Results: Eleven original trials were included involving 16 exercise groups and four control groups. Tissue saturation index (TSI) at rest remained unchanged following the exercise interventions. Exercise training increased time to minimum TSI during exercise (range effect sizes: +0.172 to +0.927). In addition, exercise training led to a faster recovery to half and full TSI rest values in most intervention groups (range effect sizes -0.046 to -0.558 and -0.269 to -0.665, respectively). Finally, NIRS data reproducibility and analytic methods were under reported in the included studies.

Conclusion: The available data suggest that exercise training improves de-oxygenation and re-oxygenation patterns, as measured with NIRS, in patients with LEAD. Whereas NIRS is a promising tool in the evaluation of LEAD, the low number of randomised controlled trials, as well as large heterogeneity in NIRS assessment methods, outcome measures, and instrumentation, warrants more research to better understand the role of muscle oxygenation associated with exercise induced improvements in walking capacity.

Introduction

Lower extremity artery disease (LEAD) is characterised by a gradual atherosclerotic narrowing in the lower limbs. Although this obstruction to blood flow is often asymptomatic, 10%-35% of patients with LEAD present with typical symptoms during daily activities (1). The cramping like pain, referred to as intermittent claudication (IC), is the cardinal symptom of LEAD and results from the oxygen supply/demand mismatch in muscles distal to the obstructed vessel (2). This mismatch is of great clinical interest, as the combination of an increased local anaerobic state combined with physical inactivity might result in an acquired myopathy (3,4). This peripheral myopathy is characterised by histological and metabolic changes, such as a muscle fibre type shift, reduced capillary density, higher lactate and acylcarnitine levels, and dysregulated mitochondrial capacity (2-5). Additionally, increased blood viscosity, and local endothelial and autonomic dysfunction further compromise optimal oxygen supply (2,5). Whether insufficient circulation is the main cause of peripheral myopathy is still debated (6), yet the cascade is undoubtedly detrimental.

Following this, different diagnostic techniques have been introduced to evaluate the underlying aetiology of LEAD and patients' responses to therapy. Well known evaluation methods vary in their ability to measure local haemodynamics (e.g. ankle brachial index (ABI) or imaging methods such as magnetic resonance imaging (MRI)), local metabolism, or tissue perfusion (e.g. muscle biopsies or transcutaneous oxygen pressure measurements). Yet, most methods are static or have limited penetration depth to study underlying changes in muscle perfusion during exercise (7). Therefore, non-invasive near infrared spectroscopy (NIRS) received considerable attention in vascular research starting from the early 1990s (8), with interest in it growing rapidly as new low cost and portable devices, with important clinical potential, become available (9). In short, NIRS uses near infrared light with different wavelengths (700-900 nm) to transmit photons to the muscle of interest noninvasively. As the absorption rate of the omitted photons is different for oxygenated and de-oxygenated chromophores, receiving photodetectors can differentiate between them (8). Notably, NIRS dynamically reflects oxygen supply and demand during exercise in healthy and diseased populations (10). In LEAD studies, NIRS can be used as a diagnostic tool as it is associated with clinical measures of disease severity (e.g. ABI and recovery kinetics), and can evaluate the effects of exercise interventions (11,12).

Although NIRS offers unique opportunities to gain insight into the pathophysiological state of patients with LEAD, it remains underused in today's clinical practice. Moreover, current reporting of NIRS methodology and derived outcome parameters is very heterogeneous and hinders widespread implementation. Therefore, a systematic review was conducted to summarise the literature to date on the effect of exercise therapy on NIRS derived

outcomes in patients with LEAD. A further aim was to provide a detailed summary of NIRS instrumentation and assessment methods reported in current literature to guide future work in the field.

Methodology

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and the Synthesis WIthout Meta-analysis (SWIM) guidelines were followed (13,14), and prospectively registered with PROSPERO, the International Prospective Register of Systematic reviews (registration number: CRD42020175401).

Search strategy

A comprehensive search was conducted in MEDLINE (Ovid) and Embase (Ovid), from their dates of inception until 16 March 2020, to identify relevant peer reviewed journal articles (Supplementary file 1). Reference lists from the eligible papers were manually searched for additional studies. No language restrictions were imposed on the search.

Inclusion and exclusion criteria

Eligibility criteria included 1) prospective cohort studies, and randomised and non-randomised controlled trials investigating the effect of an exercise intervention; 2) studies performed in people aged ≥18 years with LEAD and IC (classified as Rutherford 1-3 or Fontaine 2a, 2b); 3) those reporting mean and standard deviation (SD), standard error, or median and interquartile range (IQR) of at least one NIRS outcome parameter before and after the intervention; and 4) those published as a full length publication in a peer reviewed journal.

Study selection

The results from the initial search were imported into Rayyan software for systematic screening by two independent reviewers (N.C. and P.C.) (15). After removal of duplicates, titles and abstracts were screened for eligibility. In a second phase, the full texts of potentially relevant articles were retrieved, which were then reviewed by both reviewers. Disagreements were resolved by consultation with a third reviewer (V.C.).

Data extraction

A standardised Access Database file (Microsoft, Redmond, WA, USA) was used by both reviewers to extract data independently from the individual studies, including publication details (year of publication, country of origin), study design, sample size, patient characteristics, exercise characteristics, NIRS instrumentation, and assessment methodology, as well as primary and secondary outcome measures.

Primary and secondary outcomes

The main focus was on NIRS derived parameters that could be assessed at rest, during a single bout of exercise, or during recovery from exercise (**Figure 1**). For uniformity, tissue saturation index (TSI; oxygenated[haem]/total[haem]) is used as the reference term, which also includes muscle tissue oxygen saturation (StO_2) or tissue oxygenation index (TOI). Although NIRS cannot discriminate between chromophores (haemoglobin and myoglobin), outcomes are reported as published (e.g. oxygenated haemoglobin [O_2Hb], de-oxygenated haemoglobin [HHb], and total haemoglobin [tHb]) as intracellular myoglobin tends to stay constant during exercise (8,10). Arterial or venous occlusion experiments are considered as a separate category. Secondary outcomes included pain free and maximum walking time or distance, six minute walking distance (6MWD), ABI, and peak oxygen consumption (VO_2peak). In the case of missing data, authors were contacted twice over a one month period to request data.

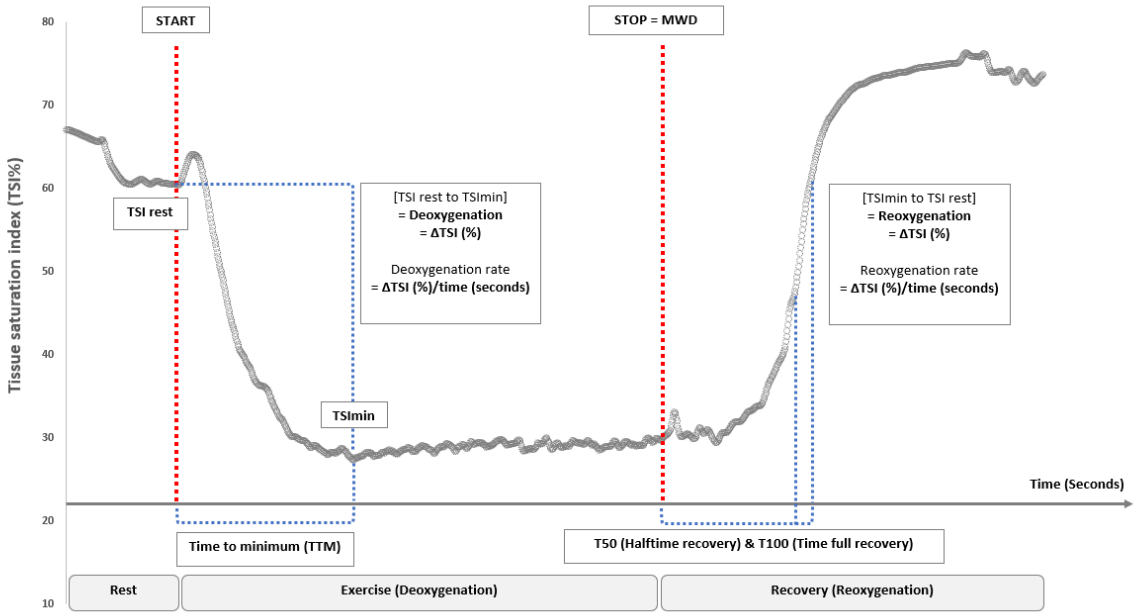

Figure 1. *Typical pattern of NIRS-derived data during a treadmill walking test (unpublished data). Outcomes are categorized following the phase in the test: at rest, during exercise or de-oxygenation and during recovery or re-oxygenation.*

Risk of bias

Study methods

Owing to the different designs of the included studies, the Cochrane risk of bias tool and the quality assessment tool for before/after studies without a control group were combined to rate the methodological quality of the included articles (16,17). This combined checklist was used by two independent reviewers (N.C. and P.C.) rating the following 12 items (rating: yes and no): objective clearly stated; eligibility criteria; representative study sample;

participants enrolment; random sequence generator; control group; description of the intervention and consistency; assessors blinded to intervention; follow up rate; statistical methods; complete outcome data; and nonselective reporting. Disagreements between reviewers were resolved by discussion with a third reviewer (V.C.). The overall score for each article was obtained by summing the number of "yes" answers.

Near infrared spectroscopy methodology

A separate analysis of the quality of the NIRS assessment methods was performed by rating the following six items: NIRS device characteristics; clear description of anatomical position; reproducibility of positioning; adipose tissue thickness (ATT) measurement; description of the specified outcomes; analysis and reporting.

Statistics

Demographic data are presented as reported in the main article. The effect sizes of all included study groups were calculated by paired standardised difference of means using Comprehensive Meta-analysis version 2.2.064. Standardised difference of means can be interpreted following Cohen's convention with the effect size being small (0.20), medium (0.50), or large (0.80) (18). To calculate the standardised effect sizes, we assumed paired data to be correlated with an r value of 0.5. The decision to not perform a meta-analysis was based on the diversity of study designs and methods, with a limited number of studies including a matched control group. Therefore, the decision was made to summarise effect sizes, in order to discuss the range and distribution of the most common outcomes. Furthermore, effects sizes were presented visually to discuss both direction of effect and heterogeneity. A conversion tool was used to calculate the mean and SD for two studies that reported median and IQR (19-21). If data were only available in figures, means or SDs were extracted using Acrobat Reader (Adobe, San Jose, CA, USA).

Results

Literature search

The original search yielded 440 studies. After removal of duplicates and exclusion of papers based on the eligibility criteria, 11 original studies involving 12 full text papers remained (**Figure 2**). Two papers from Collins et al. were included. Both involved the same population sample, but two different exercise test protocols were studied (i.e. constant and progressive work rate). Demographic data for Collins et al. were extracted from the original study (22,23). However, the NIRS substudy was selected for quantitative analysis, as it contained more information regarding the research question (23). A request for missing data was sent to nine authors and six replied (23-28).

Study characteristics

Individual study characteristics are presented in **Table 1**. Four studies were randomised controlled trials (RCTs) (20,24,26,27), three were randomised trials (22,23,29,30), two were non-RCTs (21,31), and two applied a pre-post design without a control group (25,28). Studies were published between 2009 and 2020. The majority (n = 6) were conducted in the USA (20,22-24,26,28,30), while the remainder were performed in UK (21,27), Italy (31), Brazil (29) and Japan (25). A total of 666 participants (73% men) participated in the studies. The mean age of the participants was 68.4 years, with study means ranging from 64.3 to 71.8 years. In total, 70 participants dropped out of the studies, leaving 596 available for analysis. All exercise intervention groups (n = 16) and control groups (n = 4) were analysed as individual study groups. One non-randomised control group consisted of patients that underwent angioplasty (21). Three other control groups received either best medical treatment (20), advice on physical activity (27), or attention control light resistance training (26). Comparison groups of healthy participants (n = 2) were excluded from the analysis (30,31). Traditional treadmill walking was the most frequently prescribed exercise modality (n = 7) (20,22,24,26,28-30). Three studies used alternative walking interventions with ankle loads (29), NIRS guidance (30), or pole striding (22). Two studies applied a home based walking intervention involving two structured and one self paced walking programme (26,31). The remaining three studies used ergometer cycling (25), arm cranking exercise (27), or a circuit training programme (21). All exercise interventions had a duration of 12 weeks (n = 10), except for Manfredini et al. (31), who applied a 34 week intervention. Resting levels of TSI were reported in four studies (20,21,27,28), de-oxygenation parameters during exercise in eight (20,21,23,25-29) and recovery outcomes following exercise in six (**Figure 3**) (20,21,25,26,28,29).

Table 1. *Baseline characteristics of the included studies.*

Author Year Country	Design	Exercise group (E1) **FITT-principle**	Comparison group(s) **Alternative exercise (E2) or control (C)**	Sample size **N included (N analyzed)**	Age	ABI	Sex **M/F (N)**	Test methods
Baker et al 2017 **USA**	Randomized controlled trial	**F:** 3x/week **I:** Mild-moderate pain **T:** 60 min, 12 weeks **T:** Treadmill walking	*Best medical treatment (C)*	**T:** 64 (64) **E:** 29 (29) **C:** 35 (35)	**T:** 66.5 **E:** 66 **C:** 67	**T:** 0.63 **E:** 0.645 **C:** 0.65	41/ 23	**Progressive treadmill test** 3.2 kph - 0% inclination + 2%/2 minutes
Beckitt et al 2012 **UK**	Controlled trial	**F:** 2x/week **I:** Point of claudication **T:** 50 min, 12 weeks **T:** Circuit training: step-ups, toe-walking, heel raises, wobble board and resistance cycling	*Angioplasty control (C)*	**T:** 56 (56) **E:** 42 (42) **C:** 14 (14)	**T:** 66.5 **E:** 66 **C:** 68	**T:** 0.70 **E:** 0.69 **C:** 0.72	39/ 17	**Constant work** 2.5 kph at 10% inclination **Submaximal treadmill** 100 seconds at submaximal intensity **Arterial occlusion** Acute hyperemic response
Collins et al 2012a and Collins 2012b* **USA**	Randomized trial	**F:** 3x/week **I:** Low (25-44% VO_{2peak}) to moderate (45-59% VO_{2peak}) to high (60-84% VO_{2peak}) intensity **T:** 30-60 min, 24 weeks **T:** Walking *without* poles (treadmill and hospital corridors) (E1)	**F:** 3x/week **I:** Low (25-44% VO_{2peak}) to moderate (45-59% VO_{2peak}) to high (60-84% VO_{2peak}) intensity **T:** 30-60 min, 24 weeks **T:** Walking *with* poles (outside and hospital corridors) (E2)	**T:** 103 (95) **E:** 52 (49) **C:** 51 (46)	**T:** 69.7 **E:** 68.0 **C:** 71.4	**T:** 0.63 **E:** 0.65 **C:** 0.62	*96/ 7*	**Constant work (a)** 2.9 kph at 12% inclination **Progressive work (b)** Small increases in inclination every 30 seconds; 6 minutes speed was increased every 3 min; starting speed was 2.9 km/h and inclination 0% - protocol was designed to have a 1 MET (metabolic equivalent) every 3 minutes
Figoni et al 2009 **USA**	Pre-post trial	**F:** 5x/week of which 3x/center-based and 2x/week home-based	N/A	**T:** 21 (15) **E:** 21 (15)	**T:** *68.8* **E:** *68.8*	**T:** *0.59* **E:** *0.59*	21/ 0	**Progressive work**

		I: Maximal claudication pain **T:** 12-week **T:** (Treadmill) walking + calf exercises on ergometer						3.2 kph - 0% inclination + 2%/2 minutes until a maximal inclination 14%
Gardner et al 2014 **USA**	Randomized controlled trial	**F:** 3x/week **I:** Mild-moderate pain **T:** 20-45 min, 12 weeks **T:** 15-40 minutes, 12 weeks **T:** Home-based walking using a step monitor (E1) **T:** Supervised treadmill walking (E2)	*Attention-control group (C): light resistance training (3x/week)*	**T:** 180 (180) *Intention-to-treat* **E1:** 60 (60) **E2:** 60 (60) **C:** 60 (60)	**T:** 65.7 **E1:** 67 **E2:** 65 **C:** 65	**T:** 0.70 **E1:** 0.68 **E2:** 0.68 **C:** 0.74	*96/ 84*	**Progressive work** 3.2 kph - 0% inclination + 2%/2 minutes
Haga et al 2020 **JAPAN**	Pre-post trial	**F:** 3x/week **I:** 70% maximal load **T:** 40-60 min, 12 weeks **T:** Ergometer cycling	N/A	**T:** 19 (16) **E:** 19 (16)	**T:** *67* **E:** *67*	**T:** Left: 0.77 Right: 0.79 **E:** Left: 0.77 Right: 0.79	13/ 3	**Constant work** Speed between 2.4 and 3.6 kph, 0% inclination
Manfredini et al 2012 **ITALY**	Non-randomized controlled trial	**F:** 6x/week **I:** speed 20-30% lower than pain threshold (using metronome) **T:** 20 minutes, 34 weeks	**F:** 6x/week **I:** Self-selected pace up to moderate pain **T:** 20-30 minutes, 34 weeks	**T:** 55 (45) **E1:** 36 (31) **E2:** 19 (14) **C:** 15 (15)	**T:** *71.3* **E1:** *71.9* **E2:** *70.3* **C:** *38.3*	**T:** 0.61 **E1:** *0.59* **E2:** *0.67* **C:** *1.09*	42/ 13	**Progressive work (NIRS measurements)** 1.5 kph + 0.1 kph/10 meter, 0% inclination **Venous occlusion** Muscle oxygen consumption

		T: *Structured* home-based walking (E1)	**T:** Unstructured, free pace home-based walking (E2)					
		Healthy control group with unmodified active life-style (post-hoc) (C)						
Monteiro et al 2019 **BRAZIL**	Randomized trial	**F:** 3x/week	**F:** 3x/week	**T:** 40 (32)	**T:** 64.3	**T:** Left: 0.62 Right: 0.62	*28/ 12*	**Constant work** (1 minute of warm-up with progressive increase to 3.2 km/h and 10% inclination, at moderate-to-maximum claudication one-to-two minutes of active recovery at 2.0 km/h and 0% inclination) **Arterial occlusion**
		I: Maximum claudication	**I:** Maximum claudication	**E1:** 20 (16)	**E1:** 65.5	**E1:** Left: 0.61 Right: 0.62		
				E2: 20 (16)	**E2:** 63.1	**E2:** Left: 0.62 Right: 0.61		
		T: 30 minutes, 12 weeks	**T:** 30 minutes, 12 weeks					
		T: Treadmill walking (E1)	**T:** Modified treadmill walking using ankle weights (E2)					
Murrow et al 2019 **USA**	Randomized trial	**F:** 3x/week	**F:** 3x/week	**T:** 36 (18)	**T:** *71.8*	**T:** *0.83*	14/ 4	**Progressive work** 3.2 kph - 0% inclination + 2%/2 minutes **Arterial occlusion** Muscle oxygen consumption and muscle blood flow
		I: Claudication pain ≥6/10 scale	**I:** 15% reduction from TSI rest as a lower-level threshold	**E1:** 18 (10)	**E1:** *71.6*	**E1:** *0.80*		
		T: 40 minutes, 12 weeks	**T:** 40 minutes, 12 weeks	**E2:** 18 (8)	**E2:** *72.0*	**E2:** *0.87*		
		T: Treadmill walking (E1)	**T:** NIRS-guided treadmill walking (E2)	**C:** 20 (20)	**C:** 61.0	**C:** /		
		Age-matched control group (post-hoc)						
Tew et al 2009 **UK**	Randomized controlled trial	**F:** 2x/week	*Control group with advice on PA (C)*	**T:** 57 (51)	**T:** *69.5*	**T:** *0.68*	51/ 0	**Progressive work** 3.2 kph - 0% +1% /minute
		I: 60-70% VO_2peak		**E:** 29 (27)	**E:** 69	**E:** 0.68		
		T: 20 minutes, 12 weeks		**C:** 28 (24)	**C:** 70	**C:** 0.69		
		T: Arm-cranking exercise						
Woessner et al		**F:** 3x/week		**T:** 35 (24)	**T:** *69.7*	**T:** *0.63*		**Progressive work**

2018 **USA**	Randomized controlled trial		Similar exercise group *with* nitrate supplementation				15/ 9	3.2 kph - 0% inclination + 2%/2 minutes
		I: Mild-moderate pain		**E:** 18 (13)	**E:** *71.5*	**E:** *0.70*		
		T: at least 30 minutes, 12 weeks		**C:** 17 (11)	**C:** *67.5*	**C:** *0.55*		
		T: Treadmill walking						

Note. *Numbers in italics are data on analyzed numbers of participants. ***Collins 2012b** (23): Same training characteristics except that intervention duration was 12 weeks. Sample size: T: 85(79), E1: 40(36), E2:45(35). Age. T: 69.4, E1: 66.8, E2: 71.7. ABI. T: 0.63, E1: 0.63, E2: 0.62. Sex (79 ♂/6 ♀). Abbreviations: F: frequency, I: intensity, T: time, T: type, E: exercise group, C: control group, T: total sample.*

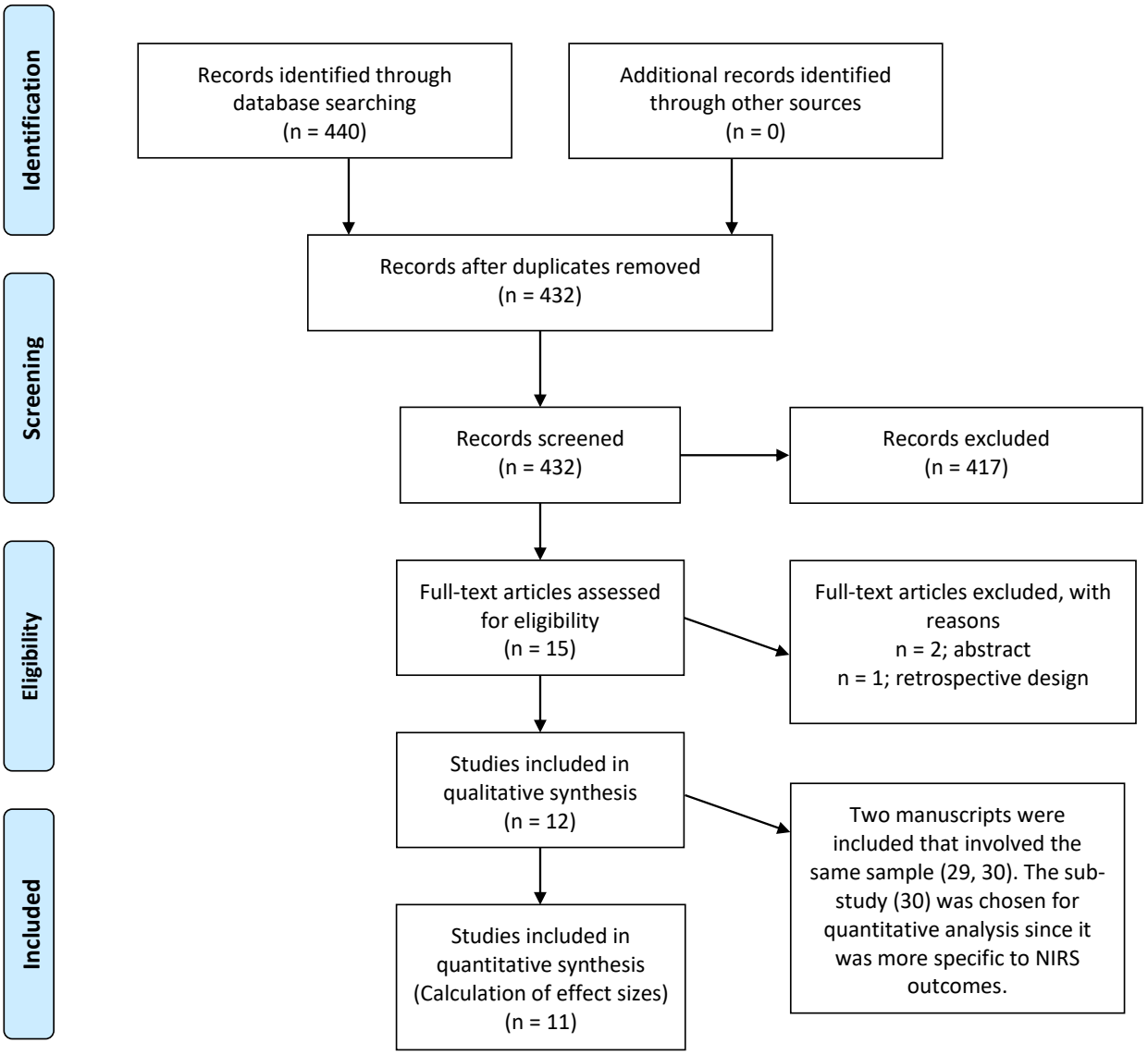

Figure 2. *Flow chart displaying the search's work flow.*

Synthesis of results

Near infrared spectroscopy parameters at rest

In all studies resting TSI remained unchanged after the exercise interventions (20,21,27,28), usual care (20), or angioplasty (21), with effect sizes ranging between -0.191 and 0.272 (**Figure 4A**). Only Baker et al. reported a between group comparison and found no difference between the exercise and control group change scores (20). Muscle oxygen consumption (mVO_2) at rest was assessed as HHb rate during venous occlusion (31), or by a combination of diffuse correlation spectroscopy and frequency domain NIRS measurements (20). Two of three study groups observed a higher mVO_2 at rest after structured walking training (20,31). The increase in mVO_2 was statistically significantly higher after exercise training compared with usual care (20). These effects were explained by a higher dynamic blood flow and oxygen extraction fraction vs. usual care (20), or an increased mitochondrial capacity after exercise, as noted by Murrow et al. (30). The latter effect was more pronounced in the traditional group vs. a walking group receiving NIRS biofeedback (interaction effect: p = .003) (30). Two other studies evaluated O_2Hb recovery after arterial occlusion and found a significantly higher recovery rate in the angioplasty group but not in the exercise group (21,29). Furthermore, no interaction, time, or group effects were observed after training on TSI recovery time, delta HHb, and delta TSI following arterial occlusion at rest (29).

Figure 3. *Distribution of the most common NIRS-derived muscle oxygenation variables in the included studies. Abbreviations: TSI rest (%): Tissue Saturation Index during resting conditions (%), mVO_2: muscle oxygen consumption, TSImin (%): minimum TSI (%) during exercise, TTM: Time to reach TSImin (%), delta TSI: TSIrest – TSImin, T100: time to reach 100% of resting TSI, T50: time to reach 50% of resting TSI.*

Near infrared spectroscopy parameters during exercise

In all studies time to minimum TSI (TTM) was increased after the exercise intervention, with five of seven exercise groups reaching statistical significance (range effect sizes: +0.172 and +0.927) (**Figure 4B**). Two RCTs reported that changes in TTM were statistically significantly larger compared with the control group (p interaction .025 and < .001, respectively) (26,27). Similarly, Tew et al. observed significantly higher TSI values at several time points during exercise after an arm cranking intervention (27). Conversely, no changes in absolute de-oxygenation were noted following seven exercise interventions (range effect sizes for delta TSI: -0.127 and +0.350; and for TSImin: -0.286 and 0.000). Although the lowest TSI value was unchanged, patients could sustain the low tissue oxygenation levels for a longer period after exercise training (time to resistance; time-effect p < .001) (29). Yet, a significant decrease in de-oxygenation, which translates to higher TSI values during exertion, was observed only after revascularisation and best medical treatment (20,21). Moreover, two studies reported the evolution of NIRS raw signals during exercise, and observed improved maintenance of O_2Hb during (sub)maximal exercise after walking training (24,31), without changes in de-oxygenation or tHb kinetics (24,31).

Near infrared spectroscopy parameters during recovery

Two RCTs reported data on T50 (i.e. time to recover 50% of resting TSI) (20,26), and three studies reported data for T100 (25,28,29), defined as time to reach 100% of resting TSI, of which none included a control group (**Figure 4C**). Contrary to Baker et al. (20), Gardner et al. found a faster recovery (T50) following either supervised or home based exercise (26), which was significantly different from the control group (p = .020). As the training interventions were similar for both studies, methodological differences most probably explain this discrepancy. That is, Baker et al. applied a frequency-domain technique to calculate half time oxygen extraction fraction, which resembled T50 (20). Although all studies showed a tendency towards an enhanced recovery following exercise training (25,28,29), assessed as T100 (range effect sizes: -0.665 and -0.269), only the conventional training intervention group reached statistical significance (29). Similarly, Beckitt et al. used T50 but defined it as half of the full recovery time (21). Following a circuit based exercise training, they found enhanced recovery after a submaximal test similar to the group that received angioplasty treatment. Yet, enhanced recovery after maximum exertion was only seen after revascularisation. Finally, relative reoxygenation, defined as the time taken to reach 100% of resting TSI relative to test duration, was significantly improved following 12 weeks of walking, three times per week, with and without ankle weights (29).

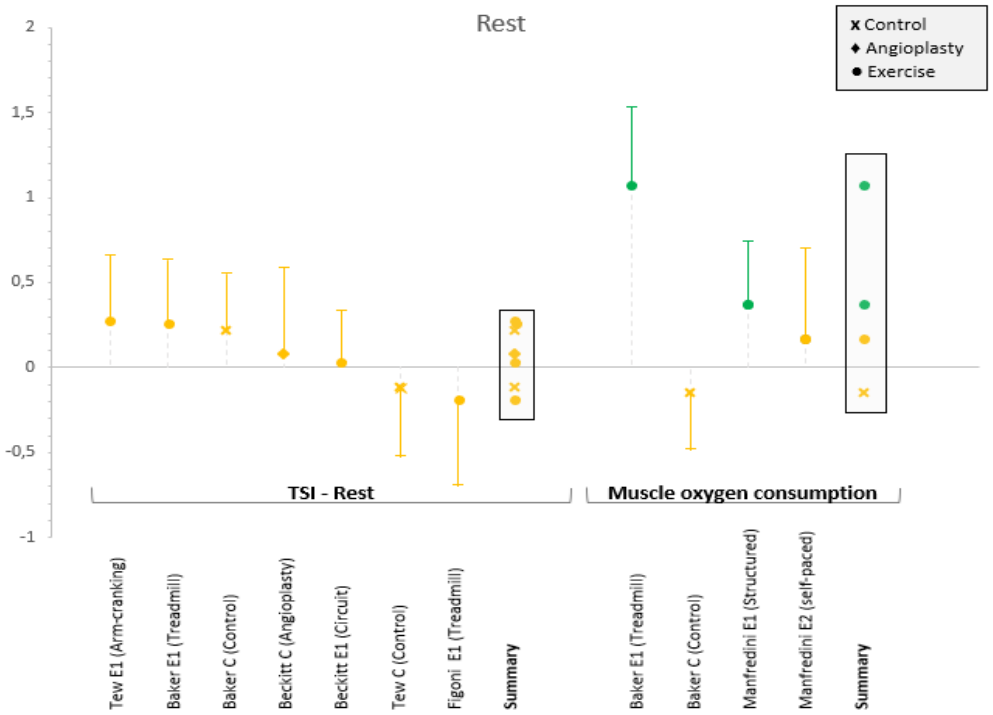

Figure 4A. *Effect sizes on TSI and muscle oxygen consumption after intervention. Results in yellow and green reflect non-significant and significant (p < .05) effect sizes respectively.*

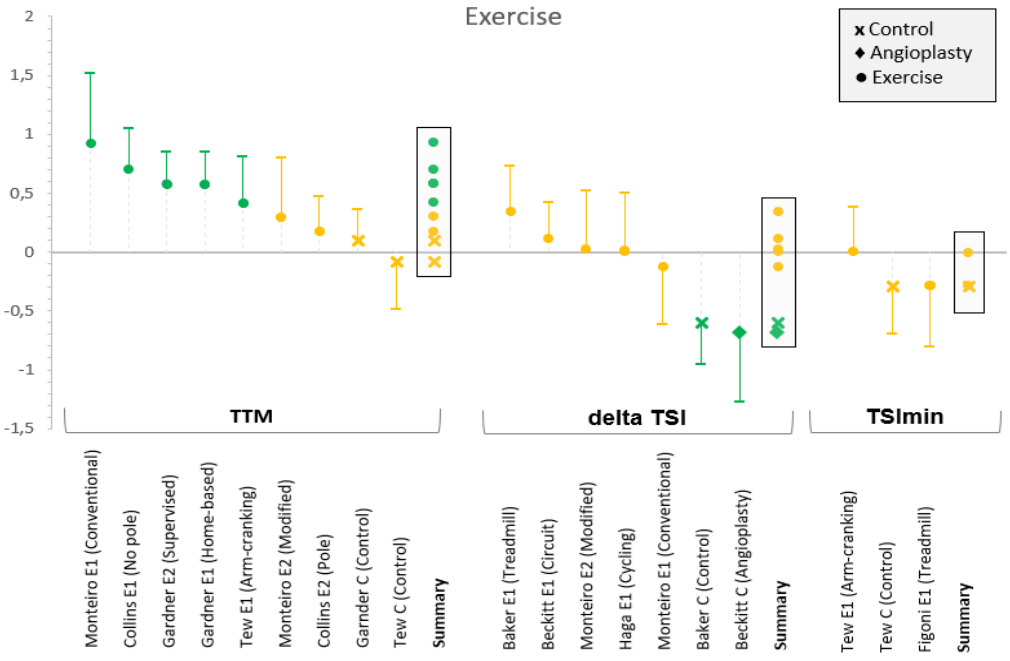

Figure 4B. *Effect sizes on time-to-minimum TSI (TTM), delta TSI and minimal TSI (TSImin) during exercise after intervention. Results in yellow and green reflect non-significant and significant (p < .05) effect sizes respectively. Data on Collins are from (30).*

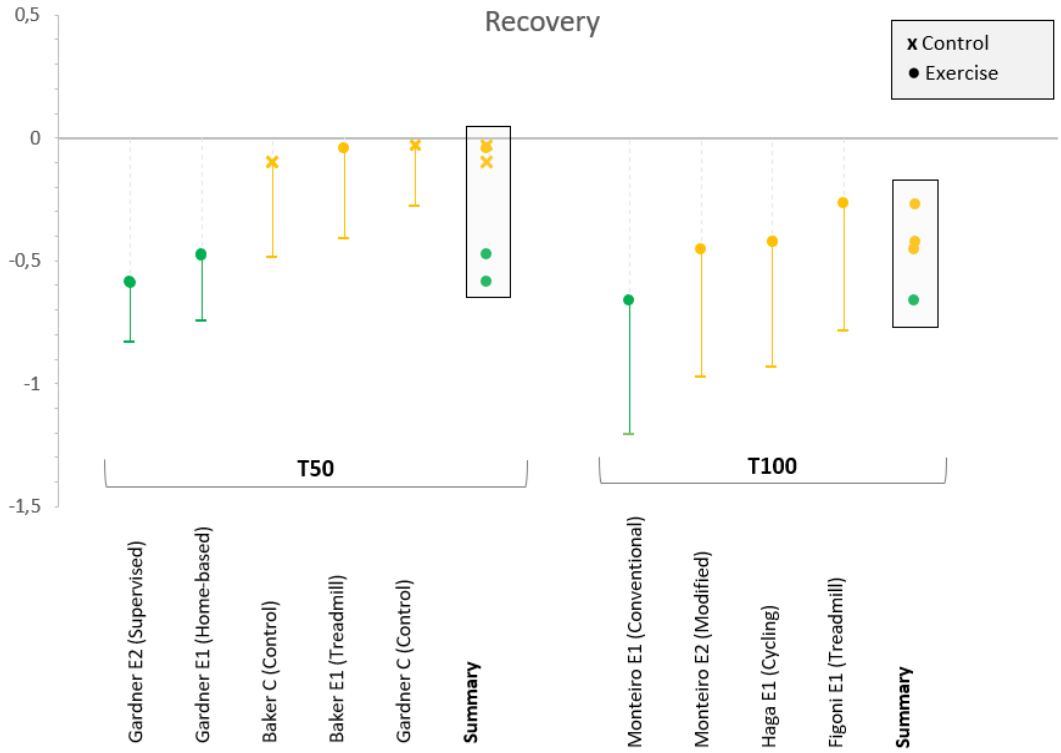

Figure 4C. *Effect sizes of halftime (T50) and total recovery time (T100) after an intervention. Results in yellow and green reflect non-significant and significant ($p < .05$) effect sizes respectively.*

Secondary outcomes

The majority of studies reported significant improvements in pain free (9/12 studies; 75%) and maximum walking capacity (14/16 studies; 87%), as well as 6MWD after the exercise interventions (24,26). Similarly, three studies applying an RCT design confirmed enhanced maximum walking capacity following walking and arm cranking exercise, respectively (20,26,27). However, a lack of improvement in maximum walking capacity during a progressive work rate test was noted after unstructured exercise (home based) (31) and after a pole striding intervention (23). Further, only one study assessed exercise capacity and found a statistically significantly improved VO_2peak following an arm cranking exercise compared with the control group (27). Although nine studies evaluated ABI, only one reported an improvement in the affected leg after 34 weeks of a structured home based walking intervention (31). Detailed information on the effects of exercise training on individual study level can be found in Supplementary files 2-4.

Risk of bias assessment

The median quality of the included studies was 8/12 (range 5-11) (Supplementary file 5). Specifically, the objective was clearly stated in nine articles, with two failing to provide a rationale and/or clear hypothesis for their study. All studies gave a clear description of

eligibility criteria, with the sample being representative of the IC population in eight. However, only two studies enrolled all eligible participants. Only four studies reported random sequence generation methods and four included an attention control group. Regarding the methodology, interventions were described in detail and delivered consistently in 10 studies, but assessors were reported to be blinded in only two. Ten studies used adequate statistical methods to assess the significance of the changes in the outcomes, although four did not have sufficient participants at follow up (dropout rate ≥ 20%). No incomplete outcome data were found when comparing the results with the protocol; however, four studies failed to report all the prespecified outcomes.

Near infrared spectroscopy methodology assessment

Although all studies (except one) reported the NIRS device used (25), almost all failed to report various device characteristics (e.g. wavelengths and sample frequency), which are important when comparing different studies (Supplementary file 6). To obtain valid and reliable results, a precise description of the anatomical placement is needed (8). Yet, only eight studies described probe position in detail, of which only four took appropriate measures to ascertain reproducibility. The remaining studies provided only a vague description regarding probe positioning (e.g. calf muscle). Two studies reported calf adipose tissue thickness (ATT) (measured with MRI and ultrasound, respectively) (20,30), and only one excluded participants with a calf ATT of > 20 mm (31). The use of raw or filtered data for analysis was not reported in any of the included articles. Regarding NIRS parameters, nine studies described the reported variables in detail, and eight reported all the prespecified outcomes.

Discussion

The aim of this review was to document systematically the effect of exercise interventions on muscle adaptations measured by NIRS after exercise interventions in patients with LEAD and to provide an overview of current NIRS methodology. Although earlier reviews have already addressed NIRS as a new method to evaluate and diagnose patients with LEAD (11,12), this is the first comprehensive review to investigate the effect of exercise therapy on NIRS outcomes.

Impact of exercise on near infrared spectroscopy parameters

Rest. Earlier studies reported comparable resting TSI in patients with IC and healthy controls (9,12). Similarly, no change was found in resting TSI after training in patients with IC. Moreover, an angioplasty treatment and an exercise group reported similar resting TSI (21). This could suggest that resting blood flow is usually sufficient for proper muscle

oxygenation, with the underlying supply demand mismatch occurring only during exercise and resembling the symptomatology of IC.

Exercise. A rapid maximum de-oxygenation in the beginning of exercise was previously specified as the hallmark NIRS pattern in patients with IC (9,10). Yet the results did not establish any improvements in absolute measures of de-oxygenation during treadmill testing. Whether de-oxygenation during exercise is related to blood flow, as evaluated by resting ABI, remains unclear, with studies reporting contrasting associations ($r = -.56$, $p = .002$; $r = -.105$, $p > .05$) (21,32). Yet, TTM substantially increased with training, meaning that patients could walk for longer before maximum de-oxygenation occurred. Similarly, O_2Hb was preserved during submaximal exercise without changes in tHb (24,31). Interestingly, early deoxygenation is associated with maximum walking capacity (32,33), as suggested earlier by Fuglestad et al. (9), who found a strong correlation between de-oxygenation one minute into exercise and maximum walking distance ($r = - .76$). In line with these findings, Gardner et al. found that the change in TTM correlated significantly with the change in maximum walking time ($r = .52$, $p < .001$ and $r = .43$, $p = .006$ for home based and supervised groups, respectively) (26). As TTM commonly appears prior to initial pain experience, these moderate correlations might be explained by the objective and subjective mismatch in pain perception and perseverance following an exercise programme (34).

Recovery. Concerning recovery, a tendency towards faster T50 and T100 following training interventions was noted. Faster re-oxygenation has previously shown clinical relevance for symptom resolution and is associated with better ambulatory outcomes (9,32,34). However, only one study achieved statistically significant results, whereas two others observed trends towards enhanced recovery after submaximal exercise intensity or recovery relative to total exercise time (21,29).

Underlying mechanisms of change using near infrared spectroscopy

Regarding resting muscle oxygen consumption, two studies showed increased values after an exercise intervention (20,31). Yet, muscle oxygen consumption is composed of blood flow and arteriovenous oxygen extraction, and therefore may involve various physiological adaptations (10). NIRS derived outcomes during exercise present local alterations that are expected after 12 weeks of exercise, such as improved capillarisation and microvascular haemodynamics (20,23,24,26,29), oxidative capacity (21,29,30), and oxygen extraction (20). In line with local adaptations involved, a 2020 study from Gardner et al. reported associations between TTM and ambulatory function, independent of resting ABI and common health burdens (33). Of note, Murrow et al. evaluated mitochondrial oxidative capacity at recovery using an exponential model to plot NIRS derived O_2Hb following repeated arterial occlusions after a bout of exercise (30). They showed a trend towards

improved mitochondrial capacity after an exercise intervention, which is similar to the improvement seen in other clinical populations with underlying mitochondrial dysfunction (30,35).

Still, this topic is part of a historical debate in which both muscle oxidative capacity and macrocirculation are opposed (6). Interestingly, the role of increased endothelial function and rheology has been suggested by the cross transfer effect of an arm cranking exercise (27), with similar improvements in NIRS de-oxygenation and recovery patterns. On the contrary, ABI analyses in all but one of the included samples did not reveal an augmented resting blood supply (20), which is in line with the available evidence (36,37). However, Manfredini et al. could discriminate two groups of responders after structured home based exercise (31): 1) 20 patients who had increased ABI had a blunted decrease of O_2Hb during submaximal exercise and a lower heart rate response; 2) 10 patients without a change in ABI increased their muscle oxygen consumption. These findings were confirmed by the study of Baker et al. (20), which reported both enhanced superficial blood flow and oxygen extraction levels during exercise. Collectively, redundancy of exercise responses and its physiological mechanisms may have an important role regarding increased walking capacity in patients with IC (38).

Study biases and methodology

Proper reporting of NIRS instrumentation, testing, and analysis is important as different technology and applied algorithms may affect the results and will hinder comparison among studies (8). In the included studies, the reproducibility of study protocols in a pre-post setting was often insufficient, with poor description of probe positioning (24,25,30), and without measures to ensure reproducibility for follow up assessments (21,23,26,31). The latter is of the utmost importance as reproducibility of the signals largely depends on a fixed probe location as oxygenation responses display large heterogeneity between different muscles, even within different regions of the same muscle (8). Additionally, the impact of adipose tissue thickness in the region of interest should be acknowledged when interpreting absolute concentrations of haemoglobin, as a thicker adipose layer can reduce the penetration depth of NIRS emitted wavelengths (8). However, the majority of included studies reported TSI outcomes, which are less prone to measurement error (8). Furthermore, a lack of uniformity of NIRS parameters reported across the different studies was noted, which makes comparisons among studies difficult. Therefore, it is recommended that researchers and clinicians should try to address these issues when performing NIRS measurements during exercise tests. Some examples of common issues and their potential solutions are presented in **Table 2**.

Limitations

The included studies had different methodologies and outcomes. To address this limitation, the sample effect sizes were calculated to present the direction of effect for most reported outcomes. The inclusion of non-randomised or non-controlled trials could introduce some bias yet was prespecified and is in line with the exploratory nature of this review. In addition, it is becoming difficult to get ethical approval for controlled studies in LEAD as exercise is now a class IA recommendation in IC treatment (21). However, it should be acknowledged that these pre-post studies without a randomised control group risk regression to the mean. This phenomenon can be minimised by performing familiarisation and multiple measurements at baseline, which were only performed in two non-controlled studies (22,28).

Conclusions

Evidence to date seems to suggest that exercise interventions may improve de-oxygenation and re-oxygenation patterns in patients with IC, measured by NIRS applications during various exercise testing protocols. NIRS therefore appears to have potency as an evaluation tool of peripheral muscle oxygenation following exercise interventions. Yet, given the scarcity of data, further research by means of larger, robust RCTs is needed. New trials should focus on better methodologies, with harmonised NIRS outcomes, and take into consideration transparency and reproducibility.

Table 2. *Common issues in NIRS methodology and application found in the literature, and their potential solutions. For a more detailed list of recommendations we refer to the review written by Barstow (8).*

Practical recommendations
• Report the technology used and the specific device characteristics: sample frequency, number of optodes, inter-optode distance and wavelength • Describe in detail the anatomical position of the probe placement and ensure methods for reproducibility for subsequent measurements and/or studies. • Adipose tissue thickness (ATT) should be measured at the site of interest and reported. Whenever possible, subject recruitment should be based on homogeneous ATT values or else a physiological calibration of the NIRS signals may be required. • Data from all raw NIRS signals (O_2Hb, HHb, tHb, diffHb) should be provided either in the main manuscript or in supplementary files. • Outcome variables should be clearly defined and replicable. In case of experimental variables or analyses, variables should be described in detail to avoid confusion. • The software used and the exact methods to analyze the data should be reported to ensure reproducibility and transparency. • Analyze and report changes from a timepoint of interest, amplitude of responses, and slopes. These are more insensitive to confounding factors such as adipose tissue thickness or random noise in the signal.

Appendices

***Supplementary file 1**: Search Strategy.*

1) Medline (Pubmed)

(((((((intermittent claudication[Title/Abstract]) OR (lower extremity artery disease[Title/Abstract])) OR (peripheral artery disease[Title/Abstract])) OR (peripheral vascular disease[Title/Abstract])) OR (peripheral arterial disease[Title/Abstract])) OR (peripheral obliterative arteriopathy[Title/Abstract])) OR (arterial occlusive disease[Title/Abstract])) AND ((((((((((exercise[Title/Abstract]) OR (walking[Title/Abstract])) OR (rehabilitation[Title/Abstract])) OR (physical activity[Title/Abstract])) OR (endurance[Title/Abstract])) OR (aerobic[Title/Abstract])) OR (strength[Title/Abstract])) OR (resistance[Title/Abstract])) OR (training[Title/Abstract])) OR (cycling[Title/Abstract])) OR (swimming[Title/Abstract]))) AND ((((((near-infrared spectroscopy) OR (near infrared spectroscopy)) OR (NIRS)) OR (muscle oxygenation)) OR (oximetry)) OR (spectroscopy)) (**363 HITS**)

2) Embase

#1 'lower extremity artery disease'/exp OR 'lower extremity artery disease'

#2 'intermittent claudication'/exp OR 'intermittent claudication'

#3 'peripheral occlusive artery disease'/exp OR 'peripheral occlusive artery disease'

#4: #1 OR #2 OR #3 (173814 HITS)

#5 exercise:ab,ti OR rehabilitation OR training:ab,ti OR swimming:ab,ti OR cycling:ab,ti OR walking:ab,ti OR 'physical activity':ab,ti OR strength:ab,ti OR resistance:ab,ti OR aerobic:ab,ti OR endurance:ab,ti (2403529 HITS)

#6 'near infrared spectroscopy' OR oximetry:ab,ti OR 'muscle oxygenation' OR 'spectroscopy' OR nirs(637974 HITS)

#7: #4 AND #5 AND #6

#8: #7 AND 'human'/de AND [embase]/lim NOT [medline]/lim (**77 HITS**)

TOTAL HITS: 440 HITS

***Supplementary file 2**: NIRS outcomes, results, comments and statistics.*

Author	At Rest	During Exercise	Recovery	Other outcomes	Comments	Applied Statistics
Baker et al 2017	E1: TSI **=** C: TSI =	E1: ΔTSI ↑ C: ΔTSI ↓ *In between group difference (p < .001)*	E1: T50 (T_R) **=** C: T50 (T_R) =	**Frequency-domain outcomes (NIRS):** Oxygen extraction fraction (**OEF**) Ratio: exercise ↑ and control ↓ Total hemoglobin/myoglobin count (**THC**) At rest: both in exercise and control = Delta hemoglobin/myoglobin count (**ΔTHC**) During Exercise: both in exercise and control **=**	-Data was converted from original median & IQR but no changes were noted in statistical significance values reported -T_R was used as the outcome of interest regarding recovery and approaches TSI T50 -Flow measurements using DCS (diffuse correlation spectroscopy) did not show any blood flow changes at rest (**F_o**). A significant in between group difference was noted when comparing ratio (**F_{ex}/ F_o**) change scores, in favor of the exercise group. -Combining NIRS and DCS measurements, a dynamic outcome for local muscle oxygen consumption (**rVO_2**) was significantly altered in favor of the exercise group.	-Wilcoxon signed rank test of ratios from both baseline and follow-up tests -TSI rest was the same at baseline and follow-up in both the E1 (p > .05) and C (p > .05). -ΔTSI was shown to be significantly different in-between groups (p < .001) but no group-specific data was provided
Beckitt et al 2012	E1: TSI = Angioplasty C: TSI **=**	E1: during both maximal and submaximal tests: ΔTSI **=** *Angioplasty C:* ΔTSI = (Maximal test) ΔTSI ↓ (Submaximal test)	E1: T50 **=** (Maximal) E1: T50 ↓ (Submaximal) *Angioplasty C*: T50 ↓	**Arterial occlusion** **O_2Hb recovery rate (after ischemia reperfusion)**: E1: = Angioplasty: ↑	-Data was converted from median & IQR	-Wilcoxon signed rank test -TSI rest was the same at baseline and follow-up in both the E1 (p > .5) and C (p > .3). -ΔTSI had a statistical tendency (**p= .10** and **p= .02**) to decrease during maximal and submaximal exercise in the angioplasty control-group. -T50 was significantly lower (**p= .02**) after a submaximal effort and a tendency to decrease after maximal effort in the exercise group (**p > .10**). In the angioplasty control-group T50 decreased significantly after both (sub)maximal effort. Although data was only provided for the submaximal test (**p= .01**)

Collins et al 2012 (a and b)	No data	**During progressive treadmill test:** E1: TTM ↑ E2: TTM **=**	No data	**During Constant-work rate test:** **Isotime TSI:** level of TSI recorded at a time consistent at baseline and follow-up Both in E1 and E2 =	-Data was provided in two separate manuscripts on the NIRS response during a progressive, graded treadmill test and a constant work-rate test. Time-point taken were 12-weeks and 24-weeks respectively.	-In the manuscript covering the progressive treadmill test (Collins et al, 2012 b) the authors used paired t-test in an intention-to-treat sample. In the manuscript covering the constant work-rate test (Collins et al, 2012a) the authors used both ANOVA/ANCOVA models -For progressive test a TTM improvement has been found in the traditional walking group only (**p= .00 vs p= .22**). Data on the constant-work rate test lacks independent pre-post comparison but our analysis of ES suggests a similar trend (ES: **p= .003** vs **p= .155**). A time-effect for both groups is reported to be significant (**p < .001**).
Figoni et al 2009	No data	E1: TSI_{min} **=**	E1: T100 **=**	**TSI exercise**: the mean TSI during exercise E1: ↓ **TSI exercise area**: area over the StO2 curve during exercise, %minutes E1: ↓	-The authors report that TSI exercise and TSI exercise area were significantly lower after the exercise intervention (**p= .01** respectively)	-Paired t-test -No significant changes were found for minimum TSI value during exercise after the intervention (**p= .24)**. Recovery time showed a statistical tendency (**p= .04**) after correcting for multiple testing.
Gardner et al 2014	No data	Both in E1 and E2: TTM ↑ C: TTM **=**	Both in E1 and E2: T50 ↓ C: T50 **=**		-Significant different responses on exercise and recovery parameters after both home-based and supervised exercise interventions compared to an attention-controlled group.	-Paired t-test (with ITT to substitute missing values) -Statistically significant increase in time to minimum TSI with faster recovery (T50) for both exercise groups (**p < .001**). No changes in the control group (**P not reported**). ANOVA for change scores (**p= .025** and **p= .020** respectively)
Haga et al 2020	No data	E1: ΔTSI **=**	E1: T100 **=**			-Paired t-test -ΔTSI was presented for both the left and right leg without significant changes after the exercise intervention (**p= .847** and **p= .947**) -T100 was statistically unaltered with **p= .144** after exercise

Manfredini et al 2012	No data	No data	No data	**Deoxygenation (O_2Hb AUC) and total hemoglobin (tHb AUC)** E1: O_2Hb AUC ↑, tHB AUC **=** E2: O_2Hb AUC **=,** tHB AUC **=** **Venous occlusion** **Muscle oxygen consumption (mVO_2):** E1: ↑ E2: **=**	-Healthy control group with unmodified active lifestyle -Muscle oxygen consumption was assessed after venous occlusion and was significantly increased in the structured exercise group only (**p= .03, with p not reported** in the self-paced and control group respectively).	-Paired t-test -Data was provided on Area Under Curve (AUC) for total hemoglobin and oxygen saturated hemoglobin during submaximal exercise (1.7-3.0 km/h), with significant changes in AUC O_2Hb in the structured exercise group (**p= .006**) but not in the self-paced or control group (**p not reported**). Baseline AUC for O_2Hb was significantly higher in the healthy control group (**p < .001**)
Monteiro et al 2019	No data	E1: TTM ↑ E1: ΔTSI = E2: TTM = E2: ΔTSI =	Both in E1 and E2: T100 ↓	**Arterial occlusion** **ΔHHb** Both in E1 and E2: = **ΔTSI** Both in E1 and E2: = **T100** Both in E1 and E2: = **Treadmill exercise** **ΔHHb** Both in E1 and E2: = **Time of resistance** Both in E1 and E2: ↑ **Deoxygenation rate (ΔTSI/sec)** Both in E1 and E2: ↓ **Re-oxygenation rate (ΔTSI/min)** Both in E1 and E2: = **Relative re-oxygenation rate** Both in E1 and E2: ↑ **Waking economy (m/ΔHHb)** Both in E1 and E2: = **Waking economy (m/ΔTSI)** Both in E1 and E2: ↑	-The authors report different outcomes during exercise with no change in ΔHHb (deoxygenated haemoglobin) but an increased time of resistance (after reaching lowest TSI values) in both groups (situation-effect: **p= .001** and pre-post for both groups **p < .05**). -Reoxygenation rate (ΔTSI/exercise + recovery time) was not altered after exercise. Yet, when corrected for total walking time (relative reoxygenation rate) the authors found a significantly shorter recovery time in both groups (situation-effect: **p= .017** and pre-post for both groups **p < .05**)	-Linear mixed models and between and post treatment statistical test are described -TTM was significantly different after the intervention for both groups (situation-effect: **p= .01**) with a significant between group-difference (interaction-effect: **p= .020**). TTM significantly increased in the conventional group alone (**p < .05**) -ΔTSI did not change after the intervention in both groups (situation-effect: **p= .709**) -Recovery was significantly faster after both interventions (situation-effect: **p= .002** and pre-post for both groups **p < .05**)

Murrow et al 2019	No data	No data	No data	**Arterial occlusion** **Muscle oxygen consumption (mVO_2)** E1: ↑ E2: = **O_2HB recovery half-time** E1: = E1: =	-The authors limited NIRS assessment to arterial occlusion maneuvers -O_2Hb (oxygenated hemoglobin) recovery half-time was not significantly altered after exercise in both groups (interaction-effect: **p= .90**) -Muscle oxygen consumption was increased (interaction-effect: **p= .003**) the conventional group alone *(***p= .004***)* compared to the NIRS-trained group *(***p= .183***)* with p-values derived from the calculated effect sizes.	-Mixed effect model
Tew et al 2009	E1: TSI = C: TSI **=**	E1: TTM ↑ E1: TSI_{min} **=** C: TTM = C: TSI_{min} **=**	No data	**Isotime TSI%** **(30, 60, 120, 180 and 240 seconds)** E1: ↑ (for 30, 60, 120, 180 seconds) C: = (for 30, 60, 120, 180 seconds)	-TSI was significantly higher after intervention on all time-points except for the 240 seconds mark (**p < .05**). In comparison, controls did have a higher TSI at 240 seconds alone.	-ANCOVA and paired t-test -TTM was significantly increased in the intervention group alone (**p=< .05**) with an interaction-effect of **p < .001**. -No changes were noted in TSI_{min} (interaction-effect: **p= .186**) (pre-post p-values not reported)
Woessner et al 2018	No data	No data	No data	**Deoxygenation characteristics** E1: = **Oxygenation characteristics** (parameter a, parameter b in f=a*x/(b+x)) E1: ↑	-The authors examined the oxygenated and deoxygenated hemoglobin response (fitted to an exponential decay and single rectangular hyperbola respectively) during exercise and observed a significant increase in O_2Hb-maintainance following exercise intervention in the placebo-controlled nitrate group.	-Chi-square test between groups

***Supplementary file 3**: NIRS effect sizes.*

At rest	Sample size	Effect size (SMD)	Confidence intervals (95%)	Pre Mean ± SD	Post Mean ± SD	Group P-value	Group comparison P-value	Measurement method
Tissue Saturation Index								
Tew E1	27	0.272	(-0.113, +0.656)	47.9 ± 9.0	50.8 ± 11.8	NR	NR	NR
Tew C	24	-0.122	(-0.523, +0.280)	46.0 ± 6.3	45.2 ± 6.8	NR		NR
Baker E1	29	0.259	(-0.111, +0.630)	59.7 ± 20.3*	64.3 ± 14.0*	> .05	> .05	Standing
Baker C	35	0.217	(-0.119, +0.552)	55.3 ± 20.1*	59.3 ± 16.2*	> .05		Standing
Beckitt C	14	0.073	(-0.452, +0.579)	55.3 ± 12.4*	56.3 ± 14.8*	> .3	NR	Standing
Beckitt E1	42	0.030	(-0.273, +0.332)	55.7 ± 11.5*	56.0 ± 10.7*	> .5		Standing
Figoni E1	15	-0.191	(-0.702, +0.320)	84.0 ± 14.0	81.0 ± 17.0	NR	NA	Supine
Muscle oxygen consumption (ml/100g/min in Manfredini et al, in Baker et al units are not reported)								
Baker E1	29	**1.069**	(+0.612, +1.525)	2.406 ± 0.920*	3.343 ± 0.826*	NR	**< .001**	DCS/FD-NIRS
Baker C	35	-0.150	(-0.483, +0.183)	2.583 ± 0.973	2.403 ± 1.344	NR		DCS/FD-NIRS
Manfredini E1	31	**0.370**	**(+0.006, +0.733)**	0.044 ± 0.028	0.054 ± 0.026	**.03**	NR	Venous occlusion
Manfredini E2	14	0.169	(-0.358, +0.697)	0.040 ± 0.022	0.044 ± 0.025	NS		Venous occlusion
Mitochondrial function								
Murrow E1	10	**1.166**	**(+0.362, +1.969)**	0.87 ± 0.51	1.46 ± 0.51	NR	**.003**	Arterial occlusion
Murrow E2	8	0.499	(-0.236, +1.234)	1.07 ± 0.48	1.31 ± 0.48	NR		Arterial occlusion

***Abbreviations:** SMD: Standardized Mean Difference, E: exercise group, C: control group, NR (not reported), NA (not applicable) and NS (not significant)/ *Converted from median and IQR. Group P-value and Group Comparison P-value are presented as reported in their main manuscripts. Statistically significant values (p<.05) are expressed in bold.*

Exercise	Sample size	Effect size (SMD)	Confidence interval	Pre Mean ± SD	Post Mean ± SD	Group P-value Manuscript	Group comparison P-value	Testing protocol
TTM								
Monteiro E1	16	**0.927**	**(+0.341, +1.513)**	150 ± 91.9	772 ± 712	**< .05**	**.020**	Constant work-rate
Monteiro E2	16	0.297	(-0.204, +0.798)	104 ± 89.6	140.6 ± 140.6	NR		Constant work-rate
Collins E1	40	**0.704**	**(+0.358, +1.050)**	255 ± 249.6	476.4 ± 353.4	**.000**	**.002**	Progressive work
Collins E2	45	0.172	(-0.122, +0.467)	221.4 ± 184.2	258 ± 232.2	.22		Progressive work
Gardner E1	60	**0.577**	**(+0.303, +0.850)**	195 ± 247	341 ± 259	**< .001**		Progressive work
Gardner E2	60	**0.579**	**(+0.306, +0.852)**	166 ± 196	308 ± 275	**< .001**	**.025**	Progressive work
Gardner C	60	0.103	(-0.151, +0.356)	245 ± 283	272 ± 236	NR		Progressive work
Tew E1	27	**0.418**	**(+0.025, +0.811)**	268 ± 305	410 ± 366	**.05**	**< .001**	Progressive work
Tew C	24	-0.083	(-0.483, +0.318)	497 ± 372	466 ± 379	NR		Progressive work
delta TSI								
Baker E1	29	0.350	(-0.025, +0.725)	12.3 ± 8.58*	16.00 ± 11.70*	> .05	**< .001**	Progressive work
Baker C	35	**-0.593**	**(-0.952, -0.234)**	14.0 ± 6.18*	10.3 ± 6.18*	> .05		Progressive work
Beckitt E1	42	0.113	(-0.191, +0.417)	38.3 ± 8.44*	39.3 ± 9.21*	> .3	NR	Constant work-rate
Beckitt C	14	**-0.690**	**(-1.273, -0.107)**	38.0 ± 9.88	31.7 ± 8.24	**.046**		Constant work-rate
Monteiro E1	16	0.026	(-0.464, +0.516)	19.1 ± 8.40	18 ± 8.80	NR	.575	Constant work-rate
Monteiro E2	16	-0.127	(-0.619, +0.365)	21.1 ± 8.17	21.3 ± 8.50	NR		Constant work-rate
Haga E1 (Left)	16	0.008	(-0.482, +0.498)	17.7 ± 12.8	17.8 ± 13.3	0.947	NA	Constant work-rate
TSImin								
Tew E1	27	0.000	(-0.377, +0.377)	39 ± 14	39 ± 15	NR	.186	Progressive work
Tew C	24	-0.285	(-0.693, +0.123)	38 ± 10	35 ± 11	NR		Progressive work
Figoni E1	15	-0.286	(-0.802, +0.231)	11 ± 14	7 ± 14	.24	NA	Progressive work

Abbreviations: *SMD: Standardized Mean Difference, E: exercise group, C: control group, NR (not reported), NA (not applicable) and NS (not significant)/ *Converted from median and IQR. Group P-value and Group Comparison P-value are presented as reported in their main manuscripts. Statistically significant values (p<.05) are expressed in bold.* ***Collins 2012a****: similar results on TTM as Collins 2012b for a constant rate treadmill test (only time-effect presented with p=.05).*

Recovery	Sample size	Effect size (SMD)	Confidence intervals	Pre Mean ± SD	Post Mean ± SD	Group P-value	Group comparison P-value	Testing protocol
T50								
Gardner E2	60	**-0.558**	(-0.830, -0.286)	165 ± 147	94 ± 76	**< .001**		Progressive work
Gardner E1	60	**-0.477**	(-0.744, -0.210)	168 ± 184	92 ± 94	**< .001**	**.020**	Progressive work
Gardner C	60	-0.027	(-0.280, +0.226)	145 ± 149	141 ± 145	NR		Progressive work
Baker C	35	-0.101	(-0.485, +0.283)	108.7 ± 86.6*	100 ± 85.0*	> .05	> .05	Progressive work
Baker E1	29	-0.046	(-0.410, +0.318)	95.3 ± 61.6*	92.7 ± 53.8*	> .05		Progressive work
T100								
Monteiro E1	16	**-0.665**	(-1.207, -0.124)	720.7 ± 921.8	155.1 ± 168.5	**< .05**	.601	Constant work-rate
Monteiro E2	16	-0.457	(-0.972, +0.058)	637.8 ± 974.5	223.8 ± 157.6	**< .05**		Constant work-rate
Haga E1	16	-0.424	(-0.935, +0.088)	200.1 ± 151.6	143.1 ± 104.8	.144	NA	Constant work-rate
Figoni E1	15	-0.269	(-0.784, +0.246)	444 ± 403.2	343.8 ± 330.6	.04	NA	Progressive work

Abbreviations: *SMD: Standardized Mean Difference, E: exercise group, C: control group, NR (not reported), NA (not applicable) and NS (not significant)/ *Converted from median and IQR. Group P-value and Group Comparison P-value are presented as reported in their main manuscripts. Statistically significant values (p<.05) are expressed in bold.*

Supplementary file 4: *Secondary outcomes effect sizes.*

Secondary outcomes	Sample size (n)	Effect size (SMD)	Confidence interval (95%)	Pre Mean ± SD	Post Mean ± SD	Group P-value	Group comparison P-value	Testing protocol
Pain Free Walking distance (meter)								
Beckitt E1	42	**1.880**	(+1.377, +2.383)	57.7 ± 30.7*	119.3 ± 34.5*	**.01**	NR	Constant work-rate
Beckitt C	14	**1.513**	(+0.746, +2.280)	62.3 ± 35.4*	161.7 ± 75.8*	> .3		Constant work-rate
Haga E1	16	0.411	(-0.100, +0.921)	160 ± 128	228 ± 187	.034	NA	Constant work-rate
Manfredini E1	31	**0.769**	(+0.368, +1.169)	89.2 ± 46.7	127.7 ± 52.9	.0001	NR	Progressive work
Manfredini E2	14	0.291	(-0.244, +0.826)	103.1 ± 64.1	123.2 ± 73.1	NS		Progressive work
Tew E1	27	**0.718**	(+0.295, +1.141)	147 ± 125	255 ± 167	< .05	.035	Progressive work
Tew C	24	0.083	(-0.317, +0.484)	177 ± 160	192 ± 195	NR		Progressive work
Pain Free Walking time (seconds)								
Murrow E1	10	**1.475**	(+0.580, +2.371)	150 ± 170.8	402 ± 170.8	< .01	.97†	Progressive work
Murrow E2	8	**1.107**	(+0.227, +1.987)	216 ± 169.7	414 ± 186.7	< .01		Progressive work
Collins (a) E1	49	**0.624**	(+0.318, +0.930)	252 ± 162	408 ± 288	< .001	NR	Constant work-rate
Collins (a) E2	46	**0.473**	(+0.169, +0.778)	222 ± 120	558 ± 762	< .001		Constant work-rate
Collins (b) E1	40	**0.336**	(+0.018, +0.655)	237 ± 178.2	313.8 ± 257.4	.034	.38	Progressive work
Collins (b) E2	45	0.204	(-0.092, +0.499)	199.8 ± 165	238.8 ± 210	.15		Progressive work
Gardner E1	60	**0.487**	(+0.220, +0.755)	195 ± 171	300 ± 242	< .001		Progressive work
Gardner E2	60	**0.672**	(+0.392, +0.952)	193 ± 150	363 ± 292	< .001	< .001	Progressive work
Gardner C	60	0.098	(-0.156, +0.351)	205 ± 167	222 ± 180	NR		Progressive work
Woessner E1	13	**1.033**	(+0.360, +1.706)	/	Δ59.2 ± 57.3	< .05	NA	Progressive work
Maximal Walking distance (meter)								
Beckitt E1	42	**2.240**	(+1.673, +2.806)	124.3 ± 35.5*	233 ± 55.3*	**.002**	NR	Constant work-rate
Beckitt C	14	**1.381**	(+0.649, +2.113)	133.7 ± 47.8*	323.3 ± 154.8*	**.001**		Constant work-rate
Manfredini E1	31	**0.572**	(+0.192, +0.952)	140 ± 60.1	173.2 ± 55.7	.001	NR	Progressive work
Manfredini E2	14	-0.098	(-0.623, +0.428)	147.3 ± 82.5	139.8 ± 69.7	NR		Progressive work
Haga E1	16	**0.646**	(+0.107, +1.185)	453 ± 345	702 ± 416	.006	NA	Constant work-rate
Monteiro E1	16	**1.708**	(+0.940, +2.477)	184 ± 156.4	1669.6 ± 937.2	NR††	.444	Constant work-rate
Monteiro E2	16	**1.110**	(+0.487, +1.733)	174 ± 141.9	1154.5 ± 945.9	NR††		Constant work-rate
Tew E1	27	**0.561**	(+0.155, +0.967)	496 ± 250	661 ± 324	< .05	.011	Progressive work
Tew C	24	0.091	(-0.310, +0.492)	600 ± 300	626 ± 266	NR		Progressive work
Maximal Walking time (seconds)								
Baker E1	29	**0.439**	(+0.058, +0.820)	493 ± 332.2*	718 ± 590.3*	NR†	.001	Progressive work
Baker C	35	0.297	(-0.042, +0.635)	416.7 ± 216.4*	503.7 ± 333.9*	NR†		Progressive work
Collins (a) E1	49	**0.842**	(+0.516, +1.168)	478.8 ± 216	1266 ± 1024.2	NR	NR	Constant work-rate

Collins (a) E2	46	**0.684**	(+0.363, +1.005)	443.4 ± 173.4	901.2 ± 739.2	NR		Constant work-rate
Collins (b) E1	40	**0.703**	(+0.357, +1.049)	480.6 ± 240.6	678 ± 308.4	.000	.002	Progressive work
Collins (b) E2	45	0.104	(-0.188, +0.397)	465.6 ± 240.6	469.8 ± 334.2	.92		Progressive work
Figoni E1	15	**1.000**	(+0.380, +1.620)	431.4 ± 237.6	676.2 ± 251.4	.000	NA	Progressive work
Murrow E1	10	**0.738**	(+0.039, +1.437)	508.2 ± 182.1	642.6 ± 182.1	NR	< .05	Progressive work
Murrow E2	8	**0.757**	(-0.029, +1.542)	522 ± 181.6	659.4 ± 181.6	NR		Progressive work
Gardner E1	60	**0.345**	(+0.085, +0.605)	380 ± 274	490 ± 350	< .001		Progressive work
Gardner E2	60	**0.710**	(+0.427, +0.993)	356 ± 222	547 ± 299	< .001	< .001	Progressive work
Gardner C	60	0.088	(-0.165, +0.342)	464 ± 237	486 ± 260	NR		Progressive work
Woessner	13	**1.153**	(+0.452, +1.855)	/	Δ238.7 ± 207.0	< .01	NA	Progressive work
6 Minute Walking Time								
Gardner E1	60	**0.386**	(+0.124, +0.649)	328 ± 108	372 ± 119	**< .001**		
Gardner E2	60	**0.165**	(-0.089, +0.420)	326 ± 94	341 ± 87	**< .05**	**.028**	
Gardner C	60	0.052	(-0.201, +0.305)	376 ± 73	380 ± 81	NR		
Woessner E1	13	**2.033**	(+1.081, +2.985)	/	Δ24.6 ± 12.1	**< .05**	NA	
Peak oxygen consumption (ml/kg/min)								
Tew E1	27	0.322	(-0.065, +0.708)	17.2 ± 2.7	18.2 ± 3.4	< .05	**.038**	
Tew C	24	-0.120	(-0.521, +0.282)	18.6 ± 5.1	18.0 ± 4.9	NS		
Ankle Brachial Index								
Baker E1	29	0.055	(-0.309, +0.420)	0.65 ± 0.17*	0.66 ± 0.19*	> .05	> .05	
Baker C	35	-0.072	(-0.404, +0.260)	0.61 ± 0.16*	0.60 ± 0.09*	> .05		
Manfredini E1	31	**0.638**	(+0.252, +1.024)	0.59 ± 0.13	0.68 ± 0.15	**< .0001**	NR	Baseline E1<E2
Manfredini E2	14	0.273	(-0.261, +0.806)	0.67 ± 0.11	0.70 ± 0.11	NR		
Murrow E1	10	0.000	(-0.620, +0.620)	0.80 ± 0.24	0.80 ± 0.24	NR	.52	
Murrow E2	8	0.318	(-0.392, +1.028)	0.87 ± 0.22	0.94 ± 0.22	NR		
Tew E1	27	0.231	(-0.151, +0.613)	0.68 ± 0.13	0.71 ± 0.13	NR	NR	
Tew C	24	0.000	(-0.400, +0.400)	0.69 ± 0.12	0.69 ± 0.15	NR		
Monteiro E1 Right	16	0.107	(-0.384, +0.598)	0.63 ± 0.17	0.65 ± 0.20	NR	NR	
Monteiro E2 Right	16	0.059	(-0.432, +0.549)	0.62 ± 0.18	0.63 ± 0.16	NR		Effect situation: .070
Monteiro E1 Left	16	0.303	(-0.198, +0.804)	0.63 ± 0.17	0.68 ± 0.16	NR	NR	
Monteiro E2 Left	16	-0.060	(-0.550, +0.431)	0.63 ± 0.18	0.62 ± 0.15	NR		Effect situation: .101
Haga E1 Right	16	-0.102	(-0.594, +0.389)	0.79 ± 0.19	0.77 ± 0.20	.189	NA	
Haga E2 Left	16	-0.050	(-0.540, +0.440)	0.77 ± 0.21	0.76 ± 0.19	.621	NA	
Woessner E1	13	0.290	(-0.265, +0.845)	0.70 ± 0.19	0.76 ± 0.22	NR	NA	

Abbreviations: *SMD: Standardized Mean Difference, E: exercise group, C: control group, NR (not reported), NA (not applicable) and NS (not significant) / *Converted from median and IQR /† (Murrow et al report a different p-value in the text compared to the table: p=.97 vs p<.05). Group P-value and Group Comparison P-value are presented as reported in their main manuscripts. Statistically significant values (p< .05) are expressed in bold.*

***Supplementary file 5**: Risk of bias assessment.*

***Table S5.1.** Study level.*

Study	Objective clearly stated	Eligibility clearly described	Representative study sample	All eligible participants enrolled	Random sequence generation	Control group	Clear description of intervention and delivered consistently	Assessors blinded to intervention	Sufficient follow-up rate	Statistical methods to examine pre-post with p-values	Complete outcome data	Non-selective reporting	Overall score
Baker et al 2017	YES	YES	YES	NO	NO	YES	YES	NO	YES	YES	YES	YES	9
Beckitt et al 2012	NO	YES	NO	NO	NO	NO	YES	NO	YES	YES	YES	NO	5
Collins et al 2012 (a,b)	YES	YES	YES	NO	YES	NO	YES	NO	NO	YES	YES	NO	7
Figoni et al 2009	YES	YES	NO	NO	NO	NO	YES	NO	NO	YES	YES	YES	6
Gardner et al 2014	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	NO	10
Haga et al 2020	NO	YES	NO	NO	NO	NO	YES	NO	YES	NO	YES	YES	5
Manfredini et al 2012	YES	YES	YES	NO	NO	NO	YES	NO	YES	YES	YES	YES	8
Monteiro et al 2019	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	11
Murrow et al 2019	YES	YES	YES	NO	NO	NO	NO	NO	NO	YES	YES	YES	6
Tew et al 2009	YES	YES	NO	NO	YES	YES	YES	NO	YES	YES	YES	YES	9
Woessner et al 2018	YES	YES	YES	NO	NO	YES	YES	YES	NO	YES	YES	NO	8

***Note.** The overall score for each article is calculated by summing the number of 'yes' answers.*

Table S5.2. *NIRS specific.*

Study	NIRS device characteristics				Anatomical description	Reproducibility	ATT measurement	Analysis		
	Manufacturer	Sampling frequency	Wavelengths	Optodes				Filter	Variables defined	All outcomes reported
Baker et al 2017	YES	YES	YES	YES	YES	NO	YES	NO	YES	YES
Beckitt et al 2012	YES	YES	YES**	YES	YES	YES	NO	NO	YES	NO
Collins et al 2012 (a,b)	YES	YES	NO	NO	YES	YES	NO	NO	YES	NO
Figoni et al 2009	YES	YES	YES**	NO*	YES	YES	NO	NO	YES	YES
Gardner et al 2014	YES	YES	NO	NO*	YES	NO	NO	NO	NO	NO
Haga et al 2020	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES
Manfredini et al 2012	YES	NO	YES	YES	YES	YES	NO***	NO	YES	YES
Monteiro et al 2019	YES	YES	NO	NO	YES	NO	NO	NO	YES	YES
Murrow et al 2019	YES	YES	YES	YES	NO	NO	YES	NO	YES	YES
Tew et al 2009	YES	YES	NO	NO	YES	NO	NO	NO	YES	YES
Woessner et al 2018	YES	NO	YES	NO	NO	NO	NO	NO	YES	YES

Abbreviations: *ATT: Adipose Tissue Thickness. *Optodes: only mentioning the used probe, **General statements rather than specific wavelength information, ***Not mentioned in the methods although present in the exclusion criteria*

Supplementary file 6: *Overview of NIRS devices in the included studies.*

DEVICE	TECHNIQUE	CHANNELS	WAVELENGHTS	COMPANY	STUDIES	WEBSITE
INSPECTRA 325	Multi-distance CW	/	3	Hutchinson, USA	4 (22, 23, 26, 28)	www.hutchinson.tdk.com
NIRO 300	Multi-distance CW	3	4	Hamamatsu, Japan	2 (21, 27)	www.hamamatsu.com
OXYMON MK III	Multi-distance CW	2	3	Artinis, Netherlands	2 (30, 31)	www.artinis.com
PORTAMON	Multi-distance CW	1	3	Artinis, Netherlands	2 (24, 29)	www.artinis.com
FOIRE-3000		24	3	Shimadzu, Kyoto, Japan	1 (25)	
CUSTOM-BUILT FD-NIRS	Frequency-domain	/	3	/	1 (20)	/

Abbreviations: *CW: continuous wave. Channels: the number of transmitters - receiver combinations.*

***Supplementary file 7**: PRISMA 2009 Checklist.*

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S file 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	/
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	S file 6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	/
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Chapter 3.2: Near infrared spectroscopy to evaluate the effect of a hybrid exercise program on peripheral muscle metabolism in patients with intermittent claudication: an exploratory PROSECO-IC sub study

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To be submitted

Abstract

Background: Lower-extremity artery disease (LEAD) is characterized by obstruction of blood flow in the lower limb arteries. Insufficient blood flow typically causes a lack of oxygen to reach distal muscles during activity, causing the symptom of intermittent claudication (IC). The complex interaction of blood flow and oxygenation is not completely understood, yet holds potential to improve knowledge on underlying changes after exercise therapy in patients with LEAD having complaints of IC.

Methods: This study is an exploratory analysis of a prospective cohort following a 12-week hybrid walking intervention. Patients with LEAD (Ankle-Brachial Index (ABI) ≤ 0.9 or 20% decrease in ABI after a maximal treadmill test) and complaints of IC (Rutherford I-III) were included. In short, the intervention combined a supervised, center-based and two home-based walking sessions monitored using a GPS wearable and individually adjusted on a weekly basis. Functional capacity was evaluated using (sub)maximal treadmill tests and a six-minute walk test (6MWT), with maximal walking distance (MWD) as the primary outcome. During treadmill tests, near infrared spectroscopy (NIRS) was used to assess tissue saturation index (TSI%) from rest to recovery. Next to paired analysis of intervention effects, high and low responders were compared to study underlying changes after the intervention. All tests were two-tailed and statistical significance was considered with a p-value of ≤ 0.05.

Results: Thirty-eight participants (31 men, mean 70.3 (SD 8.9) years) completed the intervention with NIRS analyses. Functional capacity during a progressive treadmill test and 6MWT (+155 (SD 177) and +18 (SD 29) meters) significantly improved in terms of MWD with concomitant changes in muscle de- and reoxygenation measures. During submaximal treadmill walking, oxygenated hemoglobin was better preserved after the intervention ($p = 0.040$). In line, deoxygenation was slower during the maximal treadmill test (+38.5 (IQR 793) seconds, $p < 0.001$), highlighting better preservation of tissue oxygen saturation during first stages of progressive exercise. Slower deoxygenation was more pronounced in high responders on the maximal treadmill test. In addition, enhanced time to total recovery of TSI was noted (-16 (IQR 109) seconds, $p = 0.045$).

Conclusion: Functional capacity was significantly improved following a 12-week walking intervention. Exploratory analysis revealed slower deoxygenation levels, which were more pronounced in high responders.

Introduction

Functional capacity of patients with lower extremity artery disease (LEAD) is severely impaired. This functional limitation cannot be explained solely by the intrinsic blood flow obstruction characterizing LEAD. Studies have reported only moderate associations between the ankle-brachial index (ABI) and maximal walking capacity in patients with LEAD (1). Further, even after restoration of blood flow through revascularization, functional capacity often remains impaired (2). Contemporary international guidelines recommend exercise therapy (IA evidence) to improve functional capacity as well as quality of life in patients with LEAD and IC (3–5). However, hemodynamic changes, assessed by means of resting ABI or hyperemic calf blood flow, are also neglectable after exercise therapy (6). On the other hand, local adaptations leading to improved oxygen distribution and/or extraction (e.g. microvascular fiber contact, mitochondrial function) are suggested to explain, at least partly, the observed benefits (7,8) in functional capacity and reverse underlying myopathies, due to chronic ischemic damage and physical inactivity (9,10). As such, an evaluation of local muscle oxygenation could provide further insights in these underlying changes and possibly help to understand the variability in functional outcomes observed following exercise interventions (11,12).

Near-infrared spectroscopy (NIRS) could offer a non-invasive method to study these local muscle oxygenation changes after an exercise intervention (13). In short, NIRS provides a dynamic assessment of tissue oxygen availability, extraction, and utilization. Earlier studies already showed the potency or potential to diagnose patients with LEAD based on time-dependent NIRS parameters such as recovery half-time (T50) (14). Moreover, recovery or reoxygenation indices have been found to be related to ABI, and deoxygenation patterns during exercise have been shown to provide additional insights in maximal walking distance beyond macrovascular blood supply (15). These findings highlight the versatility and redundancy of local mechanisms involved in defining functional status, and the different physiological events assessed by NIRS and ABI (14). Preliminary evidence is suggesting that NIRS derived changes in de- and reoxygenation are congruent with progression in ambulatory capacity after an exercise intervention (16). However, data is scarce, and NIRS derived measures show considerable heterogeneity (16–18). Given the variability in both ambulatory outcomes and NIRS patterns during exercise, NIRS outcomes can be used to explore exercise therapy responsiveness (17,19).

Thus, using NIRS during standardized functional tests, the aim of this PROSECO-IC (Determinants of **PRO**gression after **S**upervised **E**xer**C**ise training through techn**O**logy in patients with Intermittent Claudication) sub study was to evaluate the effects of a hybrid walking intervention on muscle oxygenation indices at rest, during treadmill exercise and during recovery in patients with LEAD and IC. We also sought to explore whether differences

in functional outcomes following an exercise intervention are associated to differences in NIRS parameters. We hypothesized that changes in muscle oxygenation are more pronounced in patients who show a better progression in functional capacity after the intervention.

Methodology

Design & study protocol

The current report is performed in the context of a more comprehensive prospective study, the PROSECO-IC study, which aimed to explore predictors of ambulatory improvement after walking therapy. All participants provided written informed consent before participation. The study was approved by the local Ethical Committee of the University Hospitals Leuven (s62125) and was a priori registered on clinicaltrials.gov with the following identifier: NCT03995589.

Participants

Patients were contacted after a consultation at the vascular center of the University Hospitals of Leuven. Patients (≥18 years) were included when they: I) presented with new complaints of intermittent claudication (Rutherford I-III; as diagnosed by the vascular surgeon), II) had an ABI ≤ 0.9 and/or 20% decrease in ABI after a maximal treadmill test, III) were provided with a conservative treatment plan for three months, and IV) were able to read and understand Dutch questionnaires. Patients were excluded when: I) patients presented with signs of complex arrhythmias or significant ischemia during a cardiopulmonary exercise test, or II) had a comorbidity which limited participation in an exercise program.

Intervention

The PROSECO-IC intervention was a 12-week hybrid intervention, combining home-based and supervised center-based walking sessions. A detailed description of the study design, training intervention and main results will be published elsewhere (cfr. *Acceptability, adherence and efficacy of a hybrid walking program in patients with intermittent claudication: an evaluation of the PROSECO-IC intervention*). In brief, participants were asked to complete two weekly home-based walks and one weekly supervised session at the University Hospitals of Leuven. These center-based sessions were used to provide in-person guidance, monitoring and feedback to allow an objective and progressively increase in walking volume and intensity. All sessions consisted of a short warm-up, walking intervals on the treadmill and stretching of the major lower limb muscles. In addition, participants received a walking prescription detailing the exercise characteristics of the sessions that had to be completed in the home environment. Patients were asked to record these home-

based sessions using a sport watch (Garmin®, Forerunner 30) and to upload these sessions on the online Garmin Connect platform. This allowed the researchers to evaluate adherence to the program prescription and walking progression. Walking prescription was based on prevailing exercise guidelines in LEAD (4) and included alternating periods of walking up to moderate claudication pain with passive or active recovery until pain resolved (i.e. typically 2 minutes). In general, participants were instructed to progressively increase the duration of their walking sessions from 28 to 50 minutes in the first six weeks, by increasing interval duration (e.g. from 4- to 6-minute interval blocks). During the final six weeks, duration of walking sessions remained stable, yet intensity of the bouts was increased by introducing short (2- to 3-minutes) moderate to severe claudication pain intervals throughout each session.

Measurements

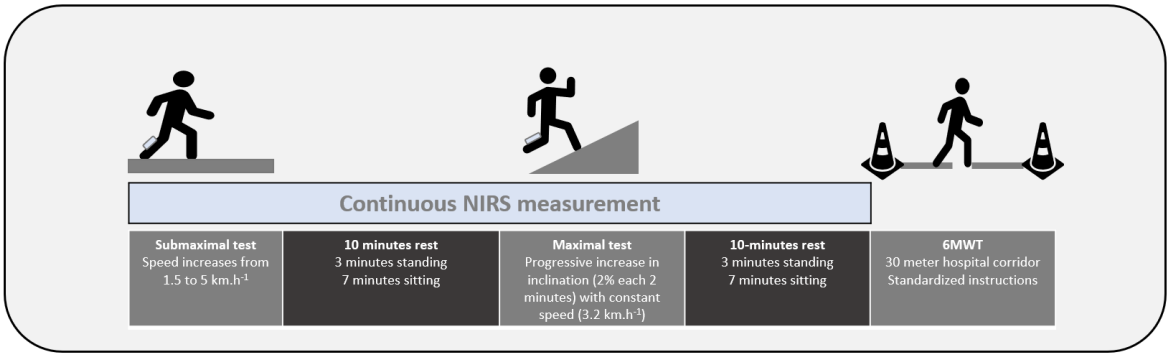


Figure 1. *Schematic illustration of the functional capacity tests protocol.*

Functional capacity tests

An overview of the functional test protocol is provided in **Figure 1**. Functional capacity was evaluated by means of two treadmill tests (20,21) and a six-minute walk test (6MWT). The tests were performed on the same day and in a standardized order (i.e. submaximal, maximal and 6MWT), while each test was interspersed by 10-minutes of rest. At the initiation of the test, participants were asked to stand for two minutes after which a standardized test protocol was applied. During each of the treadmill tests, participants were asked to report pain onset (Pain-free walking distance (PFWD)) and maximal claudication pain (Maximal walking distance (MWD)). When reaching their MWD, participants were asked to remain in standing position for three minutes followed by an additional seven minutes of recovery in seated position. Participants were allowed to use the treadmill hand rails, screens were blinded and no encouragement was provided during the entire protocol. The submaximal treadmill test was adapted from Manfredini et al to evaluate level walking speed (21) and included a one minute warm up at 1.5 $km.h^{-1}$, followed by increments of 0.1 $km.h^{-1}$ every 10 meters. The test ended when patients reached maximal claudication pain or 5.0 $km.h^{-1}$. Onset of claudication pain was recorded as pain-free walking speed (PFWS).

Then, a progressive maximal treadmill test was performed applying the Gardner protocol. This test started from a level surface, with increasing inclination of 2% every two minutes (20). Inclination was limited at 14% due to technical restraints. Speed was held constant at 3.2 $km.h^{-1}$ ± 1 $km.h^{-1}$ according to the individual fitness levels. Finally, a six-minute walk test (6MWT) was performed in a 30-meter hospital corridor according to the American Thoracic Society guideline (22). Participants were instructed to walk as far as possible within six minutes (Six-minute walking distance (6MWD)). Following standardized instructions, participants could adapt their walking speed or take a short break if needed.

Near Infrared Spectroscopy measurement

During each of the treadmill tests, calf muscle oxygenation of the most affected leg was assessed using continuous-wave near-infrared spectroscopy (NIRS) (Portamon, Artinis Medical Systems). First, the probe was covered in a transparent elastic wrap, then fixated using adhesive tape and finally covered with a black sleeve, to stabilize the probe and block exogenous lights. Reproducibility was guaranteed my marking the placement of the probe and noting the distance from the medial malleolus and the tibial crest. The Portamon has 3 optodes, emitting light at 2 wavelengths (760-850mm), and 1 receiver, with an inter-optode distance of 30, 35 and 40 mm. NIRS signals were measured continuously during both treadmill tests. Data were collected via Bluetooth at 10 Hz using Oxysoft software (version 2.3.70; Artinis Medical Systems) and were afterwards down sampled to 1 Hz for further analyses. Due to the dynamic nature of the treadmill tests we filtered the data using a moving Gaussian, with a 3 second window to remove noise. NIRS relies on the light absorption properties of chromophores in the tissue of interest (e.g. hemoglobin and myoglobin in muscle). As the underlying myoglobin concentration tends to remain constant during exercise, the changes in the oxy- or deoxygenation signals can be attributed to changes in hemoglobin content (23,24). Therefore, for the purpose of this report, we will refer to changes in raw signals as changes in oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb). In addition, the sum of the O_2Hb and HHb, defined as total hemoglobin (tHb) concentration, and the difference (dHb) between them were also calculated. Using spatial resolved spectroscopy (SRS), Tissue Saturation Index (TSI) was calculated, which reflects the oxygenation state of the muscle of interest. NIRS-derived data were analyzed for three distinct phases: at rest, during exercise, and during recovery. At rest, TSI was measured as the average of the last 30 seconds in standing position. During exercise, NIRS-derived variables for the Gardner test included: the minimum TSI (TSImin), time to reach the minimum value (TTM), and the difference between resting TSI and TSI at one and two minutes into exercise. TTM was defined as the time from exercise initiation until TSI departed from linearity, with an acceptable range of 5% and was calculated by the same blinded observer (P.C.) for all measurements. Earlier, intraclass correlation coefficient

results showed a high degree of reliability with average measures of ICC 0.956 (95% CI: 0.910, 0.978) and Cronbach's a= 0.954 between both experimenters (P.C. and N.C.) in a sample of 33 traces. In addition, we calculated the slopes of TSI from start of the test to one and two minutes of exercise using the loglinear regression function in Oxysoft. For the submaximal test, we calculated the area under the curve for the raw NIRS signals (O_2Hb, HHb, tHb and dHb) normalized for the time period covering 1.7 to 3.0 $km.h^{-1}$ (21). For the recovery phase, we calculated time to reach half (T50) and full recovery of resting TSI (T100).

Statistics

Data are reported as mean and standard deviation or median and interquartile ranges (IQR). Normality of the data was evaluated using Shapiro-Wilk and Levene's test for equal variances. Comparison of baseline and 12-week follow-up measures was performed using a paired student t test or Wilcoxon signed rank test. Further, the study population was divided into tertiles based on their improvement in MWD and 6MWD. An unpaired student t test or Mann-Whitney U test was used to determine whether there were differences in NIRS parameters between the low and high responders in MWD and 6MWD. Differences in our primary outcomes were calculated as follow-up minus baseline values. All statistical analyses were performed in JASP (Version 0.14.1). Data processing, analyses and visualizations were performed in R (Version 4.1.0; R Core Team, 2021) and RStudio (Version 1.4.1717; RStudio Team, 2021) with the packages *tidyverse* (25) and *raincloudplots* (26). All tests were two-tailed and statistical significance was considered with a p-value of ≤ 0.05.

Results

Patient flow and NIRS procedures

A study flow chart is shown in **Figure 2**. A total of 52 participants (38 men, 14 women) agreed to participate in the PROSECO trial of which 49 patients completed baseline measures. In 13 out of 49 patients (27%) NIRS measures were complicated by optode signaling issues, requiring the selection of only 2 working optodes or even exclusion from analysis. These issues were particularly present in female (X^2-test; $p < 0.001$) and participants with an increased BMI (25.9 (SD 3.9) vs 28.8 (SD 5.0) $kg.m^{-2}$, $p = 0.037$). Following baseline measures, an additional 8 participants dropped out from the study resulting in 41 participants (32 men, 9 women; 70.3 (SD 9.2) years old) who completed the scheduled intervention and follow-up measurements. An overview of the demographic characteristics of these 41 participants is presented in **Table 1**. Patients (78% men) were on average 70 years old (range 43-84) and slightly overweight. Three patients were excluded from all NIRS analyses due to insufficient data quality in at least two out of three traces (Supplementary file 1). Regarding the submaximal test, three participants did not reach 3.0

km.h^{-1} and were excluded from analysis. Consequently, complete NIRS data was available for 35 (submaximal test) and 38 (maximal treadmill test) participants.

Table 1. *Demographic information.*

Patient information	Completed intervention N= 41	NIRS-data available N=38
Age (yrs)	70.3 (SD 9.2)	70.3 (SD 8.9)
Sex (male/female)	(32/9)	(31/7)
Body mass (kg)	74.9 (SD 14.0)	74.7 (SD 13.8)
Height (m)	1.68 (SD 0.08)	1.68 (SD 0.08)
BMI (kg/m²)	26.5 (SD 4.2)	26.4 (SD 4)
ABI rest	0.66 (SD 0.26)	0.67 (SD 0.25)
Calf complaints (%)	37 (90%)	35 (92%)
Bilateral complaints (%)	22 (54%)	21 (55%)
Duration of complaints (months) ***Median and range***	24 (0.8-120)	24 (0.8-120)

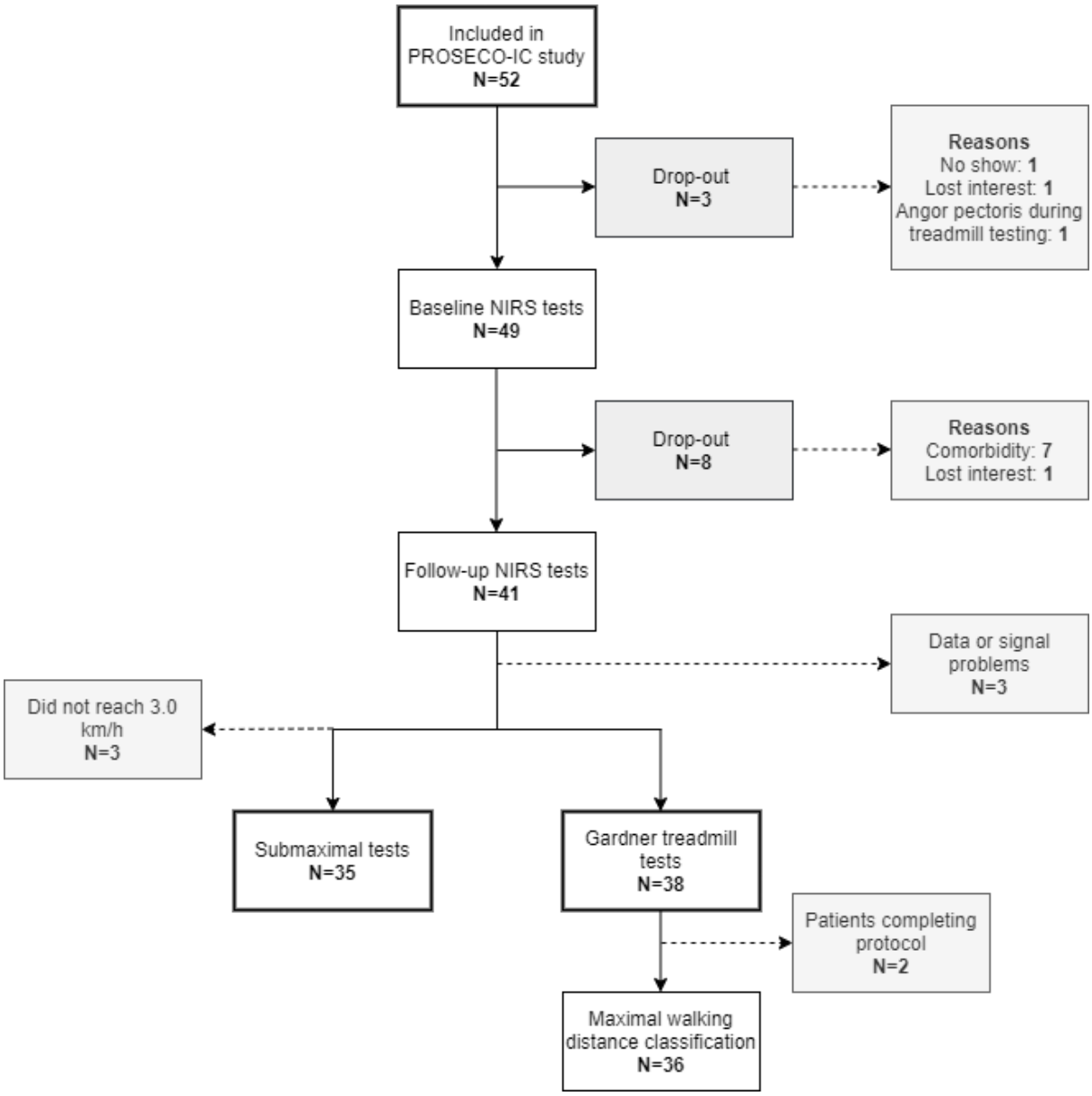


Figure 2. *Study flow chart.*

Intervention effects

At the end of the intervention, the 38 participants had completed a median of 33 (Range 11-36) training sessions (median 11.5 (Range 2-12) supervised and median 22 (Range 0-34) home-based sessions) in total. Due to federal COVID-19 quarantine measures, we had to replace supervised by unsupervised sessions and postpone follow-up visits in six participants (Range 28 to 81 days). After the intervention, ambulatory capacity in all three walking assessments was significantly improved. Participants showed a higher PFWS on the submaximal test (3.5 (IQR 1.8) to 4.5 (IQR 1.8) $km.h^{-1}$, p = 0.005), and higher PFWD (183 (SD 91) to 304 (SD 169)) and MWD (419 (SD 215) to 575 (SD 274) meters) on the maximal

treadmill test ($p < 0.001$ for both). Finally, 6MWD was also significantly increased (405 (SD 87) to 423 (SD 95), $p < 0.001$, meters) after the intervention.

Submaximal treadmill test - NIRS

Table 2 shows NIRS parameters at baseline and following the 12-week intervention. Resting TSI remained unaltered after the exercise intervention ($p = 0.319$). A better preservation of O_2Hb ($p = 0.040$) and a slower increase of HHb, though borderline not statistically significant ($p = 0.065$), was noted. Combining both oxy- and deoxygenation signals, showed a significantly higher dHb ($p = 0.030$) without a change in total hemoglobin ($p = 0.830$) when walking from 1.7 to 3.0 $km.h^{-1}$ (**Figure 3**). Significant heterogeneity in response was observed and outliers were defined as data points exceeding the first (lower) and third (higher) quartile multiplied by 1.5 times the IQR. Excluding outliers (N=2 for O_2Hb AUC change score) and participants having low-quality signals for one optode (N=5), did not affect the direction of results (O_2Hb AUC, $p = 0.054$ and HHb AUC, $p = 0.009$). No effect was noted on NIRS recovery parameters after a submaximal exertion.

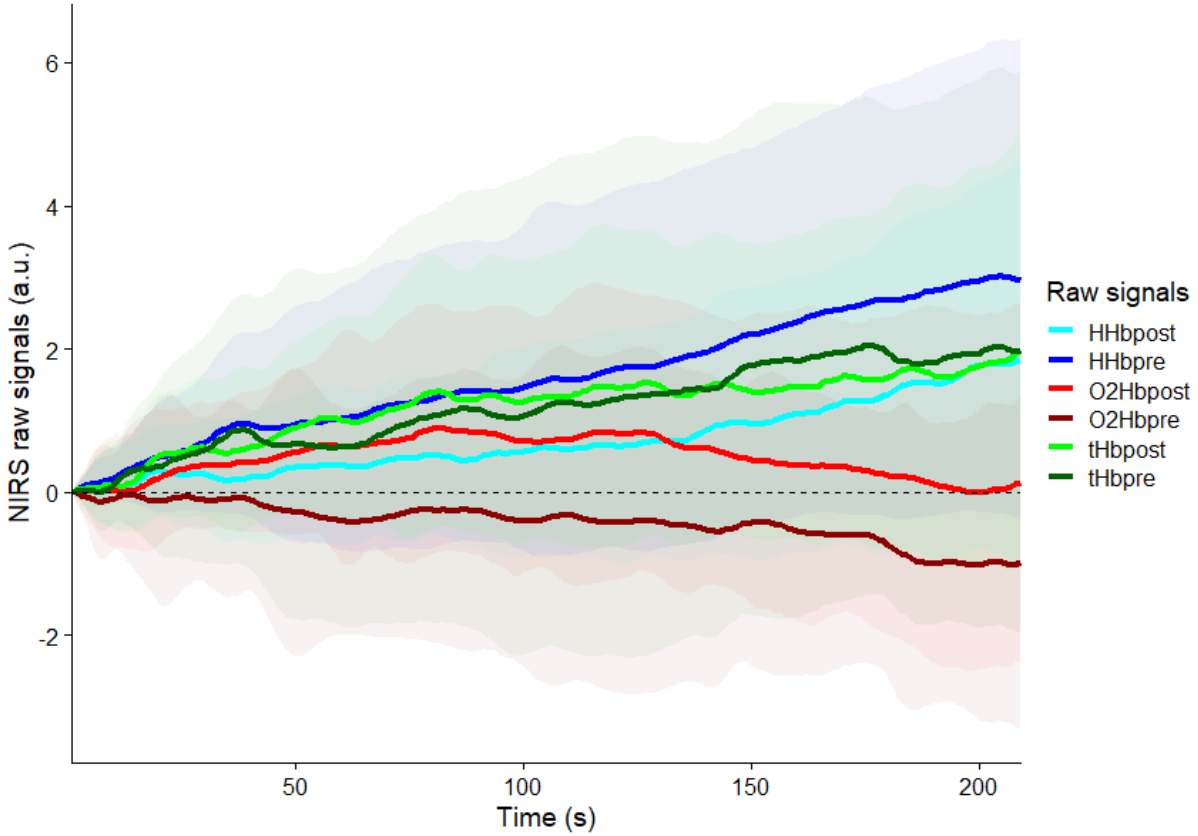


Figure 3. *Group mean exercise response (SD) for NIRS Raw Signals before (pre) and after (post) a 12-week walking intervention. Differences in area under the curve: O2HB ($p = 0.040$) and HHb ($p = 0.065$), without changes in tHb ($p = 0.830$).*

Maximal treadmill test – NIRS

As shown in **Table 2** and presented in **Figure 4,** TSI following the 10-minute recovery from the submaximal treadmill test and before the maximal treadmill test was significantly lower after the 12-week exercise intervention (p = 0.003). As minimum TSI value during the maximal test was unaltered after the intervention, a less pronounced deoxygenation (TSI rest to minimum TSI values) was observed at follow-up (21.1 (SD 8.2) vs 19.3 (SD 8.2), p = 0.028). Time to reach minimum TSI (TTM) was also significantly increased (+38.5 (IQR 193) seconds, p < 0.001) after the intervention, highlighting slower deoxygenation. Decreased slopes during the first two minutes of the exercise test are in line with a slower deoxygenation (p = 0.002 and p = 0.003 at 1 and 2-minutes respectively, Supplementary file 2). In agreement, initial two-minute AUC for O_2Hb, during the maximal test, was better preserved (p < 0.001) after the exercise intervention (Supplementary file 8). During the recovery phase, total recovery time (T100) was significantly improved after the intervention (p = 0.045, while T50 was p = 0.069). Relative recovery (i.e. ratio of T100 to total duration of treadmill test) was also significantly lower (p < 0.001) after the exercise intervention. Interestingly, one of the participants (Supplementary file 4, Participant 8) was found with clearly worsened (de)oxygenation patterns during the follow-up measurement. Specifically, this patient exhibited faster TTM (103 vs 45 seconds) and longer recovery (T50, 189 vs 512 seconds) with a concomitant decrease in ABI (0.80 vs 0.25) after the intervention.

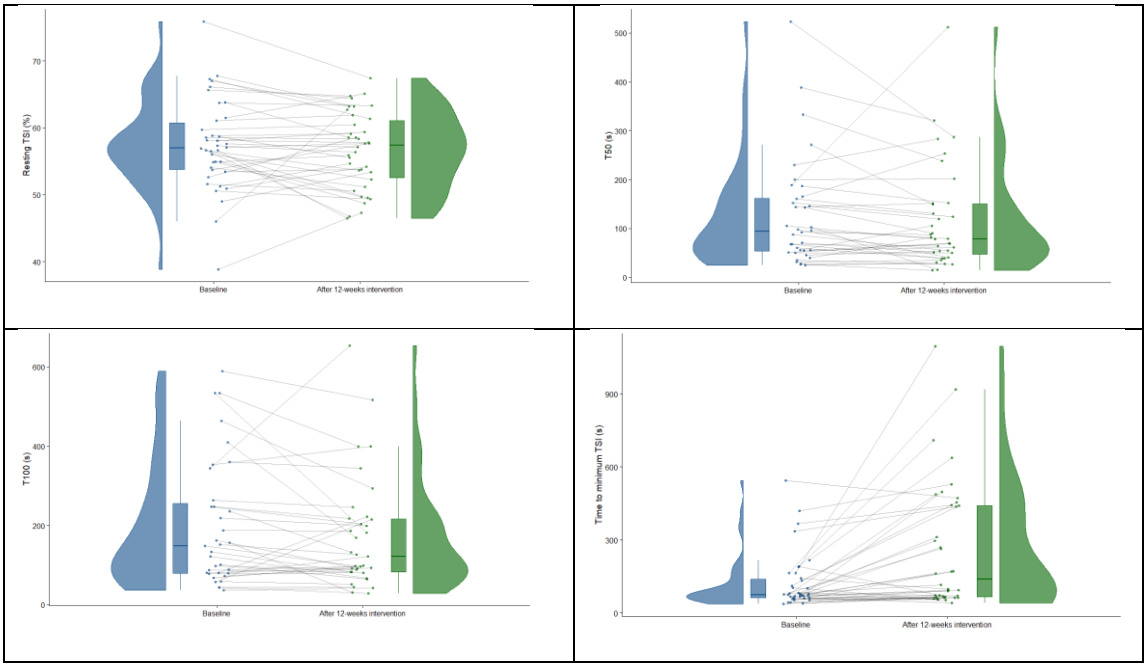


Figure 4. *Individual responses on resting (resting TSI), exercise (TTM) and recovery parameters (T50 and T100) of NIRS before and after the 12-week intervention.*

Maximal walking distance high versus low responders

A total of twelve participants were defined as high (MWD change +338 (SD 177) meters) and twelve as low responders (MWD change +5 (SD 76) meters) in MWD. Comparing the two groups at baseline (**Table 3**), no difference was noted between high and low responders regarding resting ABI (0.72 (SD 0.18) vs 0.69 (SD 0.27), p = 0.762). However, the low responder group was older (p = 0.006) and included more women (p = 0.059). Differences in baseline and NIRS change scores are depicted in **Table 4**. At baseline, time to reach minimum TSI (122 (IQR 99) vs 103 (IQR 66), p = 0.114) during the exercise test was similar in both groups. No differences between both groups could be observed for recovery NIRS parameters as documented by comparable, T50 and T100 values. Interestingly, the high responders group exhibited significantly larger improvement in TTM compared to the low responders (330 (IQR 300) vs 18 (IQR 88), p = 0.002), documenting slower deoxygenation after exercise in the high responder group (**Figure 5**). Neither at baseline, or follow-up, different patterns in submaximal raw NIRS signals were observed for high and low responders on MWD.

Table 2. *Baseline and 12-week follow-up NIRS data.*

	Baseline	12-week Follow-up	P-value
Submaximal			
Rest	**N=38**	**N=38**	
TSIrest (%)	57.5 (SD 6.8)	56.6 (SD 5.7)	0.319
Exercise	**N=35**	**N=35**	
O2Hb (AUC)	-5.5 (IQR 441)	18.7 (IQR 352)	**0.040**
HHb (AUC)	292 (IQR 297)	148 (IQR 337)	0.065
tHb (AUC)	274 (SD 295)	261 (SD 307)	0.830
dHb (AUC)	-243 (IQR 628)	-134 (IQR 491)	**0.030**
Recovery	**N=33**	**N=33**	
T50 (s)	77 (IQR 82)	65 (IQR 85)	0.317
T100 (s)*	118 (IQR 127)	107 (IQR 144)	0.304
Maximal			
Rest	**N=38**	**N=38**	
TSIrest (%)	62.7 (SD 6.3)	60.1 (SD 6.0)	**0.003**
Exercise	**N=38**	**N=38**	
TTM (s)	76 (IQR 77)	139 (IQR 375)	**<0.001**
TSImin (%)	41.6 (SD 9.9)	40.8 (SD 9.9)	0.391
TSI at 1 min (%)	44.1 (SD 10.1)	45.9 (SD 11.1)	0.110
TSI at 2 min (%)	43.4 (SD 10.3)	45.4 (SD 11.5)	0.215
Recovery	**N=36**	**N=36**	
T50 (s)	94 (IQR 108)	79 (IQR 103)	0.069
T100 (s)**	148 (IQR 176)	122 (IQR 134)	**0.045**

Note. **Data available for 32 patients **Data available for 35 patients*

Table 3. *Demographic information on high- and low responders for MWD on the treadmill and 6MWD.*

Patient information	High responders MWD N=12	Low responders MWD N=12	P-value	High responders 6MWD N=12	Low responders 6MWD N=13	P-value
Age (yrs)	66.5 (SD 6.6)	74.5 (SD 6.3)	**0.006**	67.0 (SD 10.8)	76.4 (SD 5.6)	**0.011**
Sex (male/female)	92/8%	58/42%	0.059*	83/17%	69/31%	0.409*
Body mass (kg)	73.2 (SD 16.3)	73.3 (SD 11.2)	0.978	73.7 (SD 15.0)	70.3 (SD 13.3)	0.549
Height (m)	1.71 (SD 0.09)	1.64 (SD 0.08)	0.058	1.67 (SD 0.06)	1.65 (SD 0.10)	0.860
BMI ($kg.m^{-2}$)	24.9 (SD 4.5)	27.3 (SD 4.1)	0.173	26.8 (SD 5.2)	25.6 (SD 4.2)	0.545
ABI rest	0.72 (SD 0.18)	0.69 (SD 0.27)	0.762	0.62 (SD 0.31)	0.69 (SD 0.24)	0.545

Note. **X^2-test using contingency tables*

Table 4. *Maximal walking distance responders.*

	Low responders Baseline (N=12)	High responders Baseline (N=12)	P-value	Low responders Change	High responders Change	P-value
MWD	410 (SD 213)	483 (SD 203)	0.395	+5 (SD 76)	+338 (SD 177)	**<0.001**
Submaximal						
Rest	**N=12**	**N=12**		**N=12**	**N=12**	
TSIrest (%)	61.3 (SD 7.0)	61.1 (SD 6.5)	0.957	-1.1 (SD 4.2)	-2.5 (SD 5.6)	0.517
Exercise	**N=10**	**N=12**		**N=10**	**N=12**	
O2Hb (AUC)	106 (SD 198)	-193 (SD 871)	0.283	+154 (SD 319)	+250 (SD 929)	0.923
HHb (AUC)	139 (SD 217)	511 (SD 619)	0.093	-75 (SD 296)	-368 (SD 594)	0.172
tHb (AUC)	246 (SD 261)	318 (SD 359)	0.603	+78 (SD 245)	-118 (SD 471)	0.249
dHb (AUC)	-33 (SD 324)	-704 (SD 1467)	0.228	+93 (IQR 239)	761 (IQR 1534)	0.326
Recovery	**N=11**	**N=12**		**N=11**	**N=10**	
T50 (s)	58 (IQR 99)	72 (IQR 35)	0.758	0 (IQR 32)	+2 (IQR 60)	0.916
T100 (s)	91 (IQR 122)	92 (IQR 31)	1.000	-2 (IQR 63)	+19 (IQR 113)**	0.941
Maximal						
Rest	**N=12**	**N=12**		**N=12**	**N=12**	
TSIrest (%)	61.3 (SD 7.0)	61.1 (SD 6.5)	0.957	-1.1 (SD 4.2)	-2.5 (SD 5.6)	0.517
Exercise	**N=12**	**N=12**		**N=12**	**N=12**	
TTM (s)	103 (IQR 166)	122 (IQR 99)	0.114	+18 (SD 88)	+330 (SD 300)	**0.002**
TSImin (%)	45.2 (SD 12.1)	37.9 (SD 7.0)	0.082	-1.7 (SD 5.1)	+0.6 (SD 6.9)	0.367
TSI at 1 min (%)	48.1 (SD 12.2)	42.6 (SD 8.2)	0.210	-0.9 (SD 3.9)	+5.2 (SD 8.0)	**0.028**
TSI at 2 min (%)	47.2 (SD 12.8)	40.5 (SD 6.9)	0.121	-0.6 (SD 4.4)	+6.3 (SD 8.9)	**0.045**
Recovery	**N=12**	**N=12**		**N=12**	**N=12**	
T50 (s)	120 (IQR 107)	68 (IQR 66)	0.707	-18.5 (IQR 23)	2 (IQR 52)	0.544
T100 (s)	188 (IQR 227)*	106 (IQR 94)	0.601	-28 (SD 176)*	-17 (SD 80)	0.842

Note. **Data available for 11 patients, **Data available for 9 patients*

Table 5. *Six-minute walking distance responders.*

	Low responders Baseline	**High responders Baseline**	**P-value**	**Low responders Change**	**High responders Change**	**P-value**
6MWD	387 (SD 87)	379 (SD 79)	0.809	-4 (IQR 12)	+42 (IQR 20)	**<0.001**
Submaximal						
Rest	**N=13**	**N=12**		**N=13**	**N=12**	
TSIrest (%)	-3.5 (SD 4.8)	-1.2 (SD 6.5)	0.322	-3.5 (SD 4.8)	-1.2 (SD 6.5)	0.322
Exercise	**N=12**	**N=10**		**N=12**	**N=10**	
O2Hb (AUC)	85 (IQR 255)	-245 (IQR 430)	0.140	-13 (IQR 377)	+303 (IQR 234)	0.059
HHb (AUC)	149 (SD 381)	626 (SD 545)	**0.026**	69 (IQR 129)	-389 (IQR 724)	**0.007**
tHb (AUC)	243 (SD 331)	274 (SD 295)	0.824	-14 (SD 354)	-34 (SD 384)	0.898
dHb (AUC)	-118 (IQR 697)	-624 (IQR 1075)	**0.043**	-65 (IQR 375)	+619 (IQR 957)	**0.011**
Recovery	**N=12**	**N=12**		**N=12**	**N=10**	
T50 (s)	78 (IQR 130)	56 (IQR 77)	0.603	-11 (IQR 47)	+12 (IQR 64)	0.138
T100 (s)	94 (IQR 154)	91 (IQR 127)	1.000	-8 (IQR 56)	+18.5 (IQR 112)	0.346
Maximal						
Rest	**N=13**	**N=12**		**N=13**	**N=12**	
TSIrest (%)	62.7 (SD 6.3)	59.8 (SD 6.6)	0.280	-3.5 (SD 4.8)	-1.2 (SD 6.5)	0.322
Exercise	**N=13**	**N=12**		**N=13**	**N=12**	
TTM (s)*	80 (IQR 85)	72 (IQR 154)	0.913	+25 (IQR 89)	+72 (IQR 277)	0.165
TSImin (%)	42.9 (SD 11.1)	38.0 (SD 7.8)	0.213	-2.3 (SD 5.4)	+0.8 (SD 6.8)	0.220
TSI at 1 min (%)	46.0 (SD 11.2)	40.1 (SD 8.2)	0.149	-0.5 (SD 5.4)	+4.3 (SD 9.0)	0.116
TSI at 2 min (%)	45.3 (SD 11.6)	39.3 (SD 8.4)	0.159	+0.3 (SD 7.8)	+3.8 (SD 8.5)	0.293
Recovery	**N=13**	**N=12**				
T50 (s)	96 (IQR 136)	87 (IQR 154)	0.849	-17 (IQR 33)	+4 (IQR 64)	0.538
T100 (s)	219 (IQR 332)	101 (IQR 176)*	0.817	-56 (SD 157)	-3 (SD 70)*	0.311

Note. **Data available for 11 patients*

Six-minute walk test high versus low responders

Based on the improvement on the six-minutes walk test following the intervention, twelve participants were defined as high (6MWD change +42 (IQR 20) meters) and thirteen as low responders (6MWD change -4 (IQR 12) meters). At baseline, resting ABI (0.62 (SD 0.31) vs 0.69 (SD 0.24), p = 0.545) did not differ between the two groups, as shown in **Table 3**. Low responders regarding 6MWD were generally older (p = 0.011), yet gender distribution was similar (p = 0.409). Differences in baseline and NIRS change scores can be found in **Table 5**. During exercise at baseline, TTM (72 (IQR 154) vs 80 (IQR 85), p = 0.913) was not different between the two groups. After the walking intervention, the response in TTM was not different between the two groups (p = 0.165). During recovery, there was no difference in the responses of T50 and T100 between the two groups (**Figure 5**). In comparison, submaximal raw NIRS patterns were significantly different at baseline and follow-up. High responders presented with a more pronounced increase of HHb (and thus dHb) during submaximal walking (p = 0.026 and p = 0.043, respectively). At follow-up, a more enhanced decrease in HHb was noted in high responders compared to low responders (p = 0.007).

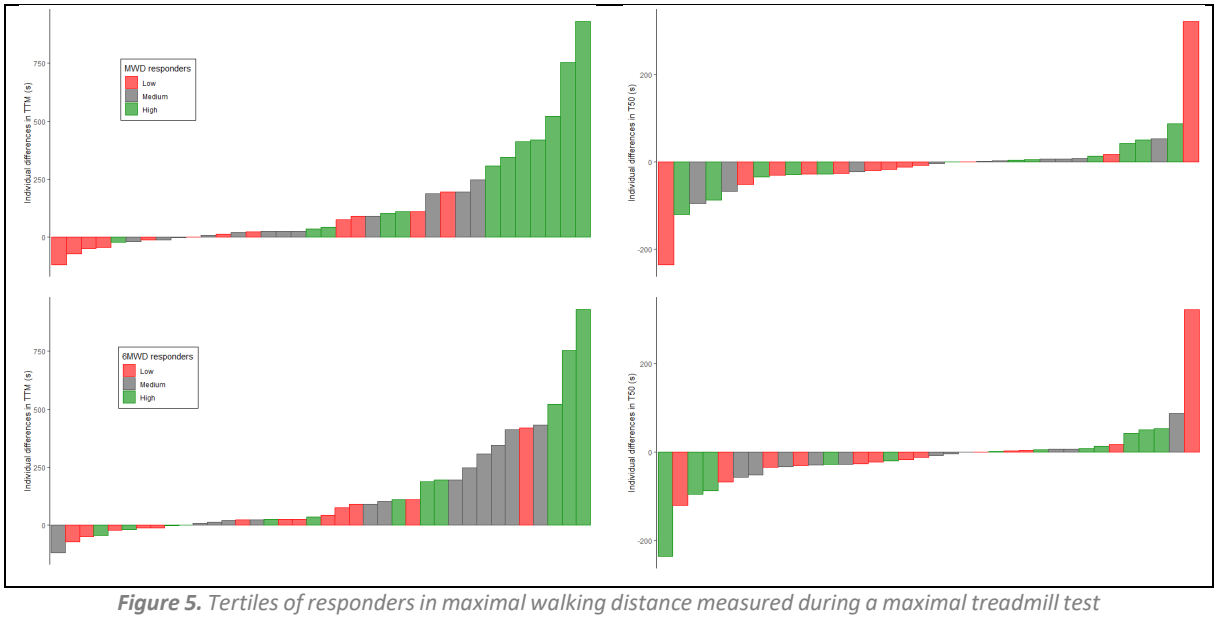


Figure 5. *Tertiles of responders in maximal walking distance measured during a maximal treadmill test and six-minute walk test and their respective change in NIRS measured deoxygenation (TTM) and recovery (T50).*

Discussion

Main findings

In this exploratory analysis we investigated NIRS changes accompanying clinically meaningful improvements in ambulatory capacity after a 12-week hybrid exercise program (27,28). A concomitant slower rate of deoxygenation during a maximal treadmill test was found, which is consistent with improved preservation of oxygenated hemoglobin during

submaximal walking. In addition, slower deoxygenation is typically observed in participants who increased the most their maximal walking distance on the treadmill and during 6MWT. Moreover, baseline TSI was not different between high and low responders for both treadmill and 6MWT outcomes.

Near Infrared Spectroscopy during exercise

Our findings on a slowed deoxygenation are in line with earlier reports on TTM in patients with LEAD and intermittent claudication (16). Given that NIRS measures provide a dynamic evaluation of oxygen supply and demand, an improved oxygen match at lower exercise intensities seems to match ambulatory improvements observed after the exercise intervention. Interestingly, TTM also represents the nadir of muscle tissue saturation, which was recently proposed as a physiological marker of critical power (29). Critical power or velocity has been defined as the highest metabolic rate achieved by oxidative metabolism (29). Hence, critical power relies on the equilibrium of oxygen supply and energetic demand of the task performed. In athletes, muscle oxygenation measures during critical power testing were used to determine the time to task failure and delineate (un)sustainable exercise intensities (29). The coincidence of critical power findings and steady-state oxygenation levels support the notion that higher responders in our sample were more likely to improve an intrinsic supply-demand mismatch, demonstrated by an improvement in TTM (29). This was also confirmed in the analysis of raw NIRS signals (Supplementary file 8). However, this was in the absence of changes in minimum TSI levels, indicating that improved supply-demand was specific for early stages during progressive exercise testing. In addition, in healthy participants it was shown that the initial slope of muscular oxygen saturation was depicting exercise intensity level (30). As such, the association of initial loglinear slope levels with maximal walking distance and six-minute walk test confirm these findings in line with TTM.

Our results in muscle oxygenation changes after walking therapy are in line with a recent systematic review, which found increased TTM after various exercise training interventions (16). Additionally, our findings are also confirmed by exercise and nitrate supplementation studies (31,32) reporting a greater preservation of O_2Hb during submaximal exercise. The improved oxygen availability could be the result of several physiological adaptations, such as increased capillary distribution and improved microvascular oxygen delivery to the muscles during exercise. Indeed, an increased capillarization has been reported after only 12 weeks of training (33). Additionally, more efficient utilization of oxygen (e.g. improved walking biomechanics (34) and/or improved mitochondrial function (35)) could also reduce the oxygen cost of submaximal exercise and explain improved (de)oxygenation patterns. As both supply and demand are object to change during exercise, TTM could be impacted by both.

Near Infrared Spectroscopy during recovery

In line with Gardner and colleagues we observed faster recovery patterns (i.e. T100) after maximal exertion (36). In addition to TTM, recovery patterns in early LEAD are particularly influenced by large vessel and diffuse oxygen supply after exercise (37). For example, in clinical studies, T50 improvements are observed after angioplasty and highly correlate with ABI recovery in LEAD ($r = 0.73$, $p < 0.001$) (38,39). This was also seen in one of our patients (Supplementary file 4, Participant 8) presenting with a worsened functional capacity after 12-weeks of exercise. While this patient exhibited a shorter TTM (meaning more rapid deoxygenation), T50 was almost 3-fold longer (meaning slower reoxygenation) with a concomitant decrease in ABI during the follow-up measurements. However anecdotical in the case of this patient, large vessel blood flow is not typically altered in patients with IC after exercise interventions (6). NIRS mainly reflects chromophores at the level of the microcirculation (23), possibly explaining the more rapid recovery compared to large vessel ABI dynamics (39). Therefore, faster recovery patterns could reflect changes on a capillary level, with improved nitric oxide (NO) bioavailability found after 12 weeks of exercise training (40). Increased NO bioavailability may improve endothelial function, blood flow, and vasodilatory responses, all of which could impact reoxygenation. Although T100 recovery patterns did change on a group level, changes are small (36) and heterogenous, with no differences between high and low responders after walking therapy. A possible explanation could be the high variability of response after LEAD treatment and discrepancy between objective and patient-reported outcomes (12) or the influence of subjective exertion during treadmill performance on recovery kinetics (38).

Individual MWD and 6MWT responses

At baseline, only raw values for HHb and dHb were significantly different between high responders and low responders on 6MWD. Specifically, an increase in deoxygenated hemoglobin and a decrease in dHb during exercise may differentiate at baseline the participants who would improve their 6MWD. Interestingly, although a wide range of responses was observed (Supplementary file 3-5), HHb levels for high responders resemble data from more diseased legs based on data from Manfredini et al (21). Normalization towards less diseased patterns (e.g. increased O_2Hb and dHb, lowered HHb and unchanged tHb) after exercise therapy was only present in high responders (21). Further, even in the absence of de- or re-oxygenation changes, functional progression was achieved in several participants possibly related to compensatory mechanisms or habituation. Therefore, whether NIRS baseline measures are capable of identifying the level of response to exercise therapy remains to be further investigated.

Limitations

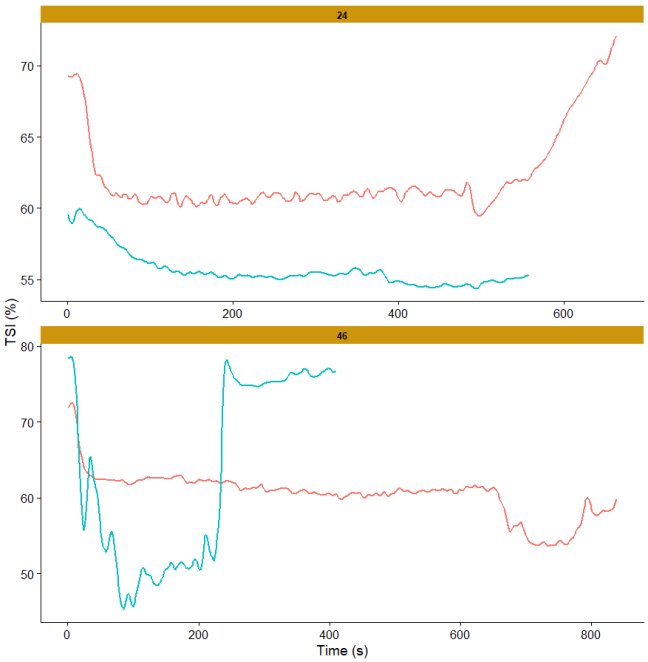
In-between comparison of raw NIRS changes using continuous wave NIRS devices has its limitations, given the confounding influence of adipose tissue thickness, hemoglobin content or even comorbidities. This is especially true in the present heterogenous group of LEAD patients characterized by increased fat mass (e.g. sarcopenia) which reduces the penetration depth of NIRS at the site of interest (41). Therefore, some patients were excluded from analysis due to signal problems during data collection (as per manufacturer instructions), with comparable demographics as earlier reported (17). In addition, low response was observed in older participants and gender distribution was imbalanced in MWD response. Suchlike demographic differences in ambulatory responses are reported earlier (42,43), yet questions remain on how they impact NIRS variables. Calf adipose tissue thickness (ATT) was measured using a Harpenden skinfold caliper (John Bull, St. Albans, England), yet given fragile skin or tight calves it was not possible to obtain reliable measurements for all included patients. However, we focused on TSI measures to calculate time-dependent changes and differences from specific timepoints, which are considered to be insensitive to ATT, are less influenced by subcutaneous blood flow (23) and therefore preferred compared to absolute values when using continuous wave systems (44). Another limitation could be the sample size, the small number of women participants and the absence of a control group, making it difficult to draw firm conclusions. More randomized controlled trials with larger sample sizes are required.

Conclusion

Walking exercise is known to increase functional capacity in patients with IC, yet the exact physiological mechanisms are still debated or unidentified. Near-infrared spectroscopy (NIRS) was used to evaluate local muscle oxygen oxygenations responses after a 12-week hybrid walking intervention. After the intervention, functional capacity in all three walking assessments (i.e. submaximal, maximal and 6MWT) was improved. Preserved oxygen availability and increased time to minimum TSI during exercise could explain some of the improvements in ambulatory outcomes. Total time of recovery was also faster after the intervention. However, some participants improved their walking capacity without noting changes in NIRS-derived outcomes, suggesting that other underlying physiological mechanisms, occurring due to the exercise intervention, could also impact ambulatory responses. More RCT's with larger samples and more integrated methodologies are required to identify the physiological determinants of ambulatory responses after an exercise therapy intervention.

Appendix

***Supplementary file 1**: Excluded due to optode problems in baseline and follow-up.*

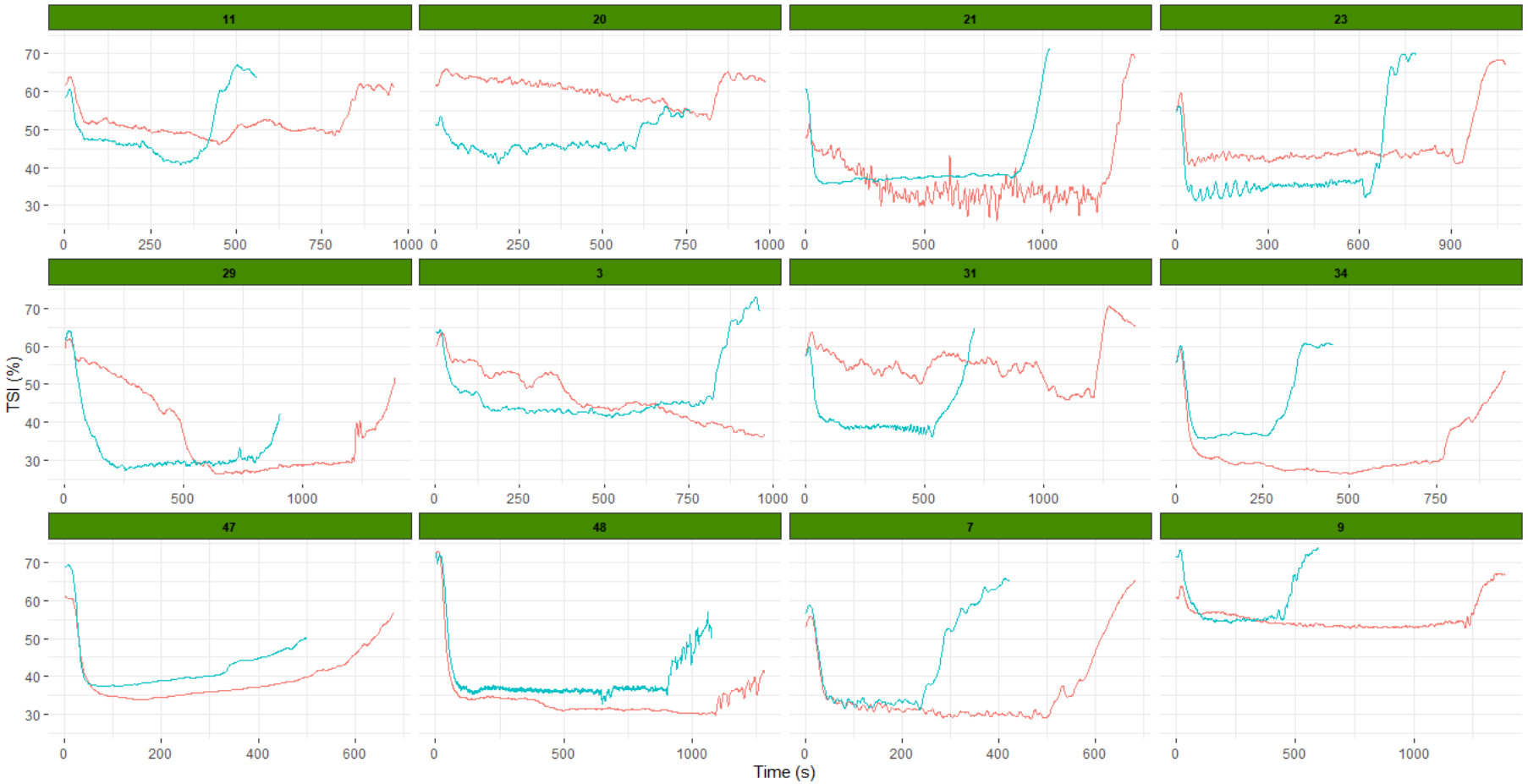


***Note.** Patients excluded due to optode problems, as per manufacturer instructions, and their respective baseline (**Green**) and 12-week follow-up (**Red**) TSI traces.*

***Supplementary file 2**: Baseline and 12-week follow-up NIRS data, supplementary analyses.*

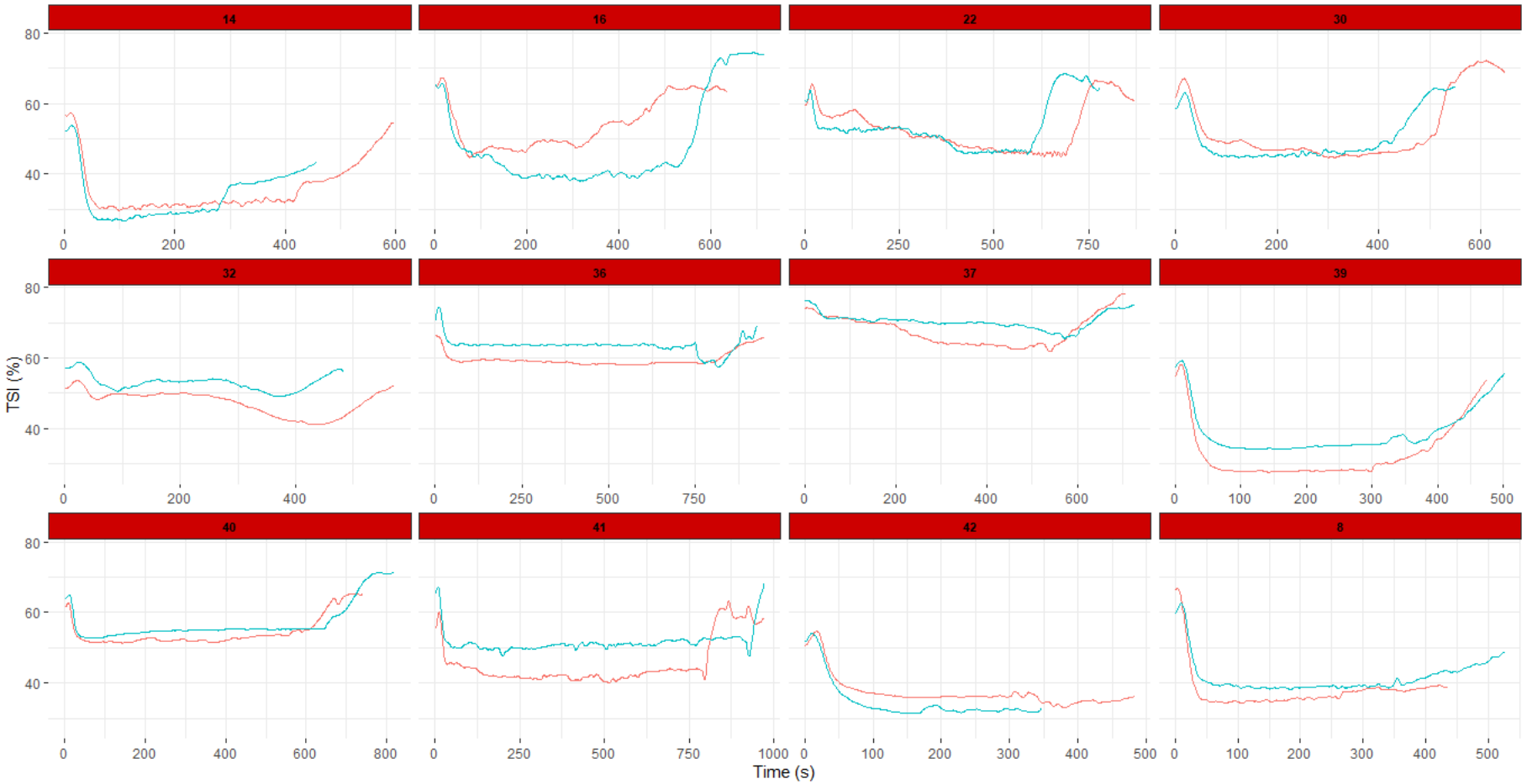
	Baseline	**12-week Follow-up**	**P-value**
Maximal			
Exercise	**N=38**	**N=38**	
O2Hb (AUC)	-2566 (IQR 1608)	-2311 (IQR 1225)	**<0.001**
HHb (AUC)	340.5 (SD 913)	170 (SD 781)	0.126
tHb (AUC)	-2370 (SD 1447)	-2021 (SD 1035)	0.081
Slope at 1 min	-0.018 (IQR 0.020)	-0.012 (IQR 0.016)	**0.002**
Slope at 2 min	-0.011 (IQR 0.011)	-0.008 (IQR 0.008)	**0.003**
ΔTSI at 1 min (%)	18.6 (SD 8.6)	14.2 (SD 9.7)	**<0.001**
ΔTSI at 2 min (%)	19.3 (SD 8.7)	14.7 (SD 10.1)	**<0.001**
Peak deoxygenation (%)	20.0 (SD 8.4)	18.2 (SD 8.4)	0.071
Relative peak deoxygenation (%)	33.9 (SD 12.9)	32.3 (SD 13.4)	0.197
Time to resistance (s)*	405.9 (SD 290)	417.3 (SD 256)	0.752
Recovery			
	N=35	**N=35**	
Relative full recovery (s)	0.302 (IQR 0.354)	0.213 (IQR 0.326)	**<0.001**

***Supplementary file 3**: High responders MWD – NIRS traces.*



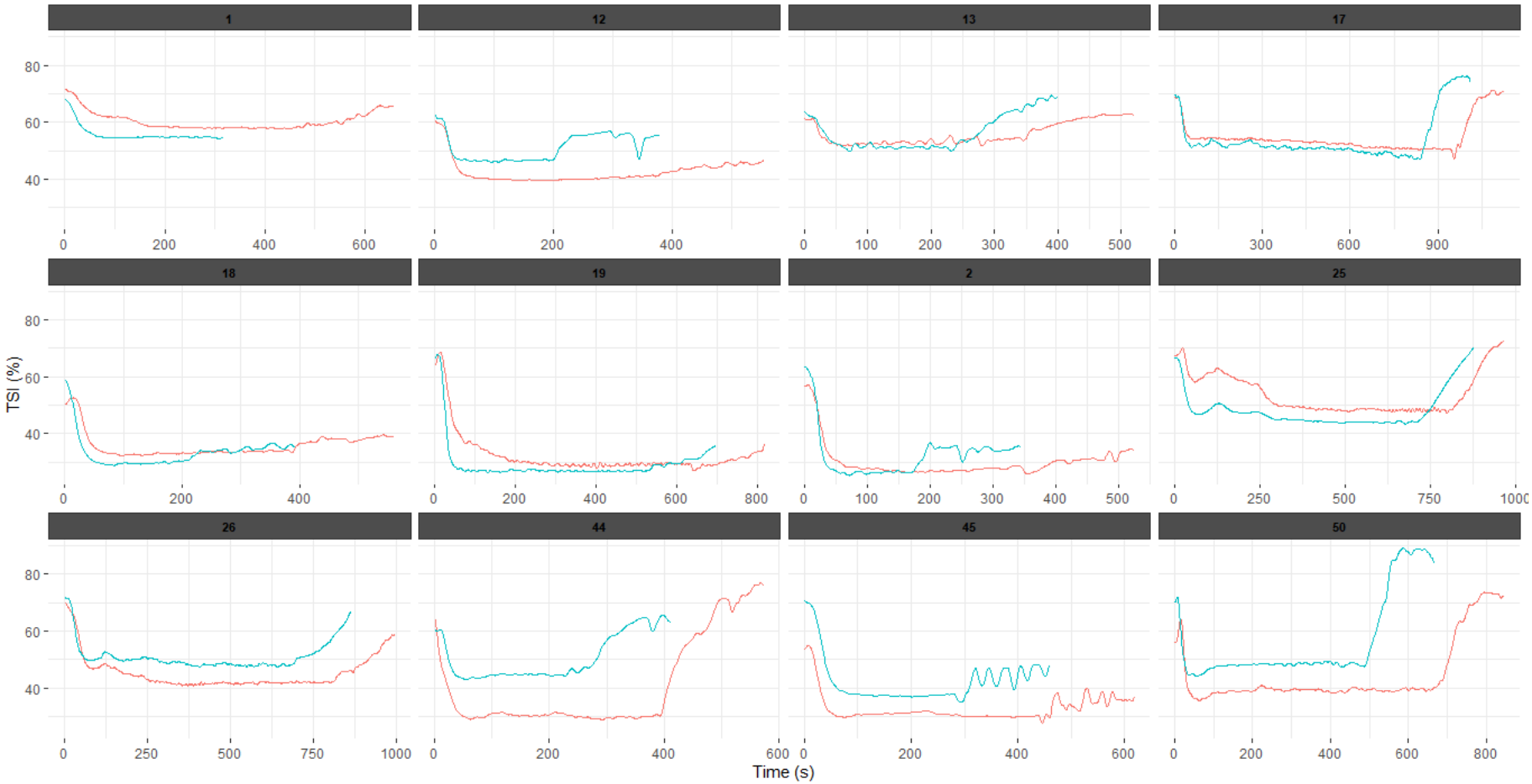
***Note.** Patients classified as high responders on MWD and their respective baseline (**Green**) and 12-week follow-up (**Red**) TSI traces.*

Supplementary file 4: *Low responders MWD – NIRS traces*.



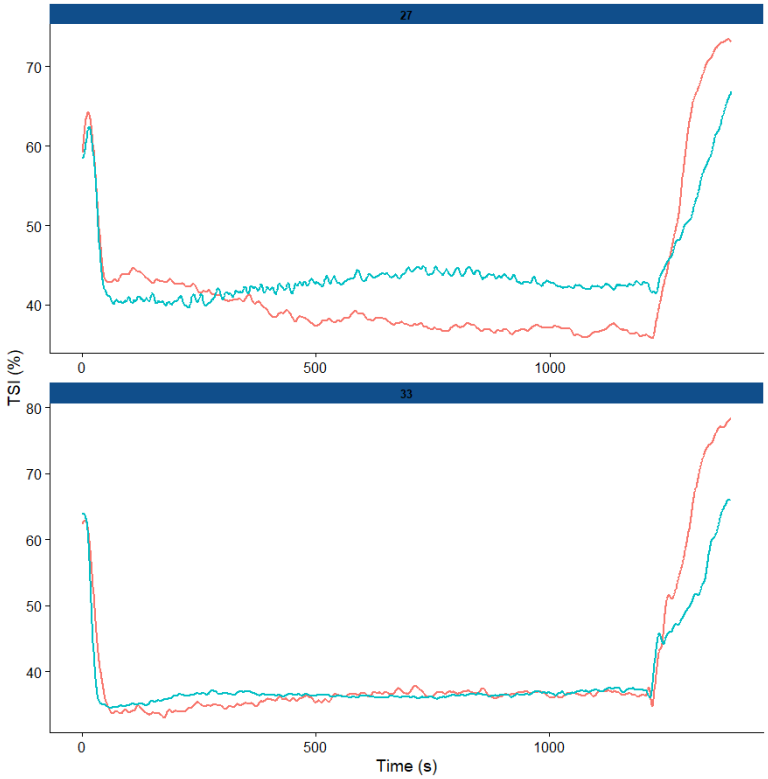
Note. *Patients classified as low responders on MWD and their respective baseline (**Green**) and 12-week follow-up (**Red**) TSI traces. In patient 24 we used different optode selections at baseline and follow-up. Therefore, absolute data (such as TSI% rest) were omitted from analysis.*

***Supplementary file 5**: Medium responders MWD – NIRS traces.*



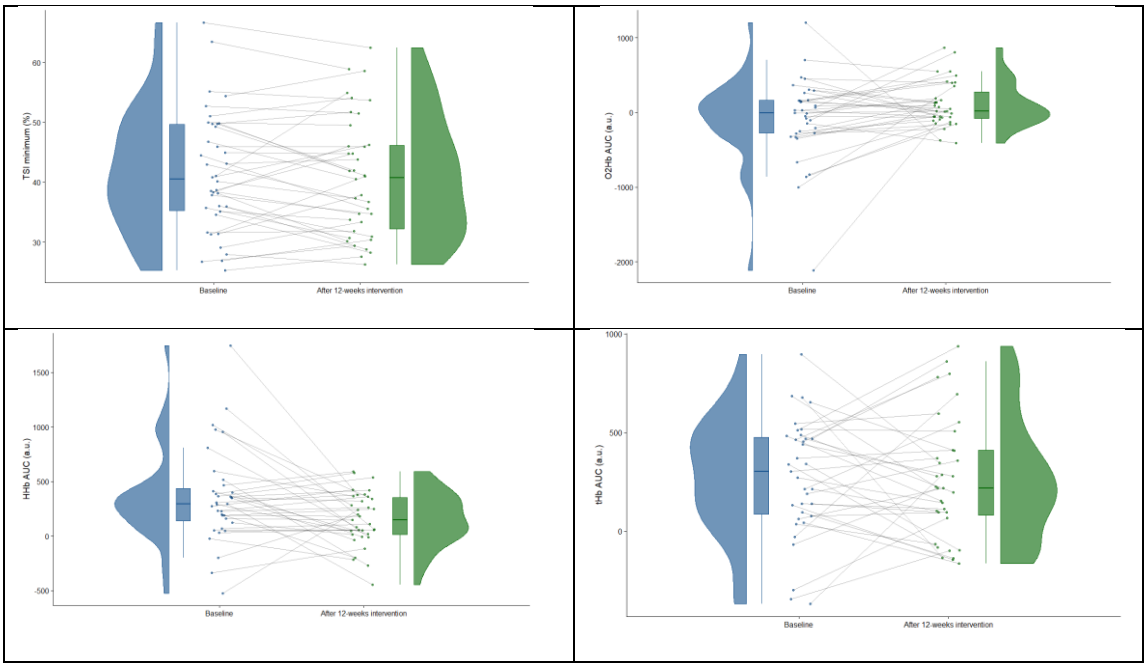
***Note.** Patients classified as medium responders on MWD and their respective baseline (**Green**) and 12-week follow-up (**Red**) TSI traces.*

***Supplementary file 6**: Excluded from categorization due to completion of Gardner protocol.*



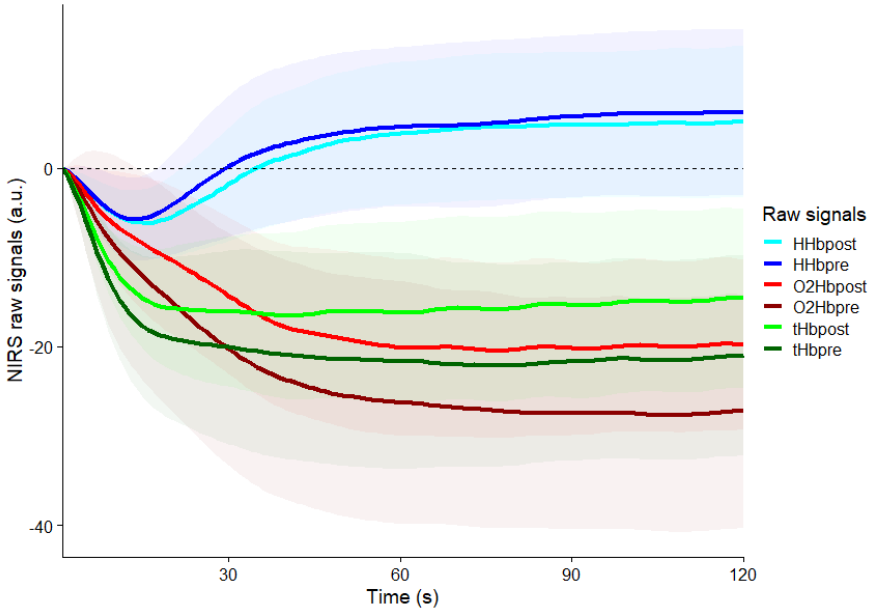
Note. Patients 27 and 33 completed the whole Gardner protocol both at Baseline and after the 12-week intervention and thus the response in MWD was zero. Therefore, they were excluded from the MWD classification because we could not regard them as low-responders.

***Supplementary file 7**: Individual responses.*



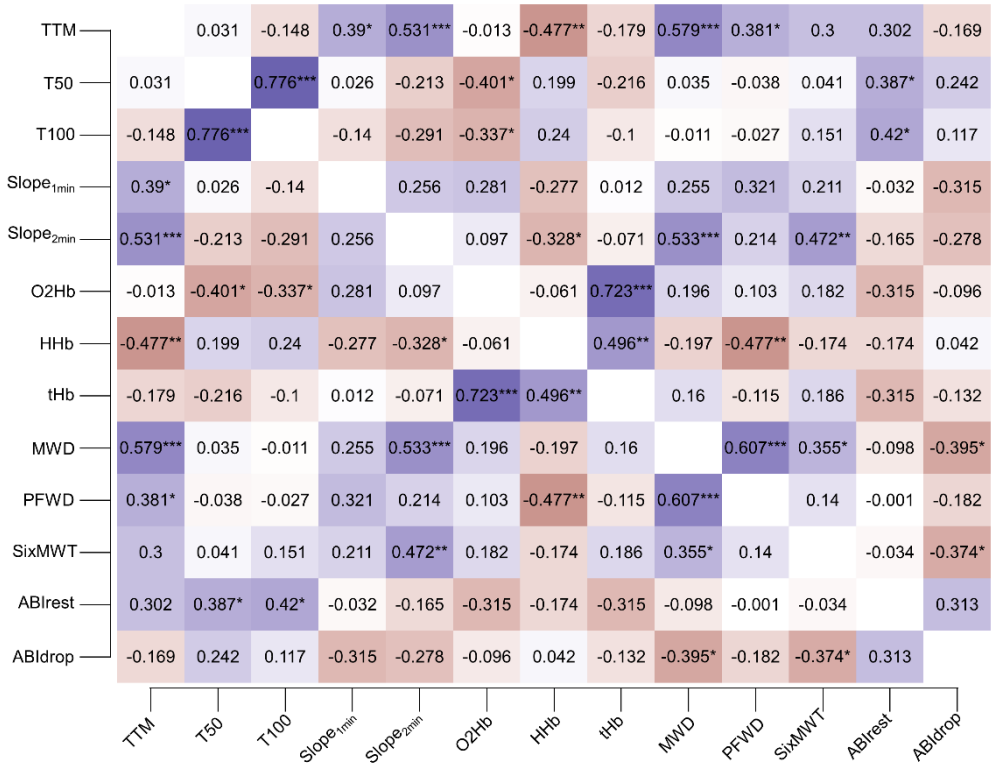
***Note.** Individual responses on minimum TSI (during the Gardner protocol) and on the area under the curve (AUC) of O2Hb, HHb and tHb (during the 1.7-3 km/h of Submaximal test), before and after the 12-week intervention.*

Supplementary file 8: *Raw NIRS signal changes during initial two minutes of Gardner protocol.*



Note. *Group mean exercise responses for NIRS Raw Signals, during the first two minutes of the Gardner protocol, before (pre) and after (post) a 12-week walking intervention. Differences in area under the curve: differences in O2HB ($p < 0.001$), without changes in HHb ($p = 0.133$) and tHb ($p = 0.126$).*

Supplementary file 9: *NIRS and functional correlation levels.*



Note. *Spearman's correlation heatmap of exercise responses. O2Hb, HHb and tHb are the area under the curve during the first two minutes of the Gardner protocol. *p<0.05, **p<0.01, ***p<0.001*

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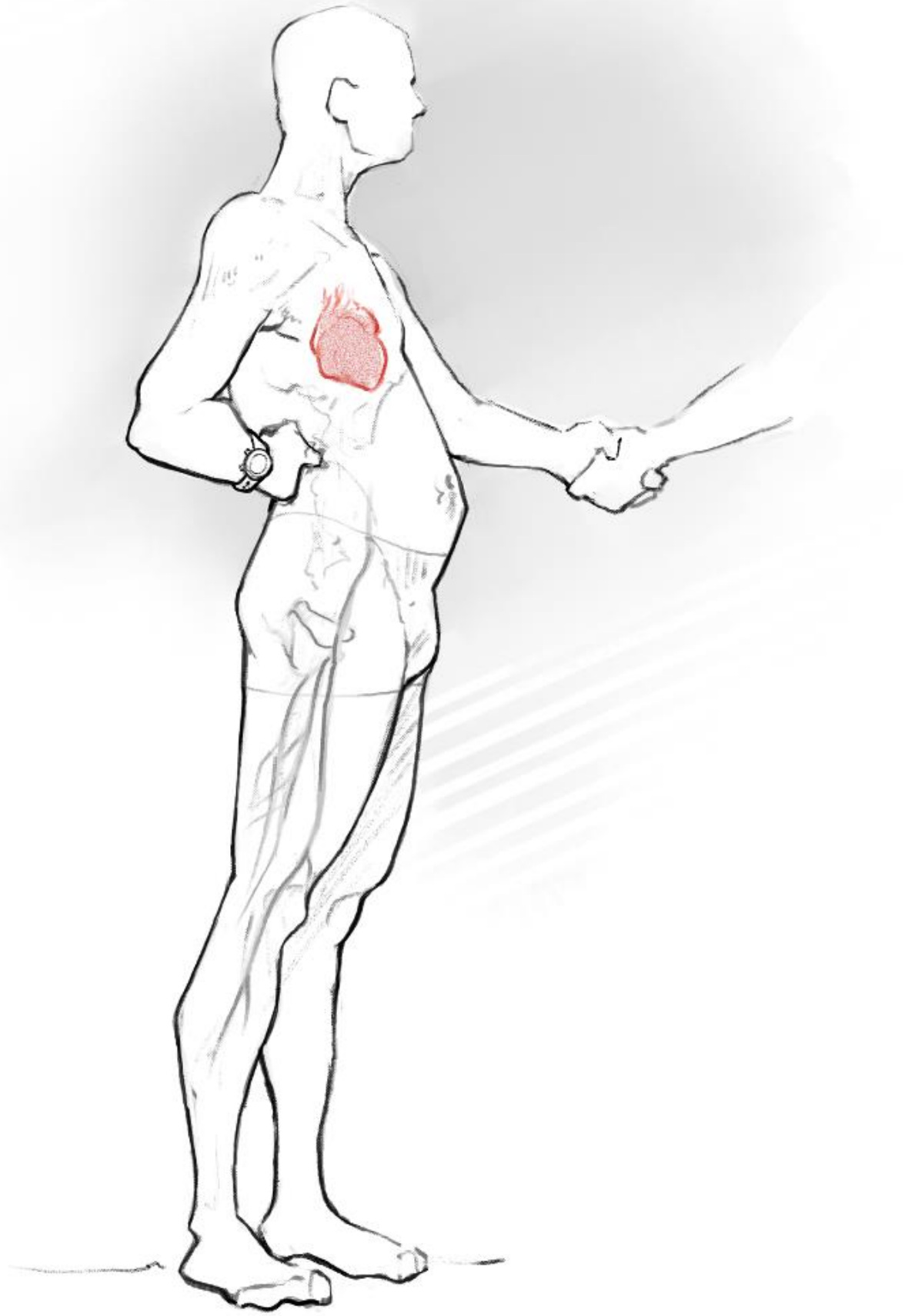
Chapter four: Exercise and cardiovascular risk profile



Chapter 4.1: The impact of supervised exercise training on traditional cardiovascular risk factors in patients with intermittent claudication: a systematic review and meta-analysis

Nils Cornelis, Julie Nassen, Roselien Buys, Inge Fourneau and Véronique Cornelissen

Published

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Abstract

Background: Patients with intermittent claudication (IC) are at increased risk of cardiovascular (CV) morbidity and mortality. Whereas extensive evidence supports the beneficial effects of supervised exercise training (SET) on walking capacity, little is known about the effect of SET on the CV risk profile of IC patients. Therefore, the aim was to evaluate the effects of SET on CV risk factors in IC patients by using meta-analysis techniques.

Methods: A systematic search in the electronic databases MEDLINE, EMBASE, CINAHL, and CENTRAL was conducted from the earliest date available until October 2, 2018. Randomised and non-randomised controlled trials lasting ≥ four weeks and investigating the effect of SET on CV risk factors in IC patients were included. Traditional CV risk factors were studied as primary outcomes; pain free walking distance (PFWD) and maximum walking distance (MWD) were included as secondary outcomes. Data were pooled using random effects models with summary data reported as weighted means and 95% confidence interval (CIs).

Results: Fifteen trials were included, involving 18 study groups (nine walking, four resistance, two aerobic training, and three combined groups), totaling 725 patients (mean age 66.3 years; mean ankle brachial index, 0.64). Exercise reduced systolic blood pressure (-5.8 mmHg; CI -9.89 to 1.67, $p < .01$) whereas all other CV risk factors (i.e. body weight, body mass index, diastolic blood pressure, and blood lipids) remained statistically unaltered. Exercise also improved PFWD (+132 m; CI 70-194, $p < .001$) and MWD (+183 m; CI 98-268, $p < .001$).

Conclusion: This meta-analysis supports the beneficial effects of SET on walking capacity. Little evidence for an improvement of the CV risk profile was found following exercise in patients with IC. However, given the scarcity of data, high quality RCTs that include an assessment of CV risk factors are urgently required to determine the effect of exercise therapy in the secondary prevention of CV disease of IC patients.

Introduction

Lower extremity artery disease (LEAD), as specified by the most recent European Society of Cardiology (ESC) and European Society for Vascular Surgery (ESVS) guidelines on peripheral arterial diseases (1), is characterised by a progressive atherosclerotic build up in arteries supplying the lower limbs. Worldwide 202 million patients are diagnosed with LEAD, with a 23.5% increase within the last decade because of a higher overall life expectancy and concomitant global rise in risk factors (2,3). Of these 202 million LEAD patients, up to 35% present with the cardinal symptom of intermittent claudication (IC), characterised by a cramp like pain when walking which only resolves through rest (4). Although not initially life threatening, the debilitating nature of IC initiates a vicious cycle of physical inactivity (5, 6) impacting functional capacity (7) and quality of life (8), and probably aggravating the already increased cardiovascular (CV) risk in these patients. Research shows that a considerable number of LEAD patients also have damage in other vessel sites, underscoring the systemic impact of atherosclerosis. Moreover, the comorbidity rate of CV and/or cerebrovascular diseases in LEAD is estimated at 61%, with the presence of LEAD itself considered as an independent risk factor equivalent to well known lifestyle related risk factors (9). It is thus most noteworthy that only a minority (20-30%) of LEAD patients will die from a non-cardiovascular disease (4).

Current treatment guidelines in LEAD patients with IC highlight the importance of supervised (10) exercise training (SET) and risk factor management as a first line treatment to improve symptomatic claudication and to slow down the progressive nature of atherosclerosis (1). Yet, a remarkable care gap regarding optimum medical treatment, risk prevention support, and healthy lifestyle promotion is still present in LEAD patients (2,11-13). There is overwhelming evidence from well controlled randomised studies that SET improves both pain free walking distance (PFWD), maximum walking distance (MWD), and quality of life in patients with IC (14). However, less attention has been paid to whether SET can also impact on the CV risk profile of these patients (15). Interestingly, one small retrospective study has shown that SET significantly altered CV morbidity and mortality in 64 patients completing SET compared with those who did not (16). The primary driver behind this observation remains unclear, but the impact of exercise on traditional CV risk factors, and therefore risk of future morbidity and mortality, has already been established in patients presenting with similar CV risk profiles (17-19). As most contemporary SET programs in IC patients are tailored to improve claudication symptoms, the systemic benefit of SET in IC remains to be determined. Therefore, this systematic review with meta-analysis will study the effect of SET on traditional CV risk factors in LEAD patients with IC. Secondary outcomes of this study will include the effect of SET on walking performance measures.

Methods

The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines were followed to conduct this systematic review and meta-analysis (20). Supplementary information S1 shows the protocol of the study.

Database and search strategy

Four electronic databases (MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL)) were searched for articles published in English from the earliest date available until October 2, 2018. The full search strategy for each of these databases is provided in Supplementary information S2. Additionally, the reference list of eligible articles and meta-analyses on the topic were manually scrutinised for other potentially eligible papers.

Eligibility

The current analysis was limited to 1) randomised controlled trials and controlled clinical trials of SET only, lasting ≥ four weeks; 2) in adult humans aged ≥ 18 years with LEAD and IC (typically classified as Rutherford 1-3 or Fontaine 2a or 2b); 3) reporting before and after mean and SD (or standard error) in exercise and control groups or mean change and SD (or standard error) in exercise and control groups or median and range in exercise and control groups of at least one traditional CV risk factor; i.e. weight, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), high density lipoprotein (HDL-C), low density lipoprotein (LDL-C), triglycerides (TGs), and fasting blood glucose (FBG); 4) published in English in a peer reviewed journal.

Study selection

After removal of duplicates, screening of all titles and abstracts from the first search (earliest date available of databases to April 27, 2017) was performed by two independent reviewers (N.C. and J.N.). Secondly, all identified articles were assessed by both reviewers and papers were selected for inclusion after consensus. An updated search was performed from April 2017 to the October 2, 2018. A third reviewer (V.C.) was consulted in case of disagreement.

Assessment of risk of bias

Studies were assessed for quality by both reviewers (N.C. and J.N.) using the Tool for the assEssment of Study qualiTy and reporting in EXercise (TESTEX scale) (21). This scale is a validated tool specifically developed for the assessment of study quality and reporting in exercise training studies. The total TESTEX score of 15 points is composed of five points on assessment of study quality and 10 points regarding study reporting. A higher score reflects

a better quality. Inter-observer agreement was determined using Kappa statistics (22). Disagreements were resolved by discussion with a third reviewer (V.C.).

Data extraction

A standardised Access Database file (Microsoft, Redmond, WA, USA) was used by both reviewers (N.C. and J.N.) to extract data related to trial and patient characteristics, intervention details, and primary and secondary outcome data. For three and five papers, data on pain free (PFWD in metres) and maximum walking distance (MWD in metres), respectively, were calculated using reported time and speed on the treadmill test. When only median and interquartile data were reported (23), these values were converted using approximation methods (24). Data presented graphically were transposed to numerical data by means of digital scaling and measurement of plots in Adobe Acrobat Reader (Adobe Systems Incorporated, San Jose, CA, USA). A request for missing data was sent to 11 authors, of which one provided the missing information.

Statistics

All meta-analyses were performed using Comprehensive Meta-Analysis software V2.2 (Biostat, Englewood, NJ, USA). When assessments were performed at different time periods, the last assessment in the analyses was used. Descriptive data are reported as weighted mean. Both Hedges' g, mean differences, and their 95% confidence intervals (CIs) were calculated as effect sizes. Each effect size was weighted by the inverse of its variance. Given the clinical heterogeneity of included studies, random effects models were used to pool the data. A two sided $p \leq .05$ was considered statistically significant. Heterogeneity among trials was assessed using Cochran Q tests with an alpha value of 0.1 indicating significant heterogeneity. In addition, the I^2 statistic was used to quantify inconsistency of treatment effect across trials. A value for $I^2 > 50\%$ was considered to indicate substantial heterogeneity. Additionally, sensitivity analyses were performed by removing studies from the model one by one. A mixed effects subgroup analysis was performed to evaluate whether exercise modes influenced the results. Publication bias was evaluated by means of visual inspection of the funnel plots of variables reported in at least five studies, supplemented by Duval and Tweedie's Trim and Fill tests to obtain an estimate of the unbiased effect size.

Results

Study selection

A PRISMA flow diagram of the literature search and selection is presented in **Figure 1**. The initial search identified 8316 potentially relevant studies of which 117 were retrieved for full text review. Eleven studies were omitted from the meta-analysis since five of them were

ancillary studies of included trials (25-29) and another six did not report the required data. One extra eligible study was identified after updating the initial search (30). Details on this updated search can be found in Supplementary information S2. In total, 15 publications were included for the quantitative analyses.

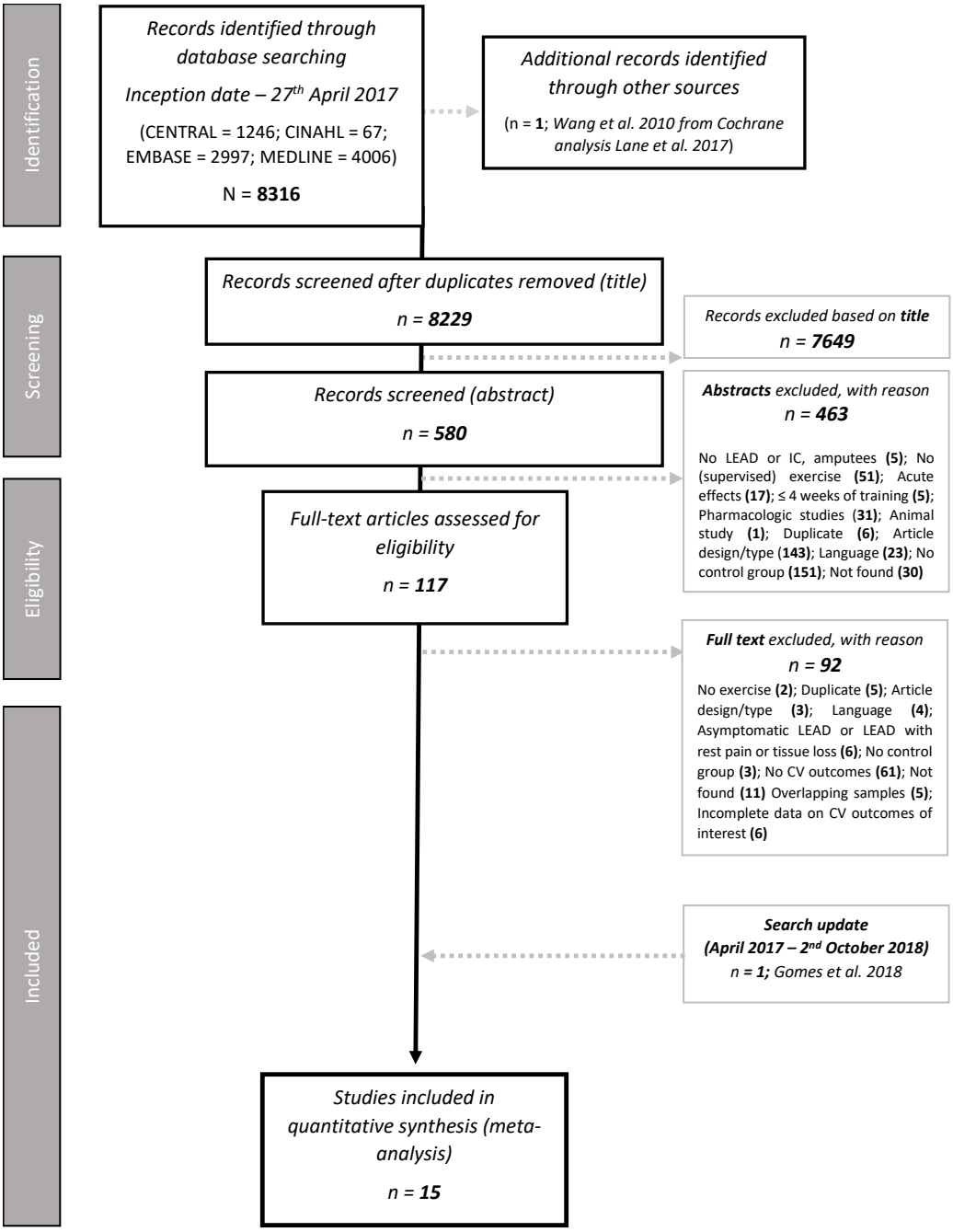


Figure 1. *PRISMA flow diagram for selection of articles. LEAD = lower extremity artery disease; CV = cardiovascular; IC = intermittent claudication.*

Study design and participant characteristics

A summary of the study characteristics of the included trials is shown in **Table 1**. All 15 trials were published between 2000 and 2018. Twelve trials were randomised controlled trials and the remaining three (20%) were non-randomised controlled trials (31-33). Except for one that applied a cross over design (33) all studies used a parallel design. Sample sizes of the studies ranged from 10 to 177 (median 45) totalling 725 randomised patients (mean age 66.3 years; range 61.8-70.5). The majority of the included patients in the studies were male (72%; range 40-100%). The total dropout rate was 17% (range 0-36%), resulting in 604 patients that completed the allocated intervention. Eleven studies reported ABI, ranging from 0.56 to 0.78 (mean 0.64), with IC class reported in seven trials as Fontaine II or Rutherford 1-3. **Figure 2** provides an overview of the studies reporting on each of the risk factors. In studies that reported the presence of specific risk factors, 23% (range 0-43%) of the patients were diagnosed with diabetes, with one trial excluding diabetic patients (34). 73% of participants (range 33-91%) had hypertension. Baseline values suggested that all trials included pre- and/or hypertensive patients (SBP range, 134-152 mmHg). In addition, almost 80% (range 30-96%) of patients had hypercholesterolaemia. PFWD and MWD were reported in eight and 13 studies respectively, with seven of them using the Gardner protocol for assessment.

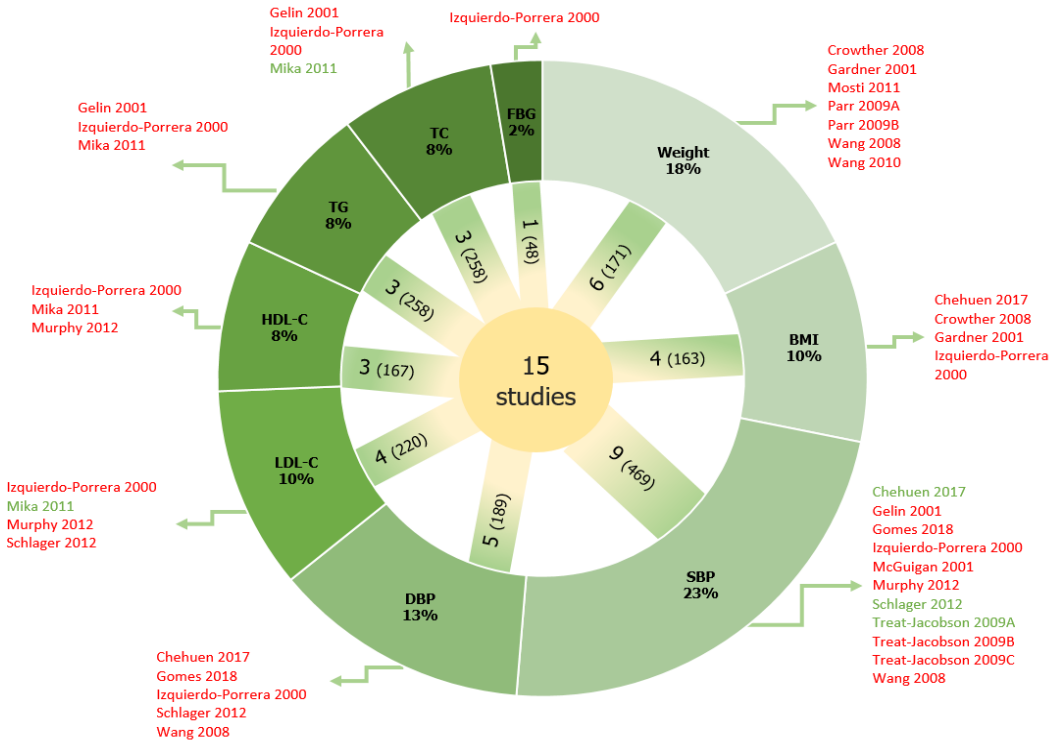


Figure 2. *Overview of cardiovascular outcomes analysed. Overview of all cardiovascular outcomes analysed (% of studies reporting a certain outcome) with the respective number of studies and the overall number of participants in meta-analysis. For each variable, between group significance of all intervention groups in the meta-analysis are shown in green, non-significant studies are shown in red. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; HDL-C = high density lipoprotein; LDL-C = low density lipoprotein; TG = triglycerides; FBG = fasting blood glucose.*

Outcome assessment and intervention characteristics

The median duration of the interventions was 12 weeks (range 8-52 weeks). Training frequency was three times per week, except in three studies performing two sessions a week (23,30,35). As shown in **Figure 3**, half (9/18) of the supervised interventions provided a walking program (23,31,34-40). Four studies implemented a resistance training intervention (30,33,41,42), two involved an aerobic training program (40,43), and three applied a combination of exercise modalities (32,40,42). Most control groups received usual care including advice to exercise.

Figure 3. *Overview of the intervention of the included studies. Study weight represented by thickness of connecting line according to number of included patients. The outer circle represents proportion of exercise intervention groups and total number of patients randomised. The inner circle represents the type of control group. N = number of patients.*

Risk of bias

The median quality of the trials was 11 (range 6-14), with incomplete reporting of point measures in seven of 15 and blinding of assessors in four of 15 studies only. Interobserver agreement, calculated using the kappa statistics, was 0.89 between both reviewers. TESTEX results and funnel plots are shown in Supplementary information S3. SBP was suggestive of publication bias. A visible trend was noted in 11 interventions, with smaller studies presenting a larger effect size left to the mean. Five studies need to be imputed according

to the Duval and Tweedie's Trim and Fill to establish symmetry with an estimated Hedges' g of -0.041 (CI -0.292 to 0.210).

Synthesis of results

Primary outcome: cardiovascular risk factors

A summary of the main effect sizes of the primary outcomes is presented in **Table 2**. Compared with controls, exercise training induced a significant decrease in office SBP with a mean reduction of -5.8 mmHg (-9.9 to -1.7). Heterogeneity and inconsistency were low for SBP. A subgroup analysis showed only a non-significant trend towards a reduction in SBP (-4.8 mmHg; range -11.1 to 1.5; $p = .14$; $I^2 = 45.7$) in the six studies that provided walking training. Conversely, the two more intense aerobic interventions (40,43), comprising 24 exercise and 19 control patients, showed a significant reduction in SBP of 11.6 mmHg (-22.3 to -1.0, $p = .03$; $I^2 = 0.0$). Five trials reporting on DBP found no effect after training (-2.2 mmHg; range -5.2 to 0.7). Changes in weight and BMI were reported in seven and four study groups respectively. There was no impact of the exercise interventions on each of these parameters compared with the control. No evidence of statistical heterogeneity was present ($I^2 = 0\%$ for both). The lipid profile was only investigated following walking interventions (23,31,34,38,39). Pooling results across these studies showed no effect on TC, HDL-C, LDL-C, and triglycerides compared with the control. Heterogeneity and inconsistency were high for TC and LDL-C and low for HDL-C and triglycerides.

Secondary outcomes: pain free and maximum walking distance

PFWD (132 m; range 70-194, $p < .01$) and MWD (183 m; range 98-268, $p < .01$) improved significantly compared with the control. As shown in **Table 2**, a separate analysis of studies using the Gardner protocol indicated even higher effect sizes. Further, pooling data from the walking interventions (7 for PFWD and 9 for MWD) showed an improvement of 160 m (89-231 m, $p < .01$ and $I^2 = 80\%$) in PFWD and 214 m (93-335, $p < .01$ and $I^2 = 96\%$) in MWD in favour of the walking group. No statistical differences were present when comparing exercise modes. The high heterogeneity with regard to MWD was reduced when omitting two studies (23,38) that found no effect of SET ($I^2 = 96\%$ vs. $I^2 = 0\%$). Similarly, omitting the study of Mika et al. (34) shifted heterogeneity for PFWD to nonsignificant ($I^2 = 80\%$ vs. $I^2 = 0\%$). Three interventions that combined modes of exercise (32,40,42) found a significant improvement in PFWD and MWD (73m, range 1-145, $p < .05$ and $I^2 = 0.0$; and 176 m, range 109-243, $p < .01$ and $I^2 = 0.0$). Combining also data of both aerobic training interventions (24 exercise and 19 control patients) showed a significant increase in MWD, whereas no effect on MWD was established for the two resistance exercise trials (19 exercise and 18 control patients). PFWD was only evaluated in two single studies regarding the aforementioned exercise modes (40,42).

***Table 3**. Included studies with trial and participant characteristics based on reported baseline data.*

Reference Country of Origin	Trial Characteristics			Patient Characteristics						
	Design	Duration (wks)	FITT	N (♂/♀)	Mean age (yrs)	Mean ABI	DM (%)	HTN (%)	BMI ($kg.m^{-2}$)	HCL (%)
Chehuen et al. 2017 (35) ***Brazil***	●	12	**Treadmill walking:** 2/w, $\%HR_{max}$ at pain threshold, 30 min (15x 2 min intervals, 2 min rest) **Control:** attention-control stretching 2/w, 30 min **Standard care:** recommendation to walk 30 min every day (assessed by weekly recall) **Test protocol:** Gardner protocol (3.2 km/h with 2% increase in inclination every 2-min)	42 (42/0)	62.5	0.60	26.2	83.3	26.2	95.2
Crowther et al. 2008† (36) ***Australia***	●	52	**Treadmill walking:** 3/w, intense to maximal pain (CPS 3-4/4), 25-40 min **Control:** not specified **Standard care:** recommendations for life-style changes **Test protocol:** Gardner protocol (3.2 km/h with 2% increase in inclination every 2-min)	21 (10/11)	69.1	0.67	19.0	33.3	28.0	N/A
Gardner et al. 2001 (37) ***USA***	●	26	**Treadmill walking:** 3/w, intense pain (CPS 3/4), at 50-80% $Workload_{max}$ 15-40 min **Control:** did not receive any recommendations regarding exercise **Mutual:** usual medical care **Test protocol:** Gardner protocol (3.2 km/h with 2% increase in inclination every 2-min)	52 (47/5)	70.5	0.68	42.3	80.8	29.9	75.0
Gelin et al. 2001† (38) ***Sweden***	●	52	**Walking:** first 26w; 3/w and last 26w; 2/w, 30 min **Control:** not specified **Standard care:** recommendations to quit smoking and risk factor management **Test protocol:** progressive increase slope from 0-12%	177 (118/59)[¤]	67.0	0.56	14.7	PoS	N/A	PoS
Gomes et al. 2018 (30) ***Brazil***	●	12	**Resistance exercise:** 2/w, 8 exercises, 3 sets of 10 repetitions, 5-7/10 on OMNI resistance exercise scale, 40 min **Control:** whole body stretching and relaxation exercises, 40 min **Test protocol:** no treadmill test	30 (18/12)[¤]	63.5	0.72	43.3	73.3	25.9	33.3
Izquierdo-Porrera et al. 2000 (31) ***USA***	○	26	**Treadmill walking:** 3/w, intense pain (CPS 3/4) at 50-80% $Workload_{max}$, 15-40 min **Control:** non-exercising control from longitudinal studies **Test protocol:** Gardner protocol (3.2 km/h with 2% increase in inclination every 2-min)	48 (44/4)	68	0.62	37.5	77.1	28.4	79.2
McGuigan et al. 2001 (41) ***Australia***	●	24	**Resistance exercise:** 3/w, 8 exercises, 2 sets with variable number of repetitions (8-15) (linear periodization), weights **Control:** non-exercising control group **Test protocol:** no data on PFWD or MWD	20 (9/11)[¤]	68.2	0.64	N/A	PoS	27.5	N/A

Mika et al. 2011[34] ***Poland***	●	**12**	**Treadmill walking:** 3/w, onset of claudication (CPS 2/5), 30-55 min (3-5 min intervals with 3 min rest) **Control:** advised not to change their usual level of activity **Standard care:** encouraged to stop smoking **Test protocol:** Gardner protocol (3.2 km/h with 2% increase in inclination every 2-min)	**61 (53/8)**	**62.8**	**0.78**	**0.0**	**N/A**	**27.7**	**PoS**
Mosti et al. 2011[32] ***Norway***	○	**8**	**Combined exercise:** 3/w, 60 min **1)** Plantar flexion ergometer: 80% $Workload_{max}$, 4x 4 min each leg at 55-65 rpm **2)** Maximal strength training: horizontal dynamic leg press, %1RM 85-90, 4 sets with 5 repetitions **Control:** non-randomized, recommendation to follow AHA exercise guidelines (Hirsch et al. 2006) **Test protocol:** Hiatt protocol (3.2 km/h with a 3.5% increase in inclination every 3-min)	**20 (14/6)**	**65.5**	**N/A**	**20.0**	**45.0**	**28.0**	**50.0***
Murphy et al. 2012†[39] ***USA***	●	**26**	**Treadmill walking:** 3/w, mild-moderate pain (CPS 3-4/5), 15-50 min **Control:** no supervised exercise **Standard care:** optimal medical management + cilostazol + recommendations for risk factor management (incl. unsupervised exercise with written and verbal instructions) **Test protocol:** Gardner protocol (3.2 km/h with 2% increase in inclination every 2-min)	**65 (37/28)[¤]**	**63.5**	**0.68**	**20.0**	**90.8**	**27.8**	**83.1**
Parr et al. 2009[42] ***South-Africa***	●	**6**	**A. Resistance exercise:** 3/w, 10 weight plated upper-body exercises and 4 dumbbell exercises with 15 (comfortably) and 10 repetitions (starting at 1.5 kg increased by 1.8-7.3 kg/week) respectively, 45 min **B. Combined exercise:** 3/w, 45 min 1) Treadmill walking: speed and incline with onset of claudication in 5-10 min, 10-20 min 2) Stationary cycling: 5 min 3) Circuit training/Floor exercises/Spinning class: 1/w, 15 min and stretching for 5 min **Control:** advice to walk as much as possible at home **Test protocol:** Gardner protocol (3.2 km/h with 2% increase in inclination every 2-min)	**25 (17/8)**	**61.8**	**N/A**	**N/A**	**N/A**	**28.0**	**N/A**
Schlager et al. 2012[23] ***Austria***	●	**26**	**Walking:** 2/w, walking speed to elicit claudication pain in 3-5 min (intermittent walking), 35-50 min **Control:** no supervised exercise **Standard care:** best medical treatment with detailed information on LEAD, risk factor management and life-style changes **Test protocol:** Constant test **(**3.2 km/h with a 12% inclination)	**53 (33/20)[¤]**	**69.5**	**0.58**	**39.6**	**PoS**	**26.8**	**96.2***

Treat-Jacobson et al. 2009 (40) ***USA***	●	**12**	**A. Aerobic exercise:** arm-ergometer, 3/w, 10 Watts below $Workload_{max}$ at 50 rpm, 60 min (2-5 min exercise, 1-2 min rest) **B. Treadmill walking:** 3/w, moderately severe pain (CPS 4/5), with increase in inclination and speed when walking > 8 min, 60 min **C. Combined exercise:** 3/w, 60 min 1) Arm ergometer: 20 min 2) Treadmill walking: 40 min **Control:** continue prescribed medical care + specific standardized written walking instructions and daily exercise records (reviewed weekly) **Test protocol:** 3.2 km/h with a 3.5% inclination increase every 3-min. When 10.5% inclination was reached, speed was increased with 0.8 km/h every 3-min	**41 (29/12)**	**67.5**	**0.67**	**36.6**	**80.5**	**28.3**	**90.2**
Wang et al. 2008 (43) ***Norway***	●	**8**	**Aerobic exercise:** plantar flexion ergometer, 3/w, 80% $Workload_{max}$,40 min (4x 4 min each leg) at 55-65 rpm **Control:** recommendation to follow AHA exercise guidelines (Hirsch et al. 2006) **Test protocol:** Hiatt protocol **(**3.2 km/h with a 3.5% increase in inclination every 3-min)	**25 (19/6)**	**66.4**	**N/A**	**12.0**	**40.0**	**30.0**	**N/A**
Wang et al. 2010 (33) ***Norway***	○	**8**	**Resistance exercise:** horizontal dynamic leg press, 3/w, %1RM 85-90, 4 sets with 5 repetitions **Control:** non-randomized, recommendation to follow AHA exercise guidelines (Hirsch et al. 2006) **Test protocol:** Hiatt protocol **(**3.2 km/h with a 3.5% increase in inclination every 3-min)	**10 (9/1)**	**67.0**	**N/A**	**20.0**	**40.0***	**31.4**	**30.0***

***Note**. Study design was a randomized controlled trial (●**)** or a prospective non-randomized controlled trial (○). Frequency, Intensity, Time and Type of training (FITT characteristics) are summarized for every intervention group. **Abbreviations:** N, analyzed or randomized numbers (ª) (male/female); CPS, claudication pain scale; ABI, ankle-brachial index; BMI, body-mass index; DM, diabetes mellitus, HTN, hypertension; OBS, obesity; HCL, hypercholesterolemia. PoS (part of sample) was used to indicate that, based on baseline data or reported medication use (*), at least part of the sample was diagnosed with the respective comorbidity. †Crowther et al. had a LEAD-free control group (n = 11). Gelin and Murphy et al. both studied a revascularization group (n = 87 and n = 46) not included in the analyses. LEAD = lower extremity artery disease.*

Table 2. *Changes in primary and secondary outcomes.*

Variable	*Studies*	*Sample size (Ex/Con)*	*Baseline Mean* ± SD	*Mean difference*	*CIs (95%)*	*Hedges' g*	*CIs (95%)*	I^2
Weight (kg)	6	89/82	**85.1 ± 5.8**	**-0.46**	-4.8;3.9	**-0.031**	-0.321;0.260	0
BMI ($kg.m^{-2}$)	4	94/69	**28.3 ± 1.5**	**0.00**	-1.3;1.3	**0.003**	-0.306;0.312	0
SBP (mmHg)	9	261/208	**143 ± 5.3**	**-5.8**	-9.9;-1.7	**-0.283**	-0.502;-0.065	17.1
DBP (mmHg)	5	108/81	**75.9 ± 5.3**	**-2.2**	-5.2;0.74	**-0.202**	-0.489;0.085	0
TC ($mmol.l^{-1}$)	3	137/121	**6.5 ± 0.94**	**-0.19**	-0.92;0.53	**-0.291**	-1.105;0.523	**86.6***
LDL-C ($mmol.l^{-1}$)	4	129/91	**3.1 ± 0.70**	**-0.25**	-0.64;0.14	**-0.320**	-0.812;0.171	**70.0***
HDL-C ($mmol.l^{-1}$)	3	102/65	**1.1 ± 0.16**	**0.03**	-0.055;0.12	**0.090**	-0.235;0.415	1
TG ($mmol.l^{-1}$)	3	137/121	**2.1 ± 0.26**	**-0.19**	-0.43;0.058	**-0.204**	-0.451;0.043	5.98
PFWD (m)	8	212/160	**174 ± 65**	**132**	70.0;194	**1.115**	0.562;1.667	**83.6***
PFWD Gardner (m)	7	179/136	**176 ± 70**	**157**	90.5;224	**1.208**	0.489;1.927	**76.4***
MWD (m)	13	346/293	**404 ± 288**	**183**	98.4;268	**1.049**	0.568;1.531	**92.7***
MWD Gardner (m)	7	179/136	**431 ± 145**	**269**	214;324	**1.418**	0.683;2.154	33.0

Note. *Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; TG, triglycerides; PFWD, pain-free walking distance; and MWD, maximal walking distance. Weighted means were calculated using baseline values and analyzed numbers. * Significant heterogeneity Cochran Q-test (<0.10).*

Discussion

This systematic review with meta-analysis is the first to pool data on CV risk factors following SET in a population of IC patients. The results confirm the findings from previous systematic reviews showing improved PFWD and MWD following SET (10,14). However, only little evidence was found to support the potential of SET as an adjunctive therapy in the secondary prevention of IC patients.

An abundance of studies highlights the key role of regular physical activity and exercise in the prevention of all cause and CV mortality in the general population and in patients with established cardiac diseases (44). The benefits of exercise on the presence and severity of CV risk factors is one of the main drivers underlying this inverse association (45). In this meta-analysis little evidence was found to support these findings in IC patients, with engagement in exercise training being associated with a significant and clinically relevant decrease in SBP (-5.8 mmHg). A recent meta-analysis in coronary artery disease patients demonstrated similar reductions in SBP following endurance training (19). Walking was the most applied exercise mode, involving 74% of included IC participants. This would suggest that low intensity exercise could already suffice to improve blood pressure levels. In line with this, Cornelissen and Smart (46) found no significant differences in BP reductions in subgroups of healthy individuals participating in low, moderate, or high intensity endurance training. However, effect sizes were smallest in the low intensity group. In IC patients included in this meta-analysis, exercise intensity was mostly prescribed based on pain perception, which makes interpretation of intensity difficult. Yet, based on GPS data, Le Faucheur et al. (47) found IC patients to walk at approximately 3.6 km/h outdoors, with a quarter of patients exceeding 4.2 km/h. Combined with the evidence that most LEAD patients are physically inactive (5) and that the metabolic cost of walking after pain onset is increased (48), one could assume that walking is performed at least at a moderate intensity by many IC patients. The lack of an effect on DBP can be explained by the fact that baseline DBP was already in the optimal range (76 mmHg) and the scant number of studies (n = 5) reducing the power.

Previous research in patients with hypercholesterolaemia suggests a decrease of 6-18% in triglycerides and 7-16% increase in HDL-C (45). As most lipid changes are expected with a >900 kcal/week energy expenditure, prolonged exercise sessions for at least 40 weeks are recommended (49). The meta-analyses did not establish any significant improvement in the blood lipid profiles of IC patients. However, baseline values of HDL-C and TG were already in the (high) normal range. Recent recommendations state that the greatest improvements in blood lipid profile may be anticipated in patients with the worst blood lipid profile, which could explain the lack of results (49). Moreover, walking interventions in a broad range of health conditions did not find any effect on HDL-C or triglycerides (50,51).

Next, obesity in IC patients is an important risk factor since it is directly associated with walking ability (52), improvement during SET (52,53), sedentary behavior (54), and subsequent development of other CV risk factors (55). More specifically, this progression of CV risk factors is linked with body composition and the visceral distribution of fat mass (55). No effect of the exercise interventions was found on body weight in the overall overweight IC patients. This is in contrast with a recent review showing that walking lowered BMI in sedentary but otherwise healthy individuals with -0.53 kg/m^2 (51). A possible explanation for this discrepancy could be the higher walking frequency in this review (median, five days/week vs. three days/week), resulting in a higher total energy expenditure (51). More specifically, a recent consensus statement from the EXPERT panel recommends an aerobic exercise volume of more than 250 min/week to target obesity (49). Therefore, SET induced body weight changes in IC patients seem to be hampered by low exercise volumes and the lack of whole body workouts included in analysis. Further, overall body weight changes do not reflect changes at a tissue level (49). This illustrates the limitations of using BMI and body weight without measuring body composition and waist circumference. Therefore, as no studies investigated changes in waist circumference or fat percentage and distribution, future studies in IC patients are warranted to elucidate the effect on body composition.

Finally, the findings confirm the results from a recent systematic review that also documented a significant improvement in PFWD and MWD at 140 and 210 m respectively (10). Significant heterogeneity observed in ambulatory outcomes can be explained by the various exercise interventions included, although heterogeneity was also found when isolating walking interventions. This was due to two studies in which no effect of walking training was found (23,38), possibly caused by a large dropout rate (51%) in the exercise group (38), the approximation method which was used to convert non-parametric outcomes, and a non-optimal walking frequency of two days/week (23). Moreover, both studies had a lower mean ABI than the other studies (0.56 and 0.58).

Limitations

The results presented in this meta-analysis should be interpreted with the following limitations: 1) The number of studies that could be included and their sample sizes is small, which limits the statistical power for most parameters. 2) Whereas almost 75% of exercise patients were included in walking groups, data on the impact of other types of exercise are scarce or absent. Since exercise characteristics are known to influence the impact of exercise on specific CV risk factors, more studies are warranted investigating the effect of other modes of exercise in IC patients. 3) Most outcome measures were secondary, which could have resulted in selective reporting. 4) The results cannot be generalised to all LEAD patients, as only LEAD patients with IC were included. 5) A lack of data on risk factor management can limit the interpretation of results. However, the majority of studies

(11/15) either reported that patients were stable, had no change in pharmacological treatment, or had optimal medical treatment as standard care. 6) As different treadmill protocols were used to evaluate MWD and PFWD, mean differences presented might lack external validity. Therefore, standardised Hedges' g values complement crude outcomes. In addition, the majority of trials (11/13) used either the Gardner or the (adjusted) Hiatt protocol to evaluate MWD. These protocols tend to have a similar energy expenditure (56) and therefore pooled mean differences are intuitively meaningful. Furthermore, a separate analysis of the studies that used the Gardner protocol further confirmed the beneficial effect of exercise therapy on walking capacity. In summary, although being the best representation of available evidence through increasing power and assessing heterogeneity, meta-analysis reviews should always be complemented with rigorous RCTs evaluating the subject. Therefore future research to include and report CV measures in exercise trials in LEAD patients should be encouraged.

Conclusion

In summary, the findings emphasise the importance of exercise training in IC patients to improve ambulatory capacity. In addition, some evidence was found suggesting that CV risk factors could ameliorate after SET. However, studies reporting on CV risk outcomes are scarce. Therefore, high quality RCTs are required to elucidate the CV risk-reducing effect of different exercise programs in IC patients.

Appendices

***Supplementary file 1**: Protocol.*

- *Types of studies*: non-randomized prospective cohort studies and randomized controlled trails (RCT's) comparing supervised exercise training (SET) with a control group receiving no exercise intervention.
- *Participants*: Adult patients with **peripheral artery disease** (ABI < 0.9) experiencing **intermittent claudication** will be included, typically Rutherford 1-3 or Fontaine 2a or 2b. When patients are asymptomatic or having critical limb ischemia with rest pains or tissue loss, the study will be excluded.
- *Interventions*: **supervised exercise training for at least 4 weeks**.
    - *Supervised exercise training*: **center-based**, either a hospital or outpatient-facility (community-based) with **direct supervision of a healthcare professional**. Although most programs will consist of interval walking training to moderate-high claudication pain, inclusion of studies will be irrespective of specific tailored exercise mode and will be specified according to the prescribed program using the FITT-P model (F=frequency/week, I=intensity of exercise, Type=mode of exercise, Time=time spend exercising without warm-up and cool-down, P=progress during the program). Supplementation of behavioral change or motivational models to the program will not lead to exclusion **but will be specified**. SET either without any previous revascularization method **or after any type of revascularization** (endovascular therapy or surgery).
    - **Exclusion of home- or community-based exercise programs**, characterized by patient's self-direction with guidance of a healthcare professional, **without direct supervision.**
- *Control*:
    - Control group receiving **no supervised exercise training**
    - Surgery
- *Outcomes*: **office blood pressure** (systolic blood pressure (mmHg) and diastolic blood pressure (mmHg)), **lipid-levels** (Low-density lipids (mg/dl or mmol/l), **high density lipids** (mg/dl or mmol/l), **triglycerides** (mg/dl or mmol/l) and **total cholesterol** (mg/dl or mmol/l)), **glucose levels** (fasting glucose levels (mg/dl or mmol/l)), **obesity** (BMI (kg/m^2) and **abdominal circumference** (cm)). **Body mass** (kg) *was added during the review process*.

Search strategy:

Search will be done using electronical databases from **PubMed MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL)** from inception date until **…** + manually identified papers when meeting inclusion criteria. (Search done **28/04)**

P: *peripheral artery disease* AND *intermittent claudication*

Synonyms: peripheral arterial disease, peripheral vascular disease, peripheral artery occlusive disease, peripheral obliterative arteriopathy, arterial occlusive disease, artery occlusive disease, PAD and PVD.

Synonyms: intermittent claudication and claudication.

I: *supervised exercise training*

Synonyms: supervised exercise program, exercise training, supervised rehabilitation, rehabilitation, walking training, walking, exercise, exercise intervention.

C: *usual care, control group*

O: cardiovascular risk factors (blood pressure, systolic blood pressure, diastolic blood pressure, SBP, DBP, hypertension; lipids, cholesterol, HDL, LDL, triglycerides; glucose, diabetes; weight, obesity, abdominal circumference)

Conduct the search:

Stage 1: combining studies in one excel file (Pubmed, CINAHL, EMBASE and CENTRAL)

= 4006 + 2994 + 67 + 1246 = **8313 (DATABASESearch_CVRF&PAD_8313.xlsx)**

Stage 2: removal of duplicate studies based on title/author (highlight in red and delete)

= 8313 – **84 (Author & Title)** = **8229**

= further duplicates will be **manually indicated** in red in stage 3

Stage 3: DATABASESearch_CVRF&PAD_Start.xlsx

Two independent researchers will examine the full list of search results exported in an excel file in the following order:

3.1) Title/abstract – exclusion when:

- No amputees
- No peripheral artery disease or intermittent claudication
- No exercise
- Acute effects
- ≤ 4 weeks of training

- Pharmacologic studies (NO combination studies with drugs)
- Animal studies
- Duplicate
- Type of paper: thesis, meta-analysis, review, book-chapter,…
- Language other than English
- Control group

No cardiovascular risk factor outcome is not included as an exclusion factor in this stage of literature search.

3.2) Abstract/full paper – exclusion when:

Factors analogous to title examination but supplemented with:

- No cardiovascular risk factors as outcomes *(Full paper)*
- No supervised training *(Full paper)*
- Asymptomatic PAD or PAD with rest pain or tissue loss (Rutherford 0 or Rutherford 4-6/Fontaine 1 or Fontaine 3-4) *(Full paper)*
- Control group

Supplementary file 2: Search strategy.

1. Medline (using Pubmed)

((((((((((((((((peripheral artery disease[Title/Abstract]) OR peripheral arterial disease[Title/Abstract]) OR peripheral vascular disease[Title/Abstract]) OR peripheral artery occlusive disease[Title/Abstract]) OR peripheral obliterative arteriopathy[Title/Abstract]) OR arterial occlusive disease[Title/Abstract]) OR claudicatio [Title/Abstract]) OR intermittent claudication[Title/Abstract]) OR claudication[Title/Abstract]) OR artery occlusive disease[Title/Abstract]) AND Humans[Mesh])) AND (((((((((exercise[Title/Abstract]) OR training[Title/Abstract]) OR physical activity[Title/Abstract]) OR walking[Title/Abstract]) OR cycling[Title/Abstract]) OR swimming[Title/Abstract]) OR strength[Title/Abstract]) OR resistance[Title/Abstract]) OR rehabilitation[Title/Abstract]) AND Humans[Mesh]))) AND Humans[Mesh])) AND Humans[Mesh]) Filters: Humans

2. EMBASE (excl. medline)

#1: peripheral:ab,ti AND artery:ab,ti AND disease:ab,ti OR (peripheral:ab,ti AND arterial:ab,ti AND disease:ab,ti) OR (peripheral:ab,ti AND vascular:ab,ti AND disease:ab,ti) OR 'peripheral occlusive artery disease':ab,ti OR (peripheral:ab,ti AND obliterative:ab,ti AND arteriopathy:ab,ti) OR (arterial:ab,ti AND occlusive:ab,ti AND disease:ab,ti) OR 'intermittent claudication':ab,ti OR claudication:ab,ti OR claudicatio OR ('artery'/exp OR artery AND occlusive AND ('disease'/exp OR disease))

#: #1 AND 'human'/de AND [embase]/lim NOT [medline]/lim

#3: exercise:ab,ti OR rehabilitation:ab,ti OR training:ab,ti OR swimming:ab,ti OR cycling:ab,ti OR walking:ab,ti OR 'physical activity':ab,ti OR strength:ab,ti OR resistance:ab,ti

#4: #3 AND 'human'/de AND [embase]/lim NOT [medline]/lim

#5: #2 AND #4

3. CINAHL

#1: TI peripheral artery disease OR AB peripheral artery disease OR TI peripheral arterial disease OR AB peripheral arterial disease OR TI peripheral vascular disease OR AB peripheral vascular disease OR TI peripheral occlusive artery disease OR AB peripheral occlusive artery disease OR TI peripheral obliterative arteriopathy OR AB peripheral obliterative arteriopathy OR TI arterial occlusive disease OR AB arterial occlusive disease

Limiters - English Language; Exclude MEDLINE records; Human

***Supplementary file 3**: Assessment of bias.*

Table S3.1. TESTEX.

	Study Quality					Study Reporting										
	1	**2**	**3**	**4**	**5**	**6**			**7**	**8**		**9**	**10**	**11**	**12**	**Total**
Chehuen 2017	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	**14**
*Crowther 2008**	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	**14**
Gardner 2001	1	0	1	1	0	1	1	1	1	1	1	0	1	1	1	**12**
Gelin 2001	1	1	1	1	0	0	1	0	1	1	1	1	0	0	0	**9**
Gomes 2018	1	1	0	1	1	0	1	0	1	1	1	1	0	1	1	**11**
Izquierdo-Porrera 2000	0	0[#]	0[#]	1	0	1	1	0	1	1	1	1	0	1	1	**9**
McGuigan 2001	1	0	0	1	0	0	1	0	0	1	0	0	0	1	1	**6**
Mika 2011	1	0	0	1	1	1	1	0	0	0	0	0	0	1	1	**7**
Mosti 2011	1	0[#]	0[#]	0	0	1	1	1	0	1	1	1	0	1	1	**9**
Murphy 2012	1	1	0	1	0	1	1	1	1	1	1	0	1	1	1	**12**
Parr 2009	1	1	1	1	0	0	1	1	0	1	1	0	0	0	0	**8**
Schlager 2012	1	1	1	1	1	1	1	0	1	1	1	0	0	1	1	**12**
Treat-Jacobsen 2009	1	1	1	1	0	1	1	1	0	1	1	0	1	1	1	**12**
Wang 2008	1	0	0	1	0	1	1	0	0	1	1	1	0	1	1	**9**
Wang 2010	1	0[#]	0[#]	1	0	1	1	1	1	1	1	1	0	1	1	**11**

*more information on methodology in Leicht et al. 2015 & Crowther et al. 2009

[#] no RCT

1. Eligibility criteria specified (=1)
2. Randomization specified (=1)
3. Allocation concealment (=1)
4. Groups similar at baseline (=1)
5. Blinding of assessors (=1)
6. Outcome measures assessed in 85% of patients: 6.1 No point – if withdrawals are > 15% (no point), 1 point – if adherence > 85%, 6.2 if adverse events are reported (=1), and 6.3 if exercise attendance is reported (=1)
7. Intention-to-treat analysis (=1)
8. Between-group statistical comparisons reported: 8.1 primary outcome (=1), 8.2 secondary outcome (=1)
9. Point measures and measures of variability for all reported outcome measures (=1)
10. Activity monitoring in control groups (=1)
11. Relative exercise intensity remained constant (=1)
12. Exercise volume and energy expenditure (=1)

S3.2 Funnel plots

Figure S3.2.1. *Funnel plot with imputed studies – Systolic Blood Pressure.*

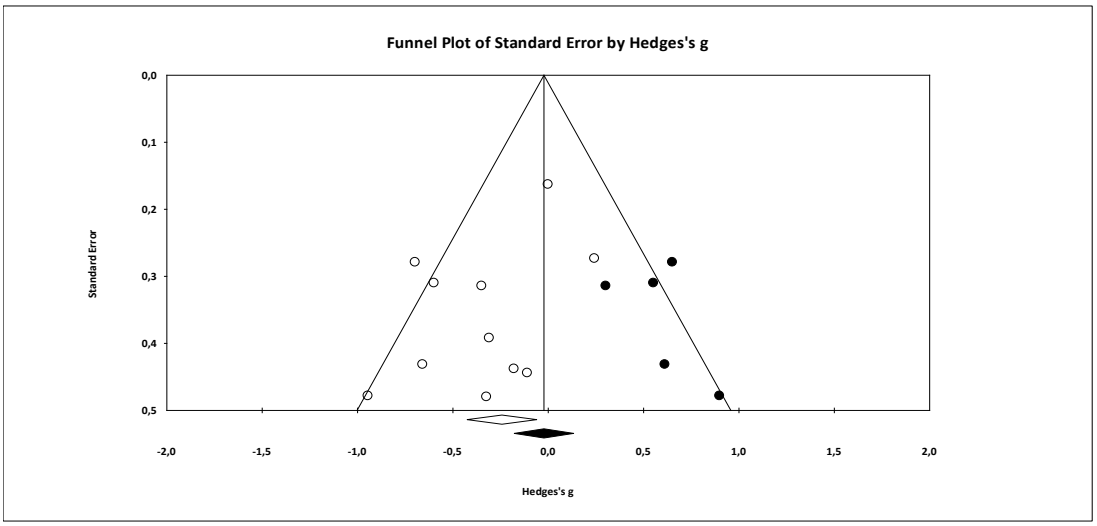


Figure S3.2.2. Funnel plot with imputed studies – Diastolic Blood Pressure.

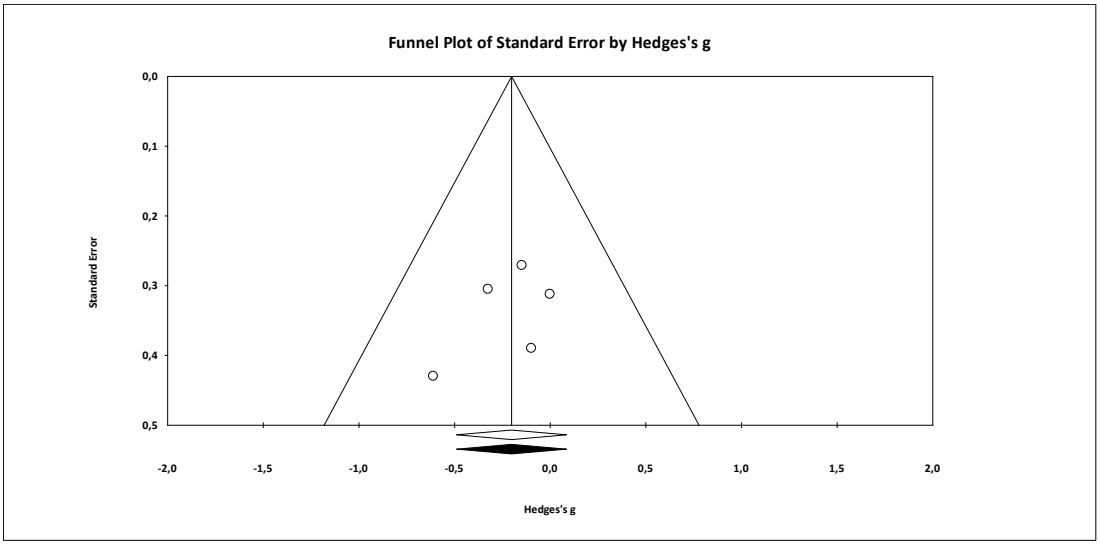


Figure S3.2.3. Funnel plot with imputed studies – Weight.

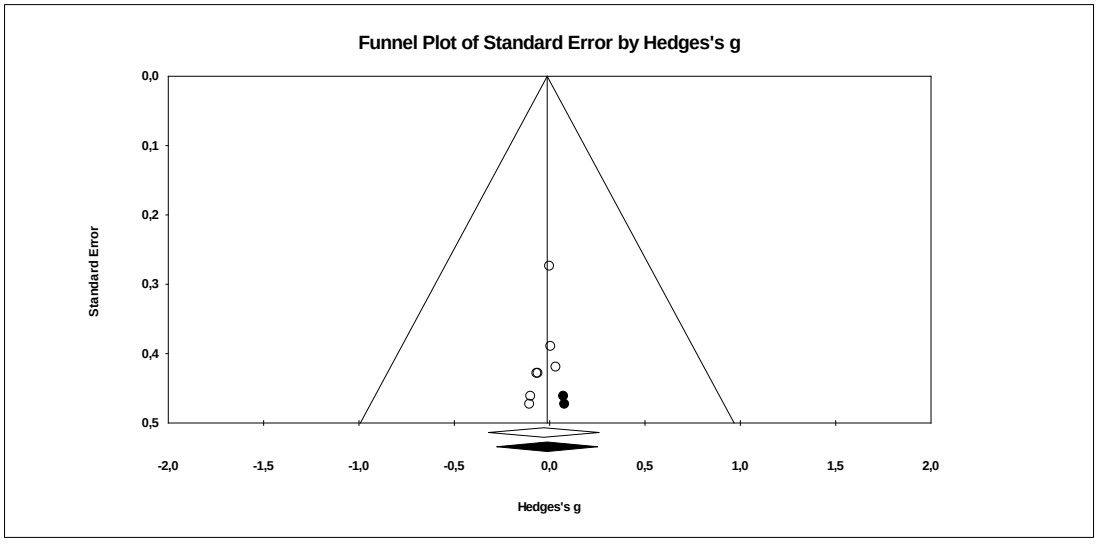


Figure S3.2.4. *Funnel plot with imputed studies – Pain-free walking distance.*

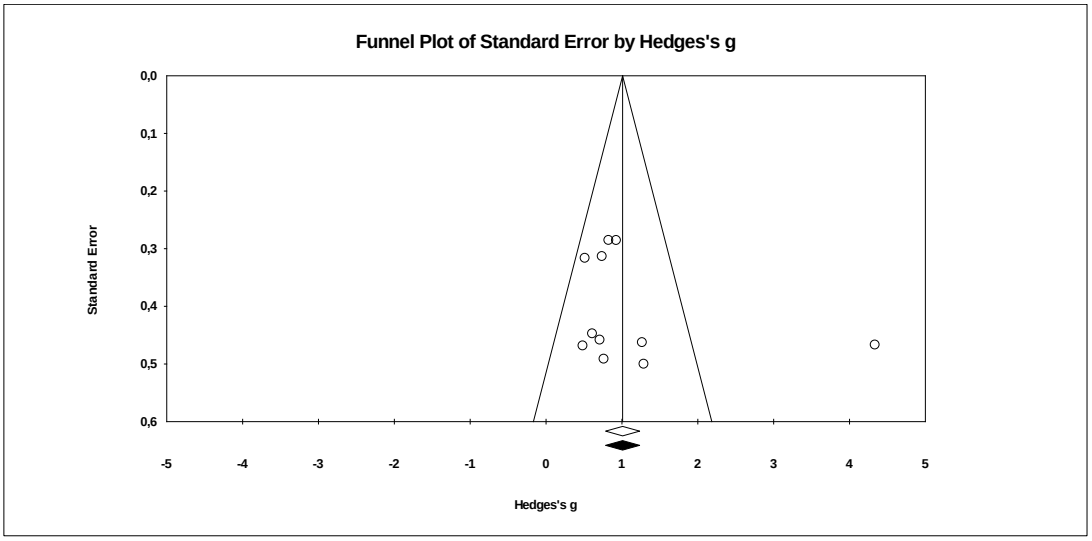


Figure S3.2.5. *Funnel plot with imputed studies –Pain-free walking distance Gardner.*

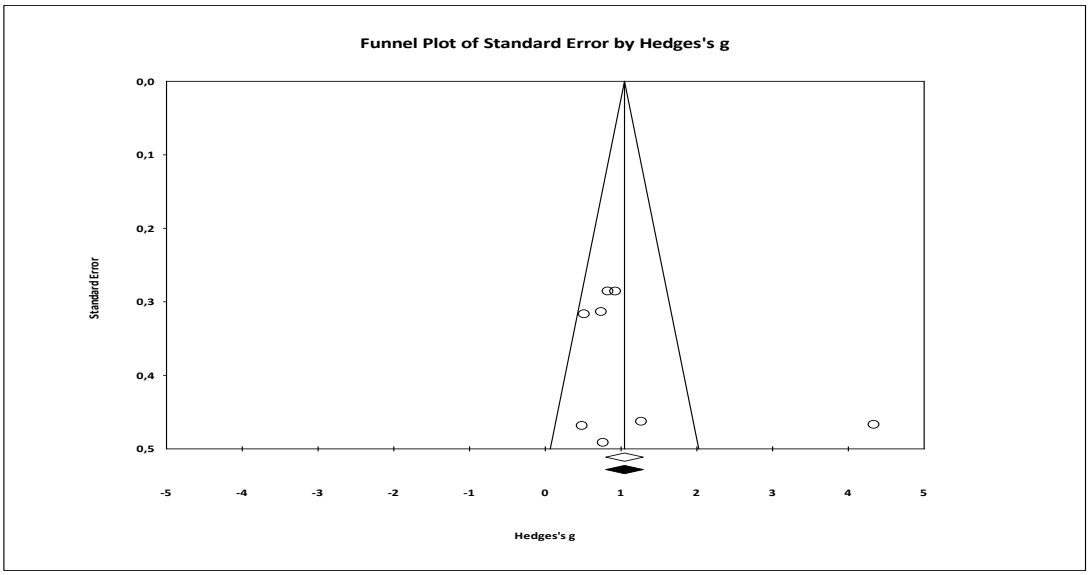


Figure S3.2.6. *Funnel plot with imputed studies – Maximal walking distance.*

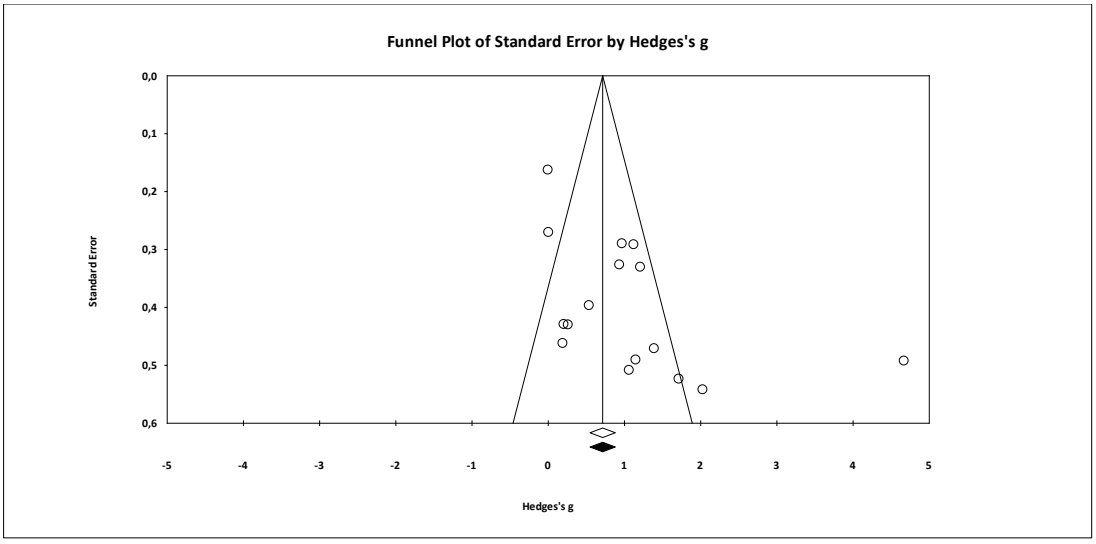
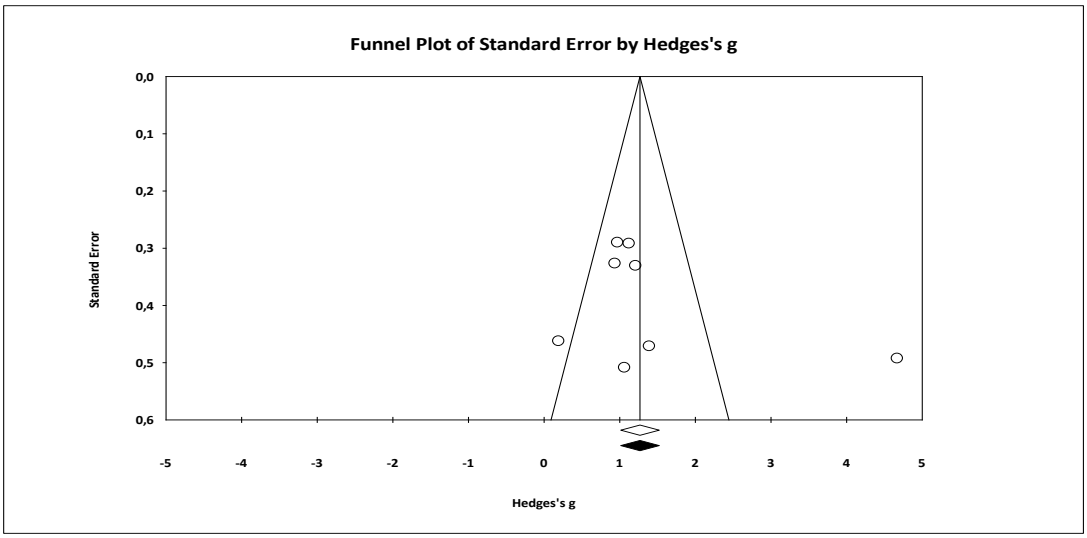


Figure S3.2.7. *Funnel plot with imputed studies – Maximal walking distance Gardner.*



Supplementary file 4: *CMA outcomes.*

Table S4.1. *Effect sizes and heterogeneity tables.*

All exercise vs control

Outcome	N	Mean Difference	Confidence Interval (95%)	P-value	Hedges' g	Confidence interval (95%)	P-value
Weight	**6** 89/82	-0.464	-4.838;3.910	**0.835**	-0.031	-0.321;0.260	**0.836**
BMI	**4** 94/69	-0.002	-1.332;1.328	**0.998**	0.003	-0.306;0.312	**0.985**
SBP	**9** 261/208	-5.781	-9.893;-1.670	**0.006**	-0.283	-0.502;-0.065	**0.011**
DBP	**5** 108/81	-2.216	-5.176;0.743	**0.141**	-0.202	-0.489;0.085	**0.168**
TC ***(Mean Mika)***	**3** 137/121	-0.191	-0.916;0.534	**0.605**	-0.291	-1.105;0.523	**0.484**
LDL ***(Mean Mika)***	**4** 129/91	-0.252	-0.640;0.135	**0.201**	-0.320	-0.812;0.171	**0.202**
HDL ***(Mean Mika)***	**3** 102/65	0.030	-0.055;0.115	**0.493**	0.090	-0.235;0.415	**0.588**
TG ***(Mean Mika)***	**3** 137/121	-0.187	-0.432;0.058	**0.134**	-0.204	-0.451;0.043	**0.106**
FBG	**1** 34/14	-0.444	-1.938;1.050	**0.560**	-0.182	-0.795;0.431	**0.561**
PFWD	**8** 212/160	132.195	69.954;194.437	**0.000**	1.115	0.562;1.667	**0.000**
PFWD Gardner	**7** 179/136	157.371	90.475;224.268	**0.000**	1.208	0.489;1.927	**0.001**
MWD	**13** 346/293	183.309	98.414;268.203	**0.000**	1.049	0.568;1.531	**0.000**
MWD Gardner	**7** 179/136	269.051	213.921;324.180	**0.000**	1.418	0.683;2.154	**0.000**

Walking exercise vs control

Outcome	N	Mean Difference	Confidence Interval (95%)	P-value	Hedges' g	Confidence interval (95%)	P-value
Weight	**2** 38/35	0.118	-6.438;6.674	**0.972**	0.010	-0.440;0.460	**0.965**
BMI	**4** 94/69	-0.002	-1.332;1.328	**0.998**	0.003	-0.306;0.312	**0.985**
SBP	**6** 205/164	-4.804	-11.125;1.517	**0.136**	-0.227	-0.529;0.075	**0.141**
DBP	**3** 83/60	-1.755	-5.234;1.724	**0.323**	-0.158	-0.492;0.175	**0.352**
TC ***(Mean Mika)***	**3** 137/121	-0.191	-0.916;0.534	**0.605**	-0.291	-1.105;0.523	**0.484**
LDL ***(Mean Mika)***	**4** 129/91	-0.252	-0.640;0.135	**0.201**	-0.320	-0.812;0.171	**0.202**
HDL ***(Mean Mika)***	**3** 102/65	0.030	-0.055;0.115	**0.493**	0.090	-0.235;0.415	**0.588**

TG (Mean Mika)	**3** 137/121	-0.187	-0.432;0.058	**0.134**	-0.204	-0.451;0.043	**0.106**
FBG							
PFWD	**7** 173/128	159.632	88.535;230.729	**0.000**	1.297	0.507;2.088	**0.001**
PFWD Gardner	**6** 162/120	171.503	97.941;245.065	**0.000**	1.393	0.497;2.289	**0.002**
MWD	**9** 273/230	213.949	92.761;335.136	**0.001**	1.277	0.554;1.999	**0.001**
MWD Gardner	**6** 162/120	303.901	274.307;333.494	**0.000**	1.668	0.784;2.551	**0.000**

Aerobic exercise vs control

Outcome	N	Mean Difference	Confidence Interval (95%)	P-value	Hedges' g	Confidence interval (95%)	P-value
Weight	**1** 14/11	0.100	-12.372;12.572	**0.987**	0.006	-0.758;0.770	**0.987**
BMI							
SBP	**2** 24/19	-11.606	-22.258;-0.955	**0.033**	-0.567	-1.180;0.045	**0.069**
DBP	**1** 14/11	-1.000	-8.849;6.849	**0.803**	-0.097	-0.861;0.667	**0.803**
TC							
LDL							
HDL							
TG							
FBG							
PFWD	**1** 10/8	85.600	26.933;144.267	**0.004**	1.292	0.311;2.273	**0.010**
MWD	**2** 24/19	140.060	45.333;234.788	**0.004**	0.781	0.176;1.387	**0.011**

Resistance exercise vs control

Outcome	N	Mean Difference	Confidence Interval (95%)	P-value	Hedges' g	Confidence interval (95%)	P-value
Weight	**3** 29/28	-1.134	-8.823;6.556	**0.773**	-0.074	-0.571;0.422	**0.769**
BMI							
SBP	**2** 20/17	-6.983	-16.143;2.177	**0.135**	-0.508	-1.137;0.121	**0.113**
DBP	**1** 11/10	-6.000	-14.088;2.088	**0.146**	-0.610	-1.452;0.233	**0.156**
TC							
LDL							
HDL							
TG							
FBG							
PFWD	**1** 9/8	74.000	-63.134;211.134	**0.290**	0.488	-0.431;1.406	**0.298**

PFWD Gardner	**1** 9/8	74.000	-63.134;211.134	**0.290**	0.488	-0.431;1.406	**0.298**
MWD	**2** 19/18	48.997	-111.252;209.246	**0.549**	0.201	-0.416;0.818	**0.523**
MWD Gardner	**1** 9/8	39.000	-142.896;220.896	**0.674**	0.194	-0.712;1.100	**0.675**

Combined exercise vs control

Outcome	N	Mean Difference	Confidence Interval (95%)	P-value	Hedges' g	Confidence interval (95%)	P-value
Weight	**1** 8/8	-1.500	-14.793;11.793	**0.825**	-0.105	-1.032;0.823	**0.825**
BMI							
SBP	**1** 12/8	-3.250	-18.832;12.332	**0.683**	-0.179	-1.037;0.680	**0.683**
DBP							
TC							
LDL							
HDL							
TG							
FBG							
PFWD	**2** 20/16	73.007	1.016;144.998	**0.047**	0.682	0.033;1.331	**0.039**
PFWD Gardner	**1** 8/8	130.000	-27.439;287.439	**0.106**	0.765	-0.199;1.729	**0.120**
MWD	**3** 30/26	175.982	109.178;242.786	**0.000**	1.079	0.071;2.088	**0.036**
MWD Gardner	**1** 8/8	225.000	29.203;420.797	**0.024**	1.065	0.067;2.062	**0.036**

All exercise vs control

Outcome	N	Study samples	df (Q)	P-value	I^2
Weight	**6** 89/82	7	6	**1.000**	0.000
BMI	**4** 94/69	4	3	**0.999**	0.000
SBP	**9** 261/208	11	10	**0.281**	17.098
DBP	**5** 108/81	5	4	**0.810**	0.000
TC (Mean Mika)	**3** 137/121	3	2	**0.001**	86.583
LDL (Mean Mika)	**4** 129/91	4	3	**0.019**	70.012
HDL (Mean Mika)	**3** 102/65	3	2	**0.364**	0.999
TG (Mean Mika)	**3** 137/121	3	2	**0.345**	5.981
FBG	**1** 34/14	1	0	**1.000**	0.000
PFWD	**8**	11	10	**0.000**	83.639

	212/160				
PFWD Gardner	**7** 179/136	8	7	**0.000**	76.407
MWD	**13** 346/293	16	15	**0.000**	92.662
MWD Gardner	**7** 179/136	8	7	**0.165**	33.002

Walking exercise vs control

Outcome	N	Study samples	df (Q)	P-value	I^2
Weight	**2** 38/35	2	1	0.943	0.000
BMI	**4** 94/69	4	3	0.999	0.000
SBP	**6** 205/164	6	5	0.101	45.715
DBP	**3** 83/60	3	2	0.758	0.000
TC (Mean Mika)	**3** 137/121	3	2	**0.001**	86.583
LDL (Mean Mika)	**4** 129/91	4	3	**0.019**	70.012
HDL (Mean Mika)	**3** 102/65	3	2	**0.364**	0.999
TG (Mean Mika)	**3** 137/121	3	2	**0.345**	5.981
FBG	**1** 34/14	1	0	**1.000**	0.000
PFWD	**7** 173/128	7	6	**0.000**	79.962
PFWD Gardner	**6** 162/120	6	5	**0.000**	78.939
MWD	**9** 273/230	9	8	**0.000**	96.035
MWD Gardner	**6** 162/120	6	5	**0.849**	0.000

Aerobic exercise vs control

Outcome	N	Study samples	df (Q)	P-value	I^2
Weight	**1** 14/11	1	0	**1.000**	0.000
BMI					
SBP	**2** 24/19	2	1	**0.509**	0.000
DBP	**1** 14/11	1	0	**1.000**	0.000
TC					
LDL					
HDL					
TG					
FBG					
PFWD	**1**	1	0	**1.000**	0.000

	10/8				
MWD	**2** 24/19	2	1	**0.889**	0.000

Resistance exercise vs control

Outcome	N	Study samples	df (Q)	P-value	I^2
Weight	**3** 29/28	3	2	**0.997**	0.000
BMI					
SBP	**2** 20/17	2	1	**0.408**	0.000
DBP	**1** 11/10	1	0	**1.000**	0.000
TC					
LDL					
HDL					
TG					
FBG					
PFWD	**1** 9/8	1	0	**1.000**	0.000
PFWD Gardner	**1** 9/8	1	0	**1.000**	0.000
MWD	**2** 19/18	2	1	**0.820**	0.000
MWD Gardner	**1** 9/8	1	0	**1.000**	0.000

Combined exercise vs control

Outcome	N	Study samples	df (Q)	P-value	I^2
Weight	**1** 8/8	1	0	**1.000**	0.000
BMI					
SBP	**1** 12/8	1	0	**1.000**	0.000
DBP					
TC					
LDL					
HDL					
TG					
FBG					
PFWD	**2** 20/16	2	1	**0.425**	0.000
PFWD Gardner	**1** 8/8	1	0	**1.000**	0.000
MWD	**3** 30/26	3	2	**0.828**	0.000
MWD Gardner	**1** 8/8	1	0	**1.000**	0.000

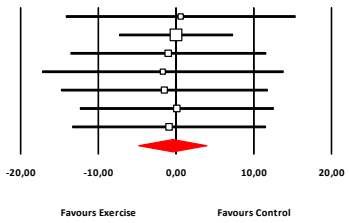
Figure S4.2. Forest plots.

Weight

All exercise vs controls

Body Weight

Study name	Comparison	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Crowther 2008	Walking vs Control	0,600	7,541	56,872	-14,181	15,381	0,080	0,937	10	11
Gardner 2001	Walking vs Control	0,000	3,732	13,927	-7,314	7,314	0,000	1,000	28	24
Mosti 2011	Combined vs Control	-1,000	6,422	41,240	-13,587	11,587	-0,156	0,876	10	10
Parr 2009 A	Resistance vs Control	-1,700	7,923	62,774	-17,229	13,829	-0,215	0,830	9	8
Parr 2009 B	Combination vs Control	-1,500	6,782	46,000	-14,793	11,793	-0,221	0,825	8	8
Wang 2008	Aerobic vs Control	0,100	6,363	40,491	-12,372	12,572	0,016	0,987	14	11
Wang 2010	Resistance vs Control	-0,900	6,352	40,352	-13,350	11,550	-0,142	0,887	10	10
		-0,464	2,232	4,981	-4,838	3,910	-0,208	0,835	89	82

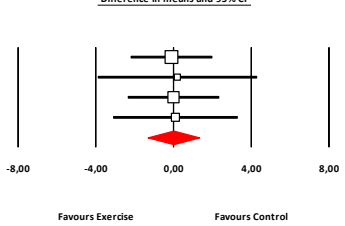


BMI

All exercise vs controls

BMI

Study name	Comparison	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Chehuen 2017	Walking vs Control	-0,100	1,070	1,144	-2,197	1,997	-0,093	0,926	22	20
Crowther 2008	Walking vs Control	0,200	2,090	4,368	-3,896	4,296	0,096	0,924	10	11
Gardner 2001	Walking vs Control	0,000	1,200	1,440	-2,352	2,352	0,000	1,000	28	24
Izquierdo-Porrera 2000	Walking vs Control	0,100	1,633	2,667	-3,101	3,301	0,061	0,951	34	14
		-0,002	0,678	0,460	-1,332	1,328	-0,003	0,998	94	69

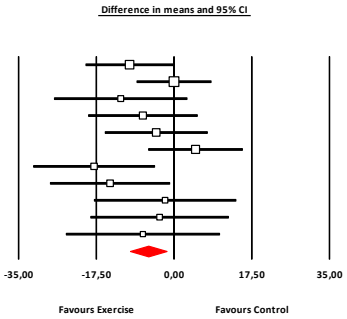


SBP

All exercise vs controls

SBP

Study name	Comparison	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Chehuen 2017	Walking vs Control	-10,000	5,070	25,701	-19,936	-0,064	-1,973	0,049	22	20
Gelin 2001	Walking vs Control	0,000	4,296	18,456	-8,420	8,420	0,000	1,000	73	76
Gomes 2018	Resistance vs Control	-12,000	7,653	58,572	-27,000	3,000	-1,568	0,117	11	10
Izquierdo-Porrera 2000	Walking vs Control	-7,000	6,282	39,468	-19,313	5,313	-1,114	0,265	34	14
McGuigan 2001	Resistance vs Control	-4,000	5,902	34,830	-15,567	7,567	-0,678	0,498	9	7
Murphy 2012	Walking vs Control	4,850	5,430	29,490	-5,793	15,493	0,893	0,372	38	20
Schlager 2012	Walking vs Control	-18,000	6,989	48,852	-31,699	-4,301	-2,575	0,010	27	26
Treat-Jacobsen 2009 A	Aerobic vs Control	-14,400	6,888	47,445	-27,900	-0,900	-2,091	0,037	10	8
Treat-Jacobsen 2009 B	Walking vs Control	-2,000	8,172	66,789	-18,018	14,018	-0,245	0,807	11	8
Treat-Jacobsen 2009 C	Combination vs Control	-3,250	7,950	63,207	-18,832	12,332	-0,409	0,683	12	8
Wang 2008	Aerobic vs Control	-7,000	8,845	78,233	-24,336	10,336	-0,791	0,429	14	11
		-5,781	2,098	4,401	-9,893	-1,670	-2,756	0,006	261	208

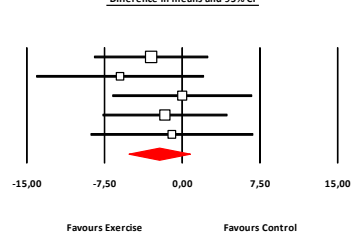


DBP

All exercise vs controls

DBP

Study name	Comparison	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Chehuen 2017	Walking vs Control	-3,000	2,808	7,882	-8,503	2,503	-1,069	0,285	22	20
Gomes 2018	Resistance vs Control	-6,000	4,126	17,027	-14,088	2,088	-1,454	0,146	11	10
Izquierdo-Porrera 2000	Walking vs Control	0,000	3,437	11,814	-6,737	6,737	0,000	1,000	34	14
Schlager 2011	Walking vs Control	-1,667	3,073	9,443	-7,690	4,356	-0,542	0,587	27	26
Wang 2008	Aerobic vs Control	-1,000	4,005	16,036	-8,849	6,849	-0,250	0,803	14	11
		-2,216	1,510	2,280	-5,176	0,743	-1,468	0,142	108	81

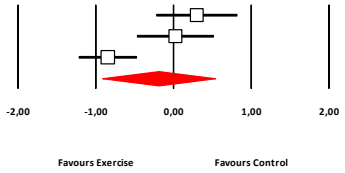


TC

All exercise vs controls

TC

Study name	Comparison	Statistics for each study							Sample size	
		Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Gelin 2001	Walking vs Control	0,300	0,266	0,071	-0,221	0,821	1,129	0,259	73	76
Izquierdo-Porrera 2000	Walking vs Control	0,025	0,252	0,063	-0,469	0,519	0,099	0,921	34	14
Mika 2011	Walking vs Control	-0,845	0,191	0,036	-1,219	-0,471	-4,434	0,000	30	31
		-0,191	0,370	0,137	-0,916	0,534	-0,517	0,605	137	121

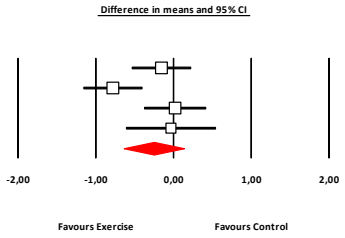


LDL-C

All exercise vs controls

LDL-C

Study name	Comparison	Statistics for each study							Sample size	
		Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Izquierdo-Porrera 2000	Walking vs Control	-0,155	0,194	0,038	-0,536	0,226	-0,796	0,426	34	14
Mika 2011	Walking vs Control	-0,780	0,193	0,037	-1,159	-0,401	-4,033	0,000	30	31
Murphy 2012	Walking vs Control	0,021	0,203	0,041	-0,377	0,419	0,104	0,918	38	20
Schlager 2012	Walking vs Revas	-0,033	0,295	0,087	-0,611	0,545	-0,112	0,911	27	26
		-0,252	0,198	0,039	-0,640	0,135	-1,278	0,201	129	91

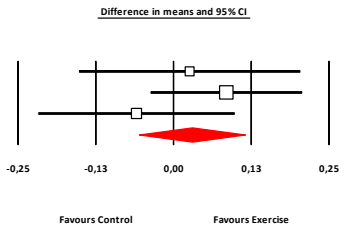


HDL-C

All exercise vs controls

HDL-C

Study name	Comparison	Statistics for each study							Sample size	
		Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Izquierdo-Porrera 2000	Walking vs Control	0,026	0,091	0,008	-0,152	0,204	0,287	0,774	34	14
Mika 2011	Walking vs Control	0,085	0,062	0,004	-0,037	0,207	1,368	0,171	30	31
Murphy 2012	Walking vs Control	-0,059	0,081	0,006	-0,217	0,098	-0,738	0,460	38	20
		0,030	0,043	0,002	-0,055	0,115	0,685	0,493	102	65

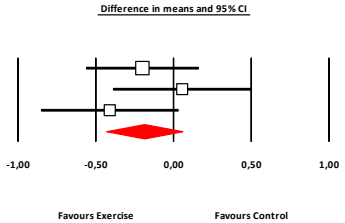


TG

All exercise vs controls

TG

Study name	Comparison	Statistics for each study							Sample size	
		Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Gelin 2001	Walking vs Control	-0,200	0,185	0,034	-0,562	0,162	-1,082	0,279	73	76
Izquierdo-Porrera 2000	Walking vs Control	0,056	0,227	0,052	-0,389	0,501	0,247	0,805	34	14
Mika 2011	Walking vs Control	-0,410	0,226	0,051	-0,852	0,032	-1,817	0,069	30	31
		-0,187	0,125	0,016	-0,432	0,058	-1,500	0,134	137	121

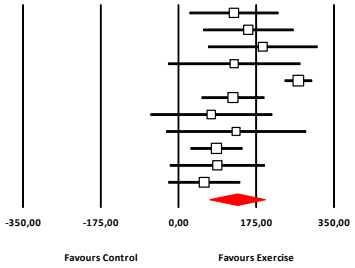


PFWD

All exercise vs controls

PFWD

Study name	Comparison	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
		Statistics for each study							Sample size	
Chehuen 2017	Walking vs Control	125,000	51,136	2614,896	24,775	225,225	2,444	0,015	22	20
Crowther 2008	Walking vs Control	157,351	51,953	2699,164	55,524	259,178	3,029	0,002	10	11
Gardner 2001	Walking vs Control	190,000	62,840	3948,906	66,835	313,165	3,024	0,002	28	24
Izquierdo-Porrera 2000	Walking vs Control	125,490	76,019	5778,816	-23,504	274,484	1,651	0,099	34	14
Mika 2011	Walking vs Control	270,020	15,732	247,497	239,186	300,854	17,164	0,000	30	31
Murphy 2012	Walking vs Control	122,820	36,036	1298,564	52,192	193,448	3,408	0,001	38	20
Parr 2009 A	Resistance vs Control	74,000	69,968	4895,481	-63,134	211,134	1,058	0,290	9	8
Parr 2009 B	Combined vs Control	130,000	80,327	6452,500	-27,439	287,439	1,618	0,106	8	8
Treat-Jacobson 2009 A	Aerobic vs Control	85,600	29,932	895,952	26,933	144,267	2,860	0,004	10	8
Treat-Jacobson 2009 B	Walking vs Control	87,600	54,591	2980,228	-19,397	194,597	1,605	0,109	11	8
Treat-Jacobson 2009 C	Combined vs Control	57,940	41,302	1705,821	-23,010	138,890	1,403	0,161	12	8
		132,195	31,757	1008,476	69,954	194,437	4,163	0,000	212	160

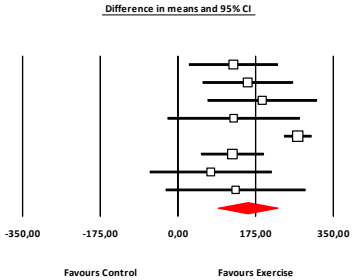


PFWD Gardner

All exercise vs controls

PFWD Gardner

Study name	Comparison	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
		Statistics for each study							Sample size	
Chehuen 2017	Walking vs Control	125,000	51,136	2614,896	24,775	225,225	2,444	0,015	22	20
Crowther 2008	Walking vs Control	157,351	51,953	2699,164	55,524	259,178	3,029	0,002	10	11
Gardner 2001	Walking vs Control	190,000	62,840	3948,906	66,835	313,165	3,024	0,002	28	24
Izquierdo-Porrera 2000	Walking vs Control	125,490	76,019	5778,816	-23,504	274,484	1,651	0,099	34	14
Mika 2011	Walking vs Control	270,020	15,732	247,497	239,186	300,854	17,164	0,000	30	31
Murphy 2012	Walking vs Control	122,820	36,036	1298,564	52,192	193,448	3,408	0,001	38	20
Parr 2009 A	Resistance vs Control	74,000	69,968	4895,481	-63,134	211,134	1,058	0,290	9	8
Parr 2009 B	Combined vs Control	130,000	80,327	6452,500	-27,439	287,439	1,618	0,106	8	8
		157,371	34,131	1164,954	90,475	224,268	4,611	0,000	179	136

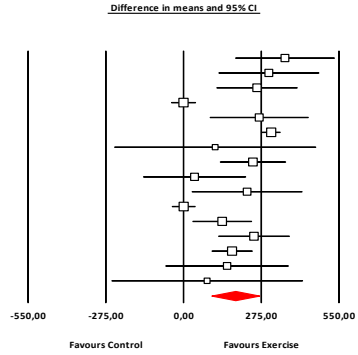


MWD

All exercise vs controls

MWD

Study name	Comparison	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
		Statistics for each study							Sample size	
Chehuen 2017	Walking vs Control	359,000	89,785	8061,380	183,024	534,976	3,998	0,000	22	20
Crowther 2008	Walking vs Control	302,066	90,928	8267,871	123,851	480,281	3,322	0,001	10	11
Gardner 2001	Walking vs Control	260,000	73,253	5365,952	116,427	403,573	3,549	0,000	28	24
Gelin 2001	Walking vs Control	0,000	22,389	501,245	-43,881	43,881	0,000	1,000	73	76
Izquierdo-Porrera 2000	Walking vs Control	267,820	89,179	7952,979	93,031	442,609	3,003	0,003	34	14
Mika 2011	Walking vs Control	310,260	16,791	281,936	277,350	343,170	18,478	0,000	30	31
Mosti 2011	Combined vs Control	112,000	182,067	33148,400	-244,845	468,845	0,615	0,538	10	10
Murphy 2012	Walking vs Control	245,640	59,511	3541,595	129,000	362,280	4,128	0,000	38	20
Parr 2009 A	Resistance vs Control	39,000	92,806	8612,940	-142,896	220,896	0,420	0,674	9	8
Parr 2009 B	Combined vs Control	225,000	99,898	9979,625	29,203	420,797	2,252	0,024	8	8
Schlager 2012	Walking vs Control	0,500	21,319	454,479	-41,284	42,284	0,023	0,981	27	26
Treat-Jacobson 2009 A	Aerobic vs Control	136,800	53,643	2877,596	31,661	241,939	2,550	0,011	10	8
Treat-Jacobson 2009 B	Walking vs Control	249,400	64,491	4159,114	123,000	375,800	3,867	0,000	11	8
Treat-Jacobson 2009 C	Combined vs Control	171,900	37,002	1369,111	99,378	244,422	4,646	0,000	12	8
Wang 2008	Aerobic vs Control	154,120	111,394	12408,525	-64,207	372,447	1,384	0,166	14	11
Wang 2010	Resistance vs Control	83,660	172,809	29862,804	-255,039	422,359	0,484	0,628	10	10
		183,309	43,314	1876,125	98,414	268,203	4,232	0,000	346	293

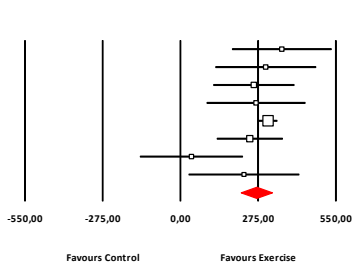


MWD Gardner

All exercise vs controls

MWD Gardner

Study name	Comparison	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
		Statistics for each study							Sample size	
Chehuen 2017	Walking vs Control	359,000	89,785	8061,380	183,024	534,976	3,998	0,000	22	20
Crowther 2008	Walking vs Control	302,066	90,928	8267,871	123,851	480,281	3,322	0,001	10	11
Gardner 2001	Walking vs Control	260,000	73,253	5365,952	116,427	403,573	3,549	0,000	28	24
Izquierdo-Porrera 2000	Walking vs Control	267,820	89,179	7952,979	93,031	442,609	3,003	0,003	34	14
Mika 2011	Walking vs Control	310,260	16,791	281,936	277,350	343,170	18,478	0,000	30	31
Murphy 2012	Walking vs Control	245,640	59,511	3541,595	129,000	362,280	4,128	0,000	38	20
Parr 2009 A	Resistance vs Control	39,000	92,806	8612,940	-142,896	220,896	0,420	0,674	9	8
Parr 2009 B	Combined vs Control	225,000	99,898	9979,625	29,203	420,797	2,252	0,024	8	8
		269,051	28,128	791,166	213,921	324,180	9,565	0,000	179	136



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Chapter 4.2: Cardiorespiratory fitness in patients with lower-extremity artery disease? It takes more than just some steps!

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Research letter

Lower extremity artery disease (LEAD) and coronary artery disease (CAD) are manifestations of the same underlying atherothrombotic vascular disease, only in a different vascular territory (1). Though characterized by a similar disease process and underlying risk profile, implementation of secondary prevention and rehabilitation is quite different among both patient groups (2). Most striking in this regard is the limited access to exercise-based rehabilitation programs for patients with LEAD compared to patients with CAD across Europe (3). Yet, a wealth of data shows that patients with CAD participating in comprehensive cardiac rehabilitation (CR) program have significantly higher survival, even in the modern era (4). These benefits appear for a large part through direct physiological effects of exercise training improving the cardiovascular (CV) risk profile, preventing progression of the atherosclerotic disease and increasing cardiorespiratory fitness (CRF) (5). Nowadays this CRF, assessed as peak oxygen uptake (peak VO_2), is considered a clinical vital sign and single best predictor for premature cardiovascular death both in healthy individuals and patients with established cardiovascular disease (6). Yet, there is a dearth of data on this vital sign in patients with LEAD. Moreover, peak VO_2 assessment during a graded cardiopulmonary exercise test (CPET) is significantly limited by the peripheral muscles in patients with LEAD (3). Especially on a treadmill, reported peak VO_2 is more a reflection of functional capacity due to claudication pain in the legs limiting peak cardiopulmonary exertion in patients with LEAD (3). To allow a better comparison of exercise capacity between patients with CAD and patients with LEAD, we aimed to compare CRF of a group of patients with LEAD to a respiratory exchange ratio (RER) effort-matched group of patients with CAD enrolling in an ambulatory CR program following an elective percutaneous coronary intervention (PCI). This study was approved by the biomedical ethical committee of UZ Leuven - KU Leuven (Reference S65065). Using propensity score matching, 50 patients with LEAD and intermittent claudication (IC) (Rutherford I-III) that enrolled in the hybrid walking program of the PROSECO-IC study (ClinicalTrials.gov: NCT03995589) were compared 1:1 with a group of 50 patients after an elective PCI, derived from a database totaling 751 patients entering phase II CR between January 2010 and November 2020. All patients performed a symptom limited graded CPET on a cycle ergometer (Oxycon Pro Jaeger) (7). Continuous measurements of ventilation, respiratory gases, and electrocardiogram were performed. Blood pressure was measured automatically every two minutes (Suntech Tango+). Peak VO_2 was defined as the highest 30-s average of VO_2 at the end of the test (7) and presented as percentage of predicted peak VO_2 according to Wasserman. The first ventilatory threshold was determined according to Binder (8). The oxygen uptake efficiency slope (OUES), an exertion-independent parameter was determined from the relation VO_2 = a log10 VE + b, in which a is the OUES and b is the intercept (9). Propensity score matching was performed applying the nearest neighbor

method (10), accounting for age, gender, height, weight and respiratory exchange ratio (RER). Comparison of the matched samples and comparison of the LEAD group to the total sample of CAD patients was performed using Chi-squared, independent sample t-tests or Mann-Whitney U-tests where applicable. Rstudio software version 1.2.5042 (R-foundation) and JASP version 0.14 (University of Amsterdam) were used for all statistical analyses. Statistical significance was set at a two-tailed p-value < 0.05.

In our IC cohort, 22 patients (44%) had a history of coronary artery bypass grafting or PCI. As shown in **Table 1**, sex distribution was similar across both groups, with the majority being male. Patients with LEAD were in general older, slightly less overweight and presented with a lower CRF. Following propensity matching both groups were well balanced for age, weight, height and effort during CPET. Yet, despite similar effort (p-value for RER=0.92, p-value for BORG=0.59), significant differences between both groups remained for all exercise capacity parameters (**Figure 1**). LEAD patients reached significantly lower peak values for VO_2 (70.3% of predicted versus 92.3%; p<0.001) and cycle load (97 W versus 131 W; p=0.002) compared to patients with CAD. Also, submaximal measures of exercise tolerance, including OUES (p=0.014) and oxygen uptake at VAT (p<0.001), were significantly lower in patients with LEAD. In line, ventilatory efficiency (VE/VCO_2-slope) was lower in LEAD. Finally, patients with LEAD reached significantly lower peak heart rates, yet, presented with higher systolic blood pressure during CPET (p=0.015 and p=0.017 respectively).

Patients with LEAD are already at very high risk for future cardiovascular morbidity or mortality (3). We show here that also their exercise capacity is moderately impaired and inferior to a matched group of patients with CAD. This underscores the urgent need for expanding the indication for CR to LEAD patients across Europe. Moreover, earlier studies showed that current exercise programs applied in LEAD patients do not elicit clinically relevant changes in levels of peak VO_2 (19 studies, +0.62 ml/kg/min (11)), with only two out of fifteen walking studies showing an improvement exceeding 15% increase in peak VO_2 (11). In line, using meta-analytic techniques we found only a modest effect of walking therapy on traditional CV risk factors in patients with LEAD (12). As a result, it could be expected that prevailing exercise interventions only have minimal impact on mortality and major CV event reduction (3). Though, this is not surprising given the overall low volume and low intensity of currently applied walking therapy. Whereas, symptom reduction is an important first step in LEAD therapy, improving CRF and other CV risk factors are crucial to support functional regain and improve long-term patient outcomes (3). Inclusion in a CR program has the potential to offer more diverse and cardiorespiratory intense exercise programs addressing not only ambulatory capacity, but also each of the underlying risk factors more adequately, CRF and as a result future mortality (13,14). Therefore, we urge the practitioners working with patients with LEAD to look beyond walking therapy as a

stand-alone exercise mode, but to tailor the exercise program also targeting the other underlying risk factors and CRF to breach a vicious cycle of physical decline to improve long-term functional and prognostic outcomes.

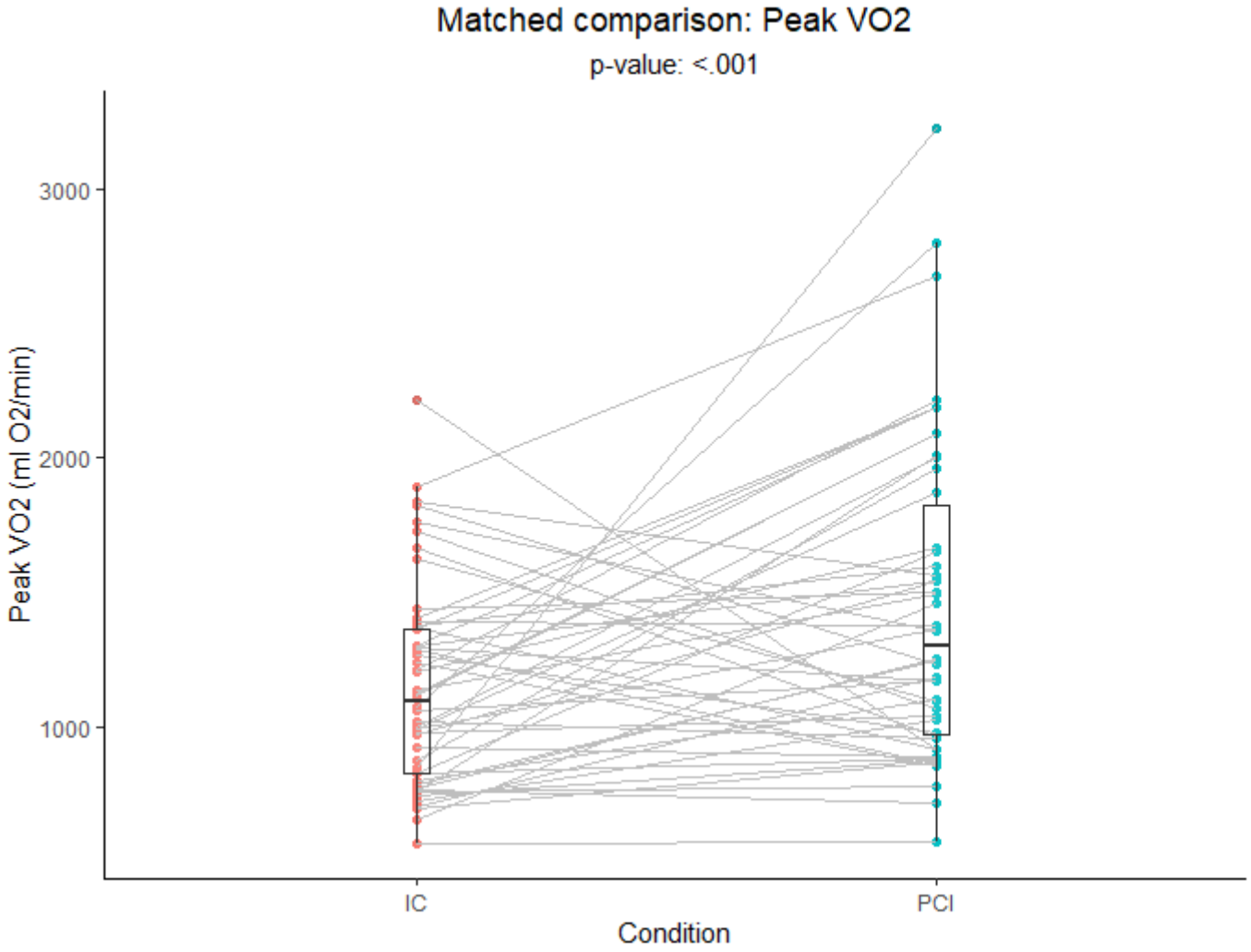
Table 1. Comparison of the unmatched and matched samples of LEAD and CAD patients.

Outcomes	LEAD patients (N=50)	Unmatched CAD: CR phase II patients (N=751)		P-value Unmatched	Matched CAD: CR phase II patients (N=50)	P-value Matched
ANTROPOMETRICS						
Gender (% male)	74%	78%		.463*	68%	.509*
Age (years)	69.3 ± 9.0	64.7 ± 9.2		**< .001**	67.5 ± 10.6	.424
Weight (kg)	75.0 ± 14.3	82.1 ± 14.2		**.001**	73.3 ± 13.2	.516
Height (cm)	167.7 ± 7.8	170.7 ± 8.4		**.012**	167.2 ± 9.4	.745
BMI (kg/m²)	26.6 ± 4.4	28.2 ± 4.3		**.007**	26.2 ± 4.0	.614
History or active smoking	96%	60%		**<.001***	54%	**<.001***
Diabetes	24%	20%		.492*	12%	.118*
EXERCISE						
Peak VO_2 (ml O_2/min)	1149 ± 380	1689 ± 568		**<.001**	1444 ± 587	**.011**
Peak VO_2 (ml O_2/kg/min)	15.4 ± 4.5	20.6 ± 6.3		**<.001**	19.7 ± 7.0	**.001**
Wasserman %	70.3 ± 21.9	99.9 ± 24.6		**<.001**	92.3 ± 26.4	**<.001**
Peak load (W)	97 ± 38	155 ± 52		**<.001**	131 ± 57	**.002**
Peak RER	1.11 ± 0.10	1.17 ± 0.10		**.001**	1.11 ± 0.12	.922
VO_2 at 1st threshold (ml O_2/min)	819 ± 237**	1137 ± 364	N=659	**<.001**	1018 ± 343	**.004**
VO_2 at 1st threshold (% predicted Peak VO_2)	50.5 ± 16.2**	68.3 ± 18.0	N=659	**<.001**	66.9 ± 17%	**<.001**
OUES	1387 ± 381			NA	1686 ± 606	**.014**
Peak HR (b.p.m.)	114 ± 24	132 ± 24	N=750	**<.001**	127 ± 29	**.015**
Rest SBP (mmHg)	132 ± 22	133 ± 20	N=741	.861	131 ± 23†	.913
Rest DBP (mmHg)	70 ± 14	76 ± 11	N=740	**<.001**	76 ± 12†	**.042**
Peak SBP (mmHg)	190 ± 33†	181 ± 30	N=745	**.036**	174 ± 32	**.017**
VE/VCO_2-slope	35.8 ± 5.7			NA	33.8 ± 6.0	**.048**
VO_2/Watt-slope	8.8 ± 1.6			NA	8.9 ± 1.4	.942
BORG scale (6-20)	15.3 ± 1.8†	15.6 ± 1.5	N=747	.208	15.2 ± 1.4	.592

Abbreviations: lower extremity artery disease = LEAD, coronary artery disease = CAD, cardiac rehabilitation = CR, body mass index = BMI, respiratory exchange ratio = RER, heart rate = HR, systolic blood pressure = SBP and diastolic blood pressure = DBP. Statistically significant ($P < 0.05$) comparisons are indicated in bold.

Matching was based on propensity score modelled to include age, gender, weight, length and RER. Slopes (OUES, VE/VCO_2-slope and VO_2/Watt-slope) were calculated using all 10-second data points during exercise. †data available for 49 patients, *Chi-square test contingency table, **data available for 47 patients (VO_2 at 1st threshold (ml O_2/min and % predicted Peak VO_2): 818 ± 246 and 50.1 ± 16.6) and 41 matched pairs. As in 29/50 patients with LEAD VT2 could not be determined, a comparison among both groups could not be performed.

Figure 1. *Matched comparison of peak VO_2 in 50 patients with LEAD and complaints of intermittent claudication (IC) and CAD peers after elective percutaneous coronary intervention (PCI).*



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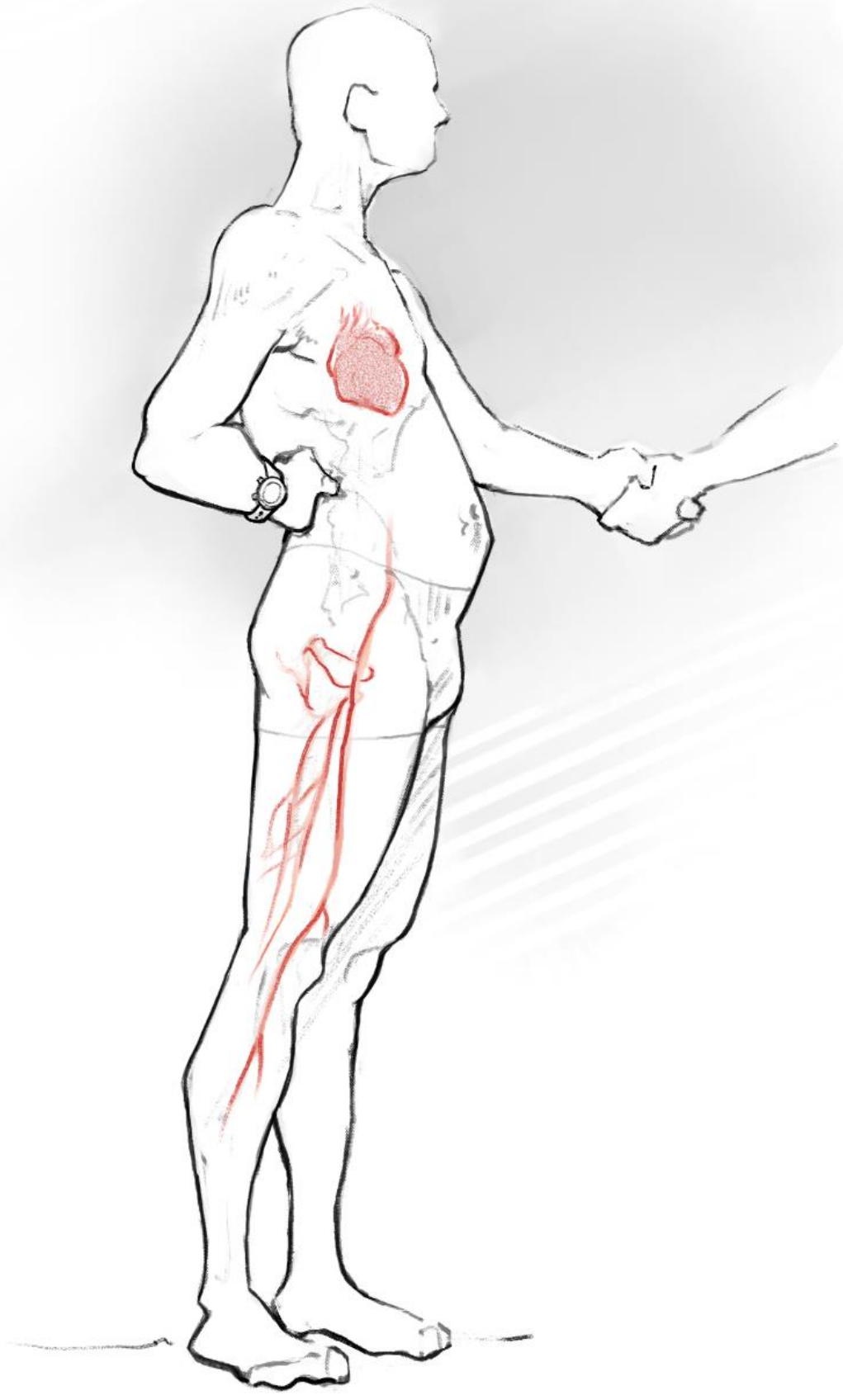
Chapter five: General discussion



General discussion

LEAD is a prevalent condition primarily caused by atherosclerosis, which affects approximately 237 million people worldwide. Although the underlying pathophysiology is similar to arterial narrowing in other vessel beds (i.e. coronary artery disease or carotid artery disease), LEAD knowledge and awareness is often limited in patients, public and even among healthcare professionals. In LEAD, atherosclerosis will cause narrowing of the lower limb arteries, creating an imbalance in blood supply and demand. This supply-demand imbalance can lead to a range of symptoms such as painful legs during physical activity or intermittent claudication, ischemic rest pain and trophic wounds. Both rest pain and trophic wounds are generally observed in more advanced LEAD and require restoration of blood supply through revascularization to avoid limb loss. Patients with intermittent claudication have been shown to benefit from exercise to improve walking capacity and quality of life. Exercise programs are typically supervised and center-based, with most evidence to support exercise therapy emerging from suchlike studies. However, a lack of widespread availability, patient uptake and adherence hampers successful implementation of supervised exercise programs. Therefore, attention has shifted to home-based exercise programs, where structured therapy, using on-site visits, telephone communication and modern wearables can offer an alternative to the effective components of a supervised, center-based program.

In this PhD work we addressed three main questions that could help us to develop and implement an accessible and effective exercise program for patients with LEAD.

How to optimally deliver home-based exercise programs? More specifically, modern technology could bridge the gap between supervised, center-based programs and the less effective recommendation to walk. As such, patient interest, needs and barriers to uptake of exercise therapy were explored in *chapter 2.1*. Following this, we conducted a 4-week pilot study with 20 participants to evaluate acceptability of and satisfaction with a combined home-based exercise program, described in *chapter 2.2*. The program was accepted and patients were satisfied with the implementation and use of a GPS wearable. However, resistance band exercises were not preferred over traditional walking instruction when conducted in the home environment. Moreover, based on published research findings from other authors, the short-term pilot and the need for additional contacts to solve technicalities we decided to add in-person visits. These new insights led to the final development of our 12-week PROSECO-IC intervention program, a hybrid solution combining on-site and home-based exercise. In line with our previous studies we analyzed acceptability and satisfaction from a patient perspective, next to the evaluation of overall efficacy. In addition, based on earlier reported heterogeneity among responses to exercise therapy, the following research question was formulated:

How does exercise work and who is to benefit? To get a closer look at the lower limb tissue oxygenation, Near Infrared Spectroscopy (NIRS) was used to evaluate acute responses to exercise before and after an exercise intervention. Findings from previous studies using this technique were first summarized in a systematic review, which is discussed in *chapter 3.1*. In line, we replicated findings in our own PROSECO-IC cohort, highlighting differences in high- and low-responders with regard to ambulatory capacity in *chapter 3.2*.

Yet another question remained: does exercise possess the ability to improve clinical status in patients, beyond ambulatory capacity and quality of life? More specifically:

Does exercise also affect the cardiovascular risk profile in patients with LEAD and intermittent claudication? In terms of secondary prevention, the rationale to improve cardiovascular risk profile was studied by comparing cardiorespiratory fitness levels of patients entering cardiac rehabilitation and our baseline PROSECO-IC cohort in *chapter 4.2*. The effects of reported exercise programs on traditional cardiovascular risk factors, including blood pressure and lipid profile, was systematically reviewed and summarized in a meta-analysis. This was presented and discussed *in chapter 4.1*.

How to optimally deliver home-based exercise programs in patients with LEAD and intermittent claudication?

5.1 Patients with LEAD and intermittent claudication are interested, satisfied and accept the implementation of technology in a home-based exercise program

The development and further implementation of home-based exercise programs including technology is trending in the field of exercise and rehabilitation. Telerehabilitation is emerging in different fields with a wide range of initiatives in cardiac (1), pulmonary (2) or oncological rehabilitation (3). In essence, common barriers regarding availability of supervised programs (i.e. reimbursement, facilities or available expertise) and uptake and adherence of patients (i.e. time and transport; 42% of non-participation PROSECO-IC contacts) limit the widespread use of center-based programs. However, the translation of key components from center-based programs, such as provision of a structured exercise program, continuous monitoring, immediate feedback and triggers to facilitate long-term behavioral change to a home-based environment is an ongoing challenge. Modern technology can provide new tools, as accelerometers or global positioning systems (GPS) can guide healthcare providers and their patients into an optimal implementation of an exercise program in the patients' home-environment. This has been confirmed by questionnaire responses by physiotherapists and vascular surgeons interested in GPS tracking of exercise sessions (89%) and an online coaching platform (67%), respectively

(4,5). Session recordings and monitoring can improve prescription and adherence to exercise, guiding the alignment of previously reported heterogeneity in home-based exercise programs for LEAD patients (6,7). In addition, self-monitoring, feedback, but also prompts to record exercise sessions using technology can improve program effectiveness (8). The development of suchlike intervention should be directed by all stakeholders, where patient input is equally important (9).

In our research group, we have some experience developing home-based exercise programs using technology in cardiac patients (10-12). However, patients with LEAD are typically older and present with specific barriers to exercise uptake (e.g. intermittent claudication). In addition, there is no formal exercise program available for LEAD patients with intermittent claudication to date. Therefore, we performed a survey among patients (99 patients, mean age 69 years) with LEAD and intermittent claudication to assess their current use of technology, barriers to be physically active and interests in different aspects of telerehabilitation (13). In line with findings from van den Houten et al in a Dutch cohort, we found that 93% of our patients (The Netherlands: 86% (5)) possessed a mobile phone and three out of four (76%) had internet access. More specifically, 37% was accessing the internet using their phone, replicating Dutch numbers that 41% of patients have a smart phone (5). These numbers are slightly lower compared to patients in cardiac rehabilitation (66%), yet, this can be explained by the difference in age (298 patients, 62 years) and the significant inverse association of age and smart phone possession or the use of applications (5,12). Next to high interest to participate in a LEAD specific exercise program, the majority of questionnaire participants reported to be interested in telecoaching and feedback (67%) with increasing numbers when both a mobile phone and internet access (81%) were available. This is somewhat in line with numbers from Harwood et al, where patients preferred home-based exercise programs, yet three out of four patients indicated the need for ongoing support (14). In our sample, the need for direct supervision and control was associated with the presence of other health issues and a lack of knowledge about the benefits of exercise. In analogy with supply-demand imbalance in LEAD, an optimal balance of technology use, supervision and the individual need of coaching and feedback is one of the challenges in the development of a structured home-based exercise program. The latter feedback can be either in-person or via technology, which can broadly range from either non-advanced (e.g. phone calls) to more advanced (e.g. application or platform) (15). In addition, patient monitoring can differ in terms of frequency and content, ranging from reported step count to objectified walking intensity, duration of intervals or terrain. This contrast in frequency of feedback and content of monitoring was present in the most recently published HONOR (2018) and LITE (2021) studies from McDermott and colleagues (16,17). Both studies used technology in structured home-based exercise to improve ambulatory capacity in LEAD. In HONOR a mismatch in prescription of exercise (i.e. bouts

of intermittent claudication induced walking) and the wearable monitor to improve overall steps was present (16). Hence, incongruity between the wearable and the exercise recommendation may result in ineffective interventions. In other words, increasing daily steps alone does not seem the major driver to improve ambulatory function. Interestingly, this was confirmed in LITE, where higher volume of pain-free walking (frequency and time) was ineffective to improve 6MWD compared to traditional intermittent claudication induced pain (17). Consequently, these results emphasize the importance of intensity above volume when prescribing exercise in LEAD. Therefore, to adequately monitor and adjust training sessions, a wearable provided with either an accelerometer or GPS-technology seems necessary. In addition, fading of telephone feedback to a monthly recall in HONOR resulted in a decrease in walking frequency, whereas LITE participants remained to be contacted weekly (16,17).

In terms of type of contact, three quarters of patients having access to the internet were particularly interested (86%) in telecoaching via e-mail. Telecoaching via telephone was attractive to half of patients owning a mobile phone, with preference for text messages (87%) to communicate. However, a recent report suggests the addition of face-to-face meetings to optimize effectiveness (18), with patients being slightly in favor for direct contact with a caregiver as well (14). Effectiveness of supervised interventions is dose-responsive based on the intensity of supervision, with more support being associated with improved walking outcomes (19). A similar trend can therefore be expected in home-based exercise programs (7), where specificity of feedback is depending on the selected technology as highlighted in the previous paragraph. The lack of supervision during resistance exercises, could also have explained our pilot findings on low interest in elastic band exercises (20). This is confirmed by Lacroix and colleagues, as they found a similar dose-response relation between supervision of resistance exercise and its effectiveness to improve strength measures in older adults (21). Interestingly, even a low number of in-person visits to guide resistance exercises are found to improve unsupervised interventions (e.g. to improve execution of exercise) (21). In our 12-week PROSECO-trial 58% (24/40) participants were neutral or not in favor of supervised sessions during our hybrid interventions. Hence, for some patients with LEAD, fading of supervised sessions could be introduced sooner with more home-based sessions. Possible reasons are similar to barriers with regard to uptake (e.g. transport and time constraint). Summarized, in-person meetings are preferable to progress exercise, discuss barriers and provide follow-up. However, non-advanced technology including feedback through timely telephone or e-mail is also accepted and offers new tools in the box in delivering exercise therapy.

Altogether, we found that patients with LEAD are interested, satisfied and accept the integration of technology in home-based exercise programs. In addition, the content,

supervision and feedback (e.g. combining barrier identification and problem solving) was (very) suitable to a large majority of the participants. By these means, technology can preserve the patient-provider relation in a home-based environment. As described by Wang and colleagues, technology can be deployed to 1) get informed about personal and environmental factors (e.g. GPS logs displaying nearby hills or obstacles worsening intermittent claudication complaints), 2) stimulate effective exchange of information, feedback and education (e.g. guiding walking pace and rest periods to balance intermittent claudication complaints throughout exercise sessions), and 3) include goal setting and action planning (e.g. discuss specific, measurable, attainable, realistic, time-depicted (SMART)) goals based on uploaded logs (22). However, future studies should investigate the appropriate level of supervised sessions and (type of) feedback, but also explore different behavioral change techniques (8) and their separate impact on effectiveness (23). From this perspective, modern technology can support different aspects of care in LEAD patients beyond exercise (24). Hence, the addition of risk factor management (e.g. healthy diet was found useful in 77% of patients), but also education to "explain the pain" (25) or contact with peers should be considered (e.g. found useful in 52% of patients). Ideally, further optimization of structured home-based exercise programs should be on an individual level, where different patient characteristics, digital literacy (26), preferences and barriers are taken into account when selecting an appropriate exercise program. One size does not fit all patients, yet, technology is widening the spectrum of choice (**Figure 15**).

As a consequence of the rapid development of different telerehabilitation solutions, a clear framework on the different components of home-based exercise programs as described is needed (15). Here different components need to be addressed: 1) the implementation of (non)-advanced technology, 2) availability of direct supervision, 3) the use of center-based or in home-visits as follow-up (15). As mentioned above, different components could be personalized, yet also adapted to different situations. By these means we kept providing feedback and monitored our participants in the PROSECO-IC trial during the first COVID-19 governmental lockdown.

5.2 Technology-monitored exercise programs can be effective

The ESC 2017 Guidelines (27) recommend the following:

In patients with intermittent claudication:

- *Supervised exercise training is recommended (IA recommendation)*
- *Unsupervised exercise training is recommended when supervised exercise training is not feasible or available (IC recommendation)*

Here the latter might be somewhat confusing, as unsupervised exercise can be adopted in different ways (7). For example, both simple advice to walk more often and structured home-based exercise programs could be considered as largely unsupervised (7). Simple advice to take up walking at home is ineffective and not always perceived as part of the treatment in LEAD patients. With regard to home-based exercise programs, early reviews in 2013 and 2015 reported that home-based exercise programs are heterogenous and the majority did not thoroughly describe all elements of the intervention (6,28). Hence, the call of the American Heart Association, to further structure home-based exercise programs (**General introduction, paragraph 1.3.2.2**). In line with improved methodology, more structured home-based exercise programs were effective in terms of ambulatory capacity and physical activity (29). This evolution was emphasized by a most recent review and meta-analysis (7). Preliminary data on studies including wearables reported effectiveness to improve ambulatory capacity and quality of life (26,30). Interestingly, Pymer and colleagues showed that home-based exercise programs including monitoring could be equally effective compared to center-based, supervised programs (7). In the PROSECO-IC trial, we found that monitoring using technology is generally accepted by patients with LEAD and intermittent claudication. Moreover, both objective and subjective ambulatory capacity and quality of life (e.g. physical functioning) was improved with clinical relevance (31,32). In addition, participants generally adhered well to the PROSECO-IC program, with a 79% adherence to home-based sessions and 99% adherence to center-based sessions. With a total combined adherence of 85%, our hybrid intervention equals the higher edge of previous reports with adherence rates ranging from 78-86% in traditional and alternative exercise programs respectively (33). A major advantage of modern wearables is that exercise sessions can be objectified, avoiding to rely on patient recall when reporting on exercise adherence (6).

However, more well-designed studies are needed to elaborate on these interesting observations. Although structured home-based exercise programs are expected to be cost-efficient compared to supervised center-based exercise programs (e.g. reduction of personnel costs, equipment, facilities and patient travel), no study to-date evaluated this in LEAD patients.

How does exercise impact the muscle and who is to benefit?

5.3 Responders

Exercise therapy has shown to be an effective first-line intervention. However highly effective on a group level, response to exercise can vary considerably in terms of ambulatory capacity, subjective ambulatory function and quality of life on the individual level (34,35). It is expected that approximately one out of three patients will not improve their 6MWD after exercise therapy (34,35). Yet, what explains this heterogeneity? In one way, variability in responses is simply a statistical phenomenon due to normal variability, as even the most stringent study methods cannot rule out all confounders (especially in studies with human participants, day-to-day variability or measurement error (36)). Hence the lack of motivation, previous activities before testing, level of dysfunction caused by existing comorbidities or other confounders could directly influence response measures.

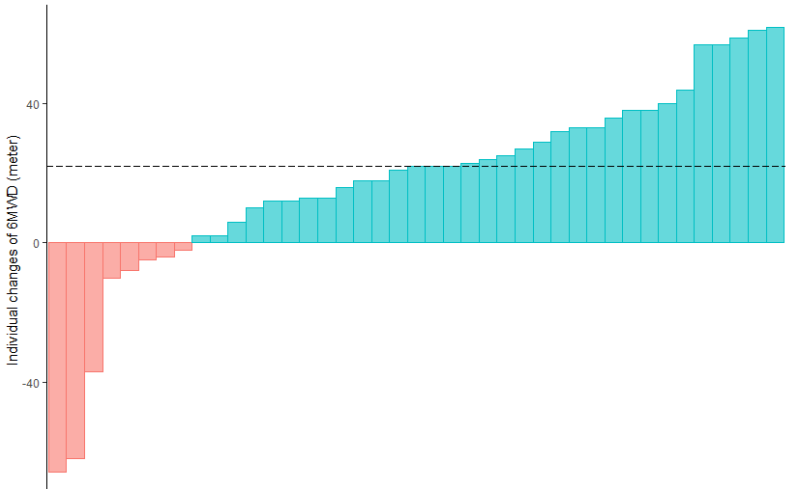


Figure 13. *PROSECO-IC responses (N=41) on six-minute walk test with 19.5% of participants (N=8/41) not increasing 6MWD. Median progression was +22 m and visualized using a dashed line.*

Moreover, response heterogeneity could be a possible explanation for discrepancy in response when comparing objective and patient-reported outcomes (37). From this perspective, several studies have attempted to delineate specific predictors of response to exercise therapy. A high baseline MWD, female gender, cardiac comorbidity and increased BMI have all been found to be predictive in terms of relative change in MWD or PFWD (38-40). Yet, accuracy of regression models to date was low (e.g. yielding an R^2 of 10.7% (38)) which is invalid for clinical practice. With regards to training characteristics, it seems intuitive that adherence to the program is mandatory for progression (41), whilst training volume and weekly step count were also put forward as a possible determinant of response (39,42). Here, the emergence of technology in exercise monitoring (e.g. pattern recognition)

could facilitate isolation of training characteristics (e.g. frequency, intensity, time, type) and the association with program response (43). Hence, program prescription could be optimized on the personal level where needed to improve patient outcomes. Moreover, a positive attitude, increased knowledge and self-efficacy was positively related with exercise therapy response (44). Interestingly, a dearth of research is available about physiological parameters and how the acute response to exercise might provide additional insights in expected benefits from exercise therapy. From this perspective, further exploration of underlying physiological changes related to improved walking is needed.

5.4 Muscle oxygenation is improved after exercise therapy, especially in high responders

The underlying biologic pathway by which exercise improves ambulatory outcomes in LEAD and intermittent claudication is a highly debated topic in the field of exercise physiology. Initially an amelioration of large vessel blood supply, most likely through formation of collateral vessels, was thought to be the driving force behind ambulatory improvement after exercise. Indeed, in epidemiological studies the amount of collateral vessels was found to be correlated with improved ambulation (45). However the formation of collateral vessels has been reported in selected cases (46), macrovascular changes are typically not detected on a group-level (e.g. peak flow and number of collaterals) after exercise training (47). In line, measures of blood supply, such as blood flow plethysmography or ABI, have not been found to be systematically associated with better functional performances (48-50). Therefore, a plethora of other mechanisms, beyond blood supply, have been proposed to explain the benefits of exercise, which are summarized in **Figure 14** (49,51,52). Since the early nineties the “metabolic theory” evolved (53), highlighting an underlying myopathy where hypoxia induced chemical, histologic and mitochondrial changes could hamper energy production in muscles distal from an arterial lesion (54-56).

Hence, the muscle as an organ, receiving oxygen through a downstream capillary network with further oxidation to form ATP, has become of major interest. From this perspective, we used Near infrared Spectroscopy (NIRS) to study the underlying supply-demand mismatch in active tissues (**more on the method in chapter 3.1 and 3.2**). NIRS devices are now portable, available at a low-cost and have the unique ability to non-invasively measure muscle oxygenation during bouts of exercise (57).

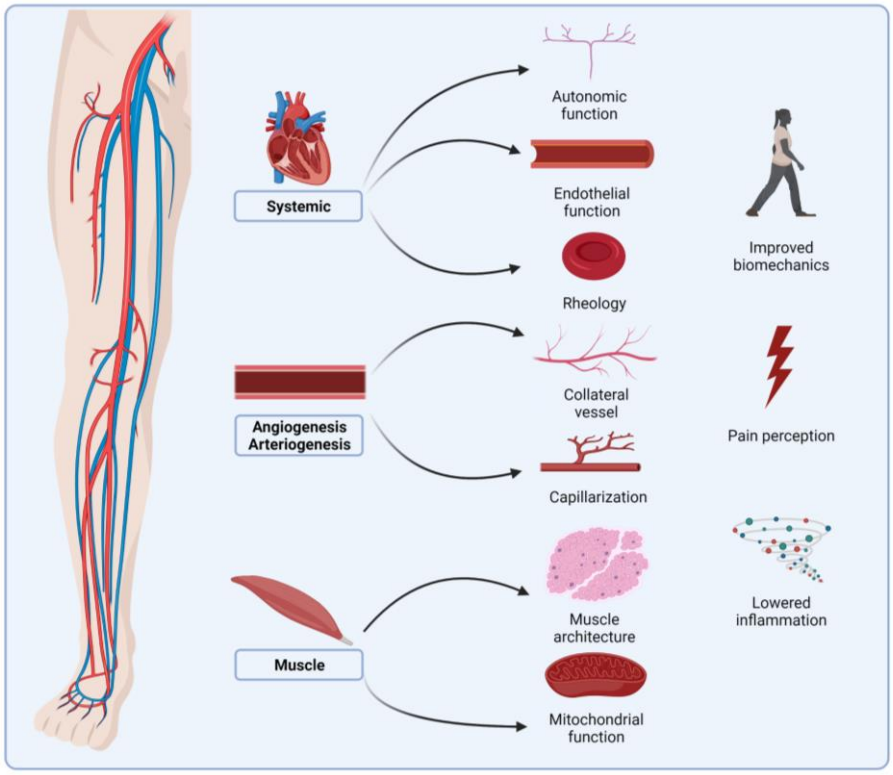


Figure 14. *Different biological pathways involved in progression of ambulatory function after exercise therapy (Created using Biorender).*

In our systematic review we evaluated the effects of exercise therapy on NIRS-derived changes in muscle oxygenation. No changes were observed in muscle oxygenation at rest, further highlighting the dynamic imbalance during activities in symptomatic LEAD (58). Besides small changes in reoxygenation, exercise therapy caused a slower deoxygenation for the same metabolic requirements (e.g. for the same exercise intensity) in the majority of included intervention groups (5 out of 7 intervention groups) (58). We confirmed these findings in our PROSECO-IC cohort, as time-to-minimum tissue oxygenation was significantly increased after the exercise intervention. Regarding raw signals, slower rates of deoxygenation were confirmed by improved preservation of oxygenated hemoglobin during submaximal walking. Of interest, improved deoxygenation was predominantly seen in participants with more pronounced ambulatory progression. This improvement seems to reflect enhanced equilibrium of oxygen demand and supply (i.e. association with critical power measures in healthy adults (59,60)) with improved aerobic capacity. Similar observations are seen in patients with heart failure, chronic kidney disease and COPD, with faster deoxygenation rates being related to decreased functional capacity (61). Hence, this metabolic rate might provide additional clinical perspective as maximal VO_2 levels are often not reached in patient populations (62). In LEAD, and possibly in other populations, improved mitochondrial function but especially fine-tuning of microcirculatory oxygen

delivery (e.g. angiogenesis, endothelial function, vasomotor control) are suggested to explain NIRS changes after an exercise program (62-65). This potency to improve the microcirculation was confirmed by a recent study by Andrade-Lima showing increased nitric oxide (NO) bioavailability after a 12-week walking program (66). Here NO is at least partially responsible for maintaining microvascular oxygen pressure and thus metabolic equilibrium during exercise (62). Similarly, dietary nitrate supplementation or upper-limb exercise leads to comparable improvements in lower-limb NIRS signaling (62,66-68). Combined, exercise therapy is hypothesized to improve local balance in oxygen delivery through an array of alterations, ultimately leading to improvement in exercise capacity (62). In other words, reciting Poiseuille's law, small changes in dynamic vascular health can have a major impact on muscle blood supply and help to explain the lack of information obtained with static measures (62). With regard to NIRS related predictors, an exploratory analysis on high responders showed a significantly higher accumulation of deoxygenated hemoglobin (more pronounced impairment of supply-demand) during submaximal walking. Yet this contrasts with earlier findings reported in pilot work from Manfredini and colleagues, and limitations to the NIRS method are present (69). In short, NIRS raw signals suffer from high heterogeneity among but also within individuals (which is also evident from wide variability measures) (62,70,71). The latter is due to several confounders (e.g. anatomical placement on the muscle, wavelength penetration depth, etc.) which are often unaccounted for as we noted in our review on current literature on NIRS in LEAD (58,70,71).

In contrast, NIRS changes do not seem a perquisite to improve ambulatory capacity based on our PROSECO-IC cohort. This observation could be explained by physiological redundancy in the exercise response, yet, could also mean that patients with LEAD and intermittent claudication improve their gait pattern. However, there is no evidence that supports this hypothesis (72). Equivalent to variety in proposed adaptive responses, the definition of a "responder" to exercise therapy is not univocal and largely depends on the outcomes assessed. For example, Hartman and colleagues have shown that improved physical function is not necessary to improve cardiovascular risk factors after exercise (73). Whipple has shown that LEAD patients with intermittent claudication improved in at least one functional outcome (34). On the other hand, approximately 40% of patients with LEAD does not reach a clinical meaningful change or has an unsatisfactory outcome after exercise (74). This cannot be overlooked and highlights the burden of intermittent claudication even in those patients with objectified improvement. The PROSECO-IC participants reached on average 79% of 6MWD predicted values after the program. Hence, for some patients, clinical benefit from exercise will not outweigh restrictions in daily life activities even after a successful exercise program. Therefore, future studies should continue to explore both patient characteristics, underlying physiological changes and how different training characteristics might impact exercise response. This seems an important step to individually

tailor LEAD therapy to elicit clinically meaningful results and realistic expectations. Moreover, even in patients requiring revascularization, the combination with exercise therapy seems highly successful, with a lower rate of future re-revascularization at follow-up compared to isolated revascularization (75). Therefore, beyond the benefit of immediate symptom resolution, a combined approach may be a window of opportunity to target long-term behavioral change. Yet, confirmation about long-term effectiveness of this synergetic effect of exercise and revascularization is needed in larger trials (75,76). Summarized, exercise is an important cornerstone throughout the entire care path of patients with LEAD having symptoms of intermittent claudication. Even in the absence of improved ambulatory capacity, exercise therapy has beneficial effects. Although highly studied in other populations it is not known whether current exercise programs improve the underlying cardiovascular risk profile in patients with LEAD and intermittent claudication.

What is the impact of exercise on the cardiovascular risk profile in patients with LEAD and intermittent claudication?

5.5 The effects of current exercise programs on the cardiovascular risk profile

Comprehensive exercise programs, such as cardiac rehabilitation, possess the ability to improve overall morbidity and mortality in a cost-effective manner (77). One reason advocating for exercise therapy in secondary prevention is the ability to improve the overall cardiovascular risk profile in patients at risk for future events (e.g. coronary artery disease (78), metabolic syndrome (79)). In line, even exercise programs with walking as the primary exercise mode have shown improvement in cardiovascular risk profile both in healthy and diseased populations (80-82). Yet, whether current exercise programs are capable of having a similar impact on traditional cardiovascular risk factors in LEAD is not clear from available literature. Therefore, we conducted a systematic review to identify exercise publications in LEAD and intermittent claudication, reporting on at least one traditional, modifiable risk factor (e.g. weight or BMI, blood pressure or lipid profile) (83). We included 15 trials with 18 intervention groups, of which 9 described a walking-based intervention including 74% of exercise patients. Publications reporting on cardiovascular risk factors were scarce, ranging from four publications on common lipid markers and nine evaluating systolic blood pressure, with concomitant small sample sizes included. In our meta-analysis, only systolic blood pressure was significantly and clinically relevant decreased after combining treatment effects (-5.8 mmHg). In comparison, we did not observe any changes in office blood pressure in our PROSECO-IC cohort (both SBP and DBP, $p = 0.563$ and $p = 0.600$). A possible explanation for this inconsistency is the difference in baseline levels. Combined

baseline systolic blood pressure in our review was 143 ± 5 mmHg whereas PROSECO-IC participants measured 122 ± 16 mmHg. Following the principle of diminished returns, previous research already indicated the higher responsiveness of hypertensive patients after dynamic aerobic training (84). Similarly, lipid levels were generally well-controlled in the PROSECO-IC cohort (e.g. 92% of participants were on prescribed statins, LDL 69 ± 29 $mg.dl^{-1}$), explaining the lack of an additional effect of exercise on overall blood lipid profile (85). As stated in **chapter 4.1**, another reason could be that actual exercise prescription in terms of volume, duration of the program and intensity was insufficient, which mandates further research.

However, even in a modern era of medicine, to reduce the atherosclerotic burden in LEAD one has to address the most proximal risk factors, typically including an unhealthy diet, cigarette smoking and physical inactivity to reach best results (86). In this prospect, it is reported that only 22% of LEAD patients receives counseling on exercise or diet (87). In comparison, advice on smoking cessation was more aggressive in LEAD compared to cardiovascular disease (88), yet, Berger and Lapado report that only one out of three active smokers with LEAD gets guidance to quit smoking (87). Still, a large group of LEAD patients reported to be interested in healthy life-style advices through technology in our preparatory questionnaire study (13). Here, ideas on stress management, advice on healthy eating or motivational support (or smoking cessation in smokers, 69%) and exercise ideas were found to be at least rather useful in approximately 60% of participants. In addition, almost half of participants thought that contact with peers would complement telecoaching using technology. Hence, to provide optimal secondary prevention in a population at high risk for future morbidity and mortality, a more comprehensive, multidisciplinary approach including dietary advice, counseling on smoking cessation and psycho-social guidance offers potential and sparks interest in LEAD.

5.6 Rationale for a more comprehensive approach

The addition of different rehabilitation components in the care for LEAD patients is justified, since atherosclerotic burden is often advanced, comorbidities add clinical complexity, functional deterioration is apparent and healthcare costs present a considerable burden to overall healthcare. Beyond control of traditional cardiovascular risk factors, counselling of physical activity to ultimately improve or maintain overall physical fitness is important in the design of cardiac rehabilitation. Interestingly, ample evidence is available about the effect of revascularization on the cardiovascular risk profile, without changes observed in physical activity levels (89,90). As stated in the previous paragraph, physical activity is an important driver in improving health and providing prevention but requires behavioral change.

Next to physical activity, cardiorespiratory fitness levels have been directly associated with future morbidity and mortality, in general, but also in LEAD (91,92). Cardiorespiratory fitness is not expected to improve after revascularization, yet, is significantly lowered in patients with LEAD and intermittent claudication as summarized in **chapter 4.2**. In this latter chapter, we matched participants from our PROSECO-IC cohort with patients enrolling in cardiac rehabilitation after an elective PCI. Comparing patients with equal levels of exertion, we found significantly lower levels of physical fitness in LEAD. Observed levels of peak oxygen consumption (15.4 $ml.kg^{-1}.min^{-1}$) were comparable with those reported in earlier trials (93). Once again, we emphasized the missed opportunity to include patients with LEAD in structured, comprehensive rehabilitation. This potential has been highlighted by Canadian researchers, reporting that inclusion in cardiac rehabilitation led to significant improvement in peak oxygen uptake (+2.4 $ml.min^{-1}.kg^{-1}$), an important change in cardiorespiratory fitness which is often absent in traditional walking programs as in our own PROSECO-IC intervention (93,94). In fact, a large retrospective analysis including 23 215 patients reported improved survival after completion of cardiac rehabilitation in LEAD (95). Moreover, provision of alternative exercise modes beyond walking, has been suggested to improve ambulatory capacity to a similar extent (96) and to increase overall adherence to exercise (33). Also in this study, a multidisciplinary approach (i.e. managing smoking and diabetes status) together with timely entry into cardiac rehabilitation has been suggested to further improve cardiorespiratory fitness outcomes (97). In contrast, numbers on actual referral and start of cardiac rehabilitation is disappointingly low (77,88). If rehabilitation programs are available, only a minority them (13.8%) provide a LEAD specific program (88).

In short, equalized care in terms of rehabilitation should be available for patients with LEAD (98), and with slight adjustments towards LEAD and the symptom of intermittent claudication, cardiac rehabilitation can become cardio*vascular* rehabilitation. A multidisciplinary approach could elicit the full potential of secondary prevention in LEAD and this option should be available for patients as part of first line conservative care or after revascularization. On the other hand, barriers to actual uptake in supervised, center-based programs remain present in cardiovascular rehabilitation. Therefore, further exploration of the ability to provide hybrid care should be done, creating the possibility for patients with LEAD to participate in different (individualized) components of a comprehensive rehabilitation program. In terms of home-based exercise programs, we already highlighted the possibility to implement technology, yet future studies should compare effectiveness in large RCTs. Interestingly, in cardiac rehabilitation, direct comparison of supervised, center-based and home-based exercise programs found equal effectiveness of the latter (99). Moreover, implementation of different components of rehabilitation is perceived as useful in LEAD patients and the possible application of technology (e.g. e-learning through educational platforms, dietary programs or medication adherence) not limited to exercise

has been successful to guide healthy living (99). Likewise, an online platform could mimic or complement social interaction, where gamification or activity sharing can motivate. Technology is ready, patients with LEAD are positive, yet further elucidation of programs combining several components is needed. Even in LEAD patients that accept the idea of supervised or technology-guided home-based training, personalized addition of timely follow-up through e-mail or telephone seems feasible and might improve the conception of exercise as therapy when recommended. Creating a more individualized approach in delivering exercise, next to adaptation and widening of the current exercise modalities, seems promising to increase patient uptake as summarized in **Figure 15**.

5.6 Limitations across studies

This PhD-research project aimed to evaluate the interest, feasibility and efficacy of exercise interventions in patients with LEAD suffering from intermittent claudication. Given the importance of patient acceptability and satisfaction in developing suchlike intervention, we focused on the development of a structured home-based exercise program integrating technology with patient feedback. In this project, we performed this research in a single cohort. Therefore, internal validity of our findings in terms of efficacy are compromised by the absence of a control group. Whereas, the original research design included a control group of patients that were not able to join the exercise group due to distance, time or interest, a low recruitment rate and the facing of the COVID-19 pandemic led to the omission of the control group. Future RCTs are now needed to compare structured exercise programs with usual care (e.g. recommendations to exercise), yet findings from current reviews (7,29) are promising and highlight the importance of including different aspects from supervised exercise programs. Deviating from our initial target number of study participants to study different physiological determinants, this setback was converted to an opportunity to focus on NIRS-related measures in the affected muscle. Although a promising method to dynamically evaluate muscle oxygenation, NIRS is characterized by several shortcomings in methodology. We highlighted these methodologic hurdles in our systematic review on NIRS (**chapter 3.1**) and described our own limitations in the exploratory analysis of PROSECO-IC data (**chapter 3.2**). In addition, COVID-19 lockdown is considered a catalyst in the implementation of digital health and technology in healthcare, as witnessed in cardiac rehabilitation (100). Also, in our PROSECO-IC study, flexibility of technology facilitated a fluent conversion to provide feedback and monitoring during the pandemic. However, it has to be acknowledged that implementation of technology suffers from several limitations beyond patients and caregivers (e.g. privacy and confidentiality, reimbursement or validity of devices (99)). Moreover, digital health literacy and active participation (recording of activities) from the end-user is still needed to optimize monitoring and feedback, which is objectified in 16% of participants in PROSECO-IC

(exercise logs < 10% compared to expected). Here, improvement in automated algorithm detection of activities might be a possible solution (42). In terms of generalizability and external validity, we only recruited participants in a tertiary care hospital (university hospitals Leuven, Leuven). Therefore, referral bias in terms of comorbidities, prescribed medication and study recruitment may be apparent. On the other hand, the high prevalence of cardiovascular, respiratory or musculoskeletal comorbidities stress the importance of multidisciplinary care in patients with LEAD. Moreover, the comorbid state in patients with LEAD might be an explanation of the observed heterogeneity in response. Selection bias is another treat to impact external validity. Although our recruitment rate was high (52% of eligible patients in PROSECO-IC) compared to earlier trials and real-world cardiovascular rehabilitation uptake, it is possible that patients with higher motivation towards a healthy active lifestyle were more likely to participate in exercise studies.

5.7 General conclusions

Exercise therapy is an important component in the management of patients with LEAD having symptoms of intermittent claudication. Though often unavailable, we further endorse the rationale to provide comprehensive rehabilitation in patients with LEAD and intermittent claudication. Comprehensive rehabilitation might provide additional health benefits beyond changes in walking capacity (e.g. better cardiorespiratory fitness and cardiovascular health). When participation in a center-based program is not possible or not preferred, home-based exercise programs supported by technology-monitoring are found to be an interesting alternative that is accepted and feasible in patients with LEAD. In terms of efficacy, we observed clinically relevant improvements in ambulatory capacity and quality of life, yet, this should be further confirmed in larger randomized controlled studies. Changes in ambulatory capacity were characterized by NIRS-derived slower rate of muscle deoxygenation during treadmill testing. However, definite conclusions on mechanisms and determinants of ambulatory progression need larger datasets. Once available, this should then result in the development of better person-tailored interventions in LEAD patients with intermittent claudication to be integrated in the current care paths.

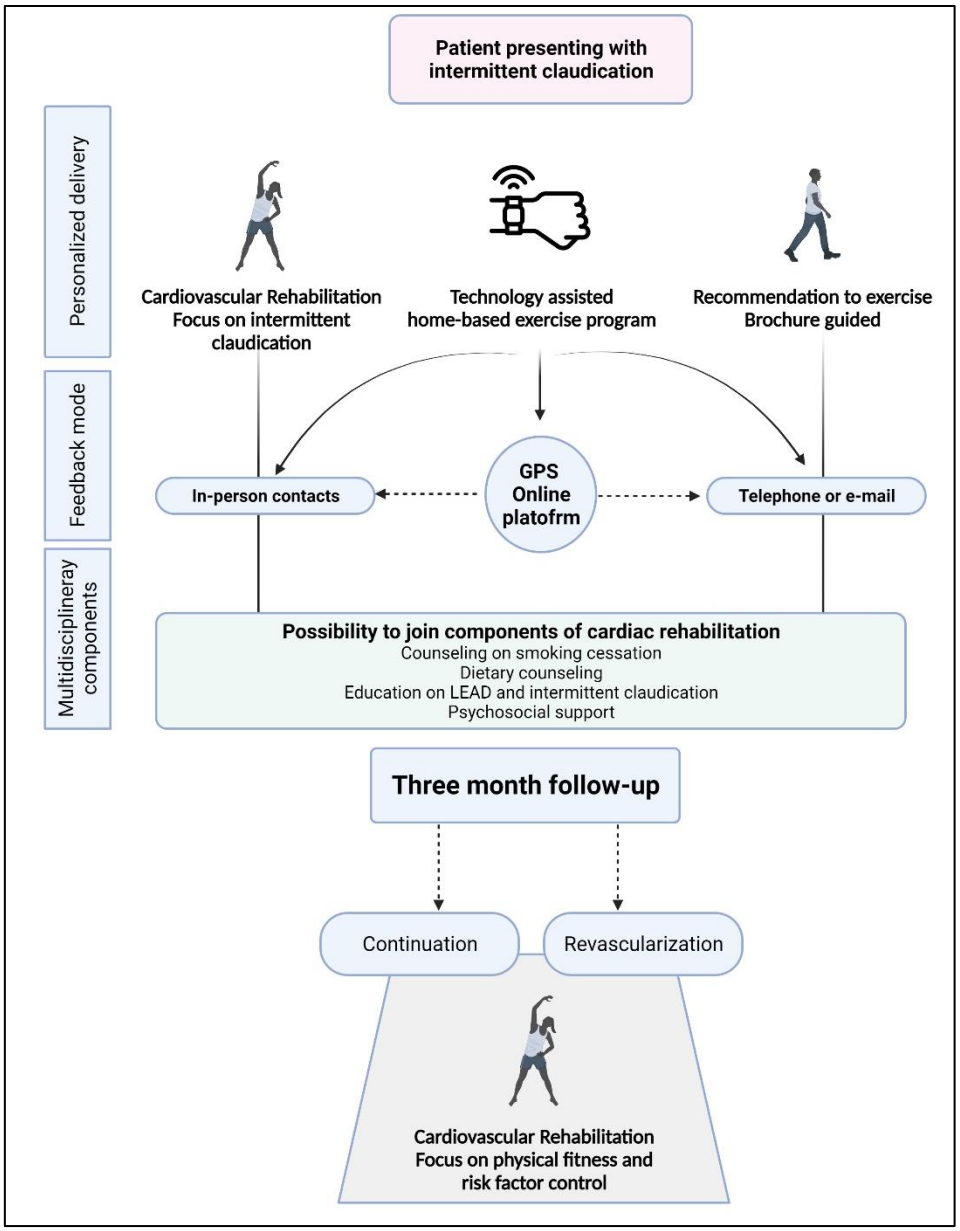


Figure 15. *Conceptual model on the introduction of LEAD in multidisciplinary, multi-component rehabilitation, with the possibility to include technology in direct monitoring and/or feedback in a home-based environment. Increased flexibility could therefore improve personalization and concurrent uptake of exercise, even when barriers are present to a supervised, center-based program (Created using Biorender).*

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Appendices

Abbreviations

6MWD	Six-minute walking distance
6MWT	Six-minute walk test
ABI	Ankle-Brachial Index
ACC	American College of Cardiology
ACSM	The American College of Sports Medicine
AHA	American Heart Association
ATP	Adenosine triphosphate
ATT	Adipose tissue thickness
BASES	British Association of Sport and Exercise Sciences
BMI	Body mass index
CAD	Coronary artery disease
CI	Confidence interval
CLEVER	The Claudication: Exercise Versus Endoluminal Revascularization
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
CPS	Claudication pain scale
CR	Cardiac rehabilitation
CRF	Cardiorespiratory fitness
CV	Cardiovascular
CVRF	Cardiovascular risk factor
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ESC	European Society of Cardiology
ESES	Exercise Self-Efficacy Scale
FBG	Fasting blood glucose
GBD	Global Burden of Disease
GHWA	Go-Home-And-Walk advice
GPS	Global positioning systems
H+	Hydron
H(B)EP	Home-based exercise program
HBET	Home-based exercise therapy
HCL	Hypercholesterolemia
HDL-C	High density lipoprotein cholesterol
HHb	De-oxygenated haemoglobin
HONOR	Home-Based Monitored Exercise for PAD
HTN	Hypertension
IC	Intermittent claudication
ICC	Intraclass correlation
IQR	Interquartile range
IRONIC	The Invasive Revascularization or Not in Intermittent Claudication
LDL-C	Low density lipoprotein cholesterol
LEAD	Lower extremity artery disease
LITE	Low-Intensity Exercise Intervention in PAD
LOE	Level of evidence
MET	Metabolic equivalent
MRI	Magnetic resonance imaging
MVPA	Moderate vigorous physical activity

MWD	Maximal walking distance
MWT	Maximal walking time
NIRS	Near infrared spectroscopy
NO	Nitric oxide
O2Hb	Oxygenated haemoglobin
OBS	Obesity
OUES	Oxygen uptake efficiency slope
PA	Physical activity
PAD	Peripheral artery (arterial) disease
PCI	Percutaneous coronary intervention
PFWD	Pain-free walking distance
PFWS	Pain-free walking speed
PFWT	Pain-free walking time
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PROSECO-IC	Determinants of PROgression after Supervised ExerCise training through technology in patients with Intermittent Claudication
PROSPERO	Prospective Register of Systematic reviews
RCT	Randomized Controlled Trial
RER	Respiratory exchange ratio
r_p	Pearson correlation
r_{pb}	Point-biserial correlation
r_s	Spearman correlation
SBP	Systolic blood pressure
SD	Standard deviation
SET	Supervised exercise therapy
SF-36	36-item Short Form Health Survey
SF-IPAQ	Short-form International Physical Activity Questionnaire
SPPB	Short Physical Performance Battery
StO2	Muscle tissue oxygen saturation
SWIM	Synthesis Without Meta Analysis
T100	Total TSI recovery
T50	Half-time TSI recovery
TASC	Trans-Atlantic Inter-Society Consensus
TC	Total choslesterol
TESTEX	Tool for the assEssment of Study qualiTy and reporting in EXercise
TG	Tryglicerides
tHb	Total haemoglobin
TOI	Tissue oxygenation index
TSI	Tissue saturation index
TSK	Tampa Scale of Kinesiophobia
TTM	Time to minimum
TUG	Timed Up and Go
TUQ	Technology Usage Questionnaire
US	United States
VascuQOL	Vascular Quality of Life Questionnaire
VAT	Ventilatory aerobic threshold
WIQ	Walking Impairment Questionnaire
X^2	Chi square

Appositions

1) Primary and secondary prevention are important to improve overall well-being and economic burden on our health system. Here, physiotherapists are educated to guide and encourage behavioral and physical change in a wide range of chronic diseases. Yet, physiotherapists should be recognized and advocate for more pronounced involvement in overall prevention strategies.

2) Mental health and stress resilience are challenged in a demanding environment such as academia. Social initiatives to connect with other young researchers within should be encouraged, not only to improve scientific skills but also to share common uncertainties and obstacles all of us encounter.

3) Empathy is the only answer when evidence-based practice and popular opinion collide.

About the author

Nils Cornelis was born on the 20th of July 1993 in Bonheiden, to grow up in Keerbergen. He graduated in latin-maths in 2011 from his high school Don Bosco ASO, Haacht. Hereafter, he started his student career in the summer of 2011 at the KU Leuven, studying Rehabilitation Sciences and Physiotherapy. Completing his Bachelor of Science degree (cum laude) in 2014, Nils started his Master of Science dissertation with his promotor Dr. Roselien Buys. During his masters he got selected to participate in a research internship in the unit cardiovascular exercise physiology (CVEP), mentored by Prof. Véronique Cornelissen. Graduated as a physiotherapist specialized in the rehabilitation of internal disorders in 2016 (summa cum laude), he started working as a research assistant in the CVEP research unit. Here he initially worked on the European Horizon 2020 project: PATHway – Technology enabled behavioral change as a pathway towards better self-management of cardiovascular disease. In august 2018, Nils started his PhD-research at the faculty of Movement and Rehabilitation Sciences at KU Leuven under the mentorship and supervision of Prof. Véronique Cornelissen (promotor), Dr. Roselien Buys (co-promotor) and Prof. dr. Inge Fourneau (co-promotor). He started to develop an exercise program using wearable technology and study its effects on intermittent claudication complaints in patients with lower extremity artery disease. From June 2020, Nils was also involved in the European Horizon 2020 project: PROTEIN, a nutrition and physical activity project. During his PhD, Nils also got involved in the skill center collaboration between university hospitals Leuven and KU Leuven. Here he worked as a physiotherapist in cardiac rehabilitation. Next to his research, Nils was also active as a coach for HARPA (phase III cardiac rehabilitation, sport club).

List of publications

Articles published in internationally reviewed journals

Cornelis, N., Buys, R., Fourneau, I., Van den Bosch, A., De Wilde, C., Goetschalckx, K., Cornelissen, V. (2021). Cardiorespiratory fitness in patients with lower-extremity artery disease? It takes more than just some steps! *Eur J Prev Cardiol. 2021; Online ahead of print.*

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Personal contribution

The PhD-researcher was involved in all aspects of the presented work, including the conception, execution, analysis and reporting of all experiments.

Conflict of interest

We declare that none of the authors mentioned in this manuscript has any conflict of interest to report. The funding source did not take part in the design, execution and reporting of the scientific experiments related in this manuscript.

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In vele opzichten kan je een PhD-traject vergelijken met een stevige wandeltocht. Een wandeltocht waarbij het reliëf eerst vlak, dan weer glooiend is, maar ook bestaat uit steile hellingen. Een wandeltocht waarbij er momenten zijn om te genieten van het uitzicht, maar ook momenten om stevig voort te maken om op tijd de volgende bestemming te bereiken. Tijdens elke trektocht beleef je dagen met stralende zon en een heldere hemel, waarbij je het gevoel hebt de wereld aan te kunnen. Anderzijds kan het weer ook wel eens tegenzitten, regen, sneeuw of zelfs storm, waarbij zowel het water, als de moed je in de schoenen zakt. Daarom is het gezelschap waarmee je een dergelijk avontuur aangaat enorm belangrijk. Enerzijds zijn er de voortrekkers, zij die jou überhaupt de kans geven om aan die enorme wandeling te beginnen en het engagement aangaan om voortdurend bij te sturen waar nodig. Te blijven navigeren, maar bovenal motiveren om samen de bestemming te bereiken. Bedankt aan alle geëngageerde juryleden om deze taak op zich te nemen en mij kritisch te laten reflecteren over welke weg ik bewandel. Onder de voortrekkers reken ik ook mijn (co)promotoren. Véronique en Roselien, die elke dag vol enthousiasme en energie starten, bedankt om mee te wandelen. Ik heb de afgelopen jaren enorm veel kunnen leren, niet alleen over wetenschap, bloedvaten en statistiek, maar ook over mezelf. Van op dag één voelde ik mij bijzonder welkom in de fijne onderzoeksgroep die CVEP is. Bij de applicatie voor mijn masterproef was dit meteen duidelijk, waar ik Dr. Buys na een eerste bericht snel moest vervangen in Roselien. Een onderzoeksgroep die duidelijk jullie stempel draagt, met een groot hart voor beweging, innovatie en technologie, maar ook een voorliefde voor de betere streekbieren. Bedankt voor de afgelopen jaren en enorm veel succes, maar uiteraard ook plezier, bij jullie verdere ondernemingen. Ook wil ik graag prof. Fourneau, Inge, bedanken, met haar rugzak aan ervaring heeft ook zij mij in de startblokken geplaatst voor dit doctoraatswerk. *If you want to go fast, go alone. If you want to go far, go together.* Een quote die ik nooit zal vergeten en ook haar werk als arts, als onderzoeker typeert. Haar sterke drang, toewijding en doorzetting om met een multidisciplinair team de zorg voor vaatpatiënten te verbeteren, zal ongetwijfeld haar bestemming vinden. Al zullen daarvoor misschien nog enkele cols worden beklommen, we zijn met dit werk al even op verkenning kunnen gaan.

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