From Karolinska Institutet, Department of Clinical Sciences,
Danderyd Hospital, Division of Rehabilitation Medicine,
Stockholm, Sweden

FEASIBILITY AND EFFICACY OF INCORPORATING AN EXOSKELETON IN GAIT TRAINING DURING SUBACUTE STROKE REHABILITATION

Anneli Wall

Stockholm 2020

Cover by Holy Grail Creative Agency in Stockholm – holygrail.se
All previously published papers were reproduced with permission from the publisher.
Pictures were published with permission from the persons in the photos and photographers.
Published by Karolinska Institutet.
Printed by Eprint AB 2020

ISBN 978-91-7831-744-8

FEASIBILITY AND EFFICACY OF INCORPORATING AN EXOSKELETON IN GAIT TRAINING DURING SUBACUTE STROKE REHABILITATION

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Anneli Wall

Principal Supervisor:
PhD Susanne Palmcrantz
Karolinska Institutet
Department of Clinical Sciences,
Danderyd Hospital
Division of Rehabilitation Medicine

Co-supervisors:
Professor Jörgen Borg
Karolinska Institutet
Department of Clinical Sciences,
Danderyd Hospital
Division of Rehabilitation Medicine

Professor Elena (Lanie) Gutierrez-Farewik
KTH MoveAbility Lab
Department of Engineering Mechanics
KTH Royal Institute of Technology

Opponent:
Professor Birgitta Langhammer
Oslo Metropolitan University, Faculty of Health Sciences, Institute of Physiotherapy, Oslo, Norway
Sunnaas HF, Research department, Bjørnemyr, Norway

Examination Board:
Maria Ekblom
The Swedish School of Sport and Health Sciences GIH, Department of Sport and Health Sciences, Stockholm, Sweden,
Karolinska Institutet, Department of Neuroscience, Stockholm, Sweden.

Jørgen Feldbæk Nielsen
Aarhus University, Faculty of Health, Department of Clinical Medicine, Hammel Neurorehabilitation Center and University Research Clinic, Denmark

Christina Brogårdh
University of Lund, Faculty of Medicine,
Department of Health Sciences, Lund, Sweden

And now, the end is near
And so I face the final curtain
My friend, I'll say it clear
I'll state my case, of which I'm certain
I've lived a life that's full
I've traveled each and every highway
But more, much more than this
I did it my way

- Frank Sinatra

ABSTRACT

Introduction: Hemiparesis is the most common acute manifestation of stroke and often has a strong negative impact on walking ability leaving one third of patients dependent in walking activities outside one's home. Improved methods for training of gait during stroke rehabilitation could tackle the challenge of achieving independent walking and promote better outcomes. Several studies have explored the value of introducing electromechanical gait machines in stroke rehabilitation to enhance gait training. One example is the exoskeleton Hybrid Assistive Limb (HAL). The HAL system has been found feasible to use during rehabilitation in the chronic stage after stroke, however knowledge of the feasibility in the subacute stage after stroke and its efficacy compared to evidence-based conventional gait training is still limited.

Aim: The overall aim of this thesis was to evaluate the safety and feasibility of HAL for gait training in the subacute stage after stroke and the effect of HAL training on functioning, disability and health compared to conventional gait training, as part of an inpatient rehabilitation program in patients with severe limitations in walking in the subacute stage after stroke.

Methods: This thesis contains two studies where one is a safety and feasibility study (Study I) and one is a prospective, randomized, open labeled, blinded evaluation study (Study II).

In Study I, eight patients performed HAL training 5 days/week. The number of training sessions were adjusted individually and varied from 6 to 31 (median 16). Safety and feasibility aspects of the training were evaluated as well as clinical outcomes on functioning and disability (e.g. independence in walking, walking speed, balance, movement functions and activities of daily living), assessed before and after the intervention period.

In Study II, 32 patients were randomized to either conventional training only or HAL training in addition to the conventional training, 4 days per week for 4 weeks. Within and between-group differences in independence in walking, walking speed/endurance, balance, movement functions and activities of daily living were investigated before and after the intervention period, as well as 6 months post stroke. In addition, gait pattern functions were evaluated after the intervention in a three-dimensional gait laboratory. At 6 months post stroke self-perceived aspects on functioning disability and health were assessed and subsequently correlated to the clinical assessments.

Results: In Study I HAL was found to be safe and feasible for gait training after stroke in patients with hemiparesis, unable to walk independently, undergoing an inpatient rehabilitation program. All patients improved in walking independence and speed, movement function, and activities of daily living during the intervention period. In addition, it was found that patients walked long distances during the HAL sessions, suggesting that HAL training may be an effective method to enhance gait training during rehabilitation of patients in the subacute stage after stroke.

In Study II substantial but equal improvements in the clinically evaluated outcomes in the two intervention groups were found. At six months post stroke, two thirds of patients were independent in walking, and a younger age but not intervention group served as the best predictor. Gait patterns were similarly impaired in both groups and in line with previous reports on gait patterns post stroke. Further, self-perceived ratings on functioning, disability and health were explained by the ability to perform self-care activities and not by intervention group.

Conclusion: To incorporate gait training with HAL is safe and feasible during inpatient rehabilitation in the subacute stage after stroke and may be a way to increase the dose (i.e. number of steps) in gait training in the subacute stage after stroke. Among these included younger patients with hemiparesis and severe limitations in walking in the subacute stage after stroke, substantial improvements in body function and activity as well as equally impaired gait patterns were observed both after incorporated HAL training and after conventional gait training only, but without between-group differences. In future studies, potential beneficial effects on cardiovascular, respiratory, and metabolic functions should be addressed. Further, as the stroke population is heterogeneous, potential subgroups of patients who may benefit the most from electromechanically-assisted gait training should be identified.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following original papers and manuscripts. They will be referred to in the text by their Roman numerals as indicated below:

I. **Nilsson A**, Vreede K S, Haglund V, Kawamoto H, Sankai Y, and Borg J. Gait training early after stroke with a new exoskeleton—the hybrid assistive limb: a study of safety and feasibility. *Journal of Neuroengineering and Rehabilitation*. 2014, 11:92. doi: 10.1186/1743-0003-11-92

II. **Wall A**, Borg J, Vreede K, Palmcrantz S. A randomized controlled study incorporating an electromechanical gait machine, the Hybrid Assistive Limb, in gait training of patients with severe limitations in walking in the sub-acute phase after stroke. *Submitted and under review*

III. **Wall A**, Palmcrantz S, Borg J, Elena M Gutierrez-Farewik. Gait Pattern after Electromechanically-assisted Gait Training with the Hybrid Assistive Limb (HAL) and Conventional Gait Training in Sub-acute Stroke Rehabilitation – a Subsample from a Randomized Controlled Trial. *In manuscript*

IV. **Wall A**, Borg J, Palmcrantz S. Self-perceived functioning and disability after randomized conventional and electromechanically-assisted gait training in subacute stroke – a 6 months follow-up. *NeuroRehabilitation.* 2019 Dec 18;45(4):501-511. doi: 10.3233/NRE-192929

CONTENTS

LIST OF ABBREVIATIONS

10MWT	10 Meter Walking Test
2MWT	2-Minute Walk Test
ADL	Activities of Daily Living
BBS	Berg Balance Scale
BI	Barthel Index
BWS	Body Weight Support
CI	Confidence Interval
CONV group	Group in Study II perfoming conventional gait training only
EAGT	Electromechanically-assisted gait training
EMG	Electromyography
EQ-5D	EuroQol 5 Dimensions Questionnaire
FAC	Functional Ambulation Categories
FES(S)	Falls Efficacy Scale Swedish version
FIM	Functional Independence Measure
FMA-LE	Fugl-Meyer assessment lower extremity
GPS	Gait Profile Score
HAL	Hybrid Assistive Limb
ICF	International Classification of Functioning, Disability and Health
IQR	Interquartile Range
MAP	Movement Analysis Profile
m/s	Meters/second
NIHSS	National Institutes of Health Stroke Scale
PROBE	Prospective, Randomized, Open labeled, Blinded evaluation
S-COVS	Clinical Outcome Variable Scale, Swedish version
SD	Standard Deviation
SIS	Stroke Impact Scale
TUG	Timed Up and Go
T (1, 2, 3)	Time point (1, 2, 3)
VAS	Visual Analog Scale

1 BACKGROUND

1.1 INTRODUCTION

Stroke is the leading cause of acquired disability among adults in developed countries [1]. Hemiparesis is the most common acute manifestation of stroke and often has a strong negative impact on mobility such as walking ability [2]. In the International Classification of Functioning, Disability and Health (ICF) [3] walking is defined as *"Moving along a surface on foot, step by step, so that one foot is always on the ground, such as when strolling, sauntering, walking forwards, backwards, or sideways"*. To regain walking ability is often a main goal expressed by patients after stroke and is a common goal set for early stroke rehabilitation interventions i.e. gait training [4, 5].

Although movement functions typically improves during the first months post stroke, more than 70% of stroke survivors experience limitations in walking three months after stroke onset [6] and about one third will be dependent in walking and remain limited in their ability to walk in a complex environment, outside one's home, so called community ambulation [2, 7, 8]. In addition, at 3 months after stroke onset 16% are still dependent in dressing and/or toilet visits [9]. These activities are included in self-care which is defined by the ICF as *"caring for oneself, washing and drying oneself, caring for one's body and body parts, dressing, eating and drinking, and looking after one's health"* [3]. Together, limitations in voluntary movement functions, walking and in the ability to perform self-care activities will result in a reduced capacity to perform activities of daily living (ADL) as compared to before stroke onset.

Apart from rehabilitation, the recovery of walking might depend on the location and extent of the lesion [10] and of restorative and compensatory mechanisms [11]. In response to an increasing understanding of recovery and neuroplasticity to regain functioning in everyday life [12-14] there is a need for further development of rehabilitation interventions to tackle the challenge of achieving independence in walking during stroke rehabilitation.

Stroke rehabilitation can be defined as *"a progressive, dynamic, goal-orientated process aimed at enabling a person with impairment to reach their optimal physical, cognitive, emotional, communicative, social and/or functional activity level"* [15]. Improved methods for training of walking during early stroke rehabilitation could result in better outcomes and have an impact on length of stay in hospital and thus result in increased cost effectiveness in stroke rehabilitation. In addition, improved walking ability and independence in walking may reduce cardiovascular risk factors and serve as secondary prevention [16] and may reduce the need for health care consumption and community support [17].

1.2 DEFINITION OF STROKE

Stroke is a clinical condition characterized by rapid occurrence of focal (or global in case of coma) neurologic dysfunction, of vascular origin, lasting more than 24 hours or leading to death [18]. Stroke is caused by an interruption of the blood supply to the brain due to block of a blood vessel causing an ischemic stroke (infarction) or a burst of a blood vessel causing an intracerebral or subarachnoid hemorrhage. In this thesis, patients with intracerebral infarction or hemorrhage, but not with subarachnoid hemorrhage, were included.

A diagnosis of stroke is based on clinical presentation and brain imaging, which is most often performed with computerized tomography examination. The clinical symptoms of stroke depend on which side and part of the brain (arterial territory) is affected. Common acute signs are paresis with contralesional weakness in the arm and/or leg, disturbed coordination and balance that may cause limited mobility. Other symptoms include difficulty in speaking or understanding speech (dysphasia/aphasia) seen in around one third of all patients, and mainly after lesions in the left (dominant) hemisphere, unilateral neglect seen mainly in patients with a lesion in the right (non-dominant) hemisphere and impairments of memory, attention and other mental functions [6, 12].

Time post stroke can be divided into different phases, where the subacute phase can be subdivided into *early subacute* (7 days – 3 months) and *late subacute* (3-6 months) [19]. In this thesis the term subacute stage after stroke (i.e. 7 days – 6 months) we will used for the patients included in our studies. The term *chronic* refers to the time beyond 6 months post stroke [19].

1.3 INCIDENCE AND PREVALENCE

In Sweden, approximately 16 500 individuals suffer a first ever stroke each year [9]. A majority, 86%, suffer an ischemic stroke and about 13% a hemorrhagic stroke. Mean age is 75 years and around 20% are younger than 65 years, thus of working age. Women tend to suffer stroke at an older age and among patients below 65 years of age, a majority are men. Most patients (63%) suffer a mild stroke, i.e scoring 0-5 points on the National Institutes of Health Stroke Scale (NIHSS) [9], a quantitative assessment of neurological deficit post stroke [20].

1.4 STROKE RECOVERY

Recovery is seen as improvements in different ICF components (body structures, body functions, activity and participation) due to restorative and/or compensatory mechanisms [11, 19]. Most recovery from stroke occurs during the first weeks after stroke and is commonly reaching a plateau within the first 3 months [21, 22] and is thereafter continuing at a slower rate. Improvements in the ability to perform a movement, with the same kinematic patterns as before stroke, can be seen as *behavioral restitution*/*true recovery* [11, 19, 23]. In contrast, *compensation* involves the use of alternative strategies, such as change in muscle activation,

different timing and kinematic patterns to perform a movement [11, 19, 23]. Clinical studies of rehabilitation interventions often fail to distinguish whether improvements achieved are due to compensation or to true recovery [11, 19, 23, 24].

Most patients exhibit some degree of spontaneous recovery, mainly occurring early (within weeks after stroke), regardless of active treatment or not [19]. Motor recovery (i.e. recovery of movement-related functioning) such as recovery of walking ability may reflect both such spontaneous processes and response to interventions [11, 19]. The development of interventions that may enhance the rate and level of true recovery beyond the spontaneous processes, taking advantage of the early time window, and the use of outcome measures that can distinguish between true recovery and compensation is thus of great interest in stroke rehabilitation.

1.5 WALKING

In healthy individuals (i.e. individuals without disabilities), walking is mainly automatically controlled by spinal networks with minimal use of executive control to accomplish a well-coordinated gait pattern [25]. However, planning, initiation and modulation of walking occurs in the cerebral cortex, basal ganglia, brainstem and cerebellum and are communicated by output in the descending, corticofugal tracts. Therefore, for motor programs to be useful in different contexts and environments they require sensory-motor-integration, continuous modification and adaptation of stereotypical gait patterns and thus integration between peripheral, supraspinal and spinal levels to enable safe walking [26-30]. In case of injury to the central nervous system, the balance between automatic and executive gait pattern control may be shifted and then safe walking requires more attention [25].

A gait cycle starts with the initial contact between one foot and the floor and ends when the same foot contacts the floor again and is divided in to stance phase and swing phase, representing 60% and 40% of the gait cycle respectively [31] (Figure 1). Walking speed (m/s) is an essential measure of walking ability and is influenced by cadence (number of steps/min) and step length (m). For healthy adults' normal walking speed is around 1.4 m/s (82 m/min)[31]. Events occurring during a gait cycle can be divided into spatial, i.e. related to distances, and temporal, i.e. related to timing. A symmetric gait pattern occurs when spatial and temporal parameters at both legs are alike [7]. Suggested prerequisites for normal gait include stability in stance, foot clearance in swing, pre-positioning of the foot for initial contact, adequate step length and energy conservation [31, 32]. Abilities such as postural control, weight shifting, forward progression and correct timing of muscle activity during repeated gait cycles are also essential [28].

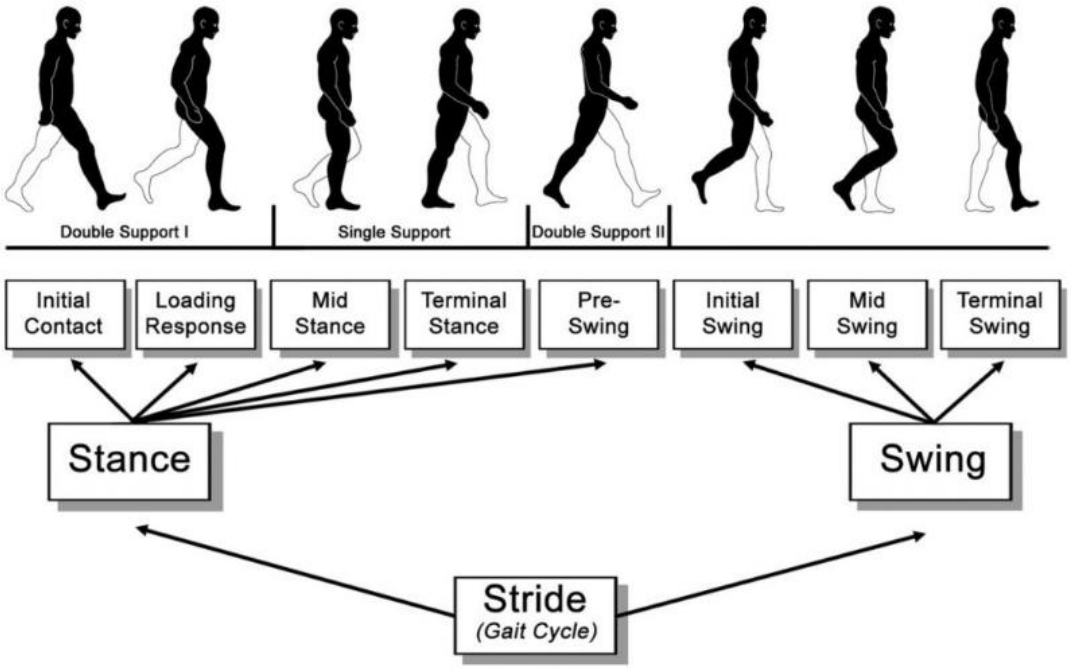

Figure 1. *A gait cycle divided into different gait events. Figure reprinted and slightly modified (cropped) with permission [33].*

1.5.1 Gait deviations after stroke

Gait pattern functions are defined as *"functions of movement patterns associated with walking, running or other whole body movements"* and includes impairments such as hemiparetic gait [3]. Compared to normal gait pattern, the hemiparetic gait pattern post stroke features decreased walking speed (due to decreased step and stride length and cadence), asymmetry (due to reduced single stance time and increased swing time on the affected limb) as well as an increased gait cycle time [28, 34, 35].

Other characteristics in gait post stroke are hyperextension or prolonged knee flexion at stance phase and hip circumduction as a strategy to achieve foot clearance during swing phase. In addition, peak moments and power generation, such as the propulsive force from plantar flexors at push off, may be decreased on the hemiparetic side [28, 34, 35]. A combination of these factors and their underlying causes, such as muscle weakness, spasticity and loss of range of motion, results in increased energy expenditure/metabolic cost in hemiparetic gait compared to normal walking [34].

The spontaneous walking speed in individuals with hemiparesis post stroke is suggested to be between 0.23-0.95 m/s, depending on the study population and often increases with time and due to structured rehabilitation approaches [28]. To be able to walk in the community, a sufficient walking speed of around 0.80 m/s [36] and interaction between physical and mental functions [37] such as orientation and visuospatial perception are required. Although increases in walking speed occur, subjects in later stages post stroke tend to still have remaining asymmetrical and compensatory gait patterns. This may be associated with an increased risk of musculoskeletal complications and falls, and increased energy

expenditure in the long term [38]. Recently, interventions aiming at improving gait symmetry after stroke have been suggested [39-41] but are most often applied and evaluated in chronic stroke. Thus, studies with interventions targeting symmetrical walking in subacute stage after stroke to overcome these compensatory gait patterns are of great interest.

1.6 PREDICTION OF WALKING RECOVERY

Investigating factors that influence recovery after stroke can guide rehabilitation strategies and interventions in the acute and subacute phase [21, 42]. However, to predict the extent of recovery after stroke is difficult [21, 43, 44]. In recent studies, prediction models for recovery of upper limb functioning, using a combination of clinical, neurophysiological and neuroimaging based measures of impairment have been introduced [45]. Recovery of walking ability after stroke is most often defined as the ability to walk independently at 6- or 12-months post stroke [46]. To predict recovery of walking ability, early presence of trunk stability (assessed with Trunk Control Test) and muscle strength in the paretic limb (assessed with the Motricity Index Leg) [47], improvement in standing balance [48] as well as younger age and less stroke severity (NIHSS score low) [42, 49] have been identified as contributing factors. A recent study has suggested an algorithm (TWIST - time to walking independently after stroke) to predict both whether and when a person will regain independent walking within the first 12 weeks post stroke, using bedside assessments at 1 week post stroke. In that study, predictors of the time to walk independently after stroke were again trunk stability (Trunk Control Test score) and hip extension strength, with an accuracy of 95% correctly predicted [50]. The TWIST-model however needs to be validated in another (larger) cohort and other predictors such as therapy dose and intensity need further investigation [50]. In addition, the results cannot be generalized to other stroke populations such as those with more severe limitations. Notably, what is predicted is the walking ability, which may depend on compensatory strategies, and thus not the recovery of gait patterns as before stroke.

1.7 REHABILITATION OF WALKING ABILITY, STRATEGIES AFTER STROKE

Early onset of repetitive, task specific individualized training, may drive functional neuroplasticity, enhance functional restitution and improve the final outcome, including walking ability [12, 51-53]. Even though issues remain, studies have suggested a dose-response relationship [54-56], where increased practice of walking, i.e. increased dose, results in better outcomes such as walking independence and speed [57]. In addition to the dose (i.e. number of steps), the intensity (i.e. heart rate and/or walking speed) and variability of task training (e.g. training in different velocities, directions and environments) should be considered as these factors together influence the result of a training intervention [58] (Figure 2).

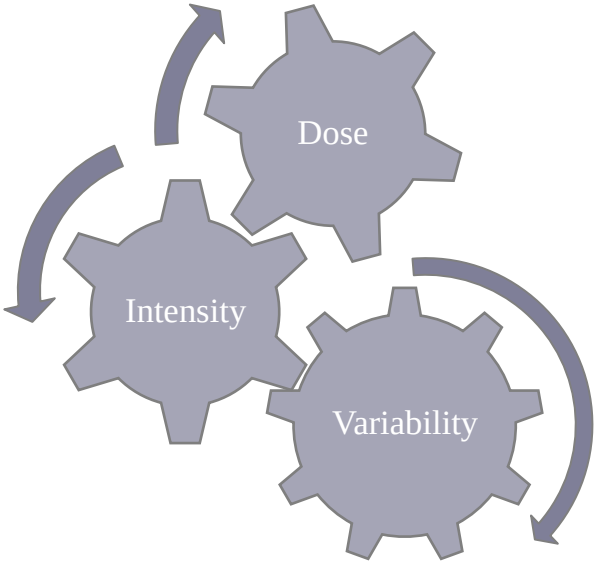

Figure 2. *Figure illustrating training parameters that influence the result of a training intervention. For gait interventions, dose can be measured in number of steps, the intensity in heart rate and/or walking speed and the variability of task training can be achieved by stepping in different directions and environments.*

Current rehabilitation strategies for improved walking ability after stroke may include task specific muscle strength and balance training, over ground walking with assistance and/or ambulatory devices (such as walking aids and orthoses) and the use of treadmill with or without body weight support (BWS). Treadmill training with BWS may allow a higher dose [58] and can be a safe way to practice walking in patients in need of great manual support. The evidence is not consistent, but data indicate that patients who are dependent in walking may not benefit neither more nor less from treadmill training (with or without BWS) in terms of regained independence, walking speed and/or endurance compared to other interventions, e.g. over ground walking [59]. In recent years, combining treadmill training with the use of electromechanical gait machines have been introduced in clinical trials as a means to increase the dose, intensity and symmetry in gait training [60, 61].

1.8 GAIT MACHINES

In a recent review [60] including 36 trials involving a total of 1472 participants, electromechanically-assisted gait training (EAGT) in combination with physiotherapy was found to increase the odds of becoming independent in walking (regardless of the type of device used) and to increase walking speed, and most so when applied in the first three months after stroke onset in patients who were unable to walk. However, the review also found that altogether, studies in subacute and chronic phase after stroke with patients dependent or independent in walking at study start, do not exhibit significant differences in walking speed and endurance as compared to conventional physiotherapy only. As recognized by the authors, the quality of the evidence is limited, and methodological limitations exists. In addition, the duration and frequency of treatment differ and there are somewhat conflicting results regarding the efficacy. Further, the use of gait machines is still

limited mostly to research-controlled trials [62]. It is also recognized that studies of EAGT most often use objective (i.e. not self-perceived), clinical outcome measures to assess the patient's impairments and limitations and data describing gait pattern functions and self-perceived functioning, disability and health in everyday life are scarce [60, 63].

Electromechanical gait machines can work according to the end-effector principle (foot plates move the feet in a controlled gait pattern) or as exoskeletons, which have joints matching the limb joints and motors that drive movements over these joints to assist, e.g. leg movements [60]. Compared to BWS treadmill training alone, the additional use of electromechanical gait machines may allow more reproducible and symmetrical gait movements than when provided by a therapist. Currently, there are several exoskeletons at various stages of development or clinical applications. In addition to differences in mechanical design and control strategies existing exoskeletons use different activation systems to produce movement of the limb.

The widely used exoskeleton, the Lokomat (Hocoma, Volketswil, Switzerland)[64] allows only limited degree of active patient participation and studies have not consistently demonstrated effects, regarding walking speed, balance, mobility and/or walking ability/independence, that are superior to those achieved with conventional training in subacute stroke [65-69].

Rather than producing preprogrammed gait trajectories, active participation [70, 71] and real-time control strategies with timely assistance [72] have been proposed, to promote motor recovery and motor learning. This is also referred to as an assistance-as-needed-approach [73], encouraging active participation from the user to reinforce voluntary muscle activation and step initiation, while the device only provides torque or support to ensure step completion. One may speculate that this approach utilizes residual capacity that otherwise may go undetected, or if not undetected gains to little practice due to muscle weakness. Thus, some recently developed exoskeletons have established intention-based control strategies using shifting of bodyweight (Ekso, Ekso Bionics, Richmond, CA, USA; ReWalk, ReWalk Robotics, Inc., Marlborough, USA; and Indego, Parker Hannifin, XX) or electromyography (HAL, Cyberdyne Inc., Ibaraki, Japan) to detect a person's intended movement and reinforce the intended step. In the studies included in this thesis we used the latter, the electromechanical gait machine called The Hybrid Assistive Limb (HAL).

1.8.1 The Hybrid Assistive Limb (HAL)

The Hybrid Assistive Limb (HAL) (Figure 3) is an intention-based exoskeleton with a hybrid system allowing both a voluntary and an autonomous mode of action to support training of gait. In total there are three different control modes called "Cybernic Autonomous Control", "Cybernic Voluntary Control" and "Cybernic Impedance Control". The HAL system is manufactured in single-leg and double-leg versions and training with HAL may be performed over ground or on a treadmill with or without BWS. The device has power units providing torque over the knee and hip joints, while the ankle-joint is unpowered hence locked in a

neutral position. A main controller of the system is used to control the power units, monitor the batteries, communicate with the system operator and modulate the assisting torque of each power unit. Key features of the HAL system have been reported in detail previously [74-76].

Figure 3. *Single leg version of the Hybrid Assistive Limb (HAL). Photo by: Johan Adelgren*

1.8.1.1 Cybernic Voluntary Control

In the voluntary control mode, movements are triggered by the user's voluntary activation of gait muscles as recorded by surface electromyography (EMG). The recorded signals are incorporated in the control algorithm and the technology enables even weak muscle activity to be used to initiate and adjust the assistive torque. The voluntary control mode allows the operator to adjust the degree of physical support for each joint (hip and knee) separately and for the flexor and extensor muscle groups respectively, to achieve a gait pattern that is as close as possible to normal gait and gradually reduce support as training progresses. If the

subject is paralytic, as may be the case early after stroke, the autonomous control mode may be used.

1.8.1.2 Cybernic Autonomous Control

The autonomous control mode utilizes voluntary weight shift to initiate gait cycles and then provides predefined movements. In this mode, the exoskeleton will e.g. swing the right leg when the left leg is in stance phase, based on output from force-pressure sensors in the shoes.

1.8.1.3 Cybernic Impedance Control

The impedance control mode provides no assistance but avoids excessive force, i.e. frictional resistance, between the suit and the limb.

1.8.2 HAL for gait training after stroke

At the time for the feasibility study (Study I), aspects on feasibility and safety of HAL was only reported for early mobilization of patients in a neurosurgical ward using a prior version of the HAL system [77] and for gait training in patients with chronic limitations after a variety of conditions including stroke [78, 79].

At the time of the start of the Prospective, Randomized, Open labeled, Blinded evaluation (PROBE) study (Study II), all previously published studies until 2014 [80] were single group studies with no control group and studies combining HAL training with evidence-based conventional training occurred later [81, 82]. As pointed out [83], EAGT should be carried out in combination with conventional physiotherapy which was applied in Study I and II in this thesis. In addition, no study had previously assessed gait pattern functions other than spatiotemporal and/or self-perceived aspects of training with HAL and/or included a long term follow up.

At present, several studies have explored the use of HAL for gait training in different stages after stroke [77-82, 84-101]. The studies differ in terms of aim, design, duration of intervention, diagnosis, setting, and patient characteristics as well as allocation, randomization, blinding and outcome measures. Fifteen are single group studies (i.e. no control group is applied) [77-79, 81, 84-88, 90, 91, 94, 95, 99, 101], one is a case study [98], five studies have a control group (but did not use strict randomization) [82, 89, 92, 97, 100] and two are randomized controlled trials [80, 93, 96]. The studies include one [98, 99] to 53 [86] patients with stroke who performed HAL training. The total number of HAL sessions range from 1 [87] to 31 [88] and with a total mean of approximately 11 sessions, using HAL 2-3 times per week with durations of ≥20 minutes (net walking time) per session. Nine of these studies include patients in the chronic phase and 14 in the acute/subacute phase after stroke. One study includes both. The mean age of participants is around 60 years.

Apart from safety and feasibility aspects, the outcome measures in the studies primarily relate to aspects of walking (10 Meter Walking Test, Functional Ambulation Categories), movement functions (Brunnström, Fugl-Meyer assessment lower extremity) and balance

(Timed Up and Go, Berg Balance Scale). Most frequently used is the 10-meter walk test [102] which is an assessment of over ground walking speed.

Ten studies [78, 79, 81, 82, 91, 92, 94, 98, 100, 101] report on a positive impact on walking speed after HAL training, however all except three [82, 92, 100] were single group studies. Two studies have found improvements in walking endurance [81, 91], one in balance [79], and two studies report increased level of independence in walking according to the Functional Ambulation Category [90, 91], however all are single group studies.

In the studies including a control group the results are conflicting showing no between-group differences in three studies [89, 93, 97], greater improvements in maximum and self-selected walking speed in the HAL group but no significant difference in independence in walking in one study [82], and using the same outcome measures, the complete opposite results are found in another study [80]. In summary, despite some positive results it is yet not determined if HAL training is superior to conventional gait training [103].

In these previous studies, data describing self-perceived aspects of the training are scarce as well as data related to self-perceived activity performance and participation in everyday life. One case-series, including one participant with stroke, explores self-perceived health assessed with the EuroQol Questionnaire (EQ-5D) and self-perceived mobility assessed with Patient-Reported Outcomes Measurement Information System (PROMIS), after HAL training [99]. They report no change in quality of life but a minor improvement less than one standarddeviation in self-perceived mobility, for that individual. Another study, including patients with different neurological diagnoses, applies a questionnaire to explore patients' experience of using HAL and finds that training with HAL can strengthen the user's motivation and sense of being able to initiate movements [104]. In addition, the potential effect of HAL training on movement functions such as gait pattern is addressed in only five studies [82, 91, 94, 95, 101]. However, these five studies mainly report on spatiotemporal data and only one [94] have used a three-dimensional motion analysis system (Vicon). In addition, to our knowledge there is currently yet no randomized controlled trials with blinded assessors published.

The accumulated results of studies demonstrate that training with the HAL system is feasible when applied in acute and chronic stage after stroke [77-79]. However, the studies show a great variation with regard to sample characteristics, timing, frequency, intensity and duration of intervention as well as different methods of evaluation and subsequent somewhat inconsistent results/benefits for improving walking.

Thus, we recognized a need for a study investigating the safety and feasibility of HAL in patients in the subacute stage after stroke and to explore potential benefits of HAL in a PROBE study with an intervention group performing both HAL training and evidence-based conventional gait training and a control group performing evidence-based conventional gait training only, in patients with severe limitations in walking after stroke. Further we identified a need to adopt an assessment protocol covering all ICF-domains [3], including

laboratory gait analysis and clinical assessments capturing both objective (i.e. not self-perceived) and self-perceived aspects with a follow-up assessment at 6 months post stroke to capture potential residual effects.

2 AIMS

The overall aim for the thesis was to evaluate the safety and feasibility of HAL for gait training in the subacute stage after stroke, and the effect of HAL training on functioning, disability and health compared to conventional gait training as part of an inpatient rehabilitation program in patients with severe limitations in walking in the subacute stage after stroke.

2.1 SPECIFIC AIMS

Paper I: To investigate the safety and feasibility of HAL for intensive gait training as part of a regular inpatient rehabilitation program for patients with hemiparesis who were unable to walk independently after stroke.

Paper II: To explore potential differences at the end of intervention and at long-term (6 months follow up) with regards to 1) movement function, 2) walking 3) balance and 4) self-care after incorporated gait training with HAL compared to conventional gait training only. Secondly, we wanted to explore self-perceived beneficial effects of incorporated HAL training.

Paper III: To explore 1) potential differences in gait pattern functions after the intervention and 2) correlations between gait patterns and standardized clinical assessments of functioning and disability, after incorporated gait training with HAL compared to conventional gait training only.

Paper IV: To explore long-term effects (6 months after stroke onset) after incorporated gait training with HAL compared to conventional gait training only, regarding self-perceived functioning, disability and recovery and predicting factors for self-perceived mobility and recovery.

3 METHODS

This thesis contains four papers (Paper I-IV), from two different studies (Study I and II) (Figure 4).

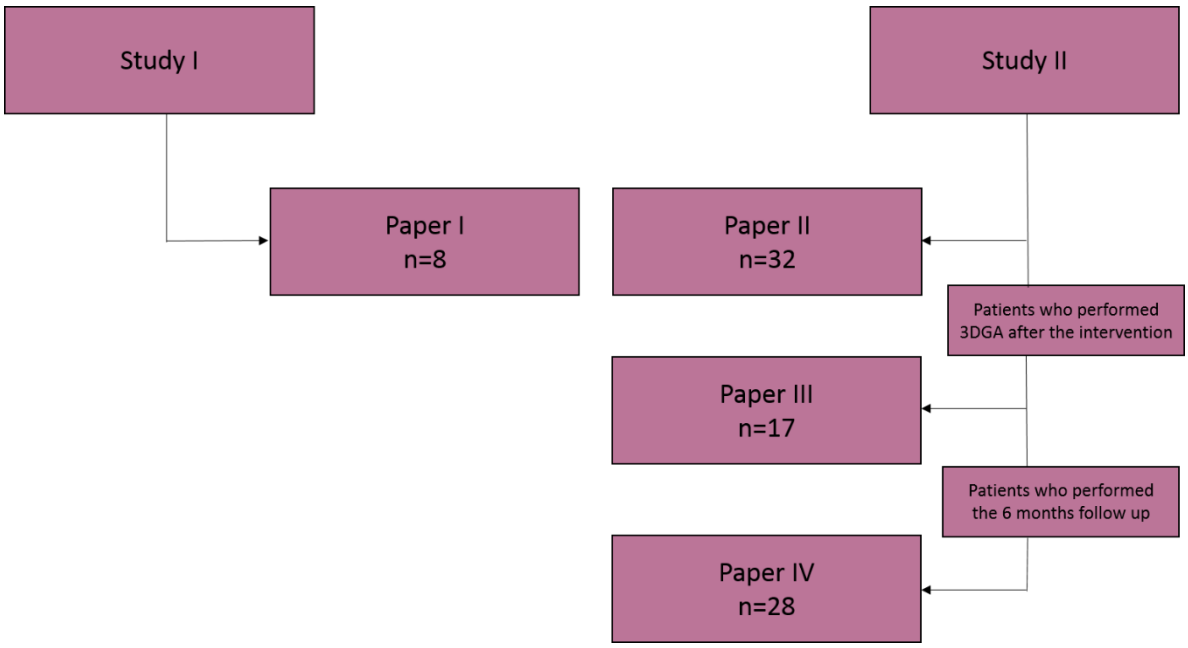

Figure 4. *Flowchart over the included studies (I and II), papers (I-IV) and number of patients in each paper.*

3.1 STUDY SETTING AND DESIGN

Patients were recruited from the University Department of Rehabilitation Medicine, Stockholm at Danderyd Hospital, Sweden. The department provides early rehabilitation services for patients with acquired brain injury, who are at working age and living in the Stockholm region. At the time of recruitment, the mean age among patients who underwent rehabilitation after a stroke, was 51 years (SD 11) and 69% were men. Most patients, 63%, suffered an ischemic stroke, and the median NIHSS score at admission to the ward was 7 points (mean 8.4, SD 6) corresponding to mild to moderately severe stroke (figures retrieved from the period of recruitment into Study II, n=273, for NIHSS n=167) [105]. Thus, the included study sample represents a younger and more severely affected group than the overall stroke population.

Study I (Paper I) was a safety and feasibility study investigating the applicability of HAL in rehabilitation of patients unable to walk independently after stroke. The study was conducted between June 2012 and August 2013.

Study II (Paper II-IV) was a PROBE study including patients with severe limitations in walking ability after stroke. The study was conducted between February 2014 and May 2017.

3.2 PATIENT RECRUITMENT

Eligible patients were consecutively sampled among those who underwent team-based, inpatient rehabilitation in the subacute stage after stroke. The study coordinator identified

possible study patients and screened for eligibility upon referral to the ward together with the team physiotherapists at the ward. Responsible for study information, both oral and written, and collecting of informed consent was a senior physician, specialized in rehabilitation medicine who also was educated in the HAL-method. Patients with dysphasia/aphasia who were found eligible were given additional simplified information about the study using pictures and if needed, a speech therapist was consulted to ensure that the patient had understood the study information and that informed consent was obtained. Patients with severe aphasia were excluded.

3.2.1 Inclusion and exclusion criteria

3.2.1.1 Study I

Inclusion criteria were: ≤7 weeks since stroke; hemiparesis, able to sit on a bench with/without supervision >5 minutes; unable to walk independently; sufficient balance control to allow upright position in standing with aids and/or manual support; cognitive ability to understand training instructions as well as written and oral study information and to express informed consent; body size compatible with the HAL suit.

Exclusion criteria were contracture restricting gait movements at any lower limb joint (hip, knee, ankle), cardiovascular or other somatic condition incompatible with intensive gait training, and/or severe contagious infections.

3.2.1.2 Study II

Inclusion criteria were ≤ 8weeks since onset of ischemic or hemorrhagic stroke (verified by computerized tomography and/or magnetic resonance imaging); hemiparesis; inability to walk or in need of continuous manual support to walk (i.e. Functional Ambulation Categories (FAC) score 0–1); ability to maintain a sitting posture with or without supervision for >5 minutes and, sufficient balance control to allow upright position in standing with aids and/or manual support; ability to understand training instructions as well as written and oral study information and express informed consent; and a body size compatible with the HAL suit.

Exclusion criteria were cerebellar stroke, primary subarachnoid bleeding, contracture restricting gait movements at any lower limb joint, cardiovascular or other somatic condition incompatible with intensive gait training, and/or severe contagious infections.

3.3 INTERVENTION AND DATA COLLECTION

3.3.1 HAL training

The HAL sessions started by attaching the EMG-electrodes to the patient's lower limb (two over hip flexors, two over hip extensor, two for knee extensor, two for knee flexor and one reference electrode over the lateral epicondyle of femur) (Figure 5 B). All patients used a harness connected to the BWS system over the treadmill (Figure 5 A+C). After putting on the

harness, the HAL suit was attached to the patient and the electrodes were connected to the suit through cables (Figure 5 B).

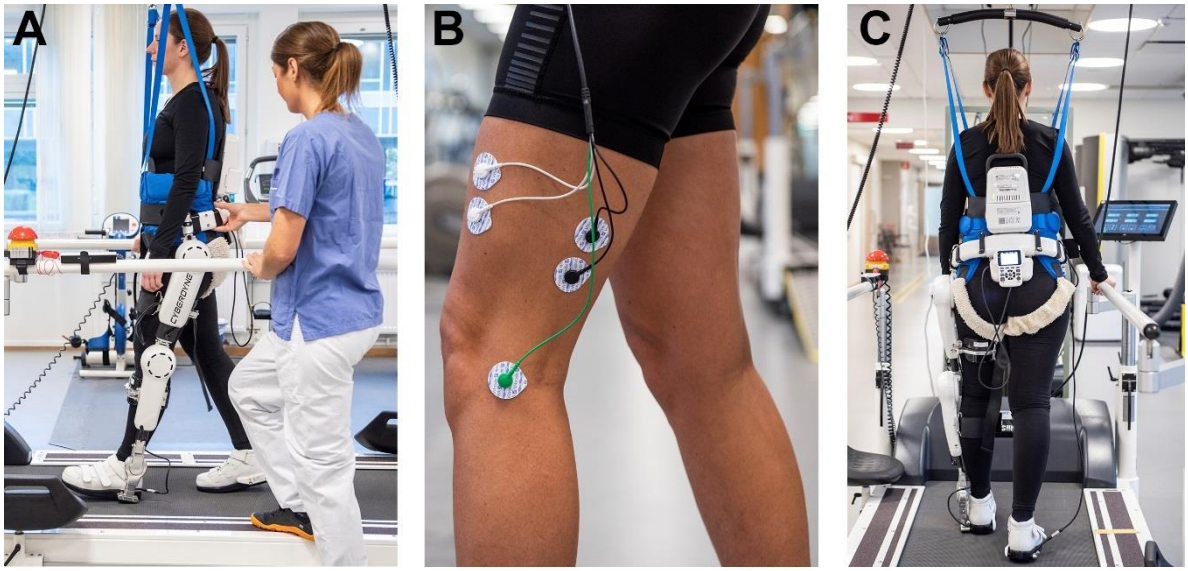

Figure 5. *A+C) Illustration of HAL training, performed on a treadmill with body weight support. B) Surface electromyography (EMG) to capture the wearer's voluntary muscle activation. EMG-electrodes were affixed over the following muscles: biceps femoris (knee flexion), quadriceps vastus lateralis (knee extension) (in picture) and rectus femoris (hip flexion), gluteus maximus (hip extension) (not in picture). A reference electrode was placed over the lateral femur condyle. Photos by: Johan Adelgren*

The patients used the handrail on the non-paretic side and got visual feedback through a mirror placed in front of them. If rest was needed during the HAL training a chair was put on the treadmill belt so the patient could rest in sitting, or if preferred rest in standing position on the treadmill. The pauses length and timing as well as the intervals of gait training length were decided by the patient, in collaboration with the physiotherapist.

All sessions were individualized regarding settings and adjustments of HAL, amount of BWS and walking speed. The therapist continuously evaluated and optimized HAL-settings to obtain a gait pattern as close to normal as possible, based on continuous observational gait analysis [106]. As the patients improved in walking ability, the amount of assistance was reduced, and the walking speed increased. One or two therapists educated in the HAL method were present during the HAL training.

3.3.1.1 Study I

The HAL training was planned daily for 5 days/week. Training was continued until the HAL-therapist found no further gain in using the HAL suit (i.e. when patients could perform gait training over ground with minimal support or supervision) or when three months had elapsed since the stroke. The double-leg version of HAL was used (since the single-leg version of HAL was yet unavailable at that time). The autonomous control mode was used on the paretic side during the first session and continuously until the voluntary control mode was possible to use in one or more joints. The possibility to switch to the voluntary control mode was determined by EMG signals obtained, the severity of the patients' gait- and balance limitations as well as presence of one additional therapist (who could adjust settings while the

other therapist supported the patient). On the non-paretic side, the impedance control mode (i.e. no support) was most often used. The degree of initial BWS was individually set to allow sufficient gait training and reduced successively. Initial speed on the treadmill was set to 0.4 km/h (i.e. 0.11 m/s) and increased as tolerated.

3.3.1.2 Study II

Training was planned for 4 days per week for 4 weeks, i.e. 16 sessions in total. Each session could at most last 1.5 hours including donning, doffing and pauses. Effective gait training time could last for a maximum of 60 minutes. The single-leg version of HAL was used. Initial BWS was set to 30% of the patient's weight and the initial speed of the treadmill was 0.5 km/h (i.e. 0.14 m/s). During the first session the autonomous control mode was used and at session number two and forward the voluntary control mode was used.

3.3.2 Conventional (gait) training

In addition to the intervention, patients included in Study I and II participated in the conventional team-based rehabilitation program (involving for example physiotherapy, occupational- and speech therapy), performed according to current best practice for inpatient rehabilitation after stroke. The physiotherapy training, including conventional gait training, was conducted by the patient's team physiotherapist and documented in the medical records (see chapter 3.3.7). The conventional gait training could include e.g. stepping, weight shifting, over ground walking as well as the use of treadmill with or without BWS.

Participation in the studies was not supposed to affect other rehabilitation sessions. No instructions were given to the team physiotherapists regarding intensity, duration and content of the conventional gait training.

3.3.3 Randomization

In Study II patients were manually randomized into conventional gait training (CONV group) or HAL training in addition to the conventional team-based rehabilitation program (HAL group). Randomization was performed by a nurse, not otherwise involved in the study. A block randomization consisting of blocks of four was used, e.g. AABB, ABAB, ABBA, BBAA etc., where A equals conventional gait training only and B equals additional HAL training. Block randomization was used for logistic reasons to allow consecutive inclusion (due to availability of HAL suits in the right size and side, i.e. left/right, at the same time).

3.3.4 Assessment procedures

3.3.4.1 Study I

Clinical assessments were performed at two time points, before (T1) and after (T2) the intervention. For practical reasons, the Barthel Index was performed by the patients' occupational therapist at T1 and T2. The NIHSS at T1 and T2 was performed by the physician who collected the informed consent. All other assessments were conducted by the

same, non-blinded physiotherapist experienced in stroke rehabilitation. Time needed for clinical assessments was normally 1-1.5 hours.

3.3.4.2 Study II

Clinical assessments were performed at three time points, before the intervention (T1), after the intervention (T2) and at 6 months post stroke (T3). For the same practical reasons, the Barthel Index was performed by the patients' occupational therapist at T1 and T2. Again, the NIHSS was performed at T1 and T2 by the physician who collected the informed consent. The FAC was, in addition to T1, T2 and T3, assessed weekly by the patient's physiotherapist at the ward and documented in the medical record. Therefore, the above described assessments were not blinded. All other assessments were blinded and performed by a physiotherapist with long experience in stroke rehabilitation. Time needed for clinical assessments was normally 1-1.5 hours.

3.3.5 Clinical assessments

The assessment methods used in the studies have been found valid and reliable and are commonly used outcome measures in stroke rehabilitation [20, 102, 107-132] and cover several aspects of body function and activity according to the ICF (Table 1). Some assessments used in the studies are not included in this thesis, such as semi-structured interviews and three-dimensional gait analysis at T3 (including EMG-recordings).

Table 1. *Assessments used in Study I and II presented in this thesis, according to the International Classification of Functioning, Disability and Health (ICF).*

ICF Components	Assessments	Study I		Study II		
		T1	T2	T1	T2	T3
Body function	• National Institutes of Health Stroke Scale	X	X	X	X	X
	• Fugl-Meyer assessment lower extremity	X	X	X	X	X
	• Three-dimensional Gait analysis **Gait Profile Score**, Kinematics, Kinetics				X	
Activity and Participation	• **Functional Ambulation Categories**	X	X	X	X	X
	• 2 minute walk test			X	X	X
	• 10 meter walk test	X	X			
	• Berg Balance Scale	X	X	X	X	X
	• Timed Up and Go	X	X			
	• Clinical Outcome Variables Scale	X	X			
	• Barthel Index	X	X	X	X	X
	• Functional Independence Measure	X	X			
	• Falls Efficacy Scale	X	X			
	• **Stroke Impact Scale**					X
	• EQ-5D and EQ VAS	X	X			
Environmental factors	• Study specific questionnaire		X		X	
Safety and feasibility	• Study specific protocol	X	X			

Primary outcomes used in the different papers (II-IV) are in bold. T1, Time point 1 (before the intervention); T2, Time point 2 (after the intervention); T3, Time point 3 (at 6 months post stroke); EQ5D, EuroQol 5 Dimensions.

3.3.5.1 National Institutes of Health Stroke Scale (NIHSS)

The NIHSS assesses stroke severity by assessing e.g. level of consciousness, visual fields, upper and lower limb movement function, limb ataxia, touch function, dysarthria, and perception. The total score is 42 points, where lower scores represent milder impairment [20, 109].

3.3.5.2 Fugl-Meyer assessment lower extremity (FMA-LE)

The FMA-LE assesses functioning in the lower extremities. The instrument includes different domains covering: muscle reflexes, voluntary movements, coordination of voluntary movements, proprioceptive and touch function, passive range of motion and pain during passive range of motion. The maximum score is 56 points and items are rated 0-2 points with higher score indicating less impairment [113]. A motor score (FMA-LE motor), used in Study II, was obtained by combining scores from muscle reflexes, voluntary movements and coordination with a maximum of 34 points.

3.3.5.3 Functional Ambulation Categories (FAC)

The FAC assesses walking ability on a six-grade-ordinal-scale, ranging from non-functional walking (score 0) to independent walking on level and non-level surfaces including stairs and inclines (score 5) [107, 108] (Table 2). The FAC is the most commonly used outcome measure in studies of EAGT for patients with severe to moderate walking limitations in both the acute and chronic phase after stroke [63]. The FAC was the primary outcome in Study II (Paper II).

The FAC evaluates the patient's level of independence and/or manual support required regardless of use of orthosis and/or walking aids. This makes the scale relevant to use in subacute stroke rehabilitation when goals involving independence in walking are common and may be more important to plan time for discharge from hospital than walking speed.

The FAC can be dichotomized into *dependent in walking* (FAC <4) and *independent in walking* (FAC 4-5) [47]. Meaningful change of the FAC score is, to the best of our knowledge, not yet established. However, one point change in score on the FAC scale can be assumed to represent a clinically meaningful difference as further discussed below, in chapter 5.7.1.

Table 2. *The Functional Ambulation Categories (FAC) according to Holden et al. [107]*

Functional Ambulation Categories		
Score	**Ambulation Description**	**Definition**
0	**Nonfunctional**	Unable to ambulate or requires help from > one person.
1	**Dependent, Level II**	Requires continuous manual contact of one person during ambulation on level surfaces, to support body weight as well as to maintain balance and/or assist coordination.
2	**Dependent, Level I**	Requires continuous manual contact or intermittent light touch of one person during ambulation on level surfaces to assist balance or coordination.
3	**Dependent, Supervision**	Ambulation occurs on level surfaces without manual contact but requires supervision because of poor judgment, questionable cardiac status, or the need for verbal cuing.
4	**Independent, Level Surfaces Only**	Ambulation is independent on level surfaces but requires help to negotiate stairs, inclines, or unlevel surfaces.
5	**Independent**	Ambulation is independent on unlevel and level surfaces, stairs, and inclines.

3.3.5.4 2 Minute Walk Test (2MWT)

The 2MWT assesses walking speed/endurance [117, 118]. Patients were instructed to walk as far as possible in 2 minutes and was timed using a stop watch. Assistive devices such as walking aids and orthoses were allowed as well as manual support, but excluded encouragement, verbal instructions or any physical help other than preventing falls.

3.3.5.5 10 Meter Walk Test (10MWT) self-selected and maximum speed

The 10MWT assesses walking speed in meters per second [102, 116]. Assistive devices such as walking aids and orthoses where allowed and, if required, manual support was provided. Two extra meters was given to accelerate and decelerate but were not timed.

3.3.5.6 Berg Balance scale (BBS)

The BBS assesses balance control during static and dynamic activities using 14 items scored 0-4 points each where a higher score indicates less disability [110-112]. Maximum score is 56 and for older adults a score of 45 can be considered a cut-off for risk of falling (to our knowledge, no cut-off is available for the stroke population) [133]. The BBS was assessed

with shoes and/or orthoses on. Patients were allowed two attempts on each item, scoring the best performance. If a patient was between two points the lower value was recorded.

3.3.5.7 Timed Up and Go (TUG)

The TUG assesses mobility, balance, walking ability and risk of falling [131]. The test was recorded with a stopwatch and includes rising up from a chair, walk 3 meters in self-selected safe pace, turn, walk back to the chair and sit down. Assistive devices such as walking aids and orthoses were allowed, but all physical assistance was prohibited.

3.3.5.8 Clinical Outcome Variables Scale, Swedish version (S-COVS), Section 5–8

The S-COVS assesses functional mobility using an ordinal scale ranging from 1-7 points with higher score meaning less limitations [115, 129, 130]. The sections 5-8 assess degree of manual support while walking, walking aids, walking endurance, and walking speed, and only these sections were used (Study I).

3.3.5.9 Barthel Index (BI)

The BI assesses degree of independence in ten activities of daily living (ADL) [119, 120]. The items involve for example dressing, bathing, toilet use, transferring oneself and climbing stairs. The total score is 100 points where a higher score indicates less disability. Different cutoff scores are used in the literature to define a favorable outcome [134]. In Paper IV 90 points was used as a cut-off for ADL independence [135].

3.3.5.10 Functional Independence Measure (FIM)

The FIM assesses the level of disability and how much assistance is required in 18 different ADL-related tasks of which 13 are physical tasks and five are cognitive tasks. Each task is scored from 1 to 7 based on level of independence, where higher scores indicates more independence and the total scores range from 18 to 126 [120, 126].

3.3.5.11 Falls-efficacy Scale Swedish version (FES(S))

The FES(S) is a questionnaire where patients are asked to rate how confident they are in performing 13 different ADL-related activities such as getting dressed and climbing a stair without falling, using a 11-point Likert scale ranging from 0 (*not confident at all*) to 10 (*very confident*) [121-123].

3.3.5.12 Stroke Impact Scale (SIS)

The SIS assesses self-perceived functioning, disability and recovery using questions that are grouped into different domains [127, 128]. The domains assessed in Paper IV were self-perceived: Strength (domain 1), ADL/IADL (Instrumental ADL) (domain 5), Mobility (domain 6), and Social participation (domain 8). The patients rate on a 5-point Likert-scale where the range for strength is from "*no strength at all*" to "*a lot of strength*"; for participation from "*none of the time*" to "*all of the time*"; and for the other domains from "*extremely difficult/cannot do at all*" to "*not difficult at all*". A summary score of each domain

is calculated using an algorithm (((mean -1) / (5-1))*100)) resulting in a minimum score of 0 points (maximum disability) and maximum score of 100 points (no disability). If ≥ 50% of the scores in one domain is missing the summary score is not calculated and that patient is omitted from the analyses.

Self-perceived percentage of stroke recovery was scored using a visual analog scale (VAS) ranging from 0 (*no recovery*) to 100 (*maximum/full recovery*).

The different SIS items in each domain have been found to cover a range of aspects relevant for the stroke population and is suggested useful for measuring a wide range of aspects of functioning and disability after stroke [127].

3.3.5.13 EuroQol Questionnaire (EQ-5D and EQ VAS)

The EQ-5D and EQ VAS assess self-perceived health in 5 domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression using a 3-point scale where lower scores mean less perceived problems/disability [124, 125]. The scores may be converted to an index value ranging from 0 to 1 where a higher score indicates a better health state. In EQ VAS the overall health status is rated on a vertical axis ranging from 0 (*Worst imaginable health state*) to 100 (*Best imaginable health state*) [124].

3.3.5.14 Study specific questionnaire

To capture the patients' attitudes towards HAL training and conventional gait training we used a questionnaire constructed by our study group, with questions responded to by using a horizontal VAS ranging from 0 to 10.

In Study I (Paper I) the patients were asked to respond to the question "*To what extent have you experienced a beneficial effect from the gait training with HAL?*" from 0 (none at all) to 10 (largest possible) and to rate their "*Overall attitude to continue training with HAL"* from 0 (negative) to 10 (positive).

In Study II (Paper II) patients responded to the questions: "*To what extent have you experienced a beneficial effect from the gait training?"* and "*To what extent have you experienced a beneficial effect from the gait training with HAL?*" from 0 (none at all) to 10 (largest possible).

3.3.6 Three-dimensional gait analysis

In combination with the clinical assessments the three-dimensional gait analysis provides detailed information about a person's gait pattern, existing gait deviations and contributing factors and may be useful to design targeted treatment and evaluate interventions [136]. In daily clinical practice, rehabilitation therapists such as physiotherapists perform observational gait analyses to evaluate patients' gait characteristics. This is a useful method to evaluate a gait pattern during the rehabilitation after stroke but is however subjective and difficult due to the number of events and aspects to be considered simultaneously in several joints [106]. The use of a three-dimensional gait analysis laboratory allows quantifications of gait patterns and

includes kinematics, kinetics, as well as spatiotemporal data. The kinematic data obtained describes linear and angular motions in three planes (sagital, frontal and transversal). Kinetics inform about forces, moments and powers through registration of ground reaction forces. Spatiotemporal data informs about e.g. step length, single limb support time and walking speed. Data from laboratory gait analysis have demonstrated good reliability also for dependent walkers in the subacute stage after stroke [137].

3.3.6.1 Procedure

Gait analysis was performed after the intervention period (T2) in Study II and was scheduled close in time to the clinical assessments, but not the same day to avoid fatigue bias. All gait analyses were conducted at the Motion Analysis Laboratory at the Karolinska University Hospital, Stockholm, by use of a motion capture system (Vicon MX40, Oxford, UK) and two force plates (Kistler, Winterthur, Switzerland). Twenty-seven passive reflective markers were placed on body segments on pre-defined anatomical landmarks on the shanks, thighs, pelvis and trunk (Vicon Plug-in-Gait model). Patients walked barefoot, at self-selected speed over a 10-meter walkway, with supervision or, if needed, minimal manual support from a physiotherapist. Walking aids (such as a crutch or hemiwalker) was allowed if needed. Video recordings with two digital cameras were performed simultaneously. Marker placement were performed by one or two of in total three investigators, using the same protocol but not blinded for intervention allocation. Time needed for the gait analysis was normally 1-1.5 hours. Approximately three gait cycles for each patient were used to calculate kinematic data. Effort was made to collect clean strikes on force plates to calculate kinetics but could not always be obtained from both sides, paretic and non-paretic, as the walking aid interfered with the force plate. Reference values were obtained from previously collected data from a group of 81 healthy subjects, described in detail in Study III. Spatiotemporal parameters were non-dimensionalized according to Hof [138] to obtain comparable numbers. Kinetics were normalized to body mass, and positive joint work was calculated as the positive integral of joint power.

3.3.6.2 Gait Parameters

The spatiotemporal, kinematic and kinetic parameters included and described in Paper III were selected with regard to clinical importance and previous research on gait post stroke [28].

3.3.6.3 Gait Profile Score (GPS)

A Gait Profile Score (GPS) was calculated for the paretic and non-paretic leg respectively to quantify overall gait deviation. The GPS quantifies the magnitude of gait deviation in degrees in the lower body (GPS-LB) or whole body (lower body and trunk) (GPS-WB). Larger GPS indicate greater deviation from normal gait. The GPS is calculated from the entire gait cycle [139, 140] and a can be divided into Gait Variable scores (GVSs) to show each gait variable's deviation throughout the gait cycle [139]. The GVSs is obtained by taking the root mean square difference between the joint angle of the patients and the average

of healthy subjects [141]. Gait indices are commonly used to assess overall gait quality in studies using three-dimensional gait analysis [140]. The GPS has previously been used mostly in children with cerebral palsy [142] but have recently been found reliable and suggested as a suitable tool for assessing gait quality post stroke [141].

3.3.7 Data describing conventional gait training and HAL training

3.3.7.1 Conventional gait training

In Study I patients participated in the conventional team-based rehabilitation program during the whole intervention period. However, data on the conventional gait training performed was not collected.

In Study II data describing the conventional gait training (for both groups) were recorded in the medical records by the patients' team physiotherapist. The physiotherapists were instructed to describe the training regarding: walking aids, orthosis used, estimated effective gait training time and distance walked during the sessions, the degree of manual support or supervision required while walking and any adverse events (like falls) if present. If gait training on a treadmill, with/without BWS was performed, additional information regarding the speed and amount of BWS applied were recorded.

3.3.7.2 HAL training

In Study I, the therapist recorded time to arrange the equipment and initiate the training session, utilization of conventional aids such as orthoses during HAL training, technical risk factors and prevention of these and other relevant comments associated with safety and feasibility.

In both Study I and II, data on HAL training were recorded using standardized protocols including time, speed, amount of BWS and individual settings within the autonomous and voluntary control mode. A standardized protocol was also used to report presence of adverse events (such as falls, skin impact, pain etc.) related to the use of HAL.

3.4 PATIENTS INCLUDED IN THE STUDIES

A total number of 40 (8+32) patients were included in the two studies. Reason for not fulfilling the inclusion criteria were mostly related to diagnosis (other than stroke) and/or ability to walk independently (Study I) or a FAC score >1 (Study II). An overview of the patients in each Paper is found in Table 3.

Table 3. *Overview of study design and patient characteristics in Paper I-IV.*

	Study I	Study II		
	Paper I	**Paper II**	**Paper III**	**Paper IV**
Design	Prospective single arm	PROBE	PROBE subsample	PROBE subsample
Patients	8	32	17	28
Age mean (range)	53 (39-64)	54 (23-66)	52 (23-64)	53 (23-66)
Group HAL/CONV	n.a.	16/16	10/7	15/13
Gender male/female	8/0	26/6	14/3	23/5
Diagnosis hemorrhage/infarction	3/5	13/19	8/9	12/16
Paretic side left/right	4/4	21/11	13/4	20/8
NIHSS Score median [IQR]	13 [9;15]	12 [9;15]	11 [9;13]	11 [8.25;14.5]

PROBE: Prospective, Randomized, Open labeled, Blinded evaluation; HAL: Hybrid Assistive Limb group; CONV: Conventional gait training group; NIHSS: the National Institutes of Health Stroke Scale; IQR: Inter quartile range.

3.4.1 Excluded patients

In Study II four patients were excluded of whom three were men and one woman, with a mean age of 51 years (SD 10). Three were excluded before the intervention start, two due to fast improvement of the FAC score (>1) between baseline testing and start of the intervention and one due to new information of medical reasons restricting intensive gait training. One patient was excluded after start of the intervention (HAL training) due to discovery of medical reasons restricting intensive gait training. All four suffered an infarction, two with left and two with right sided hemiparesis.

3.5 SAMPLE SIZE AND STATISTICAL POWER

3.5.1 Study I

This was a study of safety and feasibility. No power calculation was performed prior to the study. Eight patients were included.

3.5.2 Study II

In Paper II the sample size was determined by the primary outcome i.e. FAC. A difference of one score was considered a clinical meaningful change, based on pilot data from Study I and Hesse et al. [143]. Thus, to detect between-group differences, a sample size of 16 patients in each group was required to reach a statistical power of 0.8, with an alpha level set to 0.05.

The intention was to include 36 patients in order to handle a loss of two patients per treatment group.

Paper III and IV are based on the sample from Paper II, and no prior sample size calculations were performed for these sub studies.

3.6 STATISTICAL METHODS

A summary of the statistical methods used in each paper are presented in Table 4. Statistical analyses were performed using SPSS (IBM SPSS Statistics version 22 and 25). Variables were checked for normality using Shapiro-Wilk's test, boxplots, histogram and QQ-plots. Significant level was set to $p < 0.05$ (two-tailed) and data were analyzed using an all-available-data approach. In case of adjustment for multiple comparisons correction according to the Bonferroni method was applied.

Table 4. *Statistical methods used in Paper I-IV*

	Paper I	Paper II	Paper III	Paper IV
Differences within group(s)		Friedman test Sign-test McNemar test Wilcoxon Signed-Rank test	Wilcoxon Signed-Rank test	
Differences between groups		Mann-Whitney U-test Independent sample t-test Chi-square test/Fisher's exact test	Mann-Whitney U-test Independent sample t-test Fisher's exact test	Mann-Whitney U-test Independent sample t-test Chi-square test/Fisher's exact test
Associations		Ordinal regression Binary logistic regression	Spearman's rank correlation	Pearson's Correlation Linear regression

3.7 ETHICAL APPROVAL

Study I (Paper I) was approved by the regional ethical review board in Stockholm, Sweden (Dnr: 2012/696-31/1) and was approved and registered as a clinical trial by the Swedish Medical Products Agency (Dnr: 461:2012/518333).

Study II (Paper II-IV) was approved by the regional ethical review board in Stockholm, Sweden (Dnr: 2013/1807-31/2, 2014/1633-32 (additional application) and 2014/1267-32 (additional application)) and registered at ClinicalTrials.gov [144] (Identifier nr: NCT02410915).

Both studies were performed in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients received oral and written study information and gave their informed consent to participate in the respective study.

3.7.1 Ethical considerations

The risk of adverse events through participation in the studies was considered low and positive effects possible, why the benefits was considered outweighing potential harm. The benefits included careful and detailed evaluation of function and activity performance both during and after completed inpatient rehabilitation period, and at the 6-months follow up in Study II. Patients were also offered the possibility to intensify gait training further early after stroke, in line with current scientific evidence.

The senior physician at the ward, who approached eligible patients, was not otherwise involved in the patient's rehabilitation. The authority of a senior physician may however have affected the patient's attitude and/or decision to participate in the study. Yet, patients were informed that they could decline or withdraw study participation at any time.

In the respective written study information, the HAL training procedure was thoroughly described. This caused some patients in Study II to believe that they would all receive HAL training, despite information about randomization. This was discovered after inclusion of the first patient why additional clarifying oral information about the randomization procedure was added. There were however no dropouts due to intervention allocation.

Cyberdyne Inc. provided HAL suits but were not otherwise involved in the design of any of the two studies, data collection, data analysis or manuscript writing.

For those patients who participated in the laboratory gait analysis (Paper III) little clothing was required. Thus, before study start, information was given that participating in laboratory gait analysis requires that you wear little clothing since the reflective markers are to be placed on the surface of the skin. In addition, to use the voluntary control mode in HAL training, the physiotherapist needs to attach EMG-electrodes on the skin surface over hip and knee muscles.

We consider that the four principles in medical ethics: autonomy, justice, beneficence and non-maleficence have been fulfilled in the studies included in this thesis.

4 RESULTS

This section summarizes the main results of the thesis (Study I and II (Paper I-IV)). Detailed results are provided within each publication and manuscript.

4.1 SAFETY AND FEASIBILITY

In Study I (Paper I) HAL was found to be safe and feasible for gait training early post stroke in patients with hemiparesis, unable to walk independently, undergoing an inpatient rehabilitation program. No serious adverse events occurred. The number of training sessions varied from 6 to 31 (median 16). A typical training session lasted around 90–105 minutes of which 15-20 minutes was the time to attach the HAL suit to the patient and 25 minutes the net walking time. The patient's ability to independently move between the wheelchair and bench; ability to stand with support and cognitive skills affected the donning and doffing time.

4.2 INTERVENTIONS

4.2.1 Training dose and intensity

In Study I: HAL training was conducted by one or two physiotherapists. All patients except one could be switched from autonomous to the voluntary control mode during the training period, on average after the 6th sessions. The BWS provided was in median 27% of the patients' body weight and the patients individual walking distance per session ranged from in mean 155 to 797 meters.

In Study II: HAL training was conducted by two physiotherapists in most sessions. Most patients could be switched over to the voluntary control mode after the initial session (with autonomous control mode) as planned. The BWS was set to 30% of the patient's body weight at the first session and had at the last session been decreased to 19% in mean (SD 5). The treadmill speed was increased in mean from 0.8 km/h (0.22 m/s) to 1.5 km/h (0.42 m/s) from the first to the last sessions.

Data describing estimated time spent in walking during the conventional training sessions were limited. However, distance was recorded in the medical records in 80% of all sessions (CONV group 76%, HAL group 84%).

In the HAL group, patients walked significant longer distances during the HAL training compared to during the conventional gait training ($p = 0.001$). The overall mean distance walked per HAL session was 619 meters (SD 368) (Figure 6) and during the conventional gait training in median 30 meters [IQR 15;50]. There was no between-group difference in distance walked during the conventional gait training ($p = 0.078$) (Table 5).

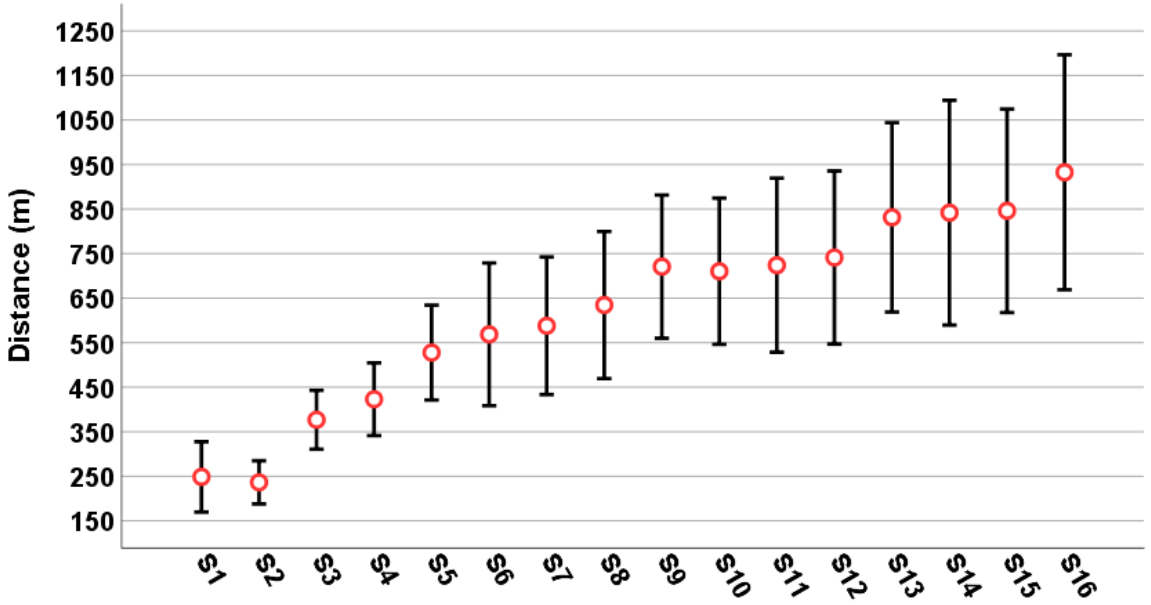

Figure 6. *Walking distance per HAL session from session one (S1) to session 16 (S16). Presented as Mean and 95% Confidence Intervals.*

The CONV group performed a greater number of conventional gait training sessions over the 4-weeks intervention period compared to the HAL group. The total number of sessions (HAL and conventional gait training) were however greater in the HAL group (Table 5).

Table 5. *Number of gait training session and distance walked per session.*

	HAL	CONV	P-value
Number of CGT sessions (median, IQR)	6 (5;8.75)	10.5 (8;14.5)	0.003
Total number of gait training session (CGT + HAL) (median, IQR)	22 (19.5;24)	10.5 (8;14.5)	<0.001
Distance (m) per session CGT (median, IQR)	30 (15;50)	60 (22;138)	0.078
Distance (m) per HAL session (mean, SD) (median, IQR)	619 (368) 564 (357;792)	-	

HAL: Hybrid Assistive Limb group; CONV: Conventional gait training group; CGT: Conventional gait training; IQR: Inter quartile range; SD: Standard deviation.

In summary, both studies showed that long walking distances were achieved during the HAL sessions (Paper I and II). In Study I it was shown that approximately 30% BWS was sufficient for most patients, why this was set as a start for all patients in Study II.

4.2.2 Patients self-perceived beneficial effect of the interventions

In Study I (Paper I): Seven patients responded to the questionnaire. The self-perceived beneficial effect from gait training with HAL was in median [IQR] 9 [7.5;9] and the overall attitude to continue training with HAL 8.5 [4;10].

In Study II (Paper II): Thirteen patients in the HAL group and nine in the CONV group responded to the questionnaire. Reasons for not responding to the questionnaire were related to dysphasia/aphasia (HAL n=2, CONV n=6) or logistic reasons (n=1 in both groups). There was no significant between-group difference for self-perceived beneficial effect of the conventional gait training (in median [IQR] for HAL 8.3 [6.7;9.5] and CONV 9.5 [8;10], p = 0.292). In the HAL group the self-perceived beneficial effect from gait training with HAL was in median 9 [7.9;10].

In summary, patients in both studies were positive and most reported a beneficial effect from HAL training. However, in Study II we found that this perceived beneficial effect of HAL training was not superior to that after conventional gait training only.

4.3 FUNCTIONING AND DISABILITY

4.3.1 Objectively assessed clinical outcomes

In Study I (Paper I): All eight patients, with moderately severe stroke according to NIHSS at inclusion, performed the assessments before and after the intervention period. Most patients (63%) had no functional walking ability (i.e. FAC 0) at inclusion. All patients exhibited improvements in walking independence and speed, balance and ADL performance after incorporated HAL training. The median FAC score improved from 0 [0;1] at baseline to 1.5 [1;2] after the intervention.

In Study II (Paper II): In total 32 patients, with moderately severe stroke according to NIHSS at inclusion, completed the intervention period (16 in each group). Thirty patients performed all three assessments whereas two patients in the CONV group were lost to follow up (at T3). Most patients (69%) had no functional walking ability (i.e. FAC 0) at inclusion. There were no statistically significant difference between the groups at baseline regarding patient characteristics or clinical assessments.

Both groups improved significantly in all clinical assessments i.e. independence in walking, control of voluntary movement in the lower extremity, walking speed/endurance, ADL and balance over time ($p < 0.001$) (Paper II).

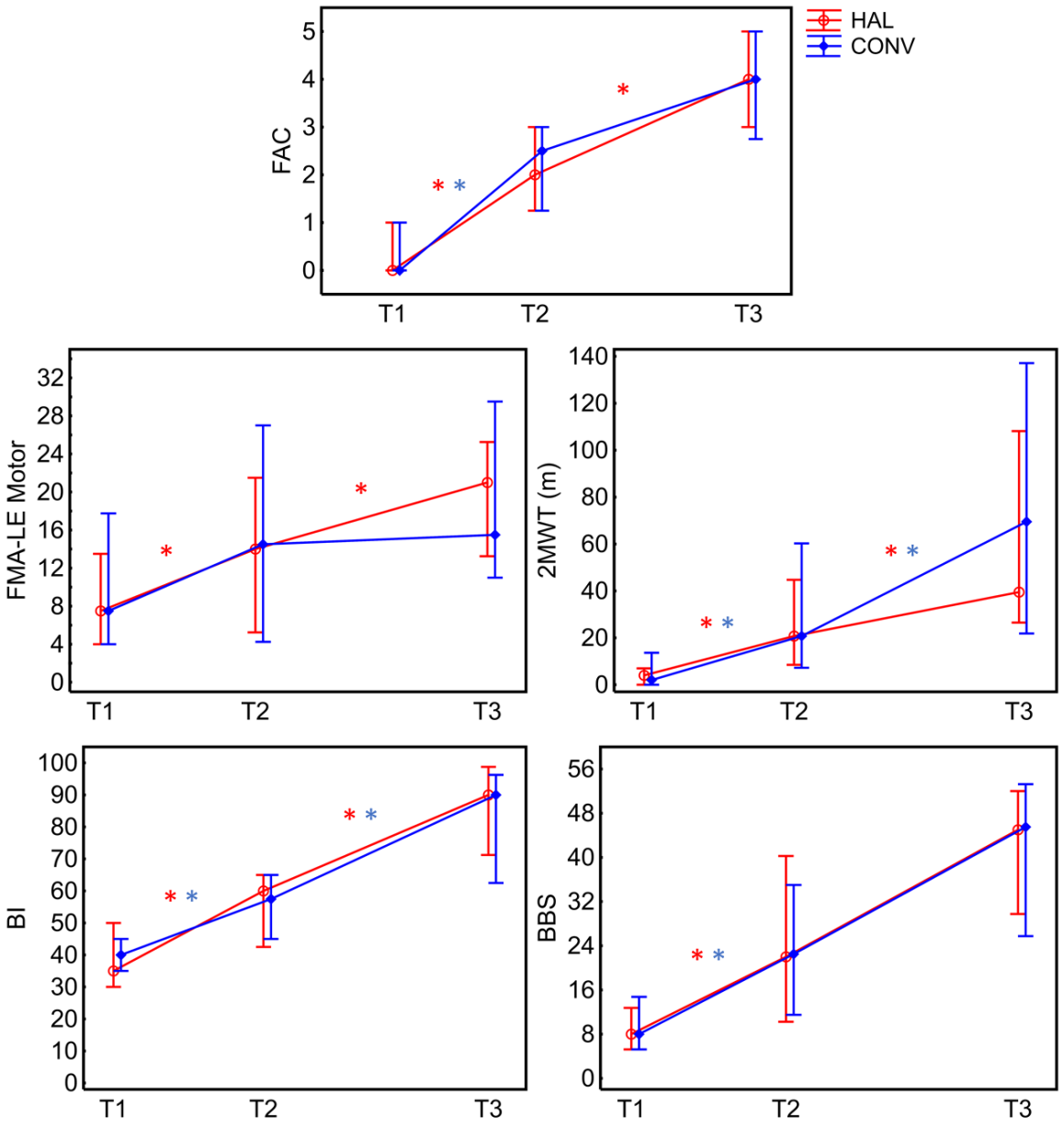

Figure 7. *Outcome assessments before (T1) and after (T2) the intervention, and at 6 months post stroke (T3). Presented as Median and Inter Quartile Range for the HAL group and CONV group respectively. HAL: Hybrid Assistive Limb group; CONV: Conventional gait training group; T1: Time point 1; FAC: Functional Ambulation Categories; FMA-LE motor: Fugl Meyer assessment lower extremity motor score; 2MWT: 2 minute walk test; BI: Barthel Index; BBS: Berg Balance Scale. *indicates significant within-group difference between T1-T2 and T2-T3 for each group after adjustment for multiple testing ($p < 0.006$). There were no significant between-group differences at T1 nor in change scores between time points (T1-T2, T2-T3, and T1-T3) for any of the above assessments.*

Except for control of voluntary movement in the lower extremity in the CONV group, both groups improved significantly in all objectively assessed clinical outcomes between T1-T3 also after the Bonferroni correction ($p < 0.006$) (Paper II).

In the HAL group there was also a significant within-group change between T1-T2 and T2-T3 ($p < 0.006$), in all objectively assessed clinical outcomes except for balance (BBS) between T2-T3 ($p = 0.007$). In the CONV group, the change in independence in walking and balance between T2-T3, as well as control of voluntary movement in the lower extremity between T1-T2 and T2-T3 were non-significant ($p > 0.006$) (Figure 7). However, there were

no significant between-group differences at T1 nor in change scores between time points (T1-T2, T2-T3, and T1-T3) (Paper II).

Both groups improved by a median of two points on the FAC between T1-T2 ending up with a median FAC score of 2 and 2.5 for the HAL group and the CONV group respectively. This denote that the patients could walk but required continuous manual contact or intermittent light touch of one person during ambulation on level surfaces to assist balance or coordination, after the intervention period. At 6 months post stroke, both groups had a median FAC score of 4, meaning they could ambulate independent on level surfaces (but required help to manage stairs, inclines, or unleveled surfaces). Accordingly, 20 patients (67%) (11 in the HAL group, 9 in the CONV group) were classified as independent in walking (i.e. FAC ≥4) at 6 months. There were however no significant between-group differences (Paper II). The proportion and number of patients in each FAC score (0-5) at baseline, after the intervention and at 6 months post stroke are displayed in Figure 8.

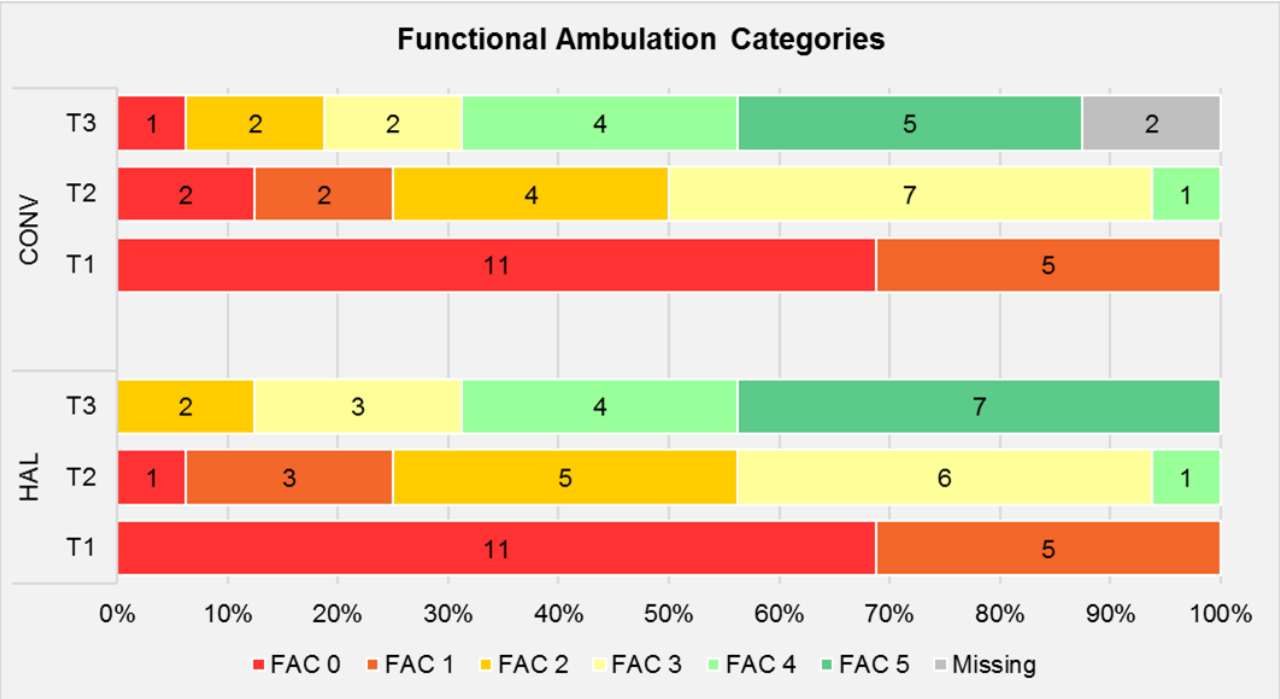

Figure 8. *Functional Ambulation Categories score at T1, T2 and T3 for the HAL group and CONV group respectively. Presented as actual number and proportion of patients within each score. FAC 0 equals no functional walking ability and FAC 5 equals independent walking including unlevel surfaces. T1: Time point 1 (before the intervention); T2: Time point 2 (after the intervention); T3: Time point 3 (at 6 months post stroke); FAC: Functional Ambulation Categories; HAL: Hybrid Assistive Limb group; CONV: Conventional gait training group*

In summary, patients in both studies improved in functioning. The median FAC score had improved more than one score (1.5-2) after the intervention. Study II however exhibited that neither the improvement on the FAC score nor improvements in other objective clinical outcome measures in the HAL group were superior to those achieved after conventional gait training alone.

4.3.2 Prediction of independence in walking

In Study II we found that having a higher FAC score after the intervention period was not associated with intervention group (OR 1.095, $p = 0.888$). Neither did intervention group, sex, diagnosis, paretic side, initial movement function (FMA-LE motor at T1), or initial balance (BBS at T1) influence the odds of being independent in walking (FAC ≥4) at 6 months. However, age and stroke severity (NIHSS at T1) was found to be key predictors (OR 0.848, CI 0.719–0.998, $p = 0.048$ and OR 0.793, CI 0.635–0.989, $p = 0.040$ respectively). However, these two predictors exhibited collinearity and when included in a multivariate model only age was left as a predictor, whereas all patients younger than 54 years of age were independent in walking at 6 months post stroke (Paper II).

4.3.3 Gait pattern functions

In Study II (Paper III) gait pattern functions were assessed after the intervention period in 17 patients (HAL n= 10, CONV n= 7), in mean 66 (SD 15) days after stroke onset. All except one used a walking aid during the three-dimensional gait analysis. Kinematic data were obtained from all patients whereas kinetics in the paretic limb were successfully collected in 13 patients (HAL n= 7, CONV n= 6). Kinetics for the non-paretic limb were only successfully collected in four patients and were therefore excluded from the analysis. All patients exhibited impaired gait kinematics, kinetics and spatiotemporal asymmetry as compared to the healthy subjects and as described previously after stroke [28, 34, 35]. However, no significant between-group differences in GPS or any GVSs for either the paretic or the non-paretic leg were found. The GPS-LB for the paretic limb (GPS-LBP) was in median [IQR] 12.9 [8.3;16.1] and 13.4 [10.5;14.7] for the CONV and HAL groups respectively (p =0.887) (Figure 9). In addition, no significant differences in any kinematic, kinetic and/or spatiotemporal parameters between the groups were demonstrated. Since lack of between-group differences, the associations were computed for the whole (merged) group. The overall gait quality (GPS-LBP) was associated with independence in walking (FAC) ($R_S = -0.625$, $p = 0.007$), walking speed/endurance (2MWT) ($R_S = -0.733$, $p = 0.001$), balance (BBS) ($R_S = -0.685$, $p = 0.002$) and movement function (FMA-LE Motor) ($R_S = -0.504$, $p = 0.039$) (Paper III).

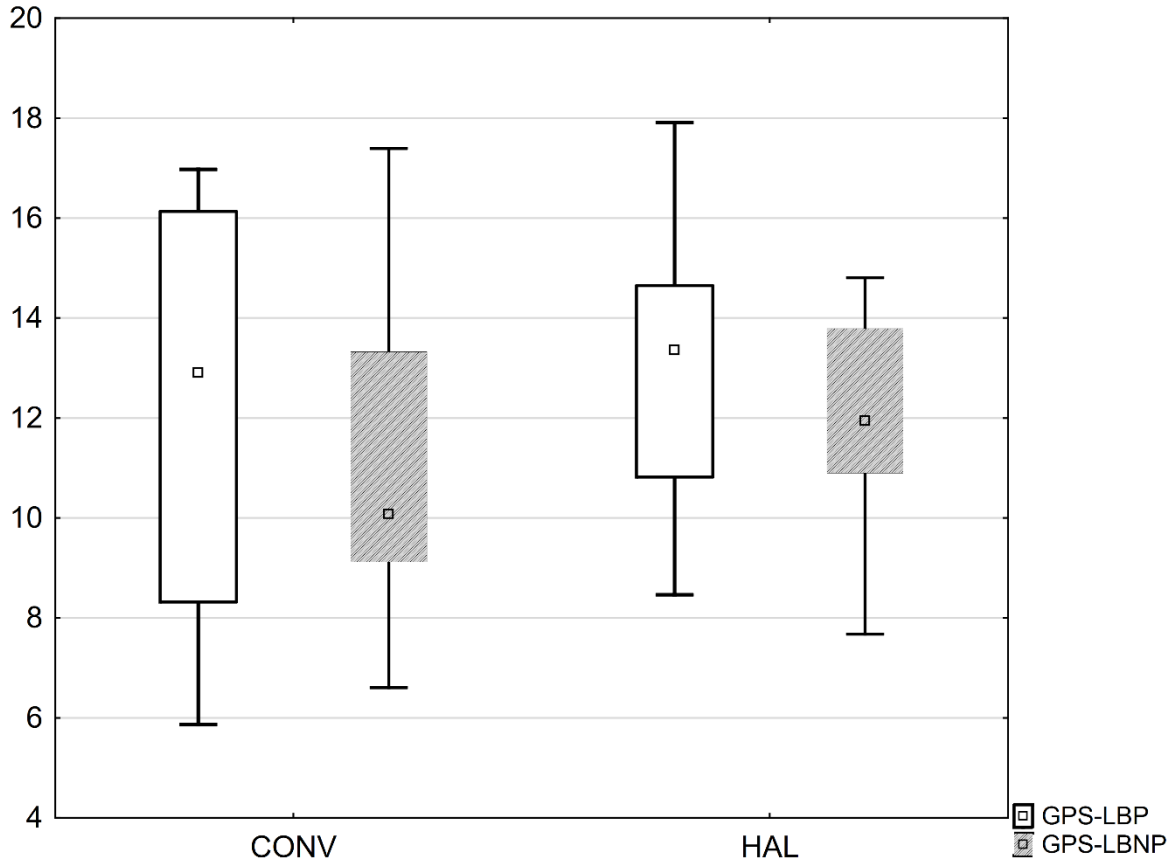

Figure 9. *Gait profile score for the paretic and non-paretic limb in both groups. The GPS-LBP was in median [IQR] 12.9 [8.3;16.1] and 13.4 [10.5;14.7] for the CONV and HAL groups respectively (p = 0.887). The GPS-LBNP was in median [IQR] 10.1 [9.1;13.3] and 11.9 [10.8;13.9] for the CONV and HAL groups respectively (p = 0.315). GPS-LBP: Gait Profile Score Lower Body Paretic Limb; GPS-LBNP: Gait Profile Score Lower Body Non-Paretic Limb; HAL: Hybrid Assistive Limb group; CONV: Conventional gait training group*

The overall positive joint work was considerably lower than in the controls, indicative of e.g. slower walking speed and reduced propulsive ankle force during pre-swing. However, there were no difference in neither total positive work nor in the proportional (%) contribution from each joint to the total positive work between the HAL and CONV group (Figure 10).

The walking speed while walking barefoot during the gait analysis compared to during over ground walking at 2MWT (performed with shoes and orthoses) were strongly associated (RS= 0.965, p <0.01).

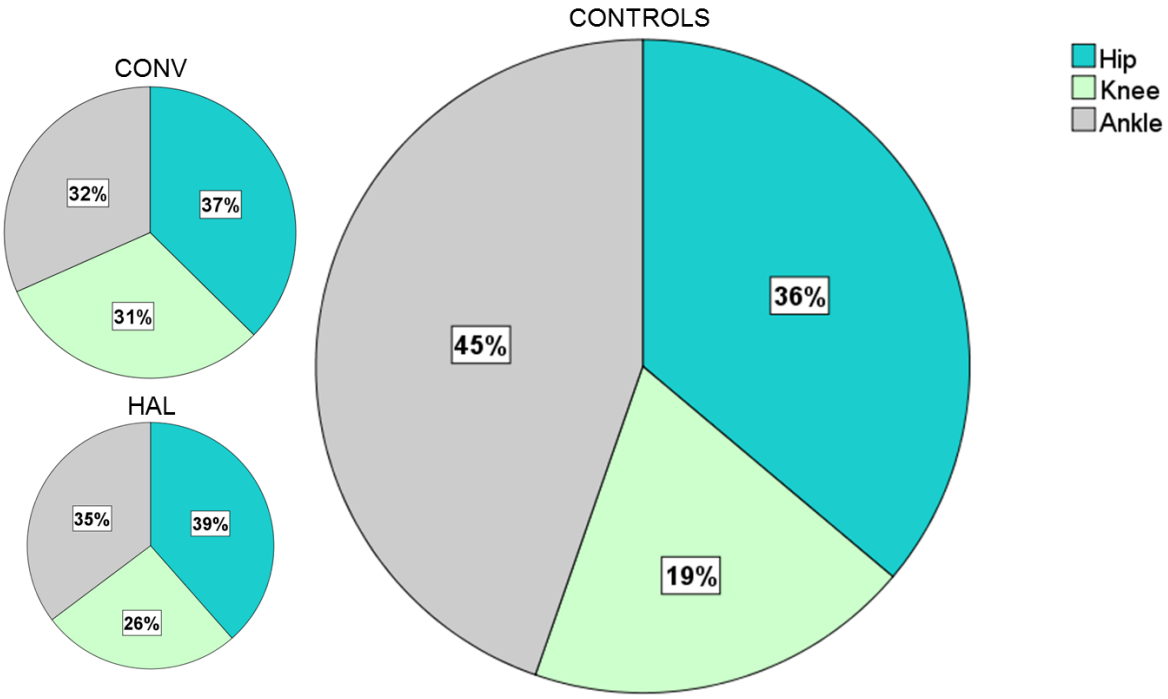

Figure 10. *Mean contribution of positive work for Hip, Knee and Ankle on the paretic side. The figures are scaled to a percent of overall positive lower limb joint work in which controls represent 100%. The CONV and HAL groups had an overall positive work of 46% and 39% that of the controls, respectively. The overall positive joint work for the HAL group was 85% that of the Conventional group (non-significant). The proportional (%) contributions of each joint to the total positive work were similar in both groups (Hip p = 0.870, Knee p = 0.594, Ankle p = 0.708). HAL: Hybrid Assistive Limb group; CONV: Conventional gait training group; CONTROLS: healthy subject group.*

4.3.4 Self-perceived functioning, disability and recovery

In total 89% of patients were dependent on assistance in personal care and/or domestic life after the inpatient rehabilitation period. Still, in Study II (Paper IV) no between-group differences in self-perceived muscle strength, ADL, mobility, participation or recovery, according to SIS were found. Both groups reported the highest perceived impact of stroke in the Strength domain and the lowest in the Mobility domain (Figure 11). Self-perceived Recovery was in median 50 [40;55] and 45 [30;60] for the HAL and CONV group respectively (p = 0.786) with a wide total range from 0 to 90.

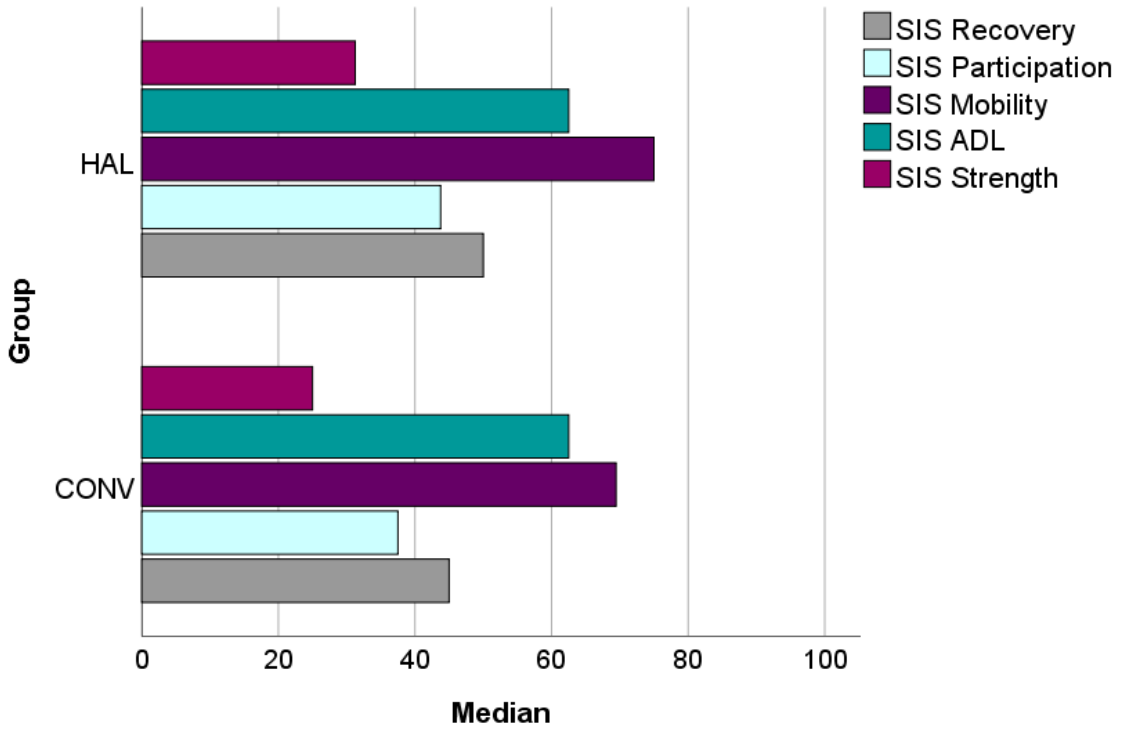

Figure 11. *Self-perceived muscle strength, ADL, mobility, participation and recovery according to the Stroke Impact Scale. Values presented as Median. A score of 0 points means maximum disability/no recovery and a score of 100 points no disability/full recovery. HAL: Hybrid Assistive Limb group; CONV: Conventional gait training group; SIS: Stroke Impact Scale. HAL n= 15, CONV n=13*

After controlling for group and baseline characteristics, we found that self-perceived mobility at 6 months was associated with change in walking speed/endurance and balance (ΔT1-T3), together explaining 72% of the variance (Adj R^2 0.717, $p = 0.002$).

The variance in self-perceived recovery at 6 months post stroke was found to be explained by objectively assessed change in ADL between T1 and T3 (BI ΔT1-T3), and self-perceived ADL at 6 months (SIS ADL), (Adj R^2 0.129, $p = 0.034$) and (R^2 0.342, $p = 0.001$) respectively. Among the items in the self-perceived ADL domain of SIS, the item *getting to the toilet on time* had the strongest association (rp 0.684, $p < 0.01$) with self-perceived recovery.

5 DISCUSSION

5.1 MAIN FINDINGS

The aim of this thesis was to investigate the safety and feasibility of HAL for gait training in the subacute stage after stroke and to explore the effect of incorporated HAL training on functioning, disability and health compared to conventional gait training alone during inpatient rehabilitation in patients with severe limitations in walking, i.e. FAC 0-1, in the subacute stage after stroke.

In study I, HAL was found to be feasible to use in an inpatient rehabilitation setting in patients unable to walk independently, who initiated HAL training within 7 weeks after stroke. The adverse events were few and negligible, such as temporary skin irritation/redness from EMG-electrodes or discomfort from a tight strap, and the training was well tolerated by the patients. In addition, we found that patients improved in walking independence and speed, balance and ADL. The findings suggested that HAL training can be incorporated in, and may be an effective gait training method during rehabilitation of younger patients in the subacute stage after stroke. An observation was that patients walked long distances during the HAL sessions despite limitations in walking over ground (Paper I).

Corroborating the results in Study I, improvements in walking independence and speed, balance, and ADL in both groups were demonstrated in Study II, but no between-group differences were found. Despite severe limitations in walking at inclusion, within 8 weeks after stroke onset, independence in walking at 6 months post stroke was achieved in 2/3 of patients and was best predicted by a younger age, regardless of intervention. Patients in the HAL group walked significantly longer distances during the HAL training as compared to during the conventional gait training. This finding suggests that HAL training may be a way to increase the dose in gait training early after stroke but that additional effects on functioning and disability are not superior to after conventional gait training alone, in these younger patients with initial severe limitations in walking (Paper II).

The gait laboratory assessment exhibited an impaired gait pattern among all patients after the intervention period, without between-group differences. Patients in both groups exhibited a gait pattern similar to what has previously been reported after stroke and the results suggest that HAL training could not be shown to induce recovery of a normal gait pattern as compared to conventional gait training alone (Paper III).

The self-perceived ratings of muscle strength, mobility, ADL, participation and recovery from stroke revealed that both groups exhibited comparable remaining disabilities at 6 months post stroke. It was also found that self-perceived recovery among these patients was best predicted and explained by their ability to perform ADL (Paper IV).

5.2 SAFTEY AND FEASIBILITY OF HAL TRAINING

Corroborating previous studies in chronic stroke as well as in other conditions [78, 79, 145, 146] we found HAL to be feasible for gait training as part of an inpatient rehabilitation program in patients in subacute stage after stroke (Study I). In this study we used the double leg version of HAL, however based on our experience and the principle of not providing more assistance nor restraint than needed during training, the use of the single leg version, is more suitable for patients with unilateral weakness, e.g. after a stroke, and should be first choice for these patients. The time to put the suit on and initiate a training session was dependent on the patients' overall stroke severity and was facilitated if, and sometimes even required two therapists present. Thus, the time and resources required for this training compared to conventional gait training need to be explored further in the light of aims, outcome assessments and results.

5.3 INTERVENTIONS

5.3.1 Training dose and intensity

The HAL training was found to enable long walking distances during the training sessions (Paper I and II), as compared to during the conventional gait training session (Paper II), thus reaching a higher dose. Current literature suggests that dose, intensity and variability are essential parameters to gain improvements from training interventions after stroke [53, 55, 56, 58]. To increase the dose and/or the intensity alone may however not be enough to enhance walking outcomes [58] since walking is a complex activity requiring integration of different abilities. To provide variability in stepping practice and assistance only as needed may promote motor learning and have been found to improve motor recovery, including walking, in experimental models in spinal cord injury and chronic stroke [147-149]. As pointed out by others, the variability in EAGT is limited [58], requires less balance control and does not meet the demands of over ground walking. In practice, few specific training interventions may provide all relevant aspects why a combination may be the most relevant.

In previous EAGT studies there is an inconsistency in applied intervention designs, frequency, intensity and duration of the training sessions as well as evaluations of outcome. This probably reflects both theoretical and practical considerations of e.g. training dose needed to achieve significant effects, patients' initial level and study resources. Reasonably, the optimal design would allow training programs to be performed at the limit of each patient's capacity with regard to the intensity and duration of each training session. The intensity and duration of the training periods must also consider the patient's functional level as well as the capacity and aims with regard to e.g. neuroplasticity, musculoskeletal function, cardiovascular function, gait pattern or independence in walking.

Even if not fully understood, the use of EAGT may be either more or less energy demanding for patients with stroke and spinal cord injury [150-154] depending on type of device, the amount of BWS applied and walking speed [150, 154]. Some previous studies have indicated positive effects on aerobic capacity after EAGT, using the Lokomat, in subacute

stroke [155, 156] and accordingly EAGT may be a way to enhance the intensity in gait training in patients dependent in walking after stroke and may contribute to secondary prevention of recurrent stroke [157]. Even if not included in this thesis (but assessed in Study II through semi-structured interviews in the HAL group) the patients found HAL training to be physically challenging and exhausting. This was also the therapists' impression and aim with the applied intervention protocol with increasing demands in terms of less assistance and BWS, and higher walking speed as patients improved. On the other hand, patients were able to walk longer distances with HAL but this could partly be explained by the extra time provided for the HAL sessions (90 minutes) compared to the conventional gait training (usually 30-60 minutes) and the extra balance support provided by the suit and the BWS (Paper II). In future EAGT studies, it would be justified to explore potential beneficial effects on cardiorespiratory functions. This requires special attention to individualized protocols controlling for e.g. intensity, level of assistance and amount of BWS.

The patients in Study II who performed HAL training spent proportionally more of their gait training time on a treadmill compared to the conventional group (Paper II). Skills obtained in one setting (such as on a treadmill) may only transfers partially and transiently to another setting (such as over ground walking) [158] why the possibility to perform EAGT over ground should be considered in future exoskeleton development and clinical studies. Some HAL studies have already applied this using a mobile suspension system over ground [78-80, 82, 91, 97]. In addition to transfer issues, the limited degrees of freedom in the HAL suit restrict the patients to movements mainly in the sagittal plane and may not be optimal to regain a normal gait pattern. Future exoskeletons designs, such as exosuits using softer fabrics [61, 159], allowing more degrees of freedom, should facilitate the possibility of increasing the variability in EAGT.

In addition, the use of EMG signals from partially paretic muscles to enable voluntary initiation of assisted walking may not be an optimal method since the recruitment of muscles per se may be abnormal after stroke and other methods for voluntary initiation and adaptive control strategies should be explored.

5.3.2 Self-perceived beneficial effect

To use EAGT may serve as a motivating factor in stroke rehabilitation. The results from the questionnaires assessing patients' attitude and perceived beneficial effect of HAL training exhibited that patients found HAL training and conventional gait training to have equally beneficial effect (Paper II). Thus, from a patient perspective the HAL training is well accepted to incorporate in clinical practice, but not superior to conventional gait training.

5.4 FUNCTIONING AND DISABILITY

5.4.1 Objectively assessed clinical outcomes

Improvements were demonstrated within both groups, however no between-group differences were found in movement function, walking independence and speed, balance, or ADL (Paper

II). These findings are in conflict with some but corroborate the results of other previous HAL studies.

In previous studies comparing HAL training to conventional gait training in the acute [97], early subacute [80] and late subacute [82] stage after stroke the results are diverse with no between-group differences in independence in walking in two studies [82, 97], while a more favorable outcome for the HAL group, regarding independence in walking, was found in one study [80]. Regarding walking speed, one study found greater increase in the HAL group [82] while the other found no between-group difference [80]. A post-hoc analysis of patients in a study by Yokota et al. 2019 [97] showed that patients with initial FMA-LE motor score below 20 points exhibited greater improvement in independence in walking after HAL training compared to after conventional gait training. Notably, as in our study the HAL group in their study received more therapy time in total. In contrast, other (single group) studies suggest that increase in walking speed [86] and improved independence in walking [90] after HAL training are less in patients with more severe hemiparesis (as assessed by Brunnström or FMA-LE) in the acute phase after stroke and in subacute stage after diseases in the central nervous system resulting in lower limb motor paresis. In Study II, patients had a FMA-LE motor score at T1 that were corresponding to a severe hemiparesis, yet improvements in independence in walking and walking speed were found, but without between-group differences. Further, in patients with chronic stroke, a randomized crossover trial [93] with 30 conventional and 30 HAL sessions over a 12-week period, exhibited neither a significant between-group difference in walking speed/endurance and independence in walking nor in balance. These conflicting results are also found in studies using other EAGT devices [66-69, 155, 156, 160-162] and highlight the need of further well-designed studies with sufficient power to identify possible subgroups of patients who might benefit more from this kind of training. As already pointed out, previous HAL studies have several limitations with regard to study sample size and non-blinded outcome assessments. Together, the findings in previous studies and the result from our Study II suggest that HAL training is not more beneficial than evidence-based conventional gait training in the subacute stage after stroke. Whether there are subgroups of patients with stroke who may respond better to HAL training than to evidence-based conventional gait training has not yet been shown.

It was found that 67% of patients were independent in walking (FAC ≥4) at 6 months post stroke (T3), representing an improvement of 83% of the possible improvement, i.e. maximal score minus the score at inclusion (Paper II). Thus, despite moderate to severe lower extremity movement impairment at study inclusion (according to the FMA-LE motor score and NIHSS) patients in both groups in our Study II improved in independence in walking in concordance with previous studies after stroke, which notably included patients earlier after the incident, and reported that 62% [163], 79% [47] and 70% [49] respectively of patients were independent in walking at 6 months. This highlights the substantial improvement seen when conventional, evidence-based training as well as HAL training are offered to non-ambulatory patients in the subacute stage after stroke. Still, variability in outcomes exists and not all patients regain independent walking ability. Therefore, we suggest that future studies

should aim to identify subgroup of best responders to different gait training strategies during stroke rehabilitation, and also explore the cost effectiveness of different interventions, with regard to time and therapists needed.

5.4.2 Prediction of independence in walking

Independence in walking could best be predicted by age but was not related to intervention group in our study sample (Study II, Paper II). All patients below 54 years of age (n=10) were independent in walking at 6 months post stroke. Age and stroke severity have previously been found to predict upper limb recovery [45], and has together with early trunk stability and hip extension strength also been suggested important for predicting independent walking [47, 49, 50, 163]. Hip extension muscle strength was not assessed in our studies but may provide proximal stability for those with poor trunk control [50] enabling walking and should be considered in future studies to facilitate stratification and/or subgroup analyses.

In addition, the degree of corticospinal tract damage according to brain imaging and transcranial magnetic stimulation has predictive value for recovery of movement function in the upper extremity after stroke [45, 164, 165] but corresponding studies have not yet consistently shown its importance for recovery of lower extremity movement function, gait outcomes and for predicting recovery of independent walking [50, 166-168]. In future studies, including data on brain structure and function together with a larger sample size may enable subgroup analysis and provide insight in who will benefit the most from EAGT and conventional gait training respectively.

Few patients (6%) in Study II (Paper II) were independent in walking at the T2 assessment. Further, the period between the T2 and T3 assessment were not monitored since most patients were discharged between those time points, which raises questions on when patients turned independent in walking. In future studies, monitoring additional interventions after discharge and the FAC score weekly from the end of intervention until the follow-up assessment, to explore potential difference in time to achieve independence in walking between patients/groups, should be considered.

5.4.3 Gait pattern functions

Gait interventions aiming at improving gait symmetry after stroke have recently been suggested [39-41] but most often been studied in chronic stroke. While the assessments in the clinic often report task accomplishment or time needed to perform a movement task, the use of a gait laboratory can reveal detailed information on how the task is performed or accomplished. In Study II (Paper III) gait patterns were assessed in detail by use of a three-dimensional gait analysis system, after four weeks of incorporated HAL training and after conventional gait training only. The aim was to explore if HAL training would imply more or less deviations from normal gait compared to conventional gait training. The primary outcome was the GPS, an index score that quantifies the magnitude of gait deviation and summarizes the overall kinematic quality.

It was found that all assessed patients exhibited impaired gait kinematics, kinetics and spatiotemporal asymmetry, compared to the healthy subjects. However, no between-group difference in gait pattern after the intervention period was found (Paper III). The GPS showed that the patients gait patterns were impaired bilaterally, with similar deviations in the paretic and non-paretic limbs, highlighting the compensatory role of the non-paretic limb post stroke. Further, overall gait quality on the paretic side (GPS-LBP) was associated with independence in walking (FAC) and the deviations in GPS are in line with previous findings [141] in patients physically independent in walking post stroke, indicating that gait deviations alone might not explain the variance in independence in walking. Thus, in patients with severe limitations in walking the use of a compensatory gait pattern may be essential to be able to walk at all, at the expense of gait symmetry.

HAL training in both subacute and chronic stroke has recently been reported to improve gait coordination (intersegmental coordination/symmetry) towards that of healthy subjects [91], and stride length and single limb support time on the affected side [101] suggesting that HAL training may change gait patterns. However, in these studies patients were less limited in walking at baseline and no control treatment was applied. Whether the reported results could be obtained by evidence-based, non-compensatory, conventional gait training remains to be studied.

Patients in Paper III had reduced propulsive force in the ankle during pre-swing compared to controls and in the HAL group there was a significant difference in foot progression between the paretic and non-paretic limb (with greater deviation in the paretic limb). As in most exoskeletons for walking, the HAL has actuators over the hip and knee, but the ankle is left unpowered. In normal gait, the role of the ankle plantar flexors is however essential in contributing to forward propulsion [28, 169]. Paretic propulsion, defined as the contribution of the paretic leg in driving the body forward during walking, has recently been suggested as an important measure of walking performance post stroke [169, 170]. Less paretic propulsion has also been associated with more severe hemiparesis, and with less leg extension with the paretic limb during terminal stance [169], again highlighting the importance of hip extensor strength during gait post stroke. Targeted training of the paretic leg, especially ankle plantar flexors and hip extensors, should be of interest in future gait intervention studies post stroke.

A newly developed light weighted, soft, exoskeleton (exosuit) with a powered ankle to assist forward propulsion and ground clearance (i.e. dorsiflexion in swing), have been applied in ambulatory chronic stroke patients. Walking with the exosuit demonstrated improvements in terms of more symmetrical and increased paretic forward propulsion, increased ankle dorsiflexion during swing phase and reduced energy cost [153] as well as reduced compensatory motions such as hip hiking and circumduction [61]. This strategy should be of interest in forthcoming exoskeleton development, in studies including also poor-ambulatory/non-ambulatory individuals in different stages after stroke, and evaluating the effect on gait patterns and walking after removing the exoskeleton.

5.4.4 Self-perceived functioning, disability and recovery

At the 6 months follow up in Study II, we found no between-group differences in self-perceived functioning, disability and recovery after HAL training compared to after conventional gait training alone (Paper IV). Previous studies on EAGT most often use assessments of functioning and disability administered by clinicians. However, assessing self-perceived aspects on functioning and disability, i.e. test instruments administered by the patients themselves, is rare [60]. One previous study assessing self-perceived aspects after EAGT in combination with conventional physiotherapy and conventional physiotherapy alone in non-ambulatory patients in the subacute stage after stroke found results corroborating ours with no between-group differences in any of the assessed SIS domains (physical, memory, emotions, communication, participation and recovery domains) over time [171].

The lower scores in self-perceived recovery compared to other studies post stroke [128, 172-174] and the wide range in self-perceived mobility (range 31-100) in Paper IV may be explained by the different requirements of life and expectations of functioning and recovery in younger compared to older individuals [175].

Both objectively assessed (BI) change and self-perceived (SIS) functioning in self-care and domestic life ability were found to be the factors with the strongest associations with self-perceived recovery at 6 months. This highlights the importance of targeting and providing evidence-based ADL practice in different contexts both during and after discharge to promote self-perceived recovery. While physiotherapy interventions to improve mobility and independence in walking are common in early stroke rehabilitation, the practice to improve movement performances related to ADL and self-care activities (such as transferring oneself specifically to the toilet) probably should gain more attention. A team-based approach would probably be most sufficient to endorse the dose and intensity of that training during subacute stroke rehabilitation. Of the patients included in Study II, 43% were still considered dependent in ADL (i.e. BI < 90) at 6 months post stroke (Paper IV). As pointed out previously, these patients represent a younger and more severely disabled subgroup potentially facing lifelong challenges and where interventions targeted at improving ADL performance might have a considerable impact over time.

Notably, previous studies have found hand function and emotions to be important explanatory factors for self-perceived recovery among younger individuals post stroke (together explaining 39%) [175]. These domains were not included here but might of course influence the self-perceived recovery in our relatively young study sample. Study II (Paper IV) highlights the importance of using both self- perceived and objective, clinical assessments during stroke rehabilitation to capture potential differences and to point out individualized goals for further training. In addition, rehabilitation goals must also change over time as demands and expectations on life and functioning might change.

The contribution of true recovery of functioning and compensation [11] in the self-perceived ratings in SIS is not fully distinguished. A person can state that he/she has no limitations or difficulties performing an activity because they are recovered, or they perform the activity in a different way i.e. compensating, or they have someone else performing the activity such as shopping and cleaning etc. The latter may also be considered as compensation. There is also a possibility to respond that you have no difficulties when the real reason is that you have never performed the activity or don't find it important. Nevertheless, self-perceived ratings are subjective and reflect the impact of stroke on a person's health and life despite differences and/or similarities in functioning/disabilities and may to some extent also reflect cognitive skills, degree of acceptance, apprehension and/or denial of once life situation. Together with objective assessments the self-perceived ratings offer a broader perspective on functioning and disability that may guide future rehabilitation and goal setting.

5.5 METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS

5.5.1 Internal validity

In Study I the inclusion was stopped after the eighth patient since it was considered sufficient numbers to answer the research questions regarding safety and feasibility, which were the main focus in that study. At that point no serious adverse events had occurred, and adequate information on the feasibility of using HAL in that specific context had been obtained.

In Study II, patients were randomized. Nevertheless, the two groups were slightly unbalanced with regard to some features e.g. stroke type and paretic side. However, none of these were considered to have a strong influence on the outcome. On the other hand, the sample sizes in the studies included in this thesis, were small, the differences less and the variances greater than expected, which influence the power. The power was calculated for Study II (Paper I) with independence in walking (FAC) as the primary outcome.

Commonly, studies of walking ability after stroke use self-selected walking speed as primary outcome and previous studies on HAL often use the 10MWT. In patients with limited mobility, the 10MWT may however have some drawbacks. Firstly, patients might need great manual support influencing the validity of the test, and secondly, patients who cannot walk at all will get a missing value. Thus, we found that the 2MWT was more useful to achieve baseline data also when patients cannot walk, i.e. 0 meters in 2 minutes, and was the reason why this test was selected in Study II.

Although walking speed (10MWT and 2MWT) remain central outcome assessments in stroke rehabilitation, they need to be considered alongside with other outcomes that reflect the broader dimension of walking [37]. In Study II (Paper II) we used independence in walking (FAC) as the primary outcome to compare intervention groups. This may be considered a more relevant and important outcome measure for patients and their significant others as well as for the health care system in order to plan discharge and further rehabilitation, than walking speed. To regain independence in walking and/or increase walking speed/endurance may represent different improvements (such as regains in balance control or muscle strength)

and are not necessarily associated over time [176]. We suggest that both outcomes assessing independence and walking speed/endurance should be used together with other relevant assessments of both functioning and disability related to walking to capture different aspects of gait that might be influenced by EAGT.

For most of the outcome assessments used in this thesis there are no established minimal clinically important difference (MCID) when used in the subacute stroke population, except for walking speed/endurance [118, 177, 178]. The MCID for walking speed in patients with subacute stroke who have severe walking speed disabilities is suggested to be 0,13m/s [177] to 0,16 m/s [178]. The change in walking independence (FAC), the primary outcome in Study II, of one score was considered to represent a meaningful change since a change from e.g. 0 to 1 would mean that the person has regained a functional walking capacity even if he/she still is dependent on another person's assistance. Further, a change from 2 to 3 would mean that the person has regained a walking capacity that only requires supervision and no longer manual assistance. These changes might result in a big difference in everyday life for that individual, their significant others and the community. Further, the score has been found to have good responsiveness and concurrent validity of each step along the scale in relation to functional mobility, walking distance and walking speed (Mehrholz 2009). Thus, in patients in Study II (Paper II) the improvement between T1 and T2 in independence in walking by in median two points on the FAC could be considered meaningful whereas the improvement in walking speed/endurance by in median 0.11 m/s cannot be considered fully clinically meaningful.

During the data collection, efforts were made to standardize assessment procedures and test conditions. After a stroke, patients may suffer fatigue which can vary throughout the day. For this reason, the assessments were as far as possible scheduled to the morning or forenoon, and the clinical tests and three-dimensional gait analysis on two separate days.

One drawback with performing three-dimensional gait analysis is the limitations in the underlying biomechanical models used to compute data, another is accuracy and consistency in marker placement. The two non-blinded investigators in the gait laboratory however followed the same protocol to obtain consistency. The included patients could not perform gait analysis before the intervention period due to their severe limitations in walking, thus precluding comparison of gait patterns before and after the intervention. In addition, to assure standardization, patients walked barefoot during the three-dimensional gait analysis. This is not the patients' best walking condition after stroke since most patients needed an orthosis while walking. Consequently, the gait cycles obtained in the laboratory do not represent the patients' everyday gait pattern and may have elevated the gait deviations, but enabled comparisons in equal conditions. The impact of walking barefoot on walking speed however seemed negligible, as a post hoc analysis indicated that walking speed assessed at the gait analysis (performed barefoot) and during 2MWT (performed with shoes and orthoses) were strongly associated (RS= 0.965, p <0.01).

The GPS could describe the overall gait quality throughout the gait cycle and enable comparisons between the intervention groups. One advantage with the GPS compared to other gait indices is the GVS where it is displayed how individual variables contribute to the GPS. However, the GPS does not provide information about the direction of the deviation and its application in the stroke population is yet limited [141]. However, together with the GVS and the other kinematic and spatiotemporal parameters we obtained sufficiently detailed information about the patients' gait pattern. Despite the use of walking aids the analysed trials were consistent and reflect the actual joint work during gait. We assessed only straight-line walking indoors and did not include assessments of arm movements. After stroke patients exhibit pathological arm movements on the paretic side compared to healthy subjects [179] which may affect the overall gait pattern. Since most of or patients used a walking aid on the non-paretic side, had limited function in the paretic arm and a whole-body marker placement were considered too time consuming and tiring for the patients, we choose not to include the arm movements and/or position in this study. The reference data from healthy subjects (in Paper III) were not speed matched with the study patients. This may have affected the comparisons with study patients but highlights the impairments in gait pattern seen after stroke, in patients with reduced walking speed compared to healthy subjects.

Previous studies of EAGT often use dose matched interventions [60] meaning that the control group receives the same amount of time/steps as the intervention group. A limitation in our Study II is the difference in the amount of total time spent in gait training between the two groups, with more sessions in total and longer walking distances performed by the HAL group. Higher number of steps and/or longer walking distances during mechanically assisted gait training (i.e. both treadmill and EAGT) compared to during conventional over ground gait practice in early stages post stroke have also been reported previously [180]. However, in those studies the gait outcomes, i.e. independence in walking and walking speed/endurance, were, unlike our findings, in favor of the experimental group. Thus, the optimal frequency and duration of training remain to be clarified [60], and individualization of training versus generalizations of possible findings should also be considered.

The repeated use of the same cohort in Paper II, III and IV and the repeated testing may increase the risk of a type I error, i.e. rejection of a true null hypothesis, in the present thesis. In Paper II and Paper III, the Bonferroni correction was applied to adjust the probability value to reduce this risk.

The respective questionnaires used in Paper I and II were study specific and constructed by our study group, experienced in stroke rehabilitation, but have not been tested further for validity and reliability.

5.5.2 External validity

Some aspects regarding the criteria for inclusion to the studies require consideration. First, the setting for these studies was a regional university clinic for team-based specialized rehabilitation admitting patients in working age with acquired brain injury. Thus, patients

participating in our studies represent a younger and more severely disabled group (according to NIHSS) than the general stroke population, hence our results cannot be generalized to the stroke population as a whole. Yet, this cohort of younger patients in risk of long-term disabilities is important to target in stroke rehabilitation.

The adapted consent form was useful and made it possible to include also patients with impaired speech or cognitive functions which we consider a strength in these studies. However, a few of these patients could not fill in the questionnaire and self-perceived ratings leading to some missing data for these outcome assessments, and consequently leaving out their perspective of gait training with or without HAL. However, few (n=2) patient were lost to the follow up assessment at 6 months and there were no dropouts during the intervention (Paper II).

Although there might be similarities between different rehabilitation facilities, there may still be differences in the extent to which evidence-based conventional gait training is provided, and therefor the results in this thesis should mainly be generalized to similar study settings i.e. specialized neurorehabilitation centers for patients with acquired brain injury. The access to systems like treadmill with BWS may differ between rehabilitation centers, likewise the access to EAGT devices. Yet, the provision of accurate dose, intensity and variability during conventional gait training should be possible to achieve in standard settings. Further, since the conventional gait training was performed by the patients' team physiotherapists at the ward, different physiotherapists were involved in the conventional training of both groups in Study II. Their experience in stroke rehabilitation were diverse, however they all followed the same treatment protocol for inpatient rehabilitation after stroke outlined at our clinic. To standardize the conventional gait training in order to reduce differences is not possible, considering evidence-based training shall be individualized. However, the amount of gait training provided (in time) is possible to control in future studies to obtain dose matched interventions. In addition, the rehabilitation performed between discharge and the 6 months follow up assessment in Study II were not monitored. Most of the patients were discharged to their homes and continued training with home-based rehabilitation team and/or out-patient care yet the frequency of training may be different.

It is fair to recognize that the control method of HAL is different from other electromechanically-assisted gait machines of exoskeleton type, such as the Lokomat. Thus, our results should be interpreted with caution regarding potential effects of gait training with other devices using different mechanical designs and control approaches.

6 CONCLUSION AND CLINICAL IMPLICATIONS

Gait training with HAL is safe and feasible to use in combination with conventional gait training during inpatient rehabilitation in the subacute stage after stroke.

Both groups improved significantly over time, however incorporated HAL training did not improve mobility, self-care and/or self-perceived functioning, disability and recovery more as compared to conventional gait training alone.

The probability of being independent in walking at 6 months post stroke was not influenced by intervention group, but increased with younger age.

HAL training may enable a higher dose, i.e. more steps, and thus longer walking distances during training compared to during conventional gait training.

Both groups exhibited similar impaired gait patterns after the intervention, thus a symmetrical gait pattern might not be attainable by conventional gait training according to today's standards nor by EAGT in patients with severe limitations in walking.

Based on the results of the studies in this thesis the following clinical implications are emphasized:

- EAGT may be a way of achieving longer walking distances during training in patients with severe limitations in walking after stroke.
- EAGT may be part of a set of rehabilitation tools but should not replace the conventional therapy. If applied, one may consider perfoming EAGT over ground with individualized timing and duration of training periods, depending on treatment goals.
- The additional value of using EAGT need to be explored further especially with regard to best responders and to cost effectiveness of this kind of training.

7 FUTURE PERSPECTIVES

Rehabilitation after stroke need to provide the most effective therapy for each patient but also be able to identify the most suitable patients for and timing of a specific therapy. Future studies are needed to characterize potential subgroups of patients, who might benefit the most from EAGT. The EAGT should probably best be performed over ground to allow for more variability, with individualized timing and duration of training periods, depending on treatment goals.

In order to further increase the variability in EAGT and to achieve gait training that meets the requirements of normal gait there is a need for technical developments. Increasing the degrees of freedom in future exoskeletons by moving away from rigid structures and instead using soft textile or softer fabrics should promote the possibility of increasing the variability in EAGT. In addition, single joint exoskeletons targeting the ankle joint to assist forward propulsion and ground clearance are to be explored in subacute stroke patients, dependent in walking. Such devices should also be evaluated in terms of improved gait patterns and walking ability also after removing the exoskeleton.

To identify subgroups and to better understand the contribution of true recovery versus compensation to the regained functioning, sophisticated assessments may be applied in future research on EAGT and walking after stroke. The importance of the structural and functional integrity of the corticospinal tract for recovery of movement control in the lower extremities and recovery of independent walking in these patients with severe limitations in walking after stroke should be explored further. Identifying clinical and laboratory predictive factors may enable the design of new intervention strategies that combine physical, technological and pharmacological tools.

The finding that hip extension strength may provide proximal stability for those with poor trunk control and be a predictor for independent walking is interesting and should be specifically assessed in future studies. Moreover, the potential positive cardiovascular effects related to the longer walking distances (and possibly higher intensity) enabled by EAGT should be explored. Furthermore, using self-reported outcome assessments and capturing the patients' perspectives of EAGT may add information beyond what is achieved with outcomes administered by clinicians and should be part of standard assessment protocols in these studies.

8 SVENSK SAMMANFATTNING

Stroke drabbar omkring 25 000 personer varje år i Sverige. Det vanligaste akutsymptomet är svaghet i ena kroppshalvan. Den akuta behandlingen förbättras fortlöpande men hos mer än hälften kvarstår problem med svaghet. Kvarstående nedsatt gångförmåga efter stroke är också vanligt vilket får konsekvenser för aktiviteter i det dagliga livet.

Det är visat att tidigt påbörjad, intensiv funktionsträning på gränsen till personens förmåga förbättrar återhämtningen och slutresultatet efter stroke men det finns också ett stort behov av nya och effektivare träningsmetoder. Det finns också stöd för att träningseffekten är störst i det tidiga skedet efter stroke då möjligheten att utnyttja hjärnans förmåga till anpassning är som störst. Flera metoder har utvecklats för intensiv gångträning efter stroke däribland elektromekaniskt understödd gångträning (robotträning). Det finns visst stöd för att elektromekanisk gångträning i tidigt skede efter stroke påverkar återhämtningen av gångförmågan positivt.

Exoskelettet Hybrid Assistive Limb (HAL) är en gångrobot som har utvecklats vid Tsukuba universitet i Tokyo i samarbete med företaget Cyberdyne Inc. för att ge stöd vid träning av personer med nedsatt kraft i benet/benen. Exoskelettet spänns fast på patienten och fungerar som ett yttre skelett, med leder som matchar patientens höft- och knäled och med motorer, som driver rörelser över dessa leder för att stödja gångträning.

Syftet med avhandlingen var att undersöka användarbarheten och effekten av att träna med HAL jämför med sedvanlig gångträning under inneliggande rehabilitering för personer med nedsatt gångförmåga, i subakut skede efter stroke.

All data baseras på två studier. Båda studierna genomfördes inom ramen för slutenvårdsrehabilitering för patienter i arbetsför ålder, med kraftigt nedsatt gångförmåga efter stroke. I den första studien undersökte vi om HAL var säker och användbar för gångträning för dessa patienter. Den andra studien var en randomiserad kontrollerad interventionsstudie där vi jämförde tillägg av gångträning med HAL till sedvanlig gångträning med endast sedvanlig gångträning för denna patientgrupp.

Studie I visade att HAL var användbar och säker inom ramarna för ordinarie rehabiliteringsprogram i subakut skede efter stroke. Gångträning med HAL möjliggjorde att intensiv gångträning kunde starta tidigt och visade på förbättring på gångförmågan efter träningen. Därtill upplevde patienterna gångträning med HAL som positiv och gynnsam.

Studie II visade att gångträning med HAL i kombination med sedvanlig, evidensbaserad sjukgymnastisk träning i subakut skede efter stroke leder till förbättringar avseende självständighet i gång, gånghastighet, uthållighet i gång, balans och förmågan att utföra aktiviteter i dagliga livet. Förbättringarna hos patienterna som tränat med HAL var dock jämförbara med de i gruppen som endast tränat sedvanlig evidensbaserad gångträning. De framkom inte heller någon skillnad avseende patienternas gångmönster eller självskattad

aktivitetsförmåga och grad av återhämtning efter gångträning med HAL jämfört med efter endast sedvanlig gångträning.

Gångmönstret hos patienterna var avvikande men i linje med vad som tidigare rapporterats efter stroke. Patienternas självskattade grad av återhämtning efter 6 månader förklarades bäst av förmågan att utföra vardagliga aktiviteter, så som att självständigt kunna sköta sina toalettbesök. Under träning med HAL gick patienterna längre sträckor än under den sedvanliga träningen, vilket skulle kunna ha andra positiva hälsoeffekter så som förbättrad kondition, varför detta bör undersökas i framtida studier.

Sammanfattningsvis visar avhandlingen att evidensbaserad gångträning i tidigt skede efter stroke leder till signifikanta förbättringar trots initialt kraftigt nedsatt gångförmåga och att användningen av elektromekanisk gångträning inte nödvändigtvis påskyndar eller förstärker denna effekt. Avhandlingen visar dock att elektromekanisk gångträning kan medföra en ökad dos (antal steg) och intensitet i gångträningen hos patienter som har en kraftigt nedsatt gångförmåga.

9 ACKNOWLEDGEMENTS

First, I would like to send my greatest gratitude to all patients participating in the studies. Thank you for your contribution to this thesis but also to me as a professional and human being.

My sincere gratitude also goes to:

My main supervisor **Susanne Palmcrantz** who helped me swim through the dark, sometimes choppy ocean of research. This particular "swim challenge" I could not have done without you. Thanks for sharing your knowledge and always being available for big and small issues, with an eye for small but important details.

My Co-supervisor **Jörgen Borg.** First for letting me be a part of this project and your research group. Always sharing your great scientific knowledge with a positive and encouraging attitude. Prestigeless by nature and continuously thinking big and beyond the expected.

My Co-supervisor **Lanie Gutierrez Farewik** for sharing your energy and vast knowledge in Biomechanics and Gait analysis. A special thanks for your positive attitude and your endless patient with MATHLAB and my questions about Newtons laws and absolute angles.

My external mentor and friend **Madeleine Jonsson.** The first to capture my curiosity for research and clinical studies and who are a contributor in many aspects to this thesis project. Thank you for your calm and wise reflections and advices regarding both research and life as a whole, and for your great tasting of wine.

The **University Department of Rehabilitation Medicine,** Stockholm at Danderyd Hospital, Sweden. Especially **Vera Häglund** not only for recruiting patients but also for great collaboration at Tonusmottagningen and for providing great travel company to Japan sharing your favorite places and great karaoke skills; **Maria Sandgren** my boss for being flexible, encouraging and for facilitating the possibility to combine research with clinical practice; **Kristian Borg** for encouragement throughout the years; and **Christian Andersén** for facilitating this research project and for great balance support when I was walking around Almedalen in the HAL suit.

To fellow PhD students as well as members of our research group, **Katarina Vreede** for great team-work with practical aspects of the studies as well as carrying out HAL training together. **Jeanette Plantin** fellow PhD student whom I have shared not only office but also joy and sorrow, hope and despair (and some bottles of champagne) with throughout these years. Thank you for fruitful and unfruitful discussions and your ability to provide new perspectives, inspiration and for making statistics a bit more understandable. I could not have done this without you! **Gaia Valentina Pennati** for always having some spare chocolate to share when you need it the most and also for sharing the love for strong black coffee. **Hanna Bergling** and **Maria Pettersson** for bringing your positive attitude and never-give-up spirit

to the group. **Påvel Lindberg** for sharing your vast knowledge and adding the French touch to the research group. **Helena Hybbinette** for your positive energy and great humor. **Christian Oldenburg** and **Gabriela Markovic** for discussions and advices in big and small issues.

To **Disa Sommerfeld** – who I call my research grandma. With your sharp mind and warm heart, you have been a true asset throughout these years. Your flexible, positive attitude, always doing you very best to solve practical issues strongly contributed to the data collection. Thanks for providing manuscript and thesis feedback and discussing results, always with new perspectives and never-ending energy.

Co-workers at the ward (80/84) especially **all the physiotherapist** whom I have had the pleasure to work with during the past twelve years. Thank you for being like an extended family, providing lots of laughter and great memories. You made it a pleasure to go to work every day. A special thanks to **Ann-Britt Hedsén** who helped out with the data collection (performing interviews with the HAL group).

To colleagues at the **Motion Laboratory, Astrid Lindgrens Barnsjukhus**, **Åsa Bartonek** for your help teaching me a part of all your knowledge in gait analysis and for fruitful discussions. **Mikael Reimeringer** for providing your technical expertise, **Josefine Eriksson Naili**, **Elin Lööf**, **Cecilia Lidbeck**, **Marie Eriksson**, **Eva Broström** for exchanging experiences and knowledge and always making me feel welcome in "your" gait lab.

My new colleagues at **Neurocampus** and **CampPro** for great support these last months. I look forward spending more time with you.

SLL Innovation and **Sofie Nybom** a former collaborator and a time optimistic friend I got to share some fantastic experiences with in Japan while learning the HAL-method.

Elsy Eek for helping out with parts of the data collection.

David Najafi for helping out with structured data coding saving me a lot of time!

Karolina Krakau for carrying out the randomization from near and far.

Kanoknart (Kano) Yingcharoen for Webrehab support and encouragement.

Elisabeth Berg and **Fredrik Johansson** for statistical advice throughout these years.

Johanna Rosén, PhD student fellow at GIH. For great company, knowledge and stubbornness during a Biomechanics course ending up with friendship, fruitful talks and lovely Italian food.

Gunilla Elmgren Frykberg for thesis feedback.

Adam Hagman at Robotdalen Västerås, who introduced us to professor Sankais group at Tsukuba University (and Cyberdyne Inc.) where the Hybrid Assistive Limb was developed.

I’m grateful that **Professor Sankai** enabled access to the HAL suits for these studies. I also want to thank **Dr Hiroaki Kawamoto** and co-workers for teaching me the HAL-method and for giving me great memories and a special place in my heart for Tokyo and Tsukuba.

To **Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital (KIDS)** and **Nina Ringart** for giving me the opportunity to become a PhD student and for your support in big and small issues.

My family and friends who not fully understood what I’ve been doing all these years, but who supported me anyhow. Having you all helped me to be more effective in my work, so I could spend more time with you.

The organizations who kindly provided grants to support this thesis project: Promobilia Foundation, NEURO Sweden (Neuroförbundet), STROKE-Riksförbundet and Norrbacka-Eugenia foundation.

10 REFERENCES

1. Feigin, V.L., B. Norrving, and G.A. Mensah, *Global Burden of Stroke.* Circ Res, 2017. **120**(3): p. 439-448.
2. Jorgensen, H.S., et al., *Recovery of walking function in stroke patients: the Copenhagen Stroke Study.* Arch Phys Med Rehabil, 1995. **76**(1): p. 27-32.
3. *World Health Organization. The international Classification of functioning, disability and health (ICF).* Geneva, 2001.
4. Bohannon, R.W., M.G. Horton, and J.B. Wikholm, *Importance of four variables of walking to patients with stroke.* Int J Rehabil Res, 1991. **14**(3): p. 246-50.
5. Dobkin, B.H., *Clinical practice. Rehabilitation after stroke.* N Engl J Med, 2005. **352**(16): p. 1677-84.
6. Alguren, B., A. Lundgren-Nilsson, and K.S. Sunnerhagen, *Functioning of stroke survivors--A validation of the ICF core set for stroke in Sweden.* Disabil Rehabil, 2010. **32**(7): p. 551-9.
7. Verma, R., et al., *Understanding gait control in post-stroke: implications for management.* J Bodyw Mov Ther, 2012. **16**(1): p. 14-21.
8. Barclay, R.E., et al., *Interventions for improving community ambulation in individuals with stroke.* Cochrane Database Syst Rev, 2015(3): p. Cd010200.
9. *Riksstroke The Swedish Stroke Register*. Stroke och TIA. Årsrapport från Riksstroke, utgiven september 2019; Available from: http://www.riksstroke.org/wp-content/uploads/2019/09/Riksstroke_A%CC%8Arsrapport-2018_slutversion.pdf.
10. Nadeau, S.E., et al., *The Effects of Stroke Type, Locus, and Extent on Long-Term Outcome of Gait Rehabilitation: The LEAPS Experience.* Neurorehabil Neural Repair, 2016. **30**(7): p. 615-25.
11. Levin, M.F., J.A. Kleim, and S.L. Wolf, *What do motor "recovery" and "compensation" mean in patients following stroke?* Neurorehabil Neural Repair, 2009. **23**(4): p. 313-9.
12. Langhorne, P., J. Bernhardt, and G. Kwakkel, *Stroke rehabilitation.* Lancet, 2011. **377**(9778): p. 1693-702.
13. Krakauer, J.W., et al., *Getting neurorehabilitation right: what can be learned from animal models?* Neurorehabil Neural Repair, 2012. **26**(8): p. 923-31.
14. Bowden, M.G., M.L. Woodbury, and P.W. Duncan, *Promoting neuroplasticity and recovery after stroke: future directions for rehabilitation clinical trials.* Curr Opin Neurol, 2013. **26**(1): p. 37-42.
15. Hebert, D., et al., *Canadian stroke best practice recommendations: Stroke rehabilitation practice guidelines, update 2015.* Int J Stroke, 2016. **11**(4): p. 459-84.
16. Gordon, N.F., et al., *Physical activity and exercise recommendations for stroke survivors: an American Heart Association scientific statement from the Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention; the Council on Cardiovascular Nursing; the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council.* Stroke, 2004. **35**(5): p. 1230-40.
17. Ivey, F.M., et al., *Cardiovascular health and fitness after stroke.* Top Stroke Rehabil, 2005. **12**(1): p. 1-16.
18. *Stroke--1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders.* Stroke, 1989. **20**(10): p. 1407-31.
19. Bernhardt, J., et al., *Agreed Definitions and a Shared Vision for New Standards in Stroke Recovery Research: The Stroke Recovery and Rehabilitation Roundtable Taskforce.* Neurorehabil Neural Repair, 2017. **31**(9): p. 793-799.
20. Brott, T., et al., *Measurements of acute cerebral infarction: a clinical examination scale.* Stroke, 1989. **20**(7): p. 864-70.

21. Kwakkel, G. and B.J. Kollen, *Predicting activities after stroke: what is clinically relevant?* Int J Stroke, 2013. **8**(1): p. 25-32.
22. Kwakkel, G., B. Kollen, and J. Twisk, *Impact of time on improvement of outcome after stroke.* Stroke, 2006. **37**(9): p. 2348-53.
23. Krakauer, J.W., *Motor learning: its relevance to stroke recovery and neurorehabilitation.* Curr Opin Neurol, 2006. **19**(1): p. 84-90.
24. Frykberg, G.E. and R. Vasa, *Neuroplasticity in action post-stroke: Challenges for physiotherapists.* European Journal of Physiotherapy, 2015. **17**(2): p. 56-65.
25. Clark, D.J., *Automaticity of walking: functional significance, mechanisms, measurement and rehabilitation strategies.* Front Hum Neurosci, 2015. **9**: p. 246.
26. Grillner, S., et al., *Neural bases of goal-directed locomotion in vertebrates--an overview.* Brain Res Rev, 2008. **57**(1): p. 2-12.
27. Lacquaniti, F., Y.P. Ivanenko, and M. Zago, *Patterned control of human locomotion.* J Physiol, 2012. **590**(10): p. 2189-99.
28. Beyaert, C., R. Vasa, and G.E. Frykberg, *Gait post-stroke: Pathophysiology and rehabilitation strategies.* Neurophysiol Clin, 2015. **45**(4-5): p. 335-55.
29. Dietz, V., *Gait disorders.* Handb Clin Neurol, 2013. **110**: p. 133-43.
30. Kandel, R.E., et al., *Principles of neural science*. Fifth ed. 2013, USA: The McGraw-Hill Companies.
31. Perry, J. and J.M. Burnfield, *Gait analysis : normal and pathological function 2nd edition*. 2010, Thorofare, USA: SLACK Incorporated.
32. Gage, J.R., *Gait analysis in cerebral palsy.* Clinics in Developmental Medicine, 1991(121): p. 132-172.
33. Stockel, T., et al., *The mental representation of the human gait in young and older adults.* Front Psychol, 2015. **6**: p. 943.
34. Sheffler, L.R. and J. Chae, *Hemiparetic Gait.* Phys Med Rehabil Clin N Am, 2015. **26**(4): p. 611-23.
35. Balaban, B. and F. Tok, *Gait disturbances in patients with stroke.* Pm r, 2014. **6**(7): p. 635-42.
36. Perry, J., et al., *Classification of walking handicap in the stroke population.* Stroke, 1995. **26**(6): p. 982-9.
37. Lord, S.E. and L. Rochester, *Measurement of community ambulation after stroke: current status and future developments.* Stroke, 2005. **36**(7): p. 1457-61.
38. Patterson, K.K., et al., *Changes in gait symmetry and velocity after stroke: a cross-sectional study from weeks to years after stroke.* Neurorehabil Neural Repair, 2010. **24**(9): p. 783-90.
39. Awad, L.N., et al., *Walking speed and step length asymmetry modify the energy cost of walking after stroke.* Neurorehabil Neural Repair, 2015. **29**(5): p. 416-23.
40. Bae, J., et al., *Biomechanical mechanisms underlying exosuit-induced improvements in walking economy after stroke.* J Exp Biol, 2018. **221**(Pt 5).
41. Finley, J.M. and A.J. Bastian, *Associations Between Foot Placement Asymmetries and Metabolic Cost of Transport in Hemiparetic Gait.* Neurorehabil Neural Repair, 2017. **31**(2): p. 168-177.
42. Craig, L.E., et al., *Predictors of poststroke mobility: systematic review.* Int J Stroke, 2011. **6**(4): p. 321-7.
43. Kwakkel, G., B. Kollen, and E. Lindeman, *Understanding the pattern of functional recovery after stroke: facts and theories.* Restor Neurol Neurosci, 2004. **22**(3-5): p. 281-99.
44. Stinear, C.M. and W.D. Byblow, *Predicting and accelerating motor recovery after stroke.* Curr Opin Neurol, 2014. **27**(6): p. 624-30.
45. Stinear, C.M., et al., *PREP2: A biomarker-based algorithm for predicting upper limb function after stroke.* Ann Clin Transl Neurol, 2017. **4**(11): p. 811-820.

46. Kwah, L.K. and R.D. Herbert, *Prediction of Walking and Arm Recovery after Stroke: A Critical Review*. Brain Sci, 2016. **6**(4).
47. Veerbeek, J.M., et al., *Is accurate prediction of gait in nonambulatory stroke patients possible within 72 hours poststroke? The EPOS study.* Neurorehabil Neural Repair, 2011. **25**(3): p. 268-74.
48. Kollen, B., et al., *Predicting improvement in gait after stroke: a longitudinal prospective study.* Stroke, 2005. **36**(12): p. 2676-80.
49. Kwah, L.K., et al., *Models containing age and NIHSS predict recovery of ambulation and upper limb function six months after stroke: an observational study.* J Physiother, 2013. **59**(3): p. 189-97.
50. Smith, M.C., P.A. Barber, and C.M. Stinear, *The TWIST Algorithm Predicts Time to Walking Independently After Stroke.* Neurorehabil Neural Repair, 2017. **31**(10-11): p. 955-964.
51. Langhorne, P., F. Coupar, and A. Pollock, *Motor recovery after stroke: a systematic review.* Lancet Neurol, 2009. **8**(8): p. 741-54.
52. Peurala, S.H., et al., *Evidence for the effectiveness of walking training on walking and self-care after stroke: a systematic review and meta-analysis of randomized controlled trials.* J Rehabil Med, 2014. **46**(5): p. 387-99.
53. Veerbeek, J.M., et al., *What is the evidence for physical therapy poststroke? A systematic review and meta-analysis.* PLoS One, 2014. **9**(2): p. e87987.
54. Lohse, K.R., C.E. Lang, and L.A. Boyd, *Is more better? Using metadata to explore dose-response relationships in stroke rehabilitation.* Stroke, 2014. **45**(7): p. 2053-8.
55. Schneider, E.J., et al., *Increasing the amount of usual rehabilitation improves activity after stroke: a systematic review.* J Physiother, 2016. **62**(4): p. 182-7.
56. Hornby, T.G., et al., *Variable Intensive Early Walking Poststroke (VIEWS): A Randomized Controlled Trial.* Neurorehabil Neural Repair, 2016. **30**(5): p. 440-50.
57. Veerbeek, J.M., et al., *Effects of augmented exercise therapy on outcome of gait and gait-related activities in the first 6 months after stroke: a meta-analysis.* Stroke, 2011. **42**(11): p. 3311-5.
58. Hornby, T.G., et al., *Influence of skill and exercise training parameters on locomotor recovery during stroke rehabilitation.* Curr Opin Neurol, 2016. **29**(6): p. 677-683.
59. Mehrholz, J., M. Pohl, and B. Elsner, *Treadmill training and body weight support for walking after stroke.* Cochrane Database Syst Rev, 2014(1): p. Cd002840.
60. Mehrholz, J., et al., *Electromechanical-assisted training for walking after stroke.* Cochrane Database Syst Rev, 2017. **5**: p. Cd006185.
61. Awad, L.N., et al., *Reducing Circumduction and Hip Hiking During Hemiparetic Walking Through Targeted Assistance of the Paretic Limb Using a Soft Robotic Exosuit.* Am J Phys Med Rehabil, 2017. **96**(10 Suppl 1): p. S157-s164.
62. Morone, G., et al., *Robot-assisted gait training for stroke patients: current state of the art and perspectives of robotics.* Neuropsychiatr Dis Treat, 2017. **13**: p. 1303-1311.
63. Geroin, C., et al., *Systematic review of outcome measures of walking training using electromechanical and robotic devices in patients with stroke.* J Rehabil Med, 2013. **45**(10): p. 987-96.
64. Colombo, G., et al., *Treadmill training of paraplegic patients using a robotic orthosis.* J Rehabil Res Dev, 2000. **37**(6): p. 693-700.
65. Hidler, J., et al., *Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke.* Neurorehabil Neural Repair, 2009. **23**(1): p. 5-13.
66. Husemann, B., et al., *Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study.* Stroke, 2007. **38**(2): p. 349-54.

67. van Nunen, M.P., et al., *Recovery of walking ability using a robotic device in subacute stroke patients: a randomized controlled study.* Disabil Rehabil Assist Technol, 2015. **10**(2): p. 141-8.
68. Mayr, A., et al., *Early robot-assisted gait retraining in non-ambulatory patients with stroke: a single blind randomized controlled trial.* Eur J Phys Rehabil Med, 2018. **54**(6): p. 819-826.
69. Schwartz, I., et al., *The effectiveness of locomotor therapy using robotic-assisted gait training in subacute stroke patients: a randomized controlled trial.* Pm r, 2009. **1**(6): p. 516-23.
70. Pennycott, A., et al., *Towards more effective robotic gait training for stroke rehabilitation: a review.* J Neuroeng Rehabil, 2012. **9**: p. 65.
71. Dobkin, B.H., *Motor rehabilitation after stroke, traumatic brain, and spinal cord injury: common denominators within recent clinical trials.* Curr Opin Neurol, 2009. **22**(6): p. 563-9.
72. Chen, G., et al., *A review of lower extremity assistive robotic exoskeletons in rehabilitation therapy.* Crit Rev Biomed Eng, 2013. **41**(4-5): p. 343-63.
73. Belda-Lois, J.M., et al., *Rehabilitation of gait after stroke: a review towards a top-down approach.* J Neuroeng Rehabil, 2011. **8**: p. 66.
74. Suzuki, K., et al., *Intention-based walking support for paraplegia patients with Robot Suit HAL.* Advanced Robotics, 2007. **21**(12): p. 1441-1469.
75. Kawamoto, H.S., Y., *Power assist system HAL-3 for gait disorder person.* Lecture Notes in Computer Science, ICCHP 2002, LNCS2398, eds K. Miesenberger, J. Klaus, and W. Zagler (Berlin; Heidelberg: Springer-Verlag), 196–203., 2002.
76. Kawamoto, H., et al., *Voluntary motion support control of Robot Suit HAL triggered by bioelectrical signal for hemiplegia.* Conf Proc IEEE Eng Med Biol Soc, 2010. **2010**: p. 462-6.
77. Ueba, T., et al., *Feasibility and safety of acute phase rehabilitation after stroke using the hybrid assistive limb robot suit.* Neurol Med Chir (Tokyo), 2013. **53**(5): p. 287-90.
78. Kubota, S., et al., *Feasibility of rehabilitation training with a newly developed wearable robot for patients with limited mobility.* Arch Phys Med Rehabil, 2013. **94**(6): p. 1080-7.
79. Kawamoto, H., et al., *Pilot study of locomotion improvement using hybrid assistive limb in chronic stroke patients.* BMC Neurol, 2013. **13**: p. 141.
80. Watanabe, H., et al., *Locomotion improvement using a hybrid assistive limb in recovery phase stroke patients: a randomized controlled pilot study.* Arch Phys Med Rehabil, 2014. **95**(11): p. 2006-12.
81. Mizukami, M., et al., *Gait training of subacute stroke patients using a hybrid assistive limb: a pilot study.* Disabil Rehabil Assist Technol, 2016: p. 1-8.
82. Yoshikawa, K., et al., *Gait training with Hybrid Assistive Limb enhances the gait functions in subacute stroke patients: A pilot study.* NeuroRehabilitation, 2017. **40**(1): p. 87-97.
83. Mehrholz, J., et al., *Electromechanical-assisted training for walking after stroke.* Cochrane Database Syst Rev, 2013(7): p. Cd006185.
84. Chihara, H., et al., *Factors Predicting the Effects of Hybrid Assistive Limb Robot Suit during the Acute Phase of Central Nervous System Injury.* Neurol Med Chir (Tokyo), 2016. **56**(1): p. 33-7.
85. Fukuda, H., et al., *Tailor-made rehabilitation approach using multiple types of hybrid assistive limb robots for acute stroke patients: A pilot study.* Assist Technol, 2016. **28**(1): p. 53-6.

86. Fukuda, H., et al., *Effectiveness of Acute Phase Hybrid Assistive Limb Rehabilitation in Stroke Patients Classified by Paralysis Severity.* Neurologia Medico-Chirurgica, 2015. **55**(6): p. 487-492.
87. Maeshima, S., et al., *Efficacy of a hybrid assistive limb in post-stroke hemiplegic patients: a preliminary report.* BMC Neurol, 2011. **11**: p. 116.
88. Nilsson, A., et al., *Gait training early after stroke with a new exoskeleton--the hybrid assistive limb: a study of safety and feasibility.* J Neuroeng Rehabil, 2014. **11**: p. 92.
89. Ogata, T., et al., *Hybrid Assistive Limb (HAL) Rehabilitation in Patients with Acute Hemorrhagic Stroke.* Neurol Med Chir (Tokyo), 2015. **55**(12): p. 901-6.
90. Nishimura, M., et al., *Factors Leading to Improved Gait Function in Patients with Subacute or Chronic Central Nervous System Impairments Who Receive Functional Training with the Robot Suit Hybrid Assistive Limb.* Neurol Med Chir (Tokyo), 2018. **58**(1): p. 39-48.
91. Puentes, S., et al., *Reshaping of Bilateral Gait Coordination in Hemiparetic Stroke Patients After Early Robotic Intervention.* Front Neurosci, 2018. **12**: p. 719.
92. Yoshimoto, T., et al., *Feasibility and efficacy of high-speed gait training with a voluntary driven exoskeleton robot for gait and balance dysfunction in patients with chronic stroke: nonrandomized pilot study with concurrent control.* Int J Rehabil Res, 2015. **38**(4): p. 338-43.
93. Sczesny-Kaiser, M., et al., *A Randomized and Controlled Crossover Study Investigating the Improvement of Walking and Posture Functions in Chronic Stroke Patients Using HAL Exoskeleton - The HALESTRO Study (HAL-Exoskeleton STROke Study).* Front Neurosci, 2019. **13**: p. 259.
94. Tan, C.K., et al., *Lateral Symmetry of Synergies in Lower Limb Muscles of Acute Post-stroke Patients After Robotic Intervention.* Front Neurosci, 2018. **12**: p. 276.
95. Tanaka, H., et al., *A follow-up study of the effect of training using the Hybrid Assistive Limb on Gait ability in chronic stroke patients.* Top Stroke Rehabil, 2019: p. 1-6.
96. Watanabe, H., et al., *Effects of gait training using the Hybrid Assistive Limb(R) in recovery-phase stroke patients: A 2-month follow-up, randomized, controlled study.* NeuroRehabilitation, 2017. **40**(3): p. 363-367.
97. Yokota, C., et al., *Acute stroke rehabilitation for gait training with cyborg type robot Hybrid Assistive Limb: A pilot study.* J Neurol Sci, 2019. **404**: p. 11-15.
98. Yoshimoto, T., I. Shimizu, and Y. Hiroi, *Sustained effects of once-a-week gait training with hybrid assistive limb for rehabilitation in chronic stroke: case study.* J Phys Ther Sci, 2016. **28**(9): p. 2684-2687.
99. Yilmaz, E., et al., *Does treadmill training with Hybrid Assistive Limb (HAL) impact the quality of life? A first case series in the United States.* Disabil Rehabil Assist Technol, 2018: p. 1-5.
100. Takeda, Y., et al., *The Effect of the Robot Suit HAL in Physical Therapy for Acute Phase Stroke.* Rigakuryoho Kagaku, 2015. **30**(4): p. 577-582.
101. Tanaka, H., et al., *Spatiotemporal gait characteristic changes with gait training using the hybrid assistive limb for chronic stroke patients.* Gait Posture, 2019. **71**: p. 205-210.
102. Wade, D.T., et al., *Walking after stroke. Measurement and recovery over the first 3 months.* Scand J Rehabil Med, 1987. **19**(1): p. 25-30.
103. Morishita, T. and T. Inoue, *Interactive Bio-feedback Therapy Using Hybrid Assistive Limbs for Motor Recovery after Stroke: Current Practice and Future Perspectives.* Neurol Med Chir (Tokyo), 2016.

104. Gruneberg, P., et al., *Robot-assisted voluntary initiation reduces control-related difficulties of initiating joint movement: A phenomenal questionnaire study on shaping and compensation of forward gait.* PLoS One, 2018. **13**(3): p. e0194214.
105. *WebRehab Sweden*. Available from: https://www.ucr.uu.se/webrehab/.
106. Kirtley, C., *Clinical Gait Analysis: Theory and Practice*. 2006, Churchill Livingstone Elsevier.
107. Holden, M.K., et al., *Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness.* Phys Ther, 1984. **64**(1): p. 35-40.
108. Mehrholz, J., et al., *Predictive validity and responsiveness of the functional ambulation category in hemiparetic patients after stroke.* Arch Phys Med Rehabil, 2007. **88**(10): p. 1314-9.
109. Goldstein, L.B. and G.P. Samsa, *Reliability of the National Institutes of Health Stroke Scale. Extension to non-neurologists in the context of a clinical trial.* Stroke, 1997. **28**(2): p. 307-10.
110. Berg, K., et al., *Measuring balance in the elderly: preliminary development of an instrument.* PHYSIOTHER CANADA, 1989. **41**(6): p. 304.
111. Berg, K., S. Wood-Dauphinee, and J.I. Williams, *The Balance Scale: reliability assessment with elderly residents and patients with an acute stroke.* Scand J Rehabil Med, 1995. **27**(1): p. 27-36.
112. Mao, H.F., et al., *Analysis and comparison of the psychometric properties of three balance measures for stroke patients.* Stroke, 2002. **33**(4): p. 1022-7.
113. Fugl-Meyer, A.R., et al., *The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance.* Scand J Rehabil Med, 1975. **7**(1): p. 13-31.
114. Gladstone, D.J., C.J. Danells, and S.E. Black, *The fugl-meyer assessment of motor recovery after stroke: a critical review of its measurement properties.* Neurorehabil Neural Repair, 2002. **16**(3): p. 232-40.
115. Salter, K., et al., *Clinical Outcome Variables Scale: A retrospective validation study in patients after stroke.* J Rehabil Med, 2010. **42**(7): p. 609-13.
116. Fulk, G.D. and J.L. Echternach, *Test-retest reliability and minimal detectable change of gait speed in individuals undergoing rehabilitation after stroke.* J Neurol Phys Ther, 2008. **32**(1): p. 8-13.
117. Kosak, M. and T. Smith, *Comparison of the 2-, 6-, and 12-minute walk tests in patients with stroke.* J Rehabil Res Dev, 2005. **42**(1): p. 103-7.
118. Perera, S., et al., *Meaningful change and responsiveness in common physical performance measures in older adults.* J Am Geriatr Soc, 2006. **54**(5): p. 743-9.
119. Mahoney, F.I. and D.W. Barthel, *FUNCTIONAL EVALUATION: THE BARTHEL INDEX.* Md State Med J, 1965. **14**: p. 61-5.
120. Hsueh, I.P., et al., *Comparison of the psychometric characteristics of the functional independence measure, 5 item Barthel index, and 10 item Barthel index in patients with stroke.* J Neurol Neurosurg Psychiatry, 2002. **73**(2): p. 188-90.
121. Tinetti, M.E., D. Richman, and L. Powell, *Falls efficacy as a measure of fear of falling.* J Gerontol, 1990. **45**(6): p. P239-43.
122. Hellstrom, K. and B. Lindmark, *Fear of falling in patients with stroke: a reliability study.* Clin Rehabil, 1999. **13**(6): p. 509-17.
123. Hellstrom, K., B. Lindmark, and A. Fugl-Meyer, *The Falls-Efficacy Scale, Swedish version: does it reflect clinically meaningful changes after stroke?* Disabil Rehabil, 2002. **24**(9): p. 471-81.
124. Rabin, R. and F. de Charro, *EQ-5D: a measure of health status from the EuroQol Group.* Ann Med, 2001. **33**(5): p. 337-43.
125. Hunger, M., et al., *Validity, reliability and responsiveness of the EQ-5D in German stroke patients undergoing rehabilitation.* Qual Life Res, 2012. **21**(7): p. 1205-16.

126. Keith, R.A., et al., *The functional independence measure: a new tool for rehabilitation.* Adv Clin Rehabil, 1987. **1**: p. 6-18.
127. Duncan, P.W., et al., *Rasch analysis of a new stroke-specific outcome scale: the Stroke Impact Scale.* Arch Phys Med Rehabil, 2003. **84**(7): p. 950-63.
128. Duncan, P.W., et al., *The stroke impact scale version 2.0. Evaluation of reliability, validity, and sensitivity to change.* Stroke, 1999. **30**(10): p. 2131-40.
129. Hasselgren-Nyberg L, et al., *S-COVS: Den svenska versionen av Physiotherapy clinical outcome variables scale.* Nord Fysioter, 1997. **1**: p. 109-113.
130. Seaby, L. and G. Torrance, *Reliability of a physiotherapy functional assessment used in rehabilitation setting.* Physiotherapy Canada, 1989. **41**: p. 264-71.
131. Podsiadlo, D. and S. Richardson, *The timed "Up & Go": a test of basic functional mobility for frail elderly persons.* J Am Geriatr Soc, 1991. **39**(2): p. 142-8.
132. Sanford, J., et al., *Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke.* Phys Ther, 1993. **73**(7): p. 447-54.
133. Berg, K.O., et al., *Clinical and laboratory measures of postural balance in an elderly population.* Arch Phys Med Rehabil, 1992. **73**(11): p. 1073-80.
134. Balu, S., *Differences in psychometric properties, cut-off scores, and outcomes between the Barthel Index and Modified Rankin Scale in pharmacotherapy-based stroke trials: systematic literature review.* Curr Med Res Opin, 2009. **25**(6): p. 1329-41.
135. Celani, M.G., et al., *Different measures for assessing stroke outcome: an analysis from the International Stroke Trial in Italy.* Stroke, 2002. **33**(1): p. 218-23.
136. Baker, R., et al., *Gait analysis: clinical facts.* Eur J Phys Rehabil Med, 2016. **52**(4): p. 560-74.
137. Hoyer, E., et al., *Temporal and spatial gait parameters in patients dependent on walking assistance after stroke: reliability and agreement between simple and advanced methods of assessment.* Gait Posture, 2014. **40**(1): p. 101-6.
138. A.L, H., *Scaling gait data to body size.* Gait & Posture, 1996. **4**(3): p. 222-23.
139. Baker, R., et al., *The gait profile score and movement analysis profile.* Gait Posture, 2009. **30**(3): p. 265-9.
140. Cimolin, V. and M. Galli, *Summary measures for clinical gait analysis: a literature review.* Gait Posture, 2014. **39**(4): p. 1005-10.
141. Devetak, G.F., et al., *Reliability and minimum detectable change of the gait profile score for post-stroke patients.* Gait Posture, 2016. **49**: p. 382-387.
142. Rasmussen, H.M., et al., *Gait Deviation Index, Gait Profile Score and Gait Variable Score in children with spastic cerebral palsy: Intra-rater reliability and agreement across two repeated sessions.* Gait Posture, 2015. **42**(2): p. 133-7.
143. Hesse, S., et al., *Robot-assisted practice of gait and stair climbing in nonambulatory stroke patients.* J Rehabil Res Dev, 2012. **49**(4): p. 613-22.
144. www.clinicaltrials.gov.
145. Aach, M., et al., *Voluntary driven exoskeleton as a new tool for rehabilitation in chronic spinal cord injury: a pilot study.* Spine J, 2014. **14**(12): p. 2847-53.
146. Wall, A., J. Borg, and S. Palmcrantz, *Clinical application of the Hybrid Assistive Limb (HAL) for gait training-a systematic review.* Front Syst Neurosci, 2015. **9**: p. 48.
147. Cai, L.L., et al., *Implications of assist-as-needed robotic step training after a complete spinal cord injury on intrinsic strategies of motor learning.* J Neurosci, 2006. **26**(41): p. 10564-8.
148. Lewek, M.D., et al., *Allowing intralimb kinematic variability during locomotor training poststroke improves kinematic consistency: a subgroup analysis from a randomized clinical trial.* Phys Ther, 2009. **89**(8): p. 829-39.

149. Shah, P.K., et al., *Variability in step training enhances locomotor recovery after a spinal cord injury.* Eur J Neurosci, 2012. **36**(1): p. 2054-62.
150. Lefeber, N., E. Swinnen, and E. Kerckhofs, *The immediate effects of robot-assistance on energy consumption and cardiorespiratory load during walking compared to walking without robot-assistance: a systematic review.* Disabil Rehabil Assist Technol, 2017. **12**(7): p. 657-671.
151. Lefeber, N., et al., *Physiological responses and perceived exertion during robot-assisted treadmill walking in non-ambulatory stroke survivors.* Disabil Rehabil, 2019: p. 1-9.
152. van Nunen, M.P., et al., *Exercise intensity of robot-assisted walking versus overground walking in nonambulatory stroke patients.* J Rehabil Res Dev, 2012. **49**(10): p. 1537-46.
153. Awad, L.N., et al., *A soft robotic exosuit improves walking in patients after stroke.* Sci Transl Med, 2017. **9**(400).
154. van Kammen, K., et al., *Lokomat guided gait in hemiparetic stroke patients: the effects of training parameters on muscle activity and temporal symmetry.* Disabil Rehabil, 2019: p. 1-9.
155. Han, E.Y., et al., *Robot-assisted gait training improves brachial-ankle pulse wave velocity and peak aerobic capacity in subacute stroke patients with totally dependent ambulation: Randomized controlled trial.* Medicine (Baltimore), 2016. **95**(41): p. e5078.
156. Chang, W.H., et al., *Effects of robot-assisted gait training on cardiopulmonary fitness in subacute stroke patients: a randomized controlled study.* Neurorehabil Neural Repair, 2012. **26**(4): p. 318-24.
157. Billinger, S.A., et al., *Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association.* Stroke, 2014. **45**(8): p. 2532-53.
158. Reisman, D.S., et al., *Split-belt treadmill adaptation transfers to overground walking in persons poststroke.* Neurorehabil Neural Repair, 2009. **23**(7): p. 735-44.
159. Asbeck, A.T., et al., *Biologically-inspired soft exosuit.* IEEE Int Conf Rehabil Robot, 2013. **2013**: p. 6650455.
160. Kim, S.Y., et al., *Effects of Innovative WALKBOT Robotic-Assisted Locomotor Training on Balance and Gait Recovery in Hemiparetic Stroke: A Prospective, Randomized, Experimenter Blinded Case Control Study With a Four-Week Follow-Up.* IEEE Trans Neural Syst Rehabil Eng, 2015. **23**(4): p. 636-42.
161. Ochi, M., et al., *Gait training in subacute non-ambulatory stroke patients using a full weight-bearing gait-assistance robot: A prospective, randomized, open, blinded-endpoint trial.* J Neurol Sci, 2015. **353**(1-2): p. 130-6.
162. Taveggia, G., et al., *Conflicting results of robot-assisted versus usual gait training during postacute rehabilitation of stroke patients: a randomized clinical trial.* Int J Rehabil Res, 2016. **39**(1): p. 29-35.
163. Kollen, B., G. Kwakkel, and E. Lindeman, *Longitudinal robustness of variables predicting independent gait following severe middle cerebral artery stroke: a prospective cohort study.* Clin Rehabil, 2006. **20**(3): p. 262-8.
164. Feng, W., et al., *Corticospinal tract lesion load: An imaging biomarker for stroke motor outcomes.* Ann Neurol, 2015. **78**(6): p. 860-70.
165. Pennati, G.V., et al., *Recovery and Prediction of Dynamic Precision Grip Force Control After Stroke.* Stroke, 2020: p. Strokeaha119026205.
166. Smith, M.C., et al., *Proportional Recovery From Lower Limb Motor Impairment After Stroke.* Stroke, 2017. **48**(5): p. 1400-1403.
167. Jones, P.S., et al., *Does stroke location predict walk speed response to gait rehabilitation?* Hum Brain Mapp, 2016. **37**(2): p. 689-703.

168. Kim, E.H., J. Lee, and S.H. Jang, *Motor outcome prediction using diffusion tensor tractography of the corticospinal tract in large middle cerebral artery territory infarct.* NeuroRehabilitation, 2013. **32**(3): p. 583-90.
169. Roelker, S.A., et al., *Paretic propulsion as a measure of walking performance and functional motor recovery post-stroke: A review.* Gait Posture, 2019. **68**: p. 6-14.
170. Awad, L.N., et al., *Identifying candidates for targeted gait rehabilitation after stroke: better prediction through biomechanics-informed characterization.* J Neuroeng Rehabil, 2016. **13**(1): p. 84.
171. Chua, J., J. Culpan, and E. Menon, *Efficacy of an Electromechanical Gait Trainer Poststroke in Singapore: A Randomized Controlled Trial.* Arch Phys Med Rehabil, 2016. **97**(5): p. 683-90.
172. Baer, G.D., et al., *Treadmill training to improve mobility for people with sub-acute stroke: a phase II feasibility randomized controlled trial.* Clin Rehabil, 2018. **32**(2): p. 201-212.
173. Duncan, P.W., et al., *Body-weight-supported treadmill rehabilitation after stroke.* N Engl J Med, 2011. **364**(21): p. 2026-36.
174. Nichols-Larsen, D.S., et al., *Factors influencing stroke survivors' quality of life during subacute recovery.* Stroke, 2005. **36**(7): p. 1480-4.
175. Palmcrantz, S., et al., *Differences between younger and older individuals in their use of care and rehabilitation but not in self-perceived global recovery 1year after stroke.* J Neurol Sci, 2012. **321**(1-2): p. 29-34.
176. Kollen, B., G. Kwakkel, and E. Lindeman, *Time dependency of walking classification in stroke.* Phys Ther, 2006. **86**(5): p. 618-25.
177. Bohannon, R.W., A.W. Andrews, and S.S. Glenney, *Minimal clinically important difference for comfortable speed as a measure of gait performance in patients undergoing inpatient rehabilitation after stroke.* J Phys Ther Sci, 2013. **25**(10): p. 1223-5.
178. Tilson, J.K., et al., *Meaningful gait speed improvement during the first 60 days poststroke: minimal clinically important difference.* Phys Ther, 2010. **90**(2): p. 196-208.
179. Johansson, G.M., et al., *Assessment of arm movements during gait in stroke - the Arm Posture Score.* Gait Posture, 2014. **40**(4): p. 549-55.
180. Ada, L., et al., *Mechanically assisted walking with body weight support results in more independent walking than assisted overground walking in non-ambulatory patients early after stroke: a systematic review.* J Physiother, 2010. **56**(3): p. 153-61.