



Summary

Worldwide, 16.9 million people experience a stroke each year of which 5.9 million stroke victims die and another 5 million remain permanently disabled. The far-reaching consequences of stroke are further illustrated by the fact that it is the second cause of mortality and the third cause of disease burden. Early after stroke, a large proportion of patients is limited in walking (60% to 100%) and activities of daily living (ADL; 80%) for which they require physical rehabilitation. Although the presentation of stroke is heterogeneous, the recovery pattern of these functional abilities poststroke typically shows a course with a relatively steep increase in the first few weeks which then levels off. Generally, most of the recovery takes place within the first 3 to 6 months after stroke onset.

The majority of people who experience a stroke are admitted to a hospital stroke unit as soon as possible, where stroke care is provided by an interdisciplinary team. After the application of medical diagnostics to determine stroke type and stroke etiology, the primary goal is to prevent further cerebral damage by application of thrombolysis or thrombectomy in patients with ischemic stroke. However, early mobilization and physical rehabilitation are started as soon as the patient is medically stable. Rehabilitation is patient specific and aims to reduce impairments, limitations in activities, and restrictions in participation, in order to enable the patient to live at home and being integrated in community life.

The length of stay at a hospital stroke unit has shortened in recent years and nowadays usually amounts about 9 days. Thereafter, about half of the patients are discharged home, with some of them requiring further rehabilitation services while others do not. The other half of the patients continue rehabilitation services as inpatients in a rehabilitation center or nursing home and will subsequently be discharged to a final location of residence. The variety in discharge location shows that care for patients with stroke extends to various health care settings and the patient's home environment (i.e. consecutive care organized in stroke services), requiring coordinated transmutal, interdisciplinary collaboration. The number of professionals involved with a patient is depending on, for example, the timing poststroke, location of residence, and the existing disabilities.

Physical therapy is one of the key disciplines in the interdisciplinary team and present in all parts of poststroke care, regardless of the phase after onset. During hospital stay, physical therapists play an important role in diagnostics and functional prognosis of patient's outcomes like independent gait and independence in ADLs. The interdisciplinary team needs this information for several reasons. First of all, to determine an adequate discharge destination and rehabilitation trajectory. Second, to formulate realistic rehabilitation goals and select relevant evidence-based interventions. Third, to inform the patient and caregivers about the course of treatment and expected outcome, and

fourth, to anticipate on possible home adjustments. Due to the decreased length of hospital stay at stroke units and the aim to improve quality of health care services without increasing resources, there is need for knowledge about the patient's outcome on the basis of simple bedside tests measured early poststroke.

The predicted final outcome plays an important role in determining a realistic treatment plan for a patient, including selecting appropriate rehabilitation interventions. In pursuit of high-quality physical therapy for patients with stroke, these interventions should be evidence-based. The Royal Dutch Society for Physical Therapy (Koninklijk Nederlands Genootschap voor Fysiotherapie, KNGF) developed a Clinical Practice Guideline for physical therapy in patients with stroke (*KNGF-guideline Stroke*) in 2004. This guideline described the scientific evidence for all parts of the physical therapy process, starting with the referral of the neurologist or other physician; followed by the diagnostic phase including prognosis; goal setting; intervention; evaluation; and termination of the treatment. This guideline also provides transparency for health care insurance companies about efficacious physical therapy poststroke. These companies could use these in their care purchasing policy. Because of the explosive growth in the number of trials in stroke rehabilitation, including physical therapy, revision of the guideline was urgently needed.

The present thesis aimed to investigate two important questions in stroke rehabilitation: (1) Are we able to early predict functional outcomes after stroke, like basic ADL and walking ability? and (2) What is the current evidence for stroke rehabilitation interventions in the domain of physical therapy? The **chapters 2, 3, and 4** are focused on early measured predictive factors for final outcome in terms of independency in basic ADL and gait. The subsequent **chapters 5, 6, and 7** deal with scientific evidence for stroke rehabilitation interventions in the domain of physical therapy. For the *KNGF-guideline Stroke*, please see <http://www.fysionet-evidencebased.nl/index.php/richtlijnen/richtlijnen/beroerte-2014>; for English: <http://www.fysionet-evidencebased.nl/index.php/kngf-guidelines-in-english>.

EARLY PREDICTION OF OUTCOME AFTER STROKE

In **chapter 2**, a systematic review is described concerning factors measured within 2 weeks after stroke being predictive or not being predictive for outcome of basic ADL at least 3 months after onset. After a systematic search of the literature, a total of 48 cohort studies were included, involving 25843 patients. Prior to determining the evidence for predictive or non-predictive factors, a list was developed to assess the risk of bias of the included cohort studies. This list contained items related study participation, study attrition, predictor measurement, outcome measurement, statistical

analysis, and clinical performance and validity. Subsequently, a best-evidence synthesis was performed for each identified factor, based on both the quality of the studies and the number of studies that had identified the factor. The mean time at which the factors were assessed amounted 5.4 days after onset. The Barthel Index (BI) was the most frequently used outcome measurement for objectifying basic ADL. There was strong evidence for patients' neurological status with items relating to lower severity of (upper limb) paresis as an important component for better outcome of basic ADL. Strong evidence was also found for age, with an older age disfavoring outcome of basic ADL. Contrary, there was strong evidence that gender nor stroke risk factors such as atrial fibrillation are not likely to be predictive for outcome of basic ADL.

The BI is the most frequently used measurement instrument in hospital stroke units to assess basic ADL. The BI describes the patient's actual performance of basic ADL during the previous 24 hours, like grooming, bathing, eating, walking stairs, and bowel and bladder control. Patients are considered to be independent in basic ADL when they have a score of at least 19 out of a maximum of 20 points. However, the predictive value (i.e. diagnostic accuracy) of the BI is unclear. Therefore, the predictive value of the early measured BI for outcome of basic ADL 6 months poststroke was investigated in **chapter 3**. Analyses were performed on data of the Early Prediction of functional Outcome after Stroke (acronym: EPOS) study. In this multicenter cohort study, adult patients with a first-ever ischemic stroke and a mono or hemiparesis were recruited in nine hospital stroke units in the Netherlands. Patients were assessed with a clinimetric test battery at days 2, 5, and 9 poststroke. Final outcome was determined 6 months after onset. Based on the EPOS study, the optimal cut-off point of the early measured BI for a favorable outcome of basic ADL at 6 months was 7 points or higher. Day 5 poststroke seemed to be the earliest moment poststroke to accurately predict final outcome in terms of basic ADL 6 months after onset. Based on the negative predictive value, assessment on day 2 resulted in an underestimation of outcome of ADL 6 months after onset. This could be explained by the observation that the BI reflects the actual performance of patients', rather than what they are assumed to be able to do at day 2 poststroke. This finding is further underpinned by the knowledge that the accuracy of the National Institutes of Health Stroke Scale, as a reflection of neurological impairments, in the same cohort is quite invariant in the first 9 days poststroke. Obviously, progress of time alone is not likely to be responsible for improved predictive accuracy of the BI in the first 9 days poststroke but rather the way how the BI is assessed in these bed-bound patients at hospital stroke units.

For clinical practice, this finding suggests that the BI should not be assessed earlier than day 5 poststroke when applied for prognostic purposes.

Another main outcome in stroke rehabilitation is independent gait. In **chapter 4**, a mathematical prediction model was developed for independent gait 6 months after stroke onset in patients who were unable to walk independently within the first 72 hours poststroke. The modeling was performed based on the data of patients included in EPOS study. Independent gait was defined as a Functional Ambulation Categories score of 4 or 5. Based on a logistic regression analysis, it was shown that independent gait could be accurately predicted early after stroke based on two simple measured variables, "sitting balance" and "strength of the paretic leg." Patients who were able to sit unsupported for 30 seconds (measured with the item sitting balance from the Trunk Control Test; 25 points) and had a less severe paresis of the leg (measured with the leg subscale of the Motricity Index; ≥ 25 points) at day 2 after stroke, had a chance of 98% to regain independent gait at 6 months. Contrary, patients who lacked a positive score on both items had a chance of only 27% to regain independency in gait. In these patients with an initial bad prognosis, reassessment of sitting balance and paresis of the leg at days 5 and 9 for prediction of independent gait resulted in a chance of 23% and 10% respectively.

In daily practice, this implies that early and frequent (re)assessment of sitting balance and strength of the paretic leg is needed to accurately predict independent gait 6 months poststroke.

NEUROREHABILITATION INTERVENTIONS AFTER STROKE

In **chapter 5** an overview is given of the evidence for stroke rehabilitation interventions in the domain of physical therapy. This manuscript was based on the *KNGF-guideline Stroke 2014*, which is a revision of the 2004 guideline. To identify relevant RCTs, a systematic search of the literature was performed. This search yielded 467 RCTs with a total of 25373 patients. These RCTs were subsequently assessed for their risk of bias and only trials with at least a "fair" quality (PEDro score ≥ 4) were included in the meta-analyses to determine the summarized effects of the interventions for various clinical outcomes. Statistical pooling of data for 53 interventions showed that there was strong evidence for beneficial effects of 30 of these interventions. For the majority of interventions related to the intervention categories "gait and mobility-related functions and activities," "arm-hand activities," and "physical fitness." In addition, strong evidence was found for intensity of practice, indicating that patients who spent more time in exercise therapy had better outcomes than those patients who spent less time in training. Next to intensity of practice, specificity seemed to be another key principle that drives effective interventions in stroke rehabilitation. For neurological treatment approaches such as Bobath/Neurodevelopmental Treatment, there was strong evidence that they equal other interventions, or even lead to worse functioning and was therefore not

recommended for daily practice. Subgroup analyses for timing of the intervention after onset could not reveal a trend for a moderator effect of poststroke phase (i.e. (hyper)acute phase, early rehabilitation phase, late rehabilitation phase, and chronic phase).

The presented review showed that apart from the enormous growth in number of published RCTs in the last decade, also the number of interventions that are labeled “strong evidence” has been increasing, just like the number of outcomes. Principles like task and context specificity and intensity remain important ingredients characterizing efficacious interventions. However, many interventions have been investigated in small sized ($N < 50$) RCTs in which a defined primary outcome was lacking and no correction was made for multiple testing. Especially the vast number of RCTs with a small sample size hampers making valid recommendations regarding the efficacy of interventions. In addition, the lack of statistical power induces instability in the evidence for interventions with corresponding recommendations in guidelines for stroke. This underpins the need for updating the *KNGF-guideline Stroke* at least every 4 years.

Intensity of practice, defined as time spent in exercise therapy, is assumed to be an important characteristic of effective exercise interventions in stroke rehabilitation. Therefore, intensity of practice is the central theme in **chapter 6**. This intensive exercise therapy related to exercise interventions focused on the lower limb without use of extensive equipment. After a systematic literature search, 14 RCTs (725 patients) were included in which patients in the experimental group spent more time in exercise therapy when compared to the controls. On average, the additional therapy time amounted 37 minutes during 5.7 weeks. Statistically pooling data of the trials resulted in significant summary effects for walking ability, comfortable walking speed, and extended ADL post intervention in favor of high-intensity practice during the first 6 months after stroke. No significant effect was found for basic ADL. Additional analyses did not find a moderator effect of treatment contrast, timing poststroke, type of control intervention, nor for methodological quality of included trials.

These findings indicate that patients with a stroke within the first 6 months after onset should have access to a physical and/or occupational therapists allowing to practice intensively as long as there are meaningful rehabilitation goals. Acknowledging the dose-response relationship of practice, the *KNGF-guideline Stroke* development team recommends that patients with limitations of basic ADL activities (< 19 points on the BI) should be enabled during their admission to exercise for at least 45 minutes per working day, whether or not supervised by a physical therapist and/or occupational therapist.

A promising intervention for the upper limb applying the “intensity” principle is constraint-induced movement therapy (CIMT). In **chapter 7**, the evidence for CIMT is reviewed, i.e. original CIMT, modified versions of CIMT, and forced use of the paretic arm and hand. After a historical background of CIMT, the efficacy and hypothetical working mechanisms of these three forms of CIMT were described.

The original form of CIMT consists of three packages, including (1) repetitive, task-oriented training of the paretic upper limb for 6 hours a day on 10 consecutive working days; (2) a transfer package including adherence-enhancing behavioral strategies; and (3) constraining use of the less affected upper limb for 90% of the waking hours to stimulate the use of the more affected upper limb. The modified versions of CIMT consist of a reduced amount of hours spent in task-oriented training and mitt wear, while a transfer package is often not applied. In total, 51 RCTs (with a total of 1784 patients) were included after a systematic literature search. Statistically combining the results of the trials showed that both original CIMT and modified CIMT yielded positive significant effects for arm-hand activities, self-reported amount of arm use in daily life, and self-reported quality of arm-hand use in daily life post intervention. These effects were also sustained 4 to 5 months after termination of the intervention. However, the effects of modified CIMT for basic ADL were only statistically significant post intervention and did not sustain. In addition, for modified CIMT a significant positive effect on motor function of the paretic arm was found, but only in patients who were within the first 3 months after stroke. These effects on motor function were maintained in the long term. As for quality of life, original CIMT showed significant benefits 4 months after termination of the intervention. No trend could be detected that timing poststroke, the degree of treatment contrast between the experimental and control groups, or type of CIMT moderated the found effects. No significant effects were found in favor of forced use.

In conclusion, original CIMT and modified CIMT are treatment options for patients with limited arm-hand activities, but who have at least some extension function of one or more fingers and/or wrist.

GENERAL DISCUSSION

Chapter 8 gives a brief overview of the main results of the presented research in chapters 2 to 7. The emphasis of this final chapter is on the critical appraisal of these investigations, the consequences of the findings for clinical practice, and results in a discussion for future research. Clinicians, patients and their families, researchers, health care insurances, and policy makers would all benefit from optimized prognostic models and recovery profiles for individual patients, to allow stratified medicine: application of interventions in subgroups of patients who are assumed to

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benefit most from a certain intervention. For this purpose, systematic measuring is a prerequisite. In parallel, underlying mechanisms of recovery and subsequently their ability to be influenced by well-timed application of (innovative) rehabilitation interventions should be investigated (i.e. translational research). For this purpose, the nature of stroke recovery should be investigated from a multidimensional perspective in which improvements of meaningful activities are investigated simultaneously with changes in neuromechanics, kinematics and neurological impairments. To create these multimodal recovery profiles, professionals with a different expertise need to work together.