ADMINISTRATIVE INFORMATION

Title

TeGeCoach trial: Telephone Health Coaching with Exercise Monitoring using Wearable Activity Trackers for Improving Quality of Life in Peripheral Artery Disease

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Abbreviations: PAD: Peripheral Artery Disease; IC: Intermittent Claudication

ABSTRACT

Peripheral artery disease (PAD) is the third most prevalent cardiovascular disease worldwide and has become a serious public health issue, with over 200 million people affected. Smoking and diabetes are the strongest risk factors for the development of PAD, as well as high cholesterol, high blood pressure and sedentary lifestyle. The most prominent symptom is leg pain while walking, known as intermittent claudication, as the muscles do not get enough blood during exercise to meet the needs. To improve mobility, first line treatment for intermittent claudication are supervised exercise programs (SEPs); however, its implementation faces manifold challenges: low uptake, potentially due to lack of reimbursement by insurance companies, limited course availability and low adherence. These barriers led to the development of home-based exercise programs, which are effective when supplemented with some form of behavior change and/or observation technique. Therefore, this trial aims to determine the clinical effectiveness and cost advantage of TeGeCoach, a 12-month long home-based exercise program (HEP), compared with the usual care of PAD. It is hypothesized that TeGeCoach will improve walking impairment and will lower the need of health care resources that are spent on patients with PAD.

The investigators will conduct a pragmatic, open-label, multicenter randomized controlled clinical trial to evaluate the effectiveness and safety of TeGeCoach. 1760 patients with PAD at Fontaine stage II will be randomly assigned either to TeGeCoach or Treatment-as-Usual (usual care). TeGeCoach consists of telephone-based health coaching that is supplemented with remote walking exercise monitoring using wearable activity trackers, as well as intensified primary care. The health coaching is a patient-centered approach by using shared decision making, active listening and motivational interviewing, based on the transtheoretical model of behavior change. Depending on the individual functional status and exercise capacity, participants will be advised to walk up to seven times a week while using a wearable activity tracker. Primary outcomes are functional capacity measured by the Walking Impairment Questionnaire, alongside with total health care costs based upon routine health insurance data. Secondary outcome measures include quality of life, health literacy and health behavior. Outcomes will be measured at three time points (0, 12, and 24 months).

Clearly, the current routine care of intermittent claudication in patients with PAD is partly ineffective und insufficient, with the consequence of a poorly served patient population and worsening disease condition. TeGeCoach may provide an effective and feasible alternative in the management of

intermittent claudication by improving access to structured exercise while potentially reducing health care costs.

INTRODUCTION

Peripheral Artery Disease (PAD) is the third most prevalent atherosclerotic cardiovascular disease worldwide after coronary heart disease and stroke and has become one of the leading causes of disability and death. With over 200 million people worldwide affected, PAD is increasingly recognized as a serious public health burden (Criqui & Aboyans, 2015; Fowkes et al., 2013). PAD is characterized by the progressive narrowing of the peripheral arteries resulting in the reduction of blood supply, eventually leading to functional impairment and mobility loss. The most common etiology of PAD is atherosclerosis, which carries an increased risk for subsequent cardiovascular events and mortality. If not intervened sufficiently early, the atherosclerotic processes can affect other vascular beds with potentially fatal consequences (Criqui et al., 2010).The number one risk factor for PAD tobacco is smoking, followed by diabetes mellitus. Other risk factors include high cholesterol, hypertension, history of cardiovascular disease (i.e., coronary heart disease, stroke), chronic kidney disorder (Criqui & Aboyans, 2015; Eraso et al., 2014; Fowkes et al., 2013; Joosten et al., 2012). Recently, low socioeconomic status has also been identified as another determinant of PAD (Pande & Creager, 2014).

The amount of people with PAD has risen rapidly in recent years, with a sharp increase by nearly 25% between 2000 and 2010 in the general population (Fowkes et al., 2013). This increase is bigger among women than among men (Sampson et al., 2014) and disproportionally high in low- and middle-income countries (28.7%, compared to 13.1% in high-income countries) (Fowkes et al., 2013). Typically, like all atherosclerotic diseases, PAD is markedly more prevalent in the elderly population (Criqui & Aboyans, 2015; Fowkes et al., 2013), estimating that 5.4% and 18.6% of individuals aged from 45 to 49 and 85 to 89 years are affected, respectively (Fowkes et al., 2013). Likewise, in Germany, the proportion of PAD-related hospitalizations has increased from 2.7% (400 928 among 15 million hospitalizations) to 3% (483 961 among 16.2 million hospitalizations) between 2005 and 2009, particularly of last stage PAD presenting as ulcers and/or gangrene by 32%, while hospital reimbursement costs for the treatment of PAD have grown nationwide from €2.14 billion in 2007 to €2.56 billion in 2009, a 21% increase within 2 years (Malyar et al., 2013). Consequently, the economic burden of PAD placed on healthcare systems is high, and is likely continuing to rise.

Nearly 50% of patients with PAD are asymptomatic at the time patients diagnosed with PAD, (Hirsch et al., 2001; McDermott et al., 2001). The most common clinical manifestation is leg pain while walking,

known as *intermittent claudication* (IC), which reflects impaired hemodynamics and vascular dysfunction (Hamburg & Creager, 2017; Hiatt, Armstrong, Larson, & Brass, 2015). IC is associated with diminished mental health and lower quality of life, thus reducing symptoms is a cornerstone of the comprehensive care for patients with PAD (Andrew W Gardner, Montgomery, Wang, & Xu, 2018; Maksimovic et al., 2014; Regensteiner et al., 2008; Smolderen et al., 2009). At an advanced stage, symptoms include resting leg pain, ulcer formation and gangrenous necrosis (i.e., tissue loss), which is the most severe clinical manifestation of PAD when untreated.

Besides pharmacotherapy, atherosclerotic risk factor management and surgical revascularization procedures, exercise-based interventions provide substantial benefits for patients with IC (Guidon & McGee, 2010; Haas, Lloyd, Yang, & Terjung, 2012; Hamburg & Balady, 2011; Lane, Harwood, Watson, & Leng, 2017). Accordingly, formal supervised exercise programs (SEPs) can be efficacious in the treatment of PAD with IC, with positive effects on muscle function, walking performance and quality of life (Beckitt, Day, Morgan, & Lamont, 2012; Brizendine, Young, McCully, & Murrow, 2014; Fakhry et al., 2012; Kruidenier et al., 2012; Malgor et al., 2015; Parmenter, Dieberg, & Smart, 2015). Therefore, SEPs are recommended as first-line therapy in a variety of published clinical guidelines, with the highest level of evidence (Gerhard-Herman et al., 2017; Lawall, Huppert, Espinola-Klein, & Rumenapf, 2016; Lawall, Huppert, Espinola-Klein, Zemmrich, & Ruemenapf, 2017; Layden, Michaels, Bermingham, Higgins, & Group, 2012). SEPs involves the use of intermittent walking exercise and are minimum three-month commitments, with at least three sessions per week (30-60 minutes per session) provided in a clinical setting by qualified personnel (e.g. hospital outpatient setting, outpatient facility, or a physician's office). However, despite its known clinical benefits and cost-effectiveness, SEPs are generally underutilized, since its routine care implementation in daily practice remains challenging. The adoption of SEPs in the routine care is hampered by low uptake and adherence rates, possibly due to copayment requirements and lack of reimbursement, lack of available local training centers and the burden of traveling (Gerhard-Herman et al., 2017; Harwood, Smith, Cayton, Broadbent, & Chetter, 2016; Layden et al., 2012). Given the upward trend in the prevalence of classic PAD risk factors and the ageing of the population, financial and organizational barriers are likely to aggravate in the future and will continue to hamper the actual use of SEPs in routine care.

Barriers to SEPs led to the emergence of structured *home-based* exercise programs (HEPs) where SEPs are not available or impractical to deliver (McDermott & Polonsky, 2016), and is thus recommended as second-line therapy with a high level of evidence (Gerhard-Herman et al., 2017). Unlike SEPs, HEPs are take place in the personal setting of the patient and are self-directed, with an exercise regimen similar to that of SEPs, (remote) oversight of exercise with specific feedback and some form of theory-driven behavior change technique such as goal setting (e.g. walking action plans), self-monitoring of walking activity (e.g. use of wearable activity tracker or logbook), barrier identification and/or health

coaching (e.g. telephone, face-to-face). Although HEPs may be inferior to SEPs (Al-Jundi, Madbak, Beard, Nawaz, & Tew, 2013; Hageman, Fokkenrood, Gommans, & Teijink, 2018; Makris, Lattimer, Lavida, & Geroulakos, 2012), there is sound evidence that HEPs are an efficacious and thus reasonable treatment approach for PAD patients by improving quality of life, walking ability and claudication symptoms (Collins et al., 2011; Fakhry, Spronk, de Ridder, den Hoed, & Hunink, 2011; A. W. Gardner, Parker, Montgomery, & Blevins, 2014; A. W. Gardner, Parker, Montgomery, Scott, & Blevins, 2011; McDermott et al., 2014; McDermott et al., 2013). For instance, HEPs incorporating an activity tracker to monitor exercise and regular exercise counselling sessions is efficacious in improving functional and pathophysiological PAD outcomes (A. W. Gardner et al., 2014; A. W. Gardner et al., 2011). Similarly, using an activity tracker for self-monitoring purposes and regular feedback sessions leads to better functional walking performance and quality of life in PAD patients (Normahani et al., 2017). Notably, six months of weekly group-mediated meetings with a six month follow-up period of regular phone calls are effective in improving clinical (McDermott et al., 2014; McDermott et al., 2013) and psychosocial outcomes (Rejeski et al., 2014) in patients with PAD. In contrast, a recent randomized trial compared a HEP relying on a combination of telephone coaching and remote exercise monitoring with the use of wearable activity tracker against usual care demonstrated no benefit of HEP in terms of functional walking ability (McDermott, Spring, Berger, & et al., 2018). Possible explanations for conflicting results across trials are considerably heterogeneous intervention protocols in HEPs using different behavioral change techniques (e.g. health coaching, exercise monitoring), different clinical outcomes (i.e. functional, performance-based and/or patient-reported), as well as varying inclusion criteria (i.e. PAD with and/or without IC) potentially leading to different patient populations. That said, it is deemed necessary to incorporate some form of behavior change technique and exercise counselling into HEPs to ensure adherence and thus to be effective, since simple “go home and walk” approaches that include only general walking advice are not effective (Mays, Rogers, Hiatt, & Regensteiner, 2013).

Due to these conflicting results, despite promising findings, there is still some controversy surrounding the real-world effectiveness and feasibility of HEPs in real-world clinical practice, alongside economic considerations. There is therefore an urgent demand of large scale, pragmatic clinical trials in which care is delivered in routine clinical practice in order to inform real world choices in the clinical practice and to shape health care policies (Ware & Hamel, 2011). For that reason, to address the growing burden of PAD, three statutory health insurances in Germany launched a 12-month long HEP named TeGeCoach that is compared to routine care. TeGeCoach incorporates an individual intermittent walking exercise regimen, remote exercise monitoring with the use of a wearable activity tracker, extra medical support and telephone health coaching. Telephone health coaching can be a cost-efficient and effective tool in the management of diseases than can support behavior change (Härter et al., 2016). This unique approach using a variety of behavior change techniques together with regular support by qualified

personnel aims to help PAD patients with IC to enhance their individual motivation for exercise and to obtain the support needed to improve their condition.

Objectives

The primary purpose of this study is to explore the empirical evidence pertaining to the effects of TeGeCoach in the real-world management of PAD. To our knowledge, there is no existing clinical trial examining the effect of a HEP for patients with PAD in routine care. By using a pragmatic approach conducted in the context of the health insurance system, TeGeCoach could be implemented in clinical practice if successful. Along with cost analyses, this trial aims to determine the clinical effectiveness of TeGeCoach over a 24-month follow-up period, when compared with the usual care of PAD (Treatment-as-Usual, TAU). Specifically, there will be a focus on two primary outcomes: 1) walking impairment (i.e. maximum walking distance and claudication pain) and 2) health care costs per patient. It is hypothesized that TeGeCoach would improve walking impairment and simultaneously lower the need of health care resources that are spent on patients with PAD.

METHODS

Trial design

This is a pragmatic, three-site, parallel group, open-label randomized controlled clinical trial embedded within three German statutory health insurances (KKH Kaufmännische Krankenkasse, TK Techniker Krankenkasse and mhplus Krankenkasse), comparing routine care (control arm, TAU) with the TeGeCoach intervention (intervention arm) for patients with PAD. Based on baseline (t0) and two postintervention follow-up measurements at 12 months and again at 24 months (t2), this trial seeks to determine whether TeGeCoach is clinically superior to TAU, along with lower health care costs for health insurances.

This study protocol is reported in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) statement (Schulz, Altman, & Moher, 2010); the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (Chan et al., 2013); and the Template for Intervention Description and Replication (TIDieR) checklist (Hoffmann et al., 2014). To control for publication bias, TeGeCoach has been registered at www.clinicaltrials.gov (NCT03496948); protocol modifications will be added to the trial registry. Ethical approval has been obtained at the ethics committee of the Medical Association Hamburg (Ärztekammer Hamburg). TeGeCoach is designed and conducted in full compliance with Good Clinical Practice quality standards and in accordance with the Declaration of Helsinki of 2008. It is expected that final results are reported after study completion in 2021.

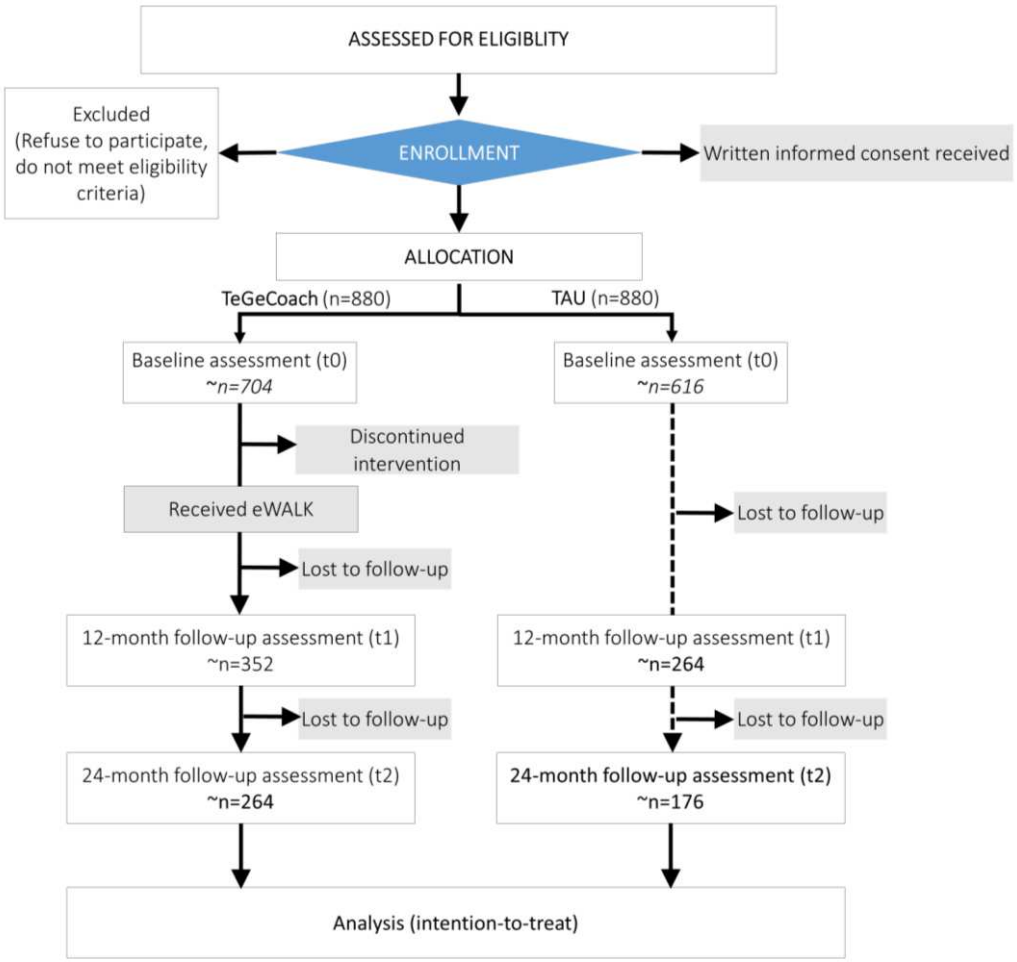

Figure 1. Study overview.

Participants

Eligible participants will be retrospectively identified through the screening of health insurance data that are routinely collected for reimbursement purposes by the statutory health insurances, containing sociodemographic characteristics and health event data (ICD-diagnosis codes). Potentially eligible participants have to fulfil the following inclusion criteria: insured at one of the recruiting statutory health insurances; aged between 35 and 80; German-speaking; access to a telephone (landline or mobile); and a primary or secondary diagnosis of PAD at Fontaine stage IIa or IIb within the last 36 months, as determined by the following German Modification of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10-GM) codes: I70.21 Atherosclerosis of native arteries of extremities with IC (> 200 m, Fontaine stage IIa); I70.22 Atherosclerosis of native arteries of extremities with IC (< 200 m, Fontaine stage IIb); I73.9 Peripheral vascular disease, unspecified (Fontaine stage IIa or IIb). To increase diagnostic accuracy, patients however should have no primary or secondary diagnosis of PAD at Fontaine stage I within the last 12 months: I70.20 Atherosclerosis of native arteries of extremities without IC (Fontaine I), and no diagnosis of Fontaine stage III or IV within the last 36

months: I70.23 Atherosclerosis of native arteries of extremities with ischemic rest pain (Fontaine III); I70.24 Atherosclerosis of native arteries of extremities with ulceration (Fontaine IV); I70.25 Atherosclerosis of native arteries of extremities with gangrene (Fontaine IV).

Ineligible patients are identified based on inpatient diagnosis only, considering the high number of diagnostic errors due to poor coding habits in outpatient settings. Exclusion criteria for participants are: immobility that goes beyond claudication (Fontaine stage III or IV; inability to carry out intervention); (chronic) physical conditions that interfere with the intervention (e.g., COPD); cognitive disorders (inability to carry out intervention); severe and persistent mental disorders (adherence reasons); suicidality (safety reasons); life-threatening illnesses (safety reasons); active or recent participation in any other PAD intervention trial; ongoing hospitalization; (self-reported) alcoholism and/or other drug dependency (adherence reasons); and heart failure graded NYHA class III and IV (inability to carry out intervention and competing risks).

Table 1. *Fontaine stages for the clinical classification of PAD.*

Grade	Symptoms	
Stage I	Asymptomatic	
Stage IIA	Claudication at a distance > 200 m	**Inclusion**
Stage IIB	Claudication at a distance < 200 m	
Stage III	Ischemic rest pain	**Exclusion**
Stage IV	Ulcer, gangrene	

Recruitment

Recruitment of participants will be undertaken by each of the three statutory health insurances: KKH Kaufmännische Krankenkasse, TK Techniker Krankenkasse and mhplus Krankenkasse. Across successive phases of recruitment, after the identification of potentially eligible trial participants with health insurance data, they will be contacted (phone, email) by their health insurance company to explain the purpose of the study, the potential benefits of the study regardless of group allocation, and to confirm that all criteria for study participation are met by undergoing further screening. Furthermore, potential participants will receive a study information letter that is supplemented with consent and permission forms (i.e. authorization for release of medical reports by the treating physician to the health coach). Potential participants will be asked to participate in the study by signing the informed consent and all permission forms, and send them back to their health insurance. Non-responders and insured individuals that are still interested in the study but have not given written consent will be followed up by phone to be reminded of the trial. Once the written consent has been received, a query is submitted

to the data warehouse of the respective health insurance, which automatically assigns a pseudonym to the participant. No participant will be enrolled without full, written informed consent. The intended recruitment period is expected to last 6 months.

In order to ensure medical attendance, participants that are allocated to TeGeCoach may elect their preferred physician. To encourage physicians to participate, they will enter into an integrated care contract (Selektivvertrag) with the respective health insurance that will provide financial incentives for the delivery of special medical services throughout the intervention (Milstein & Blankart, 2016). The enrolment and reimbursement of physicians will be coordinated by medicalnetworks (Kassel, Germany), a company that is specialized on the management of integrated care programs (ICPs) within the § 140a volume V of the German Social Security Code (SGB V). If the physician of choice refuses to participate, the participant will be referred to a nearby physician that has entered into the integrated care contract. Once enrolled, the health coach will contact the physician to discuss their tasks during the course of the study.

Treatment allocation and blinding

Participants will be allocated in a 1:1 ratio to either the intervention (TeGeCoach) or usual care arms (TAU), stratified by health coaching center (i.e. telemedicine service centers) using a permuted block method within each stratum. In order to prevent selection bias and to eliminate any predictability (allocation concealment), participants will be allocated using Sealed Envelope (London, United Kingdom), a secure internet-based randomization service including concealment, stratification and blocking for each health coaching site.

Blinding of care providers (health coaches and treating physicians) and trial participants is not possible because of obvious differences between the interventions. However, as supported by the CONSORT guidelines, blinding of the analysis will be achieved by withholding information about how the groups were coded, and by engaging an independent data analyst (Polit, 2011).

Interventions

TeGeCoach

TeGeCoach is an evidence-based HEP that is designed to inspire healthy habits and support to change unhealthy habits to improve health outcomes in patients with PAD, implemented in the personal setting of the patient. The different components of TeGeCoach have been shown to be effective in treating PAD (e.g. A. W. Gardner et al., 2014; McDermott et al., 2013; Normahani et al., 2017). The telephone health coaching will be carried out by three telemedicine centers that are located throughout Germany, with each center affiliated to one of the three statutory health insurances (KKH, TK, mhplus). The telemedicine centers are staffed with specially trained medical teams (i.e., nurses, physical therapists,

medical assistants). Upon implementation, health coaches receive … hours of training. TeGeCoach is a patient-centered approach by using shared decision making, active listening and motivational interviewing, based on the transtheoretical model of behavior change. This integrative, biopsychosocial model defines the process of intentional behavior change moving through the five stages of change: precontemplation, contemplation, preparation, action, and maintenance (Prochaska, 2013; Prochaska & Velicer, 1997).

For the purpose of monitoring exercise performance, participants will continuously wear an activity tracker device (KKH and mhplus: AS 95 Pulse by Beurer; TK: Health Watch by Philips). Through activity tracking, participants of TeGeCoach can track their personal exercise progress and retrieve feedback about their performance. These devices continuously record the number of steps per minute and automatically sync once per day with the participant's account through the health coaching platform. The health coach will initially define individually tailored walking exercise goals by taking a baseline assessment. Depending on the patient's functional status and current exercise capacity, participants will be assigned to one of three walking plans: Level A - 15 minutes of walking per day; level B - 15 – 30 minutes walking per day; or level C - 60 minutes of walking per day. The walking exercise is based on the principle of interval training; participants will be asked to walk to maximal tolerable pain, with rests between intervals. The goal is to progressively increase walking speed and distance as tolerated, with longer exercise periods and shorter rest periods between sets. The treating physician regularly reviews, and if necessary, adjusts the walking exercise plan. The treating physician checks if any contraindications to exercise exist, and whether all important comorbidities such as high blood pressure, diabetes and coronary heart disease are sufficiently treated.

Over the course of 12 months, participants will set up nine … minute phone calls with their health coach, based on evidence of the effectiveness of telephone health coaching to achieve behavior change. During these structured phone calls, the health coach will discuss the progress towards exercise goals and review of wearable activity monitor data with the participant to check whether the patient adheres to the individual walking exercise plan. In order to detect problems with the walking exercise plan and to improve adherence, additional phone calls are warranted when coaches are alerted that step frequency or the duration of exercise sessions has fallen below or went above an individual threshold range. During these calls, barriers like lack of motivation, exercise intolerance or technical issues will be discussed and how they can be overcome through behavioral support. Along with the walking exercise, patient-tailored topics of interest that are relevant to the management of PAD will be covered during these phone calls, in order to strengthen health literacy, to facilitate patient empowerment and to adopt a proactive stance in dealing with their disease. The health coaching curriculum includes: Knowledge of PAD, PAD medication, PAD and important comorbidities, and other related health topics (e.g., tobacco use, nutrition, vaccination). To ensure consistency of care, the treating physician is involved in the health

coaching by regularly releasing medical reports to the coaches. Furthermore, to add support to the health coaching, participants will be provided with informative handouts, either in electronic form or as printed output. After completion of the telephone health coaching, participants will be allowed to keep using the wearable activity tracker for another 12 months to monitor their exercise performance, although remote exercise monitoring by the health coach will be discontinued.

TeGeCoach is a low risk, non-invasive intervention with no prospectively identifiable risks. Health coaches will be regularly supervised by a team of experts, and compliance to coaching guidelines will be continuously monitored and reviewed to ensure a high-quality health coaching. The risks from use of wearable activity trackers is low; all devices have been certified (CE certificate) and thus conform to health, safety, and environmental protection standards for products sold within the European Union. That said, to ensure patient safety, participant safety will be monitored by recording (serious) adverse events that are reported during the health coaching. Over the course of the intervention, participants will also be medically monitored by their treating physician and will have regular access to the routine care of PAD. Although unlikely, in case of a (serious) adverse event, medical countermeasures will be taken in a timely manner. According to the international Good Clinical Practice guideline (ICH GCP, add REF), relevant adverse events are defined as any untoward medical occurrence in the participant administered a medicinal product, whether it is study related or not, whereas relevant serious adverse events can be any medical occurrence that results in death, requires inpatient hospitalization or prolongation of existing hospitalization, results in permanent or significant disability or is life threatening. Adverse events will be collected and analyzed, and serious adverse events (SAE) will be reported to the ethics committee of the Medical Association Hamburg.

Routine care (TAU)

Patients allocated to TAU will receive usual medical care from their own physicians. Additionally, participants will receive PAD patient information brochures from their statutory health insurance. These simple but informative leaflets will provide information about course offerings of the respective health insurances to encourage regular exercise and to promote lifestyle changes, including SEPs (vascular and cardio exercise), physical therapy, nutritional assistance programs, smoking cessation programs, weight loss programs, as well as patient education programs for obesity and diabetes. Each health insurance will have their own information leaflets. It will be thereby ensured that participants allocated to TAU will receive genuine usual care as supplied in normal everyday practice. Participants allocated to the intervention group will also have access to the usual care of PAD and will receive the same patient information (i.e., leaflets, brochures) as in TAU.

Measures

Outcome measures are listed in Table 2 along with timing of assessment; the effectiveness of TeGeCoach will be measured based upon patient-reported outcome measures, i.e., questionnaires, routine health insurance data and activity tracker data on the health coaching platform. Patient-reported outcomes will be collected via postal survey at baseline (t0), then at 12 (t1) and 24 (t2) months.

Primary Outcomes

Walking impairment (Walking Impairment Questionnaire, WIQ): The patient-reported WIQ is a valid questionnaire to classify patient-perceived walking impairment in patients with PAD in terms of pain, walking speed, walking distance and the climbing of stairs (McDermott et al., 1998; Regensteiner, Steiner, Panzer, & Hiatt, 1990; Sagar, Brown, Zelt, Pickett, & Tranmer, 2012). The WIQ has been shown to be responsive to treatment effects and thus can be used as an alternative to treadmill testing for an objective assessment of walking claudication (Nicolai et al., 2009).

Health care costs (routine health insurance data): Hospital care costs, outpatient services and primary care costs, costs for drugs and other medical supplies, and sick pay costs. The sum of these costs will give an estimation of the total cost of treating patients with PAD.

Secondary Outcomes

Generic health-related quality of life (EQ5D-5L questionnaire): The EQ5D-5L is a standardized instrument developed by the EuroQoL Group for the measurement of health-related quality of life (Herdman et al., 2011). There are five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ5D-5L has been validated for the general German population (Hinz, Kohlmann, Stöbel-Richter, Zenger, & Brähler, 2014).

Health status (SF-12 questionnaire): The SF-12 is a self-report questionnaire for the measurement of generic health status involving multiple health dimensions: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. SF-12 is a short version of the SF-36, with good psychometric properties (Ware Jr, Kosinski, & Keller, 1996). The German version has been cross-validated with the original English version (Gandek et al., 1998).

PAD-specific quality of life (VascuQoL-25 questionnaire): The VascuQol-25 is a highly-responsive validated questionnaire for the measurement of PAD-specific health-related quality of life (Morgan, Crayford, Murrin, & Fraser, 2001), with a high level of construct and convergence validity (Mehta, Subramaniam, Chetter, & McCollum, 2006). The questionnaire consists of five domains (Activity, Symptom, Pain, Emotional and Social) and has 25 items in total.

Depression (PHQ-9 questionnaire): The PHQ-9 is a brief valid questionnaire for the diagnosis of depression (Kroenke & Spitzer, 2002; Martin, Rief, Klaiberg, & Braehler, 2006) that can also be used to

identify depression outcome measures and changes over time (Löwe, Kroenke, Herzog, & Gräfe, 2004). The German version has been validated twice (Henkel et al., 2003; Lowe et al., 2004).

Generalized Anxiety Disorder (GAD-7 questionnaire): The GAD-7 is brief questionnaire for the detection of Generalized Anxiety Disorder, which has been validated in primary care setting and in the general population (Lowe et al., 2008; Spitzer, Kroenke, Williams, & Löwe, 2006).

Risk factors (AUDIT-C & FTND questionnaires): The AUDIT-C is a brief screening instrument to identify harmful alcohol consumption, consisting of three questions (Bradley et al., 2007; Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998). Regarding its psychometric properties, the AUDIT-C has been shown to be reliable and valid instrument to screen alcohol misuse in primary care settings (Dybek et al., 2006). To identify tobacco dependence, the 6-item long Fagerström Test for Nicotine Dependence (FTND) will be used, which has been shown to be validly assessing the physical addiction to nicotine (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991).

Health literacy (HLS-EU-16 questionnaire): The HLS-EU-16 is a short and comprehensive tool for the measurement of health literacy, developed by the European Health Literacy Consortium (Sørensen et al., 2013).

Patient activation (PAM-13 questionnaire): PAM-13 has been shown to be a valuable tool for the measurement of patient activation by dividing people into one of four activation levels (Hibbard, Mahoney, Stockard, & Tusler, 2005). The German version has been validated, with good psychometric properties (Brenk-Franz et al., 2013; Zill et al., 2013).

Healthcare resource use (routine health insurance data): Time period until hospitalization, probability of hospitalization, number and duration of inpatient hospitalization, outpatient medical treatment, and drug dose (defined daily dose - DDD).

Serious adverse events (routine health insurance data): e.g., death, amputation, and revascularization.

Additional outcomes (intervention arm only)

Fontaine stage (medical reports from treating physicians): The Fontaine classification is a clinical classification method which has been shown to be a useful tool for research purposes. There are five Fontaine stages (Table 1), from asymptomatic to major tissue loss.

Patient satisfaction (ZAPA questionnaire): ZAPA is a brief (4 items) and psychometrically valid German questionnaire for measuring the patient's global satisfaction with his or her outpatient care, including the quality and extent of information received and his/her involvement in clinical decisions (i.e. shared-decision making) (Scholl et al., 2011).

Walking exercise adherence (activity tracker data): e.g., number of alerts when step frequency or the duration of exercise sessions fall below or go above an individual threshold range.

Number of steps (activity tracker data): Data imported from wearable activity tracker

Table 2. *Participant timeline: Time schedule of enrolment (eligibility screen, informed consent, pseudonymization and allocation), study arms (TeGeCoach or TAU) and measurements (questionnaires and routine health insurance data).*

	Study period			
	Enrollment	Allocation	Postallocation	
Time point *[1]	**-t1**	**t0**	**t1**	**t2**
Enrollment				
Eligibility screen (routine health insurance data)	x			
Informed consent	x			
Pseudonymization		x		
Allocation		x		
Study arms				
TeGeCoach (intervention)		◆———	———	---◆
TAU (control)		----------	----------	---▶
Measurements				
Intervention and control arm				
Patient-reported outcomes (questionnaires) *[2]		x	x	x
Cost and medical outcomes (routine health insurance data) *[3]		◆———	———	———◆
Intervention arm only				
Patient-reported outcomes (questionnaires) *[4]			x	
PAD severity (medical reports from treating physicians) *[5]		x	x	
Walking exercise parameters (activity tracker data) *[6]		◆———	———◆	

*[1] -t1: ~1 month before patient in, t0: baseline; t1: 12 month follow-up t2: 24 month follow-up
*[2] WIQ, EQ5D-5L, SF-12, VascuQoL-25, PHQ-9, GHD-7, AUDIT-C, FTND, HLQ, PAM-13
*[3] Health care costs, use of medical services, (serious) adverse events
*[4] ZAPA
*[5] Fontaine stage
*[6] Walking exercise adherence, number of steps per day

Sample size

A total of 1760 patients (880 per group) will be recruited to this trial. Estimating a attrition rate of 70% (TeGeCoach) and 80% (usual care) from baseline to T2 based on prior experience with similar health coaching trials (Härter et al., 2016), it is expected to have 176 and 264 participants at T2 in the routine care and intervention arm, respectively. This sample size will provide a power of 80% (Gpower v.3.1.9.2) to detect small to moderate effects (Cohen's f = 0.15) and thus to allow clinically meaningful group comparisons on the primary outcome (Conijn et al., 2015), with an alpha of 5%.

Data collection and management

Data from three different sources will be collected: patient-reported questionnaire data, routine health insurance data and activity tracker data. Data management and storage will be carried out in compliance with the General Data Protection Regulation (GDPR) in the European Union and Good Scientific Practice guidelines by the German Research Foundation (Deutsche Forschungsgemeinschaft, 2013). To ensure confidentiality, all data will be collected, processed, analyzed and stored in

pseudonymous form by replacing personally identifying information of each participant with a unique patient identification number, allowing to combine data from multiple sources and to merge longitudinal data. Linkage to an identity (depseudonymization) is not possible without additional information, known as a pseudonymization key that is kept separately and protected by technical and organizational measures.

At each study point (t0 to t2), the data coordinators will send out a set of paper-based questionnaires to the participants. Participants will be asked to send them back to the Department of Medical Psychology at the University Medical Center Hamburg-Eppendorf, which is responsible for the external scientific evaluation of this trial. To increase response rates, participants who have not send their questionnaire back in time will receive a postal reminder. All participants will be followed up at t1 and t2, regardless of whether questionnaires have been returned at previous study points. Questionnaire data will be entered into an electronic database, with only authorized personnel being allowed to retrieve, enter or change data. For data quality and monitoring purposes, validation checks regarding out of range data, illogical and invalid responses, and data entry errors will be performed. Missing values will be analyzed and appropriate imputation strategies will be applied. It will also be checked whether missing values are missing completely at random (MCAR).

The routine health insurance data is collected for the purpose of billing of claims and contains information on all contacts with the health care system (including ICD-10 codes; operations and procedure key code – OPS, the German equivalent to the American procedure coding system—PCS), medication, and inability to work. The three health insurances assemble and pseudonymize the routine data. The statutory health insurances will share routine health insurance data from the participants with the University Medical Center Hamburg in pseudonymized form. Individual insurance information cannot be identified from this data.

Activity tracker data will be automatically uploaded to the health coaching platform via modem once per day. The statutory health insurances will share the activity tracker data that is saved on the health coaching platform with the University Medical Center Hamburg in pseudonymized form.

All data will be stored for a maximum of 10 years, securely locked in cabinets and saved on password-protected computers in areas with restricted access. Personally identifiable information of participants and decryption keys linking the individual with their pseudonym are only accessible to the data coordinators at each health insurance. The decryption keys will be deleted two years after study completion so that virtually from this point all data is fully anonymized. Regarding dissemination, all publicly available data will be fully anonymized and will not disclose identities. Participants have the right to be informed about their data. If a participant decides to withdraw from the trial prematurely, the data already collected may be used, unless requesting its deletion. If a participant decides to revoke

the informed consent, any data already collected from that participant will be deleted. Deletion of the data cannot be requested if the data has already been anonymized.

Statistical analysis

Analyses will be by intention-to-treat and in accordance with the CONSORT guidelines. That is, all participants who are enrolled to the study will be included in the analysis, regardless of conforming to the intervention protocol or not. For questionnaire data, changes from baseline to follow-up measurements in primary and secondary outcomes will be compared between study arms using linear mixed models. In order to take correlation between the observations into account, models will be adjusted for participant and telemedicine site characteristics. Missing data will be treated as missing and will not be imputed. Tests of treatment effects will be conducted at a two-sided significance level of 0.05. Predefined subgroup analyses will be added to the statistical plan to determine the influence of baseline characteristics (e.g., degree of walking impairment), health insurance affiliation (KKH + mhplus versus TK), and intention-to-treat (versus per-protocol analysis) to check robustness of the results.

For routine data, changes over time between groups will be compared between study arms using random-effects regression models (difference-in-differences method) after eliminating differences in observable baseline characteristics between groups with the use of *entropy balancing.* Entropy balancing allows a better balancing compared to conventional processes such as propensity matching (REF). Adjusting for multiple testing is not needed (Bender, Lange, & Ziegler, 2007); given that there is only one primary endpoint for patient-reported and routine health insurance data each, it is assumed that the comparisons are independent, while secondary endpoints will be interpreted in an explorative manner.

Ethics and Dissemination

The study protocol, the informed consent forms and all other documents that will be handed out to the participants have been reviewed and approved by the ethical review bodies (Medical Association Hamburg) with respect to scientific content and compliance with applicable research and human subject regulations. The ethics committee will be informed in case of any amendments made to the study protocol or informed consent forms.

Dissemination of the results of this study will occur through various channels. Results will be disseminated widely through peer-reviewed manuscripts published at leading journals in the field, reports to the funding body, international conference presentations and media press releases. Additionally, results of this trial will be made available to all insurance bodies who are interested in implementing such an intervention into routine clinical care of PAD. The study team also realizes the value of open science and feels committed to information exchange through data being accessible to

559 the research community; therefore, in an attempt to tackle the problem of hidden data, comprehensive
560 data from this trial will be made available to the public and the medical research community upon
561 request.
562
563 **DISCUSSION**
564 The aim of this trial is to inform clinical practice since the current routine care of PAD is partly
565 ineffective und insufficient, with the consequence of a poorly served patient population, worsening
566 disease condition and high mortality rates. As a result, the global burden of PAD requires substantial
567 health-care resources to be expended; the number of individuals living with PAD has increased over time
568 so has the cost of continued PAD care, while the growing aging population will inevitably let the costs
569 keep rising. With this in mind, it is expected that TeGeCoach will lead to an overall clinical improvement
570 of the patient's health status, that is, reduced claudication with better overall mobility, increased quality
571 of live, and lower costs of health care compared to the current routine care of PAD. Due to its pragmatic
572 features, this trial allows generalizability of the results to the real-world health care environment, along
573 with a heterogeneous sample of representing patients with PAD ensuring high external validity. If
574 successful, the TeGeCoach intervention may be feasible for widespread adoption by routine care.
575
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