Västra Götalandsregionen
Sahlgrenska Universitetssjukhuset, HTA-centrum
Health Technology Assessment
HTA-rapport 2014:69

Home-based versus hospital-based supervised exercise or walk advice as treatment for intermittent claudication

Bäck M, Djerf H, Jivegård L, Johansson A, Nordanstig J, Svanberg T, Wikberg Adania U, Sjögren P

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Home-based versus hospital-based supervised exercise or walk advice as treatment for intermittent claudication

[Hembaserad jämfört med sjukhusbaserad handledd fysisk träning eller träningsråd som behandling vid claudicatio intermittens]

Bäck M[1*], Djerf H[2], Jivegård L[3], Johansson A[1], Nordanstig J[2], Svanberg T[4], Wikberg Adania U[4], Sjögren P[3]

[1] Department of Physiotherapy and Occupational therapy/Physiotherapy, Sahlgrenska University Hospital/Sahlgrenska, Gothenburg, Sweden.
[2] Department of Vascular Surgery, Sahlgrenska University Hospital/Sahlgrenska, Sweden
[3] HTA-centrum, Region Västra Götaland, Sweden.
[4] Medical library, Sahlgrenska University Hospital/Sahlgrenska, Mölndal, Gothenburg, Sweden

[*]Corresponding author

Published May 2014
2014:69

Suggested citation: Bäck M, Djerf H, Jivegård L, Johansson A, Nordanstig J, Svanberg T, Wikberg Adania U, Sjögren P. Home-based versus hospital-based supervised exercise or walk advice as treatment for intermittent claudication [Hembaserad jämfört med sjukhusbaserad handledd fysisk träning eller träningsråd som behandling vid claudicatio intermittens]. Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centrum; 2014. Regional activity-based HTA 2014:69

Table of contents

Abbreviations

GHWA	Go home and walk advice
HET	Home-based supervised exercise
HRQoL	Health-related quality of life
IC	Intermittent claudication
NS	Not significant
RCT	Randomized controlled trial
SET	Hospital-based supervised exercise
SR	Systematic review
WIQ	The walking impairment questionnaire

1. Summary of the Health Technology Assessment

Method and patient group

Intermittent claudication, the most common symptomatic presentation of peripheral arterial disease, is present in 7% of Swedish people aged 60 years or older. The progressive atherosclerotic process involves the development of stenoses and/or occlusions in the arteries propagating blood to the lower limbs. This causes effort-induced pain in the affected limb(s). Treatment is usually conservative and includes exercise therapy. Today, current practice in Sweden for patients with IC usually does not include hospital-based supervised exercise programs. A home-based supervised exercise program in a self-chosen environment might bridge the gap between the highly structured and costly hospital-based supervised exercise programs and 'go home and walk advice'.

Question at issue

Is home-based supervised exercise more effective than either unsupervised 'go home and walk advice', or hospital-based supervised exercise, for patients with intermittent claudication, in terms of walking distance, health related quality of life, symptoms, and risks associated with exercise?

Studied risks and benefits for patients

Ten articles were identified: two systematic reviews, six randomized controlled trials (RCT) and two cohort studies. The systematic reviews were only commented on.
The quality of evidence (GRADE ⊕⊕○○) was low for all conclusions.

PICO 1 Home-based supervised exercise versus 'go home and walk advice'

Maximum walking distance (or time) was studied in two RCTs and one cohort study. One of the RCTs and the cohort study showed increased maximum walking distance for home-based supervised exercise versus 'go home and walk advice'.
Conclusion: Home-based supervised exercise may improve maximum walking distance in patients with intermittent claudication compared with 'go home and walk advice'.

Pain-free walking distance (or time) was studied in two RCTs and one cohort study. One of the RCTs and the cohort study showed increased pain-free walking distance for home-based supervised exercise versus 'go home and walk advice'.
Conclusion: Home-based supervised exercise may improve pain-free walking distance in patients with intermittent claudication compared with 'go home and walk advice'.

Health-related quality of life was reported in two RCTs. One of the RCTs demonstrated significantly increased health-related quality of life for home-based supervised exercise only in the mental health domain compared with 'go home and walk advice'.
Conclusion: Home-based supervised exercise may result in little or no improvement in health-related quality of life in patients with intermittent claudication compared with 'go home and walk advice'.

Symptom change according to the walking impairment questionnaire (WIQ) was reported in two RCTs. One of the RCTs showed significantly improved results for home-based supervised exercise only in the walking speed domain at six months, compared with 'go home and walk advice'.
Conclusion: Home-based supervised exercise may result in little or no improvement in functional walking ability (as measured by the WIQ) in patients with intermittent claudication compared with 'go home and walk advice'.

Risks/complications were not reported in the included studies.

PICO 2 Home-based supervised exercise versus supervised hospital-based exercise
Maximum walking distance (or time) was reported in five RCTs and one cohort study. Two RCTs and the cohort study demonstrated less improvement in maximum walking distance for home-based supervised exercise compared with supervised hospital-based exercise.
Conclusion: Home-based supervised exercise may result in less improvement in maximum walking distance in patients with intermittent claudication compared with supervised hospital-based exercise.

Pain-free walking distance (or time) was studied in four RCTs and one cohort study. Two RCTs and the cohort study showed less improvement in pain-free walking distance for home-based supervised exercise compared with supervised hospital-based exercise.
Conclusion: Home-based supervised exercise may result in less improvement in pain-free walking distance in patients with intermittent claudication compared with supervised hospital-based exercise.

Health-related quality of life was reported in four RCTs and one cohort study. The cohort study showed significantly less improvement in adjusted mean difference for home-based supervised exercise compared with supervised hospital-based exercise in the general health domain at six months, but not in any other domains.
Conclusion: Home-based supervised exercise may result in little or no difference in health-related quality of life in patients with intermittent claudication compared with supervised hospital-based exercise.

Symptom change according to the walking impairment questionnaire was reported in two RCTs, without significant differences between the study groups.
Conclusion: Home-based supervised exercise may result in little or no difference in functional walking ability measured with the WIQ in patients with intermittent claudication compared with supervised hospital-based exercise.

Risks/complications associated with exercise were not reported in the included studies.

Ethical aspects
No major ethical consequences were identified. Even if it is based on low quality of evidence only, it may constitute an ethical dilemma whether to introduce a treatment modality which may improve the walking distance as compared with the current ‘go home and walk advice’ treatment regimen. Introduction of a supervised program that would require increased monitoring resources may lead to displacement effects for other patient groups.

Economic aspects
A reliable estimate of the total cost change is not possible, given a total lack of reliable long-term data regarding the efficacy of exercise for intermittent claudication. If home-based supervised exercise, or supervised hospital-based exercise effectively improves walking capacity, as compared with ‘go home and walk advice’ this may reduce the volume of invasive interventions for intermittent claudication, thereby possibly reducing overall costs for the treatment of intermittent claudication.

Concluding remark
Home-based supervised exercise for patients with intermittent claudication was compared with hospital-based supervised exercise, or ‘go home and walk advice’. Six RCTs and two cohort studies were identified. There is low quality of evidence (GRADE ⊕⊕○○) that home-based supervised exercise, as compared with ‘go home and walk advice’, may slightly improve maximum and pain-free walking distance and result in little or no difference in health-related quality of life, and functional walking ability. There is low quality of evidence (GRADE ⊕⊕○○) that home-based supervised exercise may lead to less improvement in both maximum and pain-free walking distance than supervised hospital-based exercise, and result in little or no difference in health-related quality of life, and functional walking ability. There are no major ethical issues, and a reliable estimate of the total cost change is not possible, due to a total lack of reliable long-term data.

2. Svensk Sammanfattning– Swedish Summary

Metod och patientgrupp

Claudicatio intermittens utgör den vanligaste symtombilden vid perifer kärlsjukdom, med en förekomst av 7% i åldersgruppen 60 år eller äldre, i Sverige. Den aterosklerotiska processen innefattar utveckling av stenoser och/eller ocklusioner i de artärer som leder blodet till benen, vilket orsakar ansträngningsinducerad smärta i benet(en). Enligt nuvarande riktlinjer utgörs förstahandsbehandling vid claudicatio intermittens av medicinsk behandling, inklusive läkemedel, behandling av riskfaktorer samt handledd fysisk träning. Gällande praxis i Sverige för patienter med claudicatio intermittens brukar inte inkludera sjukhusbaserade handledda träningsprogram, på grund av kostnadsskäl samt dålig följsamhet till träningsprogrammen. Hembaserad handledd fysisk träning, i en självvald miljö, skulle kunna överbrygga klyftan mellan de strukturerade och kostsamma sjukhusbaserade handledda träningsprogrammen och de förmodligen mindre effektiva träningsråden.

Fokuserad fråga - PICO

Är hembaserad handledd fysisk träning bättre än träningsråd eller sjukhusbaserad handledd fysisk träning avseende gångsträcka, hälsorelaterad livskvalitet, symtom, samt risker förknippade med träningen?

Resultat

Tio artiklar inkluderades: Två systematiska översikter (SR), sex randomiserade kontrollerade studier (RCT) och två kohortstudier. De åtta primärstudierna granskades med checklistor, medan de två SR kommenterades. Det vetenskapliga underlaget är begränsat (GRADE ⊕⊕◯◯) för samtliga slutsatser.

PICO 1: Hembaserad handledd fysisk träning jämfört med träningsråd

Maximal gångsträcka (eller tid) studerades i två RCT och en kohortstudie, vanligen genom att gå på en gångmatta. En RCT och en kohortstudie visade ökning av den maximala gångsträckan vid hembaserad handledd fysisk träning jämfört med träningsråd.
Slutsats: Hembaserad handledd fysisk träning kan förbättra den maximala gångsträckan hos patienter med claudicatio intermittens jämfört med träningsråd.

Smärtfri gångsträcka (eller tid) studerades i två RCT och en kohortstudie, genom att gå på gångmatta. En RCT och en kohortstudie visade ökad smärtfri gångsträcka vid hembaserad handledd fysisk träning jämfört med träningsråd.
Slutsats: Hembaserad handledd fysisk träning kan förbättra den smärtfria gångsträckan hos patienter med claudicatio intermittens jämfört med träningsråd.

Hälsorelaterad livskvalitet rapporterades i två RCT, varav en visade signifikant förbättrad hälsorelaterad livskvalitet i domänen "mental hälsa" efter sex månader av hembaserad handledd fysisk träning jämfört med träningsråd. Inga andra signifikanta skillnader sågs mellan grupperna.
Slutsats: Hembaserad handledd fysisk träning kan resultera i liten eller ingen skillnad i hälsorelaterad livskvalitet hos patienter med claudicatio intermittens jämfört med träningsråd.

Symtomförändring enligt ”the walking impairment questionnaire” rapporterades i två RCT, varav en visade signifikant förbättrade resultat för hembaserad handledd fysisk träning jämfört med träningsråd i domänen "gånghastighet". Inga andra signifikanta skillnader sågs.
Slutsats: Hembaserad handledd fysisk träning kan resultera i liten eller ingen skillnad i funktionell gångförmåga hos patienter med claudicatio intermittens jämfört med träningsråd.

Träningsrelaterade risker/komplikationer rapporterades inte i studierna.

PICO 2: Hembaserad handledd fysisk träning jämfört med sjukhusbaserad handledd fysisk träning
Maximal gångsträcka (eller tid) utvärderades i fem RCT och en kohortstudie. Gångmatta användes både för träning och utvärdering i den sjukhusbaserade, men ej i den hembaserade, handledda träningsgruppen i samtliga studier. Två RCT och en kohortstudie visade att den maximala gångsträckan vid hembaserad handledd fysisk träning ökade mindre jämfört med vid sjukhusbaserad handledd träning.
Slutsats: Hembaserad handledd fysisk träning kan resultera i att den maximala gångsträckan förbättras något mindre jämfört med sjukhusbaserade handledda träningsprogram hos patienter med claudicatio intermittens.

Smärtfri gångsträcka (eller tid) studerades i fyra RCT och en kohortstudie. Gångmatta användes för träning och utvärdering i den sjukhusbaserade, men ej i den hembaserade, handledda träningsgruppen i samtliga studier. I två RCT och en kohortstudie sågs att den smärtfria gångsträckan för hembaserad handledd fysisk träning ökade mindre jämfört med vid sjukhusbaserad handledd träning.
Slutsats: Hembaserad handledd fysisk träning kan resultera i att den smärtfria gångsträckan förbättras något mindre jämfört med sjukhusbaserade handledda träningsprogram hos patienter med claudicatio intermittens.

Hälsorelaterad livskvalitet rapporterades i fyra RCT och en kohortstudie. En kohortstudie visade signifikant förbättrad (justerad) genomsnittlig skillnad för sjukhusbaserade handledd träning avseende allmän hälsa, men inte för någon annan domän, efter sex månader jämfört med hembaserad handledd fysisk träning.
Slutsats: Hembaserad handledd fysisk träning kan resultera i liten eller ingen skillnad avseende hälsorelaterad livskvalitet hos patienter med claudicatio intermittens jämfört med sjukhusbaserad handledd träning.

Symtomförändring enligt "the walking impairment questionnaire" (WIQ) rapporterades i två RCT, utan signifikanta skillnader mellan grupperna.
Slutsats: Hembaserad handledd fysisk träning kan resultera i liten eller ingen skillnad avseende funktionell gångförmåga hos patienter med claudicatio intermittens jämfört med sjukhusbaserad handledd fysisk träning.

Träningsrelaterade risker/komplikationer rapporterades inte i studierna.

Etiska aspekter
Inga betydande etiska konsekvenser identifierades. Det kan föreligga ett etiskt dilemma i huruvida det är befogat att införa en behandlingsform, baserat på begränsat vetenskapligt underlag, som kan ge förbättrad gångsträcka (hem- eller sjukhusbaserad handledd fysisk träning) jämfört med nuvarande behandlingsregim (träningsråd). Införandet av ett handlett träningsprogram som kräver ökade handledningsresurser kan leda till undanträngningseffekter för andra patientgrupper.

Ekonomiska aspekter
Det är inte möjligt att uppskatta den totala kostnaden för införandet av handledd fysisk träning vid claudicatio intermittens, på grund av den totala avsaknaden av tillförlitliga långtidsuppföljningar av träningseffekten. Om hembaserad handledd fysisk träning eller sjukhusbaserad handledd träning förbättrar gångförmågan avsevärt jämfört med träningsråd, kan det minska volymen av invasiva ingrepp, och därmed minska de totala kostnaderna för behandling vid claudicatio intermittens.

Sammanfattande slutsats
Jämfört med träningsråd kan hembaserad handledd fysisk träning förbättra den maximala och smärtfria gångsträckan, men resultera i liten eller ingen skillnad avseende hälsorelaterad livskvalitet samt funktionell gångförmåga. Hembaserad handledd fysisk träning kan resultera i att den maximala och den smärtfria gångsträckan förbättras något mindre jämfört med sjukhusbaserade handledda träningsprogram, men resulterar i liten eller ingen skillnad avseende hälsorelaterad livskvalitet och funktionell gångförmåga hos patienter med claudicatio intermittens. Det vetenskapliga underlaget är begränsat (GRADE ⊕⊕○○).
Inga betydande etiska konsekvenser kunde identifieras, och en tillförlitlig uppskattning av den totala kostnadsförändringen är inte möjlig, på grund av avsaknad av tillförlitliga långtidsdata.

Summary of the Health Technology Assessment (1&2) from The Regional Health Technology Assessment Centre (HTA-centrum)

The Regional Health Technology Assessment Centre (HTA-centrum) of Region Västra Götaland, Sweden (VGR) has the task to make statements on HTA reports carried out in VGR. The statement should summarise the question at issue, results and quality of evidence regarding efficacy and risks, and economical and ethical aspects of the particular health technology that has been assessed in the report.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, 2014-04-23

Christina Bergh
MD, Professor
Thomas Franzén
Head of hospital library
Magnus Hakeberg
OD, Professor
Lennart Jivegård
MD, Senior university lecturer
Anders Larsson
MD, PhD

Christian Rylander
MD, PhD
Ola Samuelsson
MD, Associate professor
Ninni Sernert
Associate professor
Henrik Sjövall
MD, Professor
Petteri Sjögren
DDS, PhD

Maria Skogby
RN, PhD
Annika Strandell
MD, Associate professor
Therese Svanberg
HTA librarian
Kjell-Arne Ung
MD, Associate professor

3. Participants

The question was posed by

Johan Tjärnström, MD, PhD, at the time of the nomination, chairman, Department of Vascular Surgery, Sahlgrenska University Hospital/Sahlgrenska, Göteborg, Sweden. Currently, chairman, Section of Vascular Surgery, NU Hospital Group, Uddevalla, Sweden.

Participants from the clinical departments

Maria Bäck, RPT, PhD, Department of Physiotherapy and Occupational Therapy/Physiotherapy, Sahlgrenska University Hospital/Sahlgrenska, Göteborg, Sweden.
Henrik Djerf, MD, Department of Vascular Surgery, Sahlgrenska University Hospital/Sahlgrenska, Göteborg, Sweden.
Anna Johansson, RPT, Department of Physiotherapy and Occupational Therapy/Physiotherapy, Sahlgrenska University Hospital/Sahlgrenska, Göteborg, Sweden.
Joakim Nordanstig, MD, Department of Vascular Surgery, Sahlgrenska University Hospital/Sahlgrenska, Göteborg, Sweden.

Participants, from the HTA-centrum

Petteri Sjögren, DDS, PhD, HTA-centrum, Region Västra Götaland, Sweden.
Lennart Jivegård, MD, PhD, Associate Professor, Senior University Lecturer, HTA-centrum, Region Västra Götaland, Sweden.
Therese Svanberg, HTA librarian, HTA-centrum, Region Västra Götaland, Sweden.
Ulla Wikberg Adania, librarian, Medical library, Sahlgrenska University hospital/Mölndal, Sweden.

External reviewers

Susanne Bernhardsson, RPT, Närhälsan, Öckerö Rehabmottaging, Göteborg, PhD-student IMH, Linköping University, Sweden.
Karin Manhem, MD, Associate Professor, Senior University Lecturer, Department of Medicine, Sahlgrenska University Hospital/Sahlgrenska, Göteborg, Sweden.

Conflicts of interest for the proposer or any of the participants

None reported.

Project time

HTA was accomplished during the period of 2013-12-04 – 2014-04-23.
Literature searches were made in December 2013.

4. Intermittent Claudication – Background and Treatment

Intermittent claudication and its degree of severity

Intermittent claudication (IC) is the most common symptomatic presentation of peripheral arterial disease and represents a common manifestation of atherosclerosis. The systemic nature of the atherosclerotic process confers an increased risk for suffering severe systemic vascular complications, e.g. myocardial infarction and stroke; these risks represent the largest menace to patients with IC.

The progressive atherosclerotic process involves development of stenoses and/or occlusions in the arteries propagating blood to the lower limbs, which causes reduction in blood flow. Thus less oxygen and nutrients than needed are delivered to the affected extremity during exercise. This anaerobic metabolism in the working muscle causes pain, which is the cardinal symptom in IC, reproducibly provoked by exercise in the affected limb(s).

The severity of IC symptoms range from very mild to a very severe reduction in walking capacity, which may restrict even basic activities of daily living. Although, the risk for amputation is low, and constitutes a very rare outcome in IC, the health-related quality of life (HRQoL) is often markedly reduced in patients with IC when compared with age- and gender matched controls

☑ Risk of premature death
☑ Risk of permanent illness or damage, or reduced quality of life
☑ Risk of disability and health-related quality of life

Prevalence and incidence of intermittent claudication

Peripheral arterial disease is a common health problem that globally affects over 200 million individuals. Attributable to increasing life expectancy, the prevalence has increased substantially during the last decade. Approximately 20-40 million individuals in the world experience typical IC symptoms (Fowkes *et al*., 2013). A population-based study in Sweden reported that almost a fifth of all elderly individuals (60-90 years) showed some stage of peripheral arterial disease, and that 6.8% suffered from IC (Sigvant *et al*., 2007). Applying this frequency to Region Västra Götaland, approximately 25,000 individuals in the age 60-90 years are estimated to suffer from IC.

Present treatment of intermittent claudication

The generally used first line therapy for IC in Sweden is medical therapy, including pharmacological treatment (platelet inhibitors, lipid-lowering therapy, treatment of hypertension and diabetes), risk factor management (including smoking cessation) and an unsupervised ’go home and walk‘ advice (GHWA). This treatment strategy is applied in both primary care and at the vascular surgical outpatient clinic. The patients that are evaluated by a vascular surgeon are also commonly referred for further follow-up and continuous risk factor modifying interventions within primary care.

Number of patients per year who undergo current treatment regimen

Many of the patients with IC are treated conservatively in primary care and there are no available national estimates of the total number of patients that undergo the current treatment regimen (described above). The number of individuals with IC in Sweden can be estimated to 150,000 to 200,000. At the Department of Vascular Surgery (Sahlgrenska University Hospital), approximately 200 patients with suspected IC are annually referred to the vascular surgical outpatient clinic, mainly from primary care. In approximately 150 of these patients the diagnosis of IC is confirmed, and the current treatment regimen is offered. An estimated 275 patients with IC are also referred annually from primary care to the vascular surgery outpatient clinics in SÄS, SKAS and NU Hospital Groups.

The normal pathway of a patient through the health care system

A majority of the patients with IC seek medical attention within primary care, where probably a large proportion of these patients are also managed. Referral to the vascular surgical outpatient clinic is considered e.g. when the patient demonstrates more disabling or otherwise more alarming symptoms that may require evaluation by a vascular surgeon. British guidelines recommend that all patients with IC should be offered a hospital-based (within physiotherapy departments) supervised exercise (SET) to reduce leg symptoms, as this treatment option has been shown to generate a better short-term outcome than traditional ‘go home and walk’ advice (GHWA) (NICE, 2012). This approach is recommended *before* considering vascular surgery. Currently, SET programs are scarce in Sweden, and not available in Region Västra Götaland. Home-based supervised exercise (HET) may represent an intermediate alterative, but is not currently provided in Region Västra Götaland.

Actual wait time in days for medical assessment /treatment

The actual wait time for IC patients referred from primary health care to the vascular outpatient clinic is within the stipulated time-frame of three months.

5. Home-based supervised exercise for treatment of intermittent claudication

Home-based supervised exercise

The design of the HET intervention program differs between studies and it seems there is no single established HET modality. Most typically, however, the program includes interval walking until claudication pain with a total duration of 20-40 minutes, three days/week and with follow-up after three or six months. The program also consists of regular follow-up visits and/or telephone calls to give feedback to the patient and upgrade the exercise program. Adherence to exercise in these studies is often controlled with a step activity monitor and/or an exercise diary.

The work group's understanding of the potential value of the health technology

The benefits of SET for patients with IC have almost exclusively been studied in hospital-based SET programs that include treadmill walking as training modality. A systematic review from the National Institute for Health and Care Excellence (NICE, 2012) has shown that SET improves the maximum and pain-free walking distance and health related quality of life (HRQoL) after six months, compared with an unsupervised GHWA and therefore SET is recommended as the initial treatment for patients with IC.

During the 1980s, SET was offered to patients with IC at the Sahlgrenska University Hospital. Today, SET is not included in routine clinical practice for patients with IC. Instead the patients are usually recommended a structured but not formally supervised GHWA, in combination with medical therapy.

Despite the accumulating evidence of the positive effects of SET for patients with IC, it remains an underutilized intervention. Several potential limitations of SET have been discussed in the literature, such as poor long-term adherence to the exercise protocol. In the systematic review by NICE (2012), it was also estimated that the adherence to SET after 12 months was only 22-37%. Thus, the question arises whether a HET-program in a self-chosen environment could bridge the gap between the highly structured and costly SET-programs and the simpler and less effective GHWA. If HET-programs have better or similar long-term (≥12 months) efficacy as SET-programs, they can be considered an alternative treatment strategy for patients with IC.

Diagnosis: Intermittent claudication, I73.9B

Treatment: Home-based exercise

The central question for the current HTA project

Is home-based supervised exercise (HET) more effective than either unsupervised 'go home and walk' advice (GHWA) or hospital-based supervised exercise (SET), for patients with intermittent claudication, in terms of walking distance, health related quality of life, symptoms, and risks associated with exercise?

PICO P= Patients, I= Intervention, C= Comparison, O=Outcome

P = Adult patients with intermittent claudication with current symptoms during 6 months (not recently operated)

I = Home-based supervised exercise

C1= Go home and walk advice

C2= Hospital-based supervised exercise

O = <u>Critical for decision making</u>
Maximum walking distance (or time)
Pain-free walking distance (or time)
Health-related quality of life

<u>Important but not critical for decision making</u>
Symptom change according to the walking impairment questionnaire (WIQ).
Risks/complications associated with exercise

6. Review of Quality of Evidence

Search strategy, study selection and references (Appendix 1)

In December 2013 two librarians (TS, UWA) performed systematic searches in PubMed, EMBASE, ProQuest, AMED, the Cochrane Library, and a number of HTA databases. Reference lists of relevant articles were also scrutinized for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in Appendix 1. The librarians conducted the literature searches, selected studies and independently assessed the obtained abstracts and a first selection of full-text articles for inclusion and exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to the participants that read the articles independently, and decided in a consensus meeting which articles that should be included.
The literature search identified a total of 531 articles (after removal of duplicates). The librarians then excluded 493 articles after reading their abstracts. Another 38 articles were excluded by the librarians after reading the articles in full text. The remaining 20 articles were sent to the work group, and 10 of them were finally included in the report. Six articles were RCTs and two were cohort studies. Two articles were systematic reviews that were only commented on. The primary publications were critically appraised using checklists from SBU (Swedish Council on Health Technology Assessment). The included studies are presented in Appendix 2, and the excluded articles in Appendix 3.

Ongoing research

A search in ClinicalTrials database (www.clinicaltrials.gov), January 31 2014, using the search terms *(claudication intermittent OR peripheral arterial disease* OR peripheral artery disease* OR peripheral atherosclerotic disease* OR PAD)* **AND** *(exercise OR walking OR training OR treadmill)* **AND** *(home-based OR home-training OR supervised OR supervision OR non-supervised OR advice)* identified 75 studies. Four studies were considered relevant for the PICOs in this report.

NCT00279994: Netherlands. RCT to determine if SET in a physiotherapy unit setting, with or without therapy feedback, is more (cost-) effective than exercise therapy based on a GHWA, for patients with IC stage II (Fontaine). Recruitment status unknown (updated 2008).

NCT02022423: USA. RCT to test an automated Internet-based walking program with a social media component, to improve long-term adherence to walking, walking distance, and health-related quality of life. Patients with PAD. Not open for recruitment, last verified in Dec 2013. Estimated start: Jan 2014.

NCT00618670: USA. RCT to examine the effects of a HET rehabilitation program compared with a SET on IC. Recruitment status unknown, verified December 2009.

NCT00693940: USA. RCT on the effectiveness of a home-based group mediated cognitive behavioral exercise program in helping people with lower extremity PAD to increase walking frequency and improve lower leg functioning, compared with weekly educational sessions. Ongoing, but not recruiting. Last updated, April 2013. Estimated completion date December 2012.

Medical societies or health authorities that recommend supervised exercise for treatment of intermittent claudication

☐ The National Board of Health and Welfare
☑ Medical societies
☐ Other health authority

The recently published guidelines from the UK NICE institute recommend that a supervised exercise programme should be offered to all people with intermittent claudication; however the guideline does not specify whether the program should be hospital-based or home-based (NICE, 2012).

The Transatlantic Society Consensus Document II (TASC-II) document states that 'Supervised exercise should be made available as part of the initial treatment for all patients with peripheral arterial disease (Norgren *et al*., 2007). These international guidelines also suggest that 'some level of supervision' is necessary to achieve optimal results.

In a systematic review from 2007, The Swedish Council on Technology Assessment in Health Care concluded that 'Physical training, walking or Nordic walking - particular when organized or supervised – improves walking distance' (SBU, 2007).

Present knowledge of home-based supervised exercise for treatment of intermittent claudication

Ten articles fulfilled the inclusion criteria: two systematic reviews (SR), six randomized controlled trials (RCT) and two cohort studies. The systematic reviews were only commented on. The systematic review by Makris *et al*. (2012), identified 12 studies (4 RCT and 6 cohort) that investigated the effectiveness of HET. In addition to the studies identified in this HTA, also smaller non-randomized studies were included, as well as studies that did not concur with the comparisons of the current PICO. In three studies, SET was superior to HET in improving functional capacity, but the two interventions were considered equivalent in improvements of HRQoL. Compared with GHWA and baseline measurements, HET significantly improved important aspects of functional capacity and QoL markers. The authors concluded that HET may be an effective alternative when SET is not available, but further research to establish the cost-effectiveness is warranted.

Also in the other SR by Al-Jundi *et al*. (2013) smaller non-randomized studies were included, as well as studies that did not concur with the comparisons of the current PICO. Al-Jundi *et al*. (2013) evaluated the effectiveness of HET and included 17 studies (9 RCT and 8 cohort), concluding that there is low-quality evidence that HET can improve walking capacity and HRQoL when compared with GHWA, and that the long-term clinical effect and cost-effectiveness are uncertain.

PICO 1: Home-based supervised exercise (HET) vs. 'go home and walk advice' (GHWA)

Maximum walking distance (or time) (Appendix 4:1, Appendix 5)

Two RCTs and one cohort study reported maximum walking distance. Maximum walking distance was most commonly evaluated with a graded treadmill test. Some studies reported this outcome in distance and others in time. One RCT and the cohort study showed increased maximum walking distance/time for HET versus GHWA (+124s vs. -10s, $p<0.05$ at 3 months, and +83 meters vs. + 44 meters, $p<0.0001$ at 6 months, respectively). The second RCT showed no significant differences between groups.

Conclusion: HET may improve the maximum walking distance in patients with intermittent claudication compared with GHWA. Low quality of evidence (GRADE ⊕⊕◯◯)

Pain-free walking distance (or time) (Appendix 4:2, Appendix 5)

Two RCTs and one cohort study reported pain-free walking distance. Pain-free walking distance was most commonly evaluated with a graded treadmill test. Some studies reported this outcome in distance and others in time. One RCT and the cohort study showed increased pain-free walking distance for HET versus GHWA (+134s vs. -16s, $p<0.05$ at 3 months, and +51 meters vs. + 27 meters, $p<0.0001$ at 6 months, respectively). The second RCT showed no significant differences between groups.

Conclusion: HET may improve the pain-free walking distance in patients with intermittent claudication compared with GHWA. Low quality of evidence (GRADE ⊕⊕◯◯)

Health-related quality of life (HRQoL) (Appendix 4:3, Appendix 5)

Two RCTs reported HRQoL with Short-Form 36 (SF-36). One study demonstrated significantly increased HRQoL for HET in the mental health domain, but in no other domain, at 6 months, compared with GHWA (+3.2 vs. -2.4, $p<0.01$). The other RCT showed no significant differences between groups.

Conclusion: HET may result in little or no difference in HRQoL in patients with intermittent claudication compared with GHWA. Low quality of evidence (GRADE ⊕⊕◯◯)

Symptom change - Walking impairment questionnaire (WIQ) (Appendix 4:4, Appendix 5)
Two RCTs rated patient reported functional walking ability with the WIQ. One study showed significantly improved results for HET in the walking speed domain, but in no other domain, of the WIQ at six months, compared with GHWA (+5.7 vs. -1.9 WIQ scores, p=0.034). The other RCT showed no significant differences between groups.
Conclusion: HET may result in little or no improvement in the functional walking ability (WIQ) compared with GHWA. Low quality of evidence (GRADE ⊕⊕◯◯)

Risks/complications associated with exercise
The outcome was not studied.

PICO 2: Home-based supervised exercise (HET) vs. hospital-based supervised exercise (SET)

Maximum walking distance (or time) (Appendix 4:5, Appendix 5)
Five RCTs and one cohort study reported maximum walking distance. Maximum walking distance was evaluated with a treadmill test, and treadmill walking was used as a training modality in the SET groups. Some studies reported this outcome in distance and others in time. Two RCTs and one cohort study demonstrated less improvement in maximum walking distance/time for HET compared with SET. Three RCTs showed no significant differences between the groups.
Conclusion: HET may result in less improvement in maximum walking distance in patients with intermittent claudication compared with SET. Low quality of evidence (GRADE ⊕⊕◯◯)

Pain-free walking distance (or time) (Appendix 4:6, Appendix 5)
Four RCT studies and one cohort study reported pain-free walking distance. Pain-free walking distance was evaluated with a treadmill test, and treadmill walking was used as a training modality in the SET groups. Some studies reported this outcome in distance and others in time. Two RCTs showed no significant differences between groups. Two RCTs and the cohort study showed less improvement in pain-free walking distance for HET compared with SET.
Conclusion: HET may result in less improvement in pain-free walking distance in patients with intermittent claudication compared with SET. Low quality of evidence (GRADE ⊕⊕◯◯)

Health-related quality of life (HRQoL) (Appendix 4:7, Appendix 5)
Four RCTs and one cohort study reported HRQoL with SF-36 or SF-20.
The cohort study showed significantly improved adjusted mean difference for SET versus HET in the general health domain at six months (8.39, p<0.03), but not in any other domain. The RCTs demonstrated no significant differences between the groups regarding HRQoL.
Conclusion: HET may result in little or no difference in HRQoL in patients with intermittent claudication, compared with SET. Low quality of evidence (GRADE ⊕⊕◯◯)

Symptom change - Walking impairment questionnaire (WIQ) (Appendix 4:8, Appendix 5)
Two RCTs rated patient reported functional walking ability with the WIQ, without significant differences between the study groups.
Conclusion: HET may result in little or no difference in functional walking ability measured with the WIQ in patients with intermittent claudication compared with SET.
Low quality of evidence (GRADE ⊕⊕◯◯)

Risks/complications associated with exercise
The outcome was not studied.

7. Ethical consequences

No major ethical consequences were identified. Based on low quality of evidence only, it may constitute an ethical dilemma whether to introduce a treatment modality which may improve the walking distance as compared with the current ‘go home and walk advice’ treatment regimen. On the other hand, introduction of a supervised program would require increased monitoring resources, and may lead to displacement effects for other patient groups.

8. Organisation

When HET can be put into practice

An organization to provide HET could be established within 6-12 months.

Use of HET in other hospitals in Region Västra Götaland of Sweden

Not to our knowledge.

Consequences of implementation of HET for personnel, according to the work group

Currently, patients with IC are not offered exercise at physiotherapy departments in Region Västra Götaland. If exercise is to be implemented as part of routine care for patients with IC, educational efforts for physiotherapists are needed.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland of Sweden

Uncertain at the present time. If HET is shown to be an effective treatment regimen for patients with IC, physiotherapy clinics in Region Västra Götaland may be encouraged to introduce this treatment. If a HET-program is introduced and it effectively increases walking capacity and HRQoL, a possible consequence may be fewer invasive interventions for IC. This would also reduce the numbers at risk for suffering procedure-related complications during vascular surgery.

9. Economic aspects

Present costs of currently used technologies

Currently, patients with IC at the Sahlgrenska University Hospital vascular surgical department are evaluated by a vascular surgeon and are given a structured GHWA, in combination with medical therapy and risk factor modification. It is also common that the vascular surgeon re-evaluates the patient within six or 12 months. The cost of GHWA is virtually non-existent, since the intervention only includes verbal information and a patient brochure. Patients are also commonly referred for further follow-up and continuous risk factor modification efforts in primary care.
A first-visit for evaluation at the vascular surgical outpatient clinic costs approximately 5,900 SEK. The regular follow-up visit is estimated to 4,300 SEK. In addition, costs for prescribed drugs, smoking cessation therapy and continuous follow-up within primary care at an annual basis should be added.

Expected costs of the new health technology

The stated costs in this section are to be added to the current cost estimate (stated above) which remains unchanged even if the new technology is introduced.
Physiotherapy visit for tests and review of a home-based exercise program of 60 min (280 SEK/h), at start, at three months, at six months and at one year follow-up = 1,120 SEK.
Telephone-based follow-ups 30 min every other week during 12 months = 1,680 SEK.
Walking sticks (500 SEK), and an accelerometer (4,000 SEK)
Total cost = 7,300 SEK per patient.
With approximately 150 patients a year, at the Sahlgrenska University Hospital, the added cost is estimated to 1,095,000 SEK.

Total change of cost

A reliable estimate of total cost change is not possible, given the lack of reliable long-term data with regard to efficacy of supervised exercise programs in patients with IC. Tentatively, the introduction of HET that may effectively improve walking capacity would result in a reduction in the volume of vascular surgical interventions undertaken in this patient group, and hence potential cost-reductions for vascular surgical interventions.

Possibility to adopt and use the new technology within the present budget
No.

Available analyses of health economy, cost advantages or disadvantages

There is no cost-effectiveness analysis on HET in patients with IC.

10. Unanswered questions

Important gaps in scientific knowledge

The effectiveness of HET for the here studied outcomes are supported by low quality of evidence, and long-term data are scarce. Therefore, future high quality RCT studies with more than six months follow-up are needed. The heterogeneity of study designs, exercise programs and outcome variables, in the identified studies motivate further clinical trials to establish the most optimal exercise program design for these patients. Although SET is today considered the gold standard, data on long-term (> 6 months) results and adherence to SET programmes are absent, and relevant comparisons of SET, HET and GHWA are needed. Commonly, in the identified trials the SET groups were both trained and evaluated on a graded treadmill, while the HET and unsupervised control groups exercised in other, or 'real life' circumstances, which contributed with bias. The testing and training procedures must be separated in future studies, to allow evaluation of the effects of different exercise designs and settings.

Interest to start studies or trials within the research field at issue

Based on the present information, a three-armed RCT with 12 months follow-up comparing the effectiveness of HET, SET and GHWA regarding walking distance, muscle endurance, adherence to exercise, HRQoL, the WIQ and economy aspects for patients with IC is planned. This study is a multicenter study with collaboration between physiotherapists and vascular surgeons at the Sahlgrenska University Hospital (Göteborg) and the Södra Älvsborg Hospital (Borås).

Appendix 1, Search strategy, study selection and references

Question at issue: Is home-based supervised exercise (HET) more effective than either unsupervised 'go home and walk' advice (GHWA) or hospital-based supervised exercise (SET), for patients with intermittent claudication, in terms of walking distance, health related quality of life, symptoms, and risks associated with exercise?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P = Adult patients with intermittent claudication with current symptoms during 6 months (not recently operated)

I = Home-based supervised exercise

C1 = Go home and walk advice
C2 = Hospital-based supervised exercise

O = *Critical for decision making*
Maximum walking distance (or time), pain free walking distance (or time), healthrelated quality of life (HRQoL)

Important but not critical for decision making
Symptom change according to walking impairment questionnaire (WIQ)
Risks/complications associated with exercise

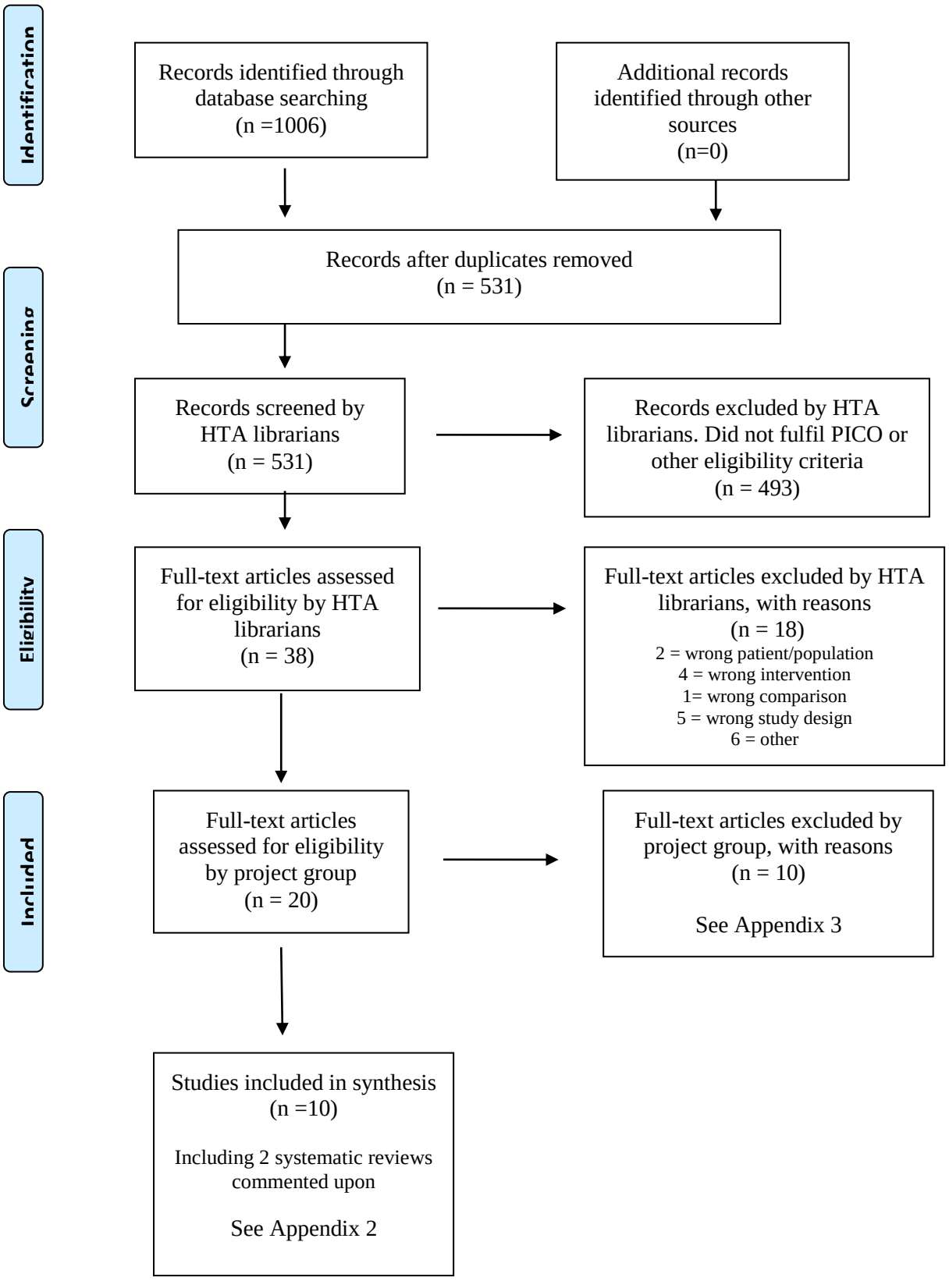
Eligibility criteria

Study design:
Systematic reviews
Randomized controlled trials
Non-randomized controlled studies with more than 100 patients

Language:
English, Swedish, Norwegian, Danish

Publication date: No limit

Selection process – flow diagram



Search strategies

Database: PubMed
Date: 2013-12-13
No of results: 333 results

Search	Query	Items found
#41	**Search #35 NOT #36 Filters: Danish; English; Norwegian; Swedish**	**333**
#38	Search #35 NOT #36	357
#36	Search Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp] OR case reports[ptyp]	2757549
#35	Search #34 AND #33 AND #31	372
#33	Search #16 OR #32	29486
#34	Search home-training[tiab] OR home[tiab] OR home-based[tiab] OR home based[tiab] OR supervised[tiab] OR supervision[tiab] OR non-supervised[tiab] OR non supervised[tiab] OR unsupervised[tiab] OR community-based[tiab] OR community based[tiab] OR advice[tiab]	232545
#32	Search claudication[Title/Abstract] OR peripheral arterial disease*[Title/Abstract] OR peripheral artery disease*[Title/Abstract] OR peripheral atherosclerotic disease*[Title/Abstract] OR PAD[Title/Abstract]	26182
#16	Search "Peripheral Arterial Disease"[Mesh] OR "Intermittent Claudication"[Mesh]	8271
#31	Search #28 OR #19	433402
#28	Search walking[Title/Abstract] OR exercise[Title/Abstract] OR treadmill[Title/Abstract] OR training[Title/Abstract]	417211
#19	Search "Exercise Therapy"[Mesh] OR "Walking"[Mesh]	44990

Database: EMBASE (OVID SP)
Date: 2013-12-13
No of results: 305 results

#	Searches	Results
1	exp kinesiotherapy/	46010
2	exp walking/	57979
3	(exercise or walking or treadmill or training).ti,ab.	511224
4	1 or 2 or 3	557349
5	exp peripheral occlusive artery disease/	114319
6	exp intermittent claudication/	8195
7	(claudication or peripheral arterial disease$ or peripheral artery disease$ or peripheral atherosclerotic disease$ or PAD).ti,ab.	34113
8	5 or 6 or 7	136648
9	(home-training or home or home-based or home based or supervised or supervision or non-supervised or non supervised or unsupervised or community-based or community based or advice).ti,ab.	291359
10	4 and 8 and 9	552
11	**limit 10 to (embase and (danish or english or norwegian or swedish) and (article or conference paper or "review"))**	**305**

Database: ProQuest Nursing & Allied Health Source
Date: 2013-12-13
No of results: 146 results

#	Searches	Results
S4	**S1 AND S2 AND S3**	**146**
S3	Ab(home-training OR home OR home-based OR home based OR supervised OR supervision OR non-supervised OR non supervised OR unsupervised OR community-based OR community based OR advice) OR ti(home-training OR home OR home-based OR home based OR supervised OR supervision OR non-supervised OR non supervised OR unsupervised OR community-based OR community based OR advice)	133264
S2	Ab(exercise OR walking OR training OR treadmill) OR ti(erercise OR walking OR training OR treadmill)	128285
S1	Ab(claudication OR peripheral arterial disease* OR peripheral artery disease* OR peripheral Atherosclerotic disease* OR PAD) OR ti(claudication OR peripheral arterial disease* OR peripheral artery disease* OR peripheral atherosclerotic disease* OR PAD	9203

Database: AMED (EBSCO)
Date: 2013-12-13
No of results: 22 results

#	Searches	Results
S4	**S1 AND S2 AND S3**	**22**
S3	TI (home-training OR home OR home-based OR home based OR supervised OR supervision OR non-supervised OR non supervised OR unsupervised OR community-based OR community based OR advice) OR AB (home-training OR home OR home-based OR home based OR supervised OR supervision OR non-supervised OR non supervised OR unsupervised OR community-based OR community based OR advice) OR KW home-training OR home OR home-based OR home based OR supervised OR supervision OR non-supervised OR non supervised OR unsupervised OR community-based OR community based OR advice)	11665
S2	TI (exercise OR walking OR training OR treadmill) OR AB (exercise OR walking OR training OR treadmill) OR KW (exercise OR walking OR training OR treadmill)	31801
S1	TI (claudication OR peripheral arterial disease* OR peripheral artery disease* OR peripheral atherosclerotic disease* OR PAD) OR AB (claudication OR peripheral arterial disease* OR peripheral artery disease* OR peripheral atherosclerotic disease* OR PAD) OR KW (claudication OR peripheral arterial disease* OR peripheral artery disease* OR peripheral atherosclerotic disease* OR PAD)	516

Database: The Cochrane Library
Date: 2013-12-13
No of results: 168 results
Cochrane reviews 12
Other reviews 2
Trials 148
Technology assessments 1
Economic evaluations 5

ID	Search	Hits
#1	claudication or peripheral arterial disease* or peripheral artery disease* or peripheral atherosclerotic disease* or PAD:ti,ab,kw (Word variations have been searched)	4067
#2	exercise or walking or training or treadmill:ti,ab,kw (Word variations have been searched)	56169
#3	#1 and #2	1175
#4	home-training or home or home-based or home based or supervised or supervision or non-supervised or non supervised or unsupervised or community-based or community based or advice:ti,ab,kw (Word variations have been searched)	22997
#5	**#3 and #4**	**168**

Database: CRD
Date: 2013-12-13
No of results: 32 results
DARE = 20
NHS EED = 10
HTA = 2

ID	Search	Hits
#1	(claudication OR peripheral arterial disease* OR peripheral artery disease* OR peripheral atherosclerotic disease* OR PAD)	373
#2	(exercise OR walking OR training OR treadmill)	5186
#3	(exercise OR walking OR training OR treadmill)	139
#4	(home-training OR home OR home-based OR home based OR supervised OR supervision OR non-supervised OR non supervised OR unsupervised OR community-based OR community based OR advice)	4176
#5	**#1 AND #2 AND #4**	**32**

The web-sites of **SBU, Kunnskapssenteret** and **Sundhedsstyrelsen** were visited 2014-03-21
One reference partly relevant to the question at issue was found.

Reference lists
A comprehensive review of reference lists brought no new records

---

Reference lists

Included studies:

Collins TC, Lunos S, Carlson T, Henderson K, Lightbourne M, Nelson B, et al. Effects of a home-based walking intervention on mobility and quality of life in people with diabetes and peripheral arterial disease: a randomized controlled trial. Diabetes Care. 2011;34(10):2174-9

Fakhry F, Spronk S, De Ridder M, Den Hoed PT, Hunink MGM. Long-term effects of structured home-based exercise program on functional capacity and quality of life in patients with intermittent claudication. Archives of Physical Medicine and Rehabilitation. 2011;92(7):1066-73.

Gardner AW, Parker DE, Montgomery PS, Scott KJ, Blevins SM. Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication: a randomized controlled trial. Circulation. 2011;123(5):491-8.

Manfredini F, Malagoni AM, Mascoli F, Mandini S, Taddia MC, Basaglia N, et al. Training rather than walking: the test in -train out program for home-based rehabilitation in peripheral arteriopathy. Circ J. 2008;72(6):946-52.

Patterson RB, Pinto B, Marcus B, Colucci A, Braun T, Roberts M, et al. Value of a supervised exercise program for the therapy of arterial claudication. Journal of Vascular Surgery. 1997;25(2):312-9.

Regensteiner JG, Meyer TJ, Krupski WC, Cranford LS, Hiatt WR. Hospital vs home-based exercise rehabilitation for patients with peripheral arterial occlusive disease. Angiology. 1997;48(4):291-300.

Sandercock GR, Hodges LD, Das SK, Brodie DA. The impact of short term supervised and home-based walking programmes on heart rate variability in patients with peripheral arterial disease. J Sports Sci Med. 2007;6(4):471-6.

Savage P, Ricci MA, Lynn M, Gardner A, Knight S, Brochu M, et al. Effects of home versus supervised exercise for patients with intermittent claudication. J Cardiopulm Rehabil. 2001;21(3):152-157.

Systematic reviews, no appraisal done, only commented on:

Al-Jundi W, Madbak K, Beard JD, Nawaz S, Tew GA. Systematic Review of Home-based Exercise Programmes for Individuals with Intermittent Claudication. Eur J Vasc Endovasc Surg. 2013;46(6):690-706.

Makris GC, Lattimer CR, Lavida A, Geroulakos G. Availability of supervised exercise programs and the role of structured home-based exercise in peripheral arterial disease. Eur J Vasc Endovasc Surg. 2012;44(6):569-75; discussion 76.

Excluded studies:

Bermingham SL, Sparrow K, Mullis R, Fox M, Shearman C, Bradbury A, et al. The Cost-effectiveness of Supervised Exercise for the Treatment of Intermittent Claudication. Eur J Vasc Endovasc Surg. 2013;46(6):707-14.

Fokkenrood HJ, Bendermacher BL, Lauret GJ, Willigendael EM, Prins MH, Teijink JA. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. Cochrane Database Syst Rev. 2013;8:Cd005263.

Gardner AW, Parker DE, Montgomery PS, Blevins SM. Diabetic women are poor responders to exercise rehabilitation in the treatment of claudication. J Vasc Surg. 2013 Nov 20. [Epub ahead of print]

Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain: a meta-analysis. Jama. 1995;274(12):975-80.

Langbein WE, Collins EG, Orebaugh C, Maloney C, Williams KJ, Littooy FN, et al. Increasing exercise tolerance of persons limited by claudication pain using polestriding. J Vasc Surg. 2002;35(5):887-93.

McDermott MM, Liu K, Guralnik JM, Criqui MH, Spring B, Tian L, et al. Home-based walking exercise intervention in peripheral artery disease: a randomized clinical trial. Jama. 2013;310(1):57-65.

Nicolai SP, Teijink JA, Prins MH. Multicenter randomized clinical trial of supervised exercise therapy with or without feedback versus walking advice for intermittent claudication. J Vasc Surg. 2010;52(2):348-55.

Nielsen SL, Larsen B, Prahl M, Jensen CT, Jensen BE, Wenkens V. [Hospital training compared with home training in patients with intermittent claudication]. Ugeskr Laeger. 1977;139(46):2733-6.

Pinto BM, Marcus BH, Patterson RB, Roberts M, Colucci A, Braun C. On-site versus home exercise programs: psychological benefits for individuals with arterial claudication. Journal of Aging & Physical Activity. 1997;5(4):311-28.

Wind J, Koelemay MJ. Exercise therapy and the additional effect of supervision on exercise therapy in patients with intermittent claudication. Systematic review of randomised controlled trials. Eur J Vasc Endovasc Surg. 2007;34(1):1-9.

Other references:

[Checklist from SBU regarding cohort studies. Version 2010:1]. [Internet]. [cited 2014 Mar 21] Available from: http://www.sahlgrenska.se/upload/SU/HTA-centrum/Hj%c3%a4lpmedel%20under%20projektet/B03_Granskningsmall%20f%c3%b6r%20kohortstudier%20med%20kontrollgrupper.doc

[Checklists from SBU regarding randomized controlled trials. [Internet]. [cited 2014 Mar 21] Available from: http://www.sahlgrenska.se/upload/SU/HTA-centrum/Hj%c3%a4lpmedel%20under%20projektet/1/B02_Granskningsmall%20f%c3%b6r%20randomiserad%20kontrollerad%20pr%c3%b6vning%20modifierad%20OS%20IT.doc

Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013 Oct 19;382(9901):1329-40.

GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490-4.

GRADE Working Group. List of GRADE working group publications and grants [Internet]. [Place unknown]: GRADE Working Group, c2005-2009 [cited 2012 Mar 8]. Available from: http://www.gradeworkinggroup.org/publications/index.htm

Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097.

National Institute for Health and Care Exellence. Lower limb peripheral arterial disease : diagnosis and management. National clinical guideline centre. Nice Clinical Guideline ; 147. London: National Institute for Health and Care Exellence, 2012.

Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-society consensus for the management of peripheral arterial disease (tasc ii). J Vasc Surg. 2007;45 Suppl S:S5-67

Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Andersson B, Persson E, et al. A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. J Vasc Surg. 2007 Jun;45(6):1185-91.

Statens beredning för medicinsk utvärdering. Benartärsjukdom - diagnostik och behandling: en systematisk litteraturöversikt. Stockholm: Statens beredning för medicinsk utvärdering (SBU); 2007.

Project: Exercise training programs in intermittent claudication
Appendix 2: Included primary publications - Design and patient characteristics.

Author, Year, Country	Study Design	Follow-up period	Study Groups; Intervention vs control	Patients (n)	Mean age (years)	Men/women	Outcome variables
Collins, 2011 USA	RCT	6 months	I = HET C1 = Go home and walk advise	145	67	100/45	Maximum walking distance Pain free walking distance HRQoL WIQ
Gardner, 2011 USA	RCT	3 months	I = HET C1 = Go home and walk advise C2 = SET	119	65	57/62	Maximum walking distance Pain free walking distance HRQoL WIQ
Patterson, 1997 USA	RCT	6 months	I = HET C2 = SET	60*	69	29/26	Maximum walking distance Pain free walking distance HRQoL
Regensteiner, 1997 USA	RCT	3 months	I = HET C2 = SET	20	64	Not reported	Maximum walking distance Pain free walking distance HRQoL WIQ
Sandercock, 2007 UK	RCT	3 months	I = HET C2 = SET	50†	62-67 group means	32/12	Maximum walking distance
Savage, 2001 USA	RCT	6 months	I = HET C2 = SET	21	66	15/6	Maximum walking distance Pain free walking distance HRQoL
Fakhry, 2011 The Netherlands	Cohort	12 months	I = HET C2 = SET	217	67-68 group means	135/82	Maximum walking distance Pain free walking distance HRQoL
Manfredini, 2008 Italy	Cohort	6 months	I = HET C1 = Go home and walk advise	143	68	117/26	Maximum walking distance Pain free walking distance

HET = Home-based supervised exercise. HRQoL = Health related quality of life. SET = Hospital-based supervised exercise. WIQ = Walking impairment questionnaire.

* Five patients were excluded at onset, after randomization (i.e. 55 were included in baseline data).

† Data for 44 patients presented in baseline characteristics.

Project: Exercise training programs in intermittent claudication
Appendix 3: Excluded studies

Study (author, publication year)	Reason for exclusion
Bermingham, 2013	Not concurrent with PICO, wrong outcome.
Fokkenrood, 2013	Not concurrent with PICO, wrong intervention.
Gardner, 2013	Not concurrent with PICO, wrong intervention and comparison.
Gardner, 1995	Not concurrent with PICO, no comparison.
Langbein, 2002	Not concurrent with PICO, wrong intervention.
McDermott, 2013	Not concurrent with PICO, wrong intervention.
Nicolai, 2010	Not concurrent with PICO, wrong intervention.
Nielsen, 1977	Not concurrent with PICO, wrong intervention.
Pinto, 1997	Duplicate publication Patterson 1997
Wind, 2007	Not concurrent with PICO, wrong intervention.

Project: Exercise programs in intermittent claudication
Appendix 4:1. PICO 1 - Home-based supervised exercise vs. go home and walk advice
Outcome variable: Maximum walking distance

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Collins, 2011	USA	RCT	n=145 I=72 C1=73	19	MWD at six months: Δ +24.5 (se 19.6) m	MWD at six months: Δ +39.2 (se 19.6) m ns. between groups	Patients with PAD + diabetes. HET vs. 'standard care' (=no formal training advice) Outcome retrieved by graded treadmill testing (Gardner protocol)	+	?/-	?/+
Gardner, 2011	USA	RCT	n=79 I=40 C1=39	I=11 C1=9	PWT at three months: Δ +124 (sd 193) s	PWT at three months: Δ-10 (sd 176) s p<0.05 between groups	Three study arms (SET, HET, 'standard care') Outcome retrieved by during graded treadmill protocol (Gardner protocol)	+	+	-
Manfredini, 2008	Italy	Prospective cohort study	n=143 I=74 C1=52	I=8 C1=9	ACD at six months: Δ +83 m	ACD at six months: Δ +44 m p=0.0001, between groups	Outcome: absolute claudication distance Monthly check-ups at hospital in home-based SET Outcome retrieved during graded treadmill testing (constant speed)	?	?/-	?

ACD = Absolute claudication distance. HET = Home-based supervised exercise. MWD = Maximum walking distance. PWT = Peak walking time. SET = Supervised hospital-based exercise.

Project: Exercise programs in intermittent claudication
Appendix 4:2. PICO 1 - Home-based supervised exercise vs. go home and walk advice
Outcome variable: Pain-free walking distance

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Collins, 2011	USA	RCT	n=145 I=72 C1=73	19	ICD at six months: Δ +66.7 (se 12.0) m	ICD at six months: Δ +52.3 m (se 23.6) m ns. between groups	Patients with PAD + diabetes. HET vs. ”standard care” (=no formal training advice) Outcome retrieved by graded treadmill testing (Gardner protocol)	+	?/-	?/+
Gardner, 2011	USA	RCT	n=79 I=40 C1=39	I=11 C1=9	COT at three months: Δ +134 (sd 197) s	COT at three months: Δ -16 (sd 125) s p<0.05 between groups	Three study arms (SET, HET, ”standard care”) Outcome retrieved by during graded treadmill protocol (constant speed)	+	+	-
Manfredini, 2008	Italy	Cohort study	n=143 I=74 C1=52	I=8 C1=9	ICD at six months: Δ +51 m	ICD at six months: Δ +27 m p<0.001 between groups	Monthly check-ups at hospital in home-based SET Outcome retrieved during graded treadmill testing (constant speed)	?	?/-	?

COT = Claudication onset time. HET = Home-based supervised exercise. ICD = Initial claudication distance. SET = Supervised hospital-based exercise.

Project: Exercise programs in intermittent claudication
Appendix 4:3. PICO 1 - Home-based supervised exercise vs. go home and walk advice
Outcome variable: Health-related quality of life

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Collins, 2011	USA	RCT	n=145 I=72 C1=73	19	SF-36 mental health domain at six months: Δ 3.2 (se 1.5)	SF-36 mental health domain at six months: Δ -2.4 (se 1.5) p=0.01 between groups All other SF-36 domains ns. between groups	Patients with PAD + diabetes. HEP vs. 'standard care' (=no formal training advice) Outcome retrieved by graded treadmill testing (Gardner protocol)	?	?/-	?/+
Gardner, 2011	USA	RCT	n=79 I=40 C1=39	I=11 C1=9	SF-36 physical function score at three months: Δ 8 (sd 15)	SF-36 physical function score at three months: Δ -1 (sd 17) ns. between groups	Three study arms (SET, HET, 'standard care'); ITT analysis Outcome retrieved by during graded treadmill protocol (constant speed)	+	+	-

HET = Home-based supervised exercise. SET = Supervised hospital-based exercise.

Project: Exercise programs in intermittent claudication
Appendix 4:4. PICO 1 - Home-based supervised exercise vs. go home and walk advice
Outcome variable: Walking Impairment Questionnaire (WIQ)

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Collins, 2011	USA	RCT	n=145 I=72 C1=73	19	WIQ subscale walking speed, at six months: Δ + 5.7 (se 2.2)	WIQ subscale walking speed, at six months: Δ -1.9 (se 2.8) p=0.034 between groups All other WIQ domain scores, ns. between groups	Patients with PAD + diabetes. HEP vs. ”standard care” (=no formal training advice) Outcome retrieved by graded treadmill testing (Gardner protocol)	?	?/-	?/+
Gardner, 2011	USA	RCT	n=79 I=40 C1=39	I=11 C1=9	WIQ at three months Distance score (%): Δ 10 (sd 25) Speed score (%): Δ 11 (sd 22) Stair climbing score (%): Δ 10 (sd 22)	WIQ at three months Distance score (%): Δ 1 (sd 34) ns. between groups Speed score (%): Δ 4 (sd 25) ns. between groups Stair climbing score (%): Δ 3 (sd 25) ns. between groups	Three study arms (SET, HET, ”standard care”); ITT analysis Outcome retrieved by during graded treadmill protocol (constant speed)	+	+	-

HET = Home-based supervised exercise. SET = Supervised hospital-based exercise. WIQ = Walking impairment questionnaire.

Project: Exercise programs in intermittent claudication
Appendix 4:5. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.
Outcome variable: maximum walking distance

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Gardner, 2011	USA	RCT	n=80 I=40 C2=40	I=11 C2=7	Peak walking time: Baseline: 402 (sd 285) s Post-test: 526 (sd 374) s p<0.01, within group At three months: Δ 124 (sd 193) s	Peak walking time (s): Baseline: 325 (sd 169) s Post-test: 540 (sd 281) s p<0.001, within group At three months: Δ 215 (sd 207) s ns. between groups	Outcome variable: Peak walking time evaluated with progressive graded treadmill protocol HET: 3 days/week. Duration 20 min increasing 5 min biweekly until a total of 45 min, self-selected pace during 12 weeks. Step activity monitor, logbook feed-back on exercise intensity SET: 3 days/week. Duration 15 min increasing 5 min biweekly until a total of 40 min, intermittent treadmill walking to near-maximal pain during 12 weeks. Step activity monitor	+	+	-
Patterson, 1997	USA	RCT	n=60 I=30 C2=30	I=11 C=11	MWT at 6 months: Δ 70% p<0.001, within group	MWT at 6 months: Δ 207% p<0.001, within group p<0.004, between groups	Outcome variable: maximum walking time (MWT) evaluated with graded progressive maximal treadmill exercise test HET: 3 days/week, duration 20-40 min/ walking at home to tolerance during 12 weeks. Exercise logs review at weekly lectures Follow-up treadmill test at 6 months SET: 3 days/week, 1 hour aerobic arm and leg ergometry + graded treadmill walking individually determined during 12 weeks. Weekly lectures. Control of adherence by a nurse Follow-up treadmill test at 6 months	+	?	-

Project: Exercise programs in intermittent claudication
Appendix 4:5. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.
Outcome variable: maximum walking distance

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Regensteiner, 1997	USA	RCT	n=20 I=10 C2=10	0	Peak walking time three months follow-up: Baseline: 372 (sd 216) s Exit: 390 (sd 252) s Δ 18 s ns. within group	Peak walking time three months follow-up: Baseline: 276 (sd 144) s Exit: 654 (sd 270) s Δ 378 s p<0.05, within group p<0.05, between groups	Outcome variable: peak walking time. Graded treadmill protocol. Stages increased 3,5% in grade every three minutes, with no change in speed to maximal claudication pain. Original data (time) calculated from minutes to seconds. HET: 3 days/week, duration 35 min, increasing to 50 min. Detailed walking prescription at as a rapid rate as possible for 3 months. Adherence controlled by nurse (weekly telephone call). SET: 3 days/week, duration 35 min, increasing to 50 min. Interval walking on graded treadmill on mild-moderate level until claudication pain for 3 months	-	?	?/-

Project: Exercise programs in intermittent claudication
Appendix 4:5. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.
Outcome variable: maximum walking distance

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Sandercock, 2007	UK	RCT	n=28 I=15 C2=13	7	Maximum walking time three months follow-up: Baseline: 366 (sd 198) s Week 12: 432 (sd 312) s Δ 66 s ns. within group	Maximum walking time three months follow-up: Baseline: 390 (sd 240) s Week 12: 726 (sd 378) s Δ 336 s p<0.001, within group ns, between groups	Outcome: Maximal walking time. Graded treadmill test increased by 2% every 2 min until test termination. Original data (time) calculated from minutes to seconds. HET: 3 days/week, duration 30 min walking sessions at RPE 12-14. Contacted weekly by telephone to control adherence. SET: 2 days/week, duration 30 min treadmill walking at 70-75% of VO2peak. Exercise diary with instruction to undertake one additional weekly 30 min walking session.	+	?	-

Project: Exercise programs in intermittent claudication
Appendix 4:5. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.
Outcome variable: maximum walking distance

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Savage, 2001	USA	RCT	n=21 I=10 C2=11	0?	Maximal claudication distance at 3 months: Δ + 204 m p<0.009, within group Maximal claudication distance at 6 months: Δ +183 m p<0.01, within group	Maximal claudication distance at 3 months: Δ + 312 m p<0.0001, within group Maximal claudication distance at 6 months: Δ + 220 m p<0.05, within group ns. between groups	Outcome measure: Maximal claudication distance. Symptom-limited treadmill exercise test. Constant walking speed of 2 miles per hour, increasing grade by 2% every 2 minutes. HET: 3 days/week, duration 15 min, increasing to 40 min. Walking until claudication pain (resting and continuing). Evaluated after 12 and 24 weeks. SET: 3 days/week, duration 15 min, increasing 40 min. Graded treadmill walking constant pace of 2 miles per hour at 60% of maximal grade. Readjusted monthly by repeating the maximal treadmill test. During exercise walking until claudication pain (resting and continuing). After 12 weeks the SET-group transitioned to the HET-program.	-	-	-

Project: Exercise programs in intermittent claudication
Appendix 4:5. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.
Outcome variable: maximum walking distance

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Fakhry, 2011	Netherlands	Cohort	n=217 I=142 C2=75	I=47	Mean relative improvement in MWD at 6 months: Δ 265 (95% CI: 180-350) % Mean relative improvement in MWD at 12 months: Δ 268 (95% CI: 140-396) %	Mean relative improvement in MWD at 6 months: Δ 750 (95% CI: 599-901) % Adjusted* mean difference: Δ -433 (95% CI: -665 to -200) % p<0.01, between groups Mean relative improvement in MWD at 12 months: Δ 666 (95% CI: 523-809) % Adjusted* mean difference: Δ -361 (95% CI: -604 to -118) % p<0.01, between groups	Outcome variable: MWD evaluated with treadmill walking, no graded incline (speed 3.5 km/h – max 30 min) HET: 1 session/day, duration 30 min near maximum pain in self-chosen environment, during 24 weeks Between group differences (relative improvement) SET: 2 sessions/week, duration 30 min near maximum pain on treadmill constant speed, during 24 weeks * Adjusted for confounders.	-	-	?

HET = home-based supervised exercise. MWD = maximum walking distance. MWT = Maximum walking time. SET = hospital-based supervised exercise.

Project: Exercise training programs in intermittent claudication
Appendix 4:6. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.
Outcome variable: Painfree walking distance (MPWD)

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Gardner 2011	USA	RCT	n=80 I=40 C2=40	I=7 C2=11	Claudication onset time: Pretest: 204 (sd 137) s Posttest: 337 (sd 250) s p<0.001, within group At three months: Δ 134 (sd 197) s	Claudication onset time: Pretest: 196 (sd 144) s Posttest: 361 (sd 264) s p<0.001, within group At three months: Δ 165 (sd 173) s ns. between groups	Outcome variable: Claudication onset time evaluated with a progressive graded treadmill protocol HET: 3 days/week, duration 20 min increasing 5 min biweekly until a total of 45 min, self-selected pace during 12 weeks. Step activity monitor, logbook feed-back on exercise intensity. SET: 3 days/week, duration 15 min increasing 5 min biweekly until a total of 40 min, intermittent treadmill walking to near-maximal pain during 12 weeks. Step activity monitor.	+	+	-
Patterson 1997	USA	RCT	n=60 I=30 C2=30	I=11 C2=11	CPT at 6 months: Δ 131% p<0.001, within group	CPT at 6 months: Δ 337% p<0.001, within group p<0.004, between groups	Outcome variable: claudication pain time (CPT) evaluated with graded progressive maximal treadmill exercise test. HET: 3 days/week, duration 20-40 min walking at home to tolerance during 12 weeks. Exercise logs review at weekly lectures SET: 3 days/week, duration 1 hour aerobic arm and leg ergometry + treadmill walking individually determined during 12 weeks. Weekly lectures. Control of adherence by a nurse.	+	?	-

Project: Exercise training programs in intermittent claudication
Appendix 4:6. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.
Outcome variable: Painfree walking distance (MPWD)

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Regensteiner, 1997	USA	RCT	n=20 I=10 C2=10	0	Pain free walking time, three months follow-up: Entry: 138 (sd 120) s Exit: 174 (sd 84) s Δ 36 s ns. within group	Pain free walking time, three months follow-up: Entry: 120 (sd 78) s Exit: 300 (sd 204) s Δ 180 s ns. within group p<0.05, between groups	Outcome variable: pain-free walking time. Graded treadmill protocol. Stages increased 3,5% in grade every three minutes, with no change in speed to maximal claudication pain. Original data (time) calculated from minutes to seconds. HET: 3 days/week, duration 35 min, increasing to 50 min. Detailed walking prescription at as a rapid rate as possible for 3 months. Adherence controlled by nurse (weekly telephone call). SET: 3 days/week, duration 35 min, increasing to 50 min. Interval walking on treadmill on mild-moderate level until claudication pain for 3 months.	-	?	?/-

Project: Exercise training programs in intermittent claudication
Appendix 4:6. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.
Outcome variable: Painfree walking distance (MPWD)

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Savage 2001	USA	RCT	n=21 I=10 C2=11	0?	Initial claudication distance at 3 months: Δ +43 m ns. within group Initial claudication distance at 6 months: Δ +81 m ns. within group	Initial claudication distance at 3 months: Δ +215 (sd 150) m ns. within group p<0.01 between groups Initial claudication distance at 6 months: Δ +243 m p<0.003, within group	Outcome measure: Initial claudication distance. Symptom-limited treadmill exercise test. Constant walking speed of 2 miles per hour, increasing grade by 2% every 2 minutes. HET: 3 days/week, duration 15 min, increasing to 40 min. Walking until claudication pain (resting and continuing). Evaluated after 12 and 24 weeks SET: 3 days/week, duration 15 min, increasing 40 min. Treadmill walking constant pace of 2 miles per hour at 60% of maximal grade. Readjusted monthly by repeating the maximal treadmill test. During exercise walking until claudication pain (resting and continuing). After 12 weeks the SET-group transitioned to the HET-program.	-	-	-

Project: Exercise training programs in intermittent claudication
Appendix 4:6. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.
Outcome variable: Painfree walking distance (MPWD)

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Fakhry 2011	Netherlands	Cohort	n=217 I=142 C2=75	I=47	Mean relative improvement in MWPD at 6 months: Δ 308 (95% CI: 139-478) % Adjusted* mean difference: -953 (95% CI: -1596 to -341) % Mean relative improvement in MWPD at 12 months Δ 370 (95% CI: 223-516) %	Mean relative improvement in MWPD at 6 months: Δ 1241 (95% CI: 894-1587) % Adjusted* mean difference: -938 (95% CI: -1495 to -381) % p<0.01, between groups Mean relative improvement in MWPD at 12 months Δ 1286 (95% CI: 908-1663) % Adjusted* mean difference: -953 (95% CI: -1565 to -341) % p<0.01, between groups	Outcome variable: MPWD evaluated with treadmill walking, no graded incline (speed 3.5 km/h – max 30 min) HET: 1 session/day, duration 30 min near maximum pain in self-chosen environment, during 24 weeks SET: 2 sessions/week, duration 30 min near maximum pain on treadmill constant speed, during 24 weeks * Adjusted for confounders.	-	-	?

HET, home-based supervised exercise; SET, hospital-based supervised exercise

Project: Exercise programs in intermittent claudication
Appendix 4:7. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.
Outcome variable: HRQoL

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Gardner, 2011	USA	RCT	n=80 I=40 C2=40	I=11 C2=7	Physical function score: Baseline: 40 (sd 22) % Post-test: 48 (sd 23) % p<0.01, within group At three months: Δ 8 (sd 15) %	Physical function score: Baseline: 37 (sd 17) % Post-test: 46 (sd 21) % p<0.01, within group At three months: Δ 9 (sd 16) % ns. between groups	Outcome variable: Physical function score according to SF-36 HET: 3 days/week. Duration 20 min increasing 5 min biweekly until a total of 45 min, self-selected pace during 12 weeks. Step activity monitor, logbook feed-back on exercise intensity SET: 3 days/week. Duration 15 min increasing 5 min biweekly until a total of 40 min, intermittent treadmill walking to near-maximal pain during 12 weeks. Step activity monitor	+	+	-

Project: Exercise programs in intermittent claudication
Appendix 4:7. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.
Outcome variable: HRQoL

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Patterson 1997	USA	RCT	n=60 I=30 C2=30	I=11 C2=11	<u>SF-36 at 12 weeks:</u> Physical function: 53 (24.4)* p<0.01, within group Pain index: 61 (21.6) * p<0.01, within group Physical component: 38 (12) * p<0.01, within group <u>SF-36 at 6 months</u>: Physical function: 54 (23.5) * p<0.01, within group Pain Index: 64 (19.3) * p<0.01, within group Physical component: 38 (11.1)* p<0.01, within group	<u>SF-36 at 12 weeks:</u> Physical function: 52 (22.2) * p<0.01, within group Pain index: 64 (23.6) * p<0.01, within group Physical component: 38 (8.3)* p<0.01, within group <u>SF-36 at 6 months</u>: Physical function: 56 (14.4) * p<0.01, within group Pain index: 62 (20.6) * p<0.01, within group Physical component: 39 (8.6) * p<0.01, within group ns. between groups for all SF-36 domains	Outcome variable: SF-36 HET: 3 days/week, duration 20-40 min walking at home to tolerance during 12 weeks. Exercise logs review at weekly lectures SET: 3 days/week, duration 1 hour aerobic arm and leg ergometry + graded treadmill walking individually determined during 12 weeks. Weekly lectures. Control of adherence by a nurse * Not specified whether se or sd.	+	?	-

Project: Exercise programs in intermittent claudication
Appendix 4:7. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.
Outcome variable: HRQoL

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Regensteiner 1997	USA	RCT	n=20 I=10 C2=10	0	SF-20, three months follow-up: Baseline: 61 (sd 25) % Exit: 71 (sd 29) % Δ 10 % ns. within group	SF-20, three months follow-up: Baseline: 52 (sd 19) % Exit: 72 (sd 18) % Δ 20 % p<0.05, within group ns. within, and between groups for all other SF-20 domains	Outcome variable: SF-20 No significant inter-group differences HET: 3 days/week, duration 35 min, increasing to 50 min. Detailed walking prescription at as a rapid rate as possible for 3 months. Adherence controlled by nurse (weekly telephone call). SET: 3 days/week, duration 35 min, increasing to 50 min. Interval walking on graded treadmill on mild-moderate level until claudication pain for 3 months.	-	?	?/-
Savage 2001	USA	RCT	n=21 I=10 C2=11	0?	SF-36 at 3 and 6 months: ns. within group ns. between groups	SF-36 at 3 and 6 months: ns. within group ns. between groups	Outcome measure: SF-36 HET: 3 days/week, duration 15 min, increasing to 40 min. Walking until claudication pain (resting and continuing). Evaluated after 12 and 24 weeks. SET: 3 days/week, duration 15 min, increasing 40 min. Graded treadmill walking constant pace of 2 miles per hour at 60% of maximal grade. Readjusted monthly by repeating the maximal treadmill test. During exercise walking until claudication pain (resting and continuing). After 12 weeks the SET-group transitioned to the HET-program.	-	-	-

Project: Exercise programs in intermittent claudication
Appendix 4:7. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.
Outcome variable: HRQoL

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Fakhry 2011	Netherlands	Cohort	n=217 I=142 C2=75	I=47	<u>Mean change in SF-36 at 6 months:</u> Physical functioning: Δ 5.74 (95% CI: 2.06-9.42) Physical role functioning: Δ 6.78 (95% CI: -0.68-14.24) Bodily pain: Δ 3.51 (95% CI: -0.55-7.57) General health: Δ -0.79 (95% CI: -3.64-2.10) <u>Mean change in SF-36 at 12 months</u>: Physical functioning: Δ 6.88 (95% CI: 2.85-10.91) Physical role functioning: Δ 8.89 (0.57-17.21)	<u>Mean change in SF-36 at 6 months:</u> Physical functioning: Δ 12.20 (95% CI: 6.78-17.62) Physical role functioning: Δ 13.93 (95% CI: 3.49-24.38) Bodily pain: Δ 6.56 (95% CI: 0.96-12.16) General health: Δ 5.13 (95% CI: 0.81-9.46) <u>Adjusted* mean difference at 6 months</u>: General health: Δ-8.39 (95% CI: -16.11 to -0.68) p=0.03, between groups ns. between groups for all other SF-36 domains <u>Mean change in SF-36 at 12 months</u>: Physical functioning: Δ 12.68 (95% CI: 7.33-18.03) Physical role functioning: Δ 5.93 (-4.74-16.61)	Outcome variable: SF-36 HET: 1 session/day, duration 30 min near maximum pain in self-chosen environment, during 24 weeks SET: 2 sessions/week, duration 30 min near maximum pain on treadmill constant speed, during 24 weeks * Adjusted for confounders	-	-	?

Project: Exercise programs in intermittent claudication

Appendix 4:7. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.

Outcome variable: HRQoL

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
					Bodily pain: Δ 6.55 (1.54-11.56) General health: Δ -1.19 (-4.45-2.07)	Bodily pain: Δ 9.67 (3.85-15.49) General health: Δ 4.88 (0.81-8.95) <u>Adjusted* mean difference at12 months:</u> ns. between groups for all SF-36 domains				

HET, home-based supervised exercise; SET, hospital-based supervised exercise; PF, physical functioning; PRF, physical role functioning; BP, bodily pain; GH, general health

Project: Exercise programs in intermittent claudication
Appendix 4:8. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.
Outcome variable: WIQ (walking impairment questionnaire)

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Gardner 2011	USA	RCT	n=80 I=40 C2=40	I=11 C2=7	WIQ distance score: Baseline: 32 (sd 29) % Post-test: 42 (sd 33) % p<0.05, within group At three months: Δ 10 (sd 25) % WIQ speed score: Baseline: 30 (sd 22) % Post-test: 41 (sd 22) % p<0.05, within group At three months: Δ 11 (sd 22) % WIQ stair climbing score: Baseline: 38 (sd 26) % Post-test: 48 (sd 27) % p<0.05, within group At three months: Δ 10 (sd 22) %	WIQ distance score: Baseline: 25 (sd 26) % Post-test: 38 (sd 31) % p<0.05, within group At three months: Δ 13 (sd 28) % ns. between groups WIQ speed score: Baseline: 27 (sd 19) % Post-test: 36 (sd 24) % p<0.01, within group At three months: Δ 9 (sd 15) % ns. between groups WIQ stair climbing score: Baseline: 32 (sd 32) % Post-test: 44 (sd 34) % p<0.001, within group At three months: Δ 12 (sd 15) % ns. between groups	Outcome variable: WIQ HET: 3 days/week. Duration 20 min increasing 5 min biweekly until a total of 45 min, self-selected pace during 12 weeks. Step activity monitor, logbook feed-back on exercise intensity SET: 3 days/week. Duration 15 min increasing 5 min biweekly until a total of 40 min, intermittent treadmill walking to near-maximal pain during 12 weeks. Step activity monitor	+	+	-

Project: Exercise programs in intermittent claudication
Appendix 4:8. PICO 2 Home-based supervised exercise vs. hospital-based supervised exercise.
Outcome variable: WIQ (walking impairment questionnaire)

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Regensteiner, 1997	USA	RCT	n=20 I=10 C=10	0	WIQ, three months follow-up: Distance: Baseline: 31 (sd 33) % Exit: 44 (sd 34) % Δ 13 % ns. within group Speed: Baseline: 32 (sd 17) % Exit: 38 (sd 14) % Δ 6 % ns. within group Claudication severity score: Baseline: 38 (sd 26) % Exit: 40 (sd 25) % Δ 2 % ns. within group	WIQ, three months follow-up: Distance: Baseline: 31 (sd 21) % Exit: 55 (sd 31) % Δ 24 % p<0.05, within group ns. between groups Speed: Baseline: 36 (sd 20) % Exit: 51 (sd 29) % Δ 15 % p<0.05, within group ns. between groups Claudication severity score: Baseline: 33 (sd 22) % Exit: 48 (sd 25) % Δ 2 % p<0.05, within group ns. between groups	Outcome variable: WIQ HET: 3 days/week, duration 35 min, increasing to 50 min. Detailed walking prescription at as a rapid rate as possible for 3 months. Adherence controlled by nurse (weekly telephone call). SET: 3 days/week, duration 35 min, increasing to 50 min. Interval walking on treadmill on mild-moderate level until claudication pain for 3 months.	-	?	?/-

HET, home-based supervised exercise; SET, hospital-based supervised exercise; WIQ, walking impairment questionnaire

Project: Exercise programs in intermittent claudication
Appendix 5: Summary of Findings

Outcome variable Number of studies	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Absolute effect	Quality of evidence GRADE
PICO 1: Home-based supervised exercise (I) vs. go home and walk advise (C)									
Maximal walking distance 3	2 RCT 1 Cohort	Some limitations (?)[1]	Some inconsistency (?)[2]	Some uncertainty (?)[3]	Serious imprecision (-1)[4]	Unlikely	Not relevant	I: Δ 25-83* m C1: Δ 39-44* m I: Δ 124* s C1: Δ -10* s	⊕⊕◯◯
Pain free walking distance 3	2 RCT 1 Cohort	Some limitations (?)[1]	Some inconsistency (?)[2]	Some uncertainty (?)[3]	Serious imprecision (-1)[5]	Unlikely	Not relevant	I: Δ 51-67* m C1: Δ 27-52* m I: Δ 134* s C1: Δ -16* s	⊕⊕◯◯
Health related quality of life 2	2 RCT	Some limitations (?)[1]	No serious inconsistency	Serious indirectness (-1)[3]	Serious imprecision (-1)[6]	Unlikely	Not relevant	SF 36 physical function* I: Δ 8 C1: Δ -1 SF 36 mental health* I: Δ 3 C1: Δ -2	⊕⊕◯◯
Walking impairment questionnaire 2	2 RCT	Some limitations (?)[1]	No serious inconsistency	Serious indirectness (-1)[3]	Serious imprecision (-1)[6]	Unlikely	Not relevant	Speed score* I: Δ 10%, or Δ 6 C1: Δ 4%, or Δ -2	⊕⊕◯◯

Project: Exercise programs in intermittent claudication
Appendix 5: Summary of Findings

Outcome variable Number of studies	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Absolute effect	Quality of evidence GRADE
PICO 2: Home-based supervised exercise (I) vs. hospital-based supervised exercise (C)									
Maximal walking distance 6	5 RCT 1 Cohort	Serious limitations (-1)[7]	Some inconsistency (?)[2]	Some uncertainty (?)[8]	Uncertain precision (?)[9]	Unlikely	Not relevant	I: Δ 18-124 s* C2: Δ 215-378 s*	⊕⊕◯◯
Pain free walking distance 5	4 RCT 1 Cohort	Serious limitations (-1)[7]	Some inconsistency (?)[2]	Some uncertainty (?)[8]	Uncertain precision (?)[9]	Unlikely	Not relevant	I: Δ 36-134 s* C2: Δ 165-180* s	⊕⊕◯◯
Health related quality of life 5	4 RCT 1 Cohort	Serious limitations (-1)[7]	No serious inconsistency	Some uncertainty (?)[8]	Uncertain precision (?)[10]	Unlikely	Not relevant	No significant differences	⊕⊕◯◯
Walking impairment questionnaire 2	2 RCT	Serious limitations (-1) [11]	No serious inconsistency	Some uncertainty (?)[12]	Uncertain precision (?)[10]	Unlikely	Not relevant	Speed score* I: Δ 6-11 % C2: Δ 9-15 %	⊕⊕◯◯

High quality of evidence = ⊕⊕⊕⊕
Moderate quality of evidence = ⊕⊕⊕◯
Low quality of evidence = ⊕⊕◯◯
Very low quality of evidence = ⊕◯◯◯

*Pooled analysis not suitable due to different outcome measures and heterogeneous interventions. Ranges of mean changes from individual studies presented in table, when applicable (see Appendix 4).

Project: Exercise programs in intermittent claudication
Appendix 5: Summary of Findings

Outcome variable Number of studies	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Absolute effect	Quality of evidence GRADE

Footnotes:
1. Problems with baseline data and randomization.
2. Different effect estimates across the studies.
3. Short follow-up period, specificity of the intervention?
4. Possible unfavorable effects, outcome measure the same as exercised in the intervention group, no power calculation for non-inferiority design for secondary outcomes.
5. Outcome measure the same as exercised in the intervention group, no power calculation for non-inferiority design for secondary outcomes.
6. Possibly unfavorable effects, no power calculation for non-inferiority design for secondary outcomes.
7. Large proportion of patients lost to follow-up, unclear randomization, no intention-to-treat analysis, comparable groups?
8. Different interventions, short follow-up.
9. Outcome measure the same as exercised in the intervention group, possibly unfavorable effects.
10. Possibly unfavorable effects.
11. Unclear randomization, comparable groups?
12. Short follow-up period.

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA

HTA

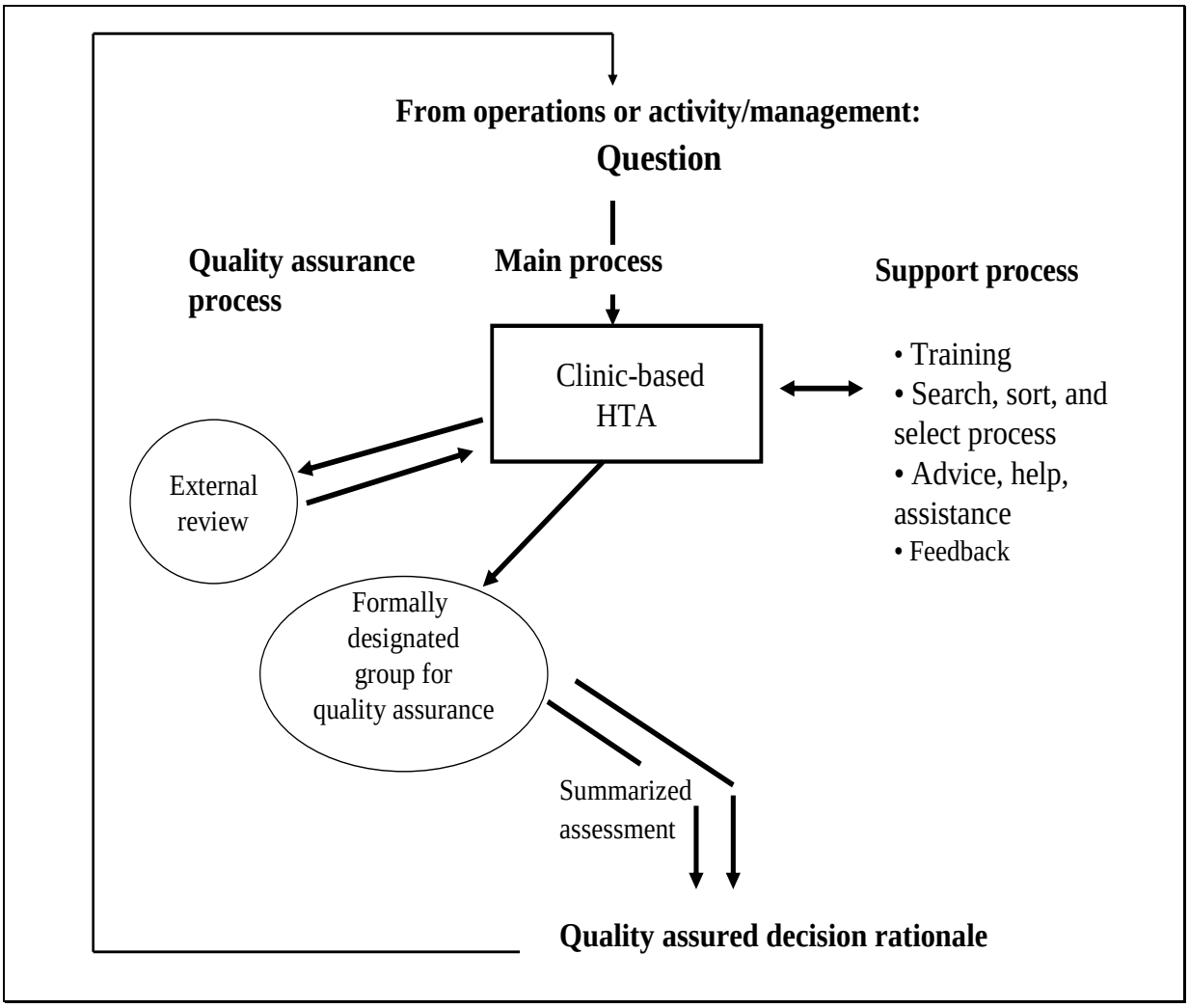
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Sahlgrenska Universitetssjukhuset, HTA-centrum
Röda Stråket 8, 413 45 Göteborg
www.sahlgrenska.se/hta-centrum