Chapter 1

Introduction
Stroke is defined by the World Health Organisation (WHO) as: “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin.” Nearly 90 percent of all strokes are ischemic, the remainder are intracerebral and subarachnoid hemorrhages. Two thirds of all ischemic strokes occur in the anterior circulation and thereof 96 percent involves the middle cerebral artery (MCA). Worldwide fifteen million people suffer a stroke each year, resulting in about 5 million deaths. Of the remaining stroke survivors another 5 million are permanently disabled. Although the incidence of stroke is declining in many developed countries, largely as a result of better control of high blood pressure and reduced levels of smoking, the absolute number of strokes continues to increase because of the ageing population.

After an MCA stroke, approximately 80% of survivors have motor impairments, such as upper or lower limb (hem)iparesis and spasticity. These motor impairments greatly affect an individual’s ability to perform activities of daily living (ADL) and to participate in daily-life situations. In particular, the severity of an upper limb paresis is strongly associated with outcome of ADL independency. Although there is a lack of good epidemiologic research about recovery rates after stroke, results from some cohort studies suggest that only 5–20% of the patients with severe upper limb paresis at stroke onset demonstrate complete functional recovery. In contrast, Nakayama et al. showed that 80% of the patients in their study with a mild upper limb paresis at stroke onset, achieved full upper limb function 6 months after stroke. In this particular study, upper limb function was evaluated using the Barthel Index by using the subscores for feeding and grooming. However, these items allow compensation strategies with the non-paretic limb. This finding suggests that the interpretation of the diverging percentages in the different prospective cohort studies largely dependent on the underlying construct of applied measurements, used for evaluating outcome. Fortunately, the WHO’s international classification of functioning, disability, and health (ICF) provides a well defined classification framework that can be used to classify the consequences of stroke in terms of body structures and functions (impairments), activities (limitations) and participation (restrictions) (Figure 1.1). Throughout this thesis, recovery of the paretic upper limb after stroke will be discussed, using the ICF as the underlying conceptual framework. The next paragraph explains how the ICF classification can be used to describe recovery of the paretic upper limb after stroke. At the end of the introduction, a brief list of definitions following the terminology as used in the ICF is provided.
What do we mean with “recovery of the paretic upper limb” in terms of the ICF classification?

To improve our understanding about what happens during upper limb recovery after stroke we have defined recovery at 3 levels of the ICF: Body Structure, Body Functions and Activities (Figure 1.2). In this schematic representation, the definitions were not extended to the participation level of the ICF, since participation refers to the societal perspective of functioning, which is more difficult to define. We propose that (upper limb) recovery can be achieved by both restitution (i.e. repair) and substitution (i.e. learning compensation strategies). For instance, at the activity level, patients may perform a certain task with the same quality of motor control as before the stroke. In this context, recovery is a consequence of restitution. However, improvement in performance of a task may also be achieved as a result of the use of adaptation or compensation strategies that the patient employs to deal with existing impairments. With that, recovery is a consequence of substitution/compensation.

How does motor recover of the paretic upper limb emerge?

The time course of upper limb recovery after stroke typically follows a non-linear pattern: most upper limb recovery is usually seen in the first weeks post stroke, with only little improvement occurring after one year. For example, in the Copenhagen Stroke Study of Nakayama and
10% of the patients reached their plateau in terms of upper limb recover already within the first three weeks after stroke. Kwakkel and colleagues found that the outcome for regaining some dexterity is optimally predicted within the first 4 weeks post-stroke, suggesting that outcome at 6 months is already defined within this time frame. Time-dependent improvements immediately after stroke are caused by some degree of spontaneous restitution of neurological function, often characterized as 'spontaneous neurological recovery.' Although spontaneous neurological recovery is not fully understood, several mechanisms, such as recovery of penumbral tissues, resolution of diaschisis, elevated levels of growth promoting factors and angiogenesis, are purportedly involved. However, upper limb recovery after stroke is more than neural repair alone and also depends on improvements in movement-related functions such as muscle strength, joint mobility, and coordination of simple and complex voluntary movements. Beyond the first months after stroke, patients can also improve in terms of substitution by using behavioural compensation strategies to deal with their existing neurological impairments.

**Figure 1.2** Definitions for motor recovery based on the ICF classification. A classification of recovery, compensation/substitution and restitution, based on the ICF framework. A stroke can cause changes in various body structures (i.e. the spinal cord, the brain and/or muscles). A change in a certain body structure can influence a body function (i.e. muscle power, muscle tone or the coordination of voluntary movements) and a change in a body function may influence the activity performance (i.e. eating, dressing). We suggest that recovery can be the result of both compensation/substitution and restitution within the defined levels of the ICF classification. Body components are defined as a collection of body structures that contribute to a specific body function.
Prediction of upper limb recovery after stroke

Knowledge about prognosis of outcome is important to inform patients and their relatives properly. Additionally, it is important for stroke management decisions, like discharge policies and intervention planning at hospital stroke units and in integrated care pathways. Positive outcomes of interventions in rehabilitation medicine are specific and largely dependent on patients’ characteristics at baseline. For instance, the favorable results reported for Constraint Induced Movement Therapy (CIMT) are probably not only caused by the content and intensity of therapy, but are especially achieved due to an a priori selection of patients with a favorable prognosis to regain some dexterity.20, 21 This suggests that patient-tailored stroke care requires not only experts’ knowledge about the effectiveness of a certain evidence-based intervention but also about the conditional factors that are required to apply that specific intervention. Early insight in the prognosis of outcome allows clinicians therefore to deliver patient-tailored stroke care already in the hospital stroke units, which can then be continued in integrated care pathways. Ultimately, implementation of suitable prognostic models, already in the hospital stroke unit, will lead to a reduction in health care costs, since it prevents that patients receive inadequate care after stroke.22, 23

Prognostic research

Several observational studies have demonstrated that initial severity of hemiparesis is a good predictor for upper limb recovery.8, 9, 16, 24, 25 However, inter-individual variability in recovery patterns makes accurate prediction difficult. Computational prediction models are developed to provide objective estimates of outcome probabilities. However, most prediction models have not gained much acceptance in clinical practice due to a lack of applicability. Application of a model requires for instance unambiguous definitions of the predictive determinants and the assessment of these determinants should be reproducible in clinical practice,22 which is not always the case with sophisticated techniques such as neuroimaging and neurophysiologic assessments. Moreover, the prognostic accuracy of models based on neuroimaging and neurophysiological assessments is shown to be similar to that of motor function assessments, when directly compared.26, 27 These findings suggest that we should primarily focus on indentifying determinants which could be obtained in a quick and simple way. An important aspect for the validity of prognostic determinants is the methodological quality of the study, which is unfortunately often poor in studies of existing models early after stroke.7 For instance, generalization of obtained outcome probabilities is often limited because of differences in the timing of assessment of clinical determinants. Measurements in a prospective cohort study about recovery after stroke should take place at fixed time points, because of the non-linearity in
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recovery patterns.28 An intensive repeated-measurements design should be used, to determine the optimal timing for the assessments and to capture changes at short timescales. The challenge is to build a prognostic model that meets above-mentioned criteria. In chapter 2 of this thesis, the development of a computational prognostic model is described. The aim of this study was to determine if outcome in terms of upper limb function at 6 months after stroke can be predicted using relatively quick and simple to obtain clinical parameters, measured within 72 hours after stroke in a hospital stroke unit. In addition, the effect of the timing of post-stroke assessment on the accuracy of prediction was investigated by re-assessments on days 5 and 9 post stroke.

In chapter 3, a study is presented that aimed to investigate which patients’ characteristics predict the recovery of upper limb capacity after discharge from the hospital stroke unit, during inpatient rehabilitation.

What is the accuracy of prediction of upper limb recovery without using a computational prediction model?

Computational prediction models are developed to complement clinical expertise and guidelines in clinical decision making processes. An important question is therefore if the use of a prediction model results in a higher accuracy of prediction, compared with the accuracy of prediction without the use of a model. Results by Kwakkel and colleagues29 suggest that predictions about functional outcome made by therapists in the second and fifth week after stroke onset are about as accurate as computational prediction models. However, current knowledge about the accuracy of therapists’ prediction in the first week post stroke, when important decisions regarding discharge policy and intervention planning have to be made, is still lacking. In chapter 4 we investigated the accuracy of predictions regarding outcome of the paretic upper limb, as made by physical therapists in hospital stroke units. In addition we investigated if the accuracy of prediction is influenced by the timing of assessment post stroke. Finally, the accuracy of predictions made by physical therapists and predictions made by computational prediction models were compared.

What is the optimal timing and intensity for upper training?

Prospective prognostic research shows that the potential for functional recovery of the upper limb is largely defined within 4 weeks post stroke.8 In addition, progress of time seems to be an independent covariate in explaining recovery of impairments such as synergism, strength, neglect and balance control in the first 6 to 10 weeks post stroke.13, 30 These findings are in line with animal studies that suggest the presence of a time window in the first weeks after stroke,
in which proteins that encourage growth related processes, such as CAP 43, MARCKS and CAP 23, are upregulated. Upregulation of growth promoting factors results in synapse strengthening and activity dependent rewiring of neuronal networks to compensate for tissue loss to injury. Moreover, the period in which growth promoting factors are expressed at the highest level is thought to be followed by a period in which negative factors that inhibit reorganization, such as the extracellular matrix factor NOGO, are presented. As a consequence, it is suggested that there is a limited time window of heightened neuroplasticity during the first weeks after stroke, which may offer an opportunity for therapists to successfully apply evidence based interventions for acute stroke survivors to enhance recovery. The importance of early intervention is confirmed by an animal study of Biernaskie and colleagues, who showed a marked improvement in forelimb reaching tasks in rats when training was started as early as 5 days post stroke. In contrast, less improvement was found when the training started at 14 days post stroke and motor recovery did not differ between rats that started their training at 30 days post stroke and rats in the control group. The control group did not receive any training. However, conflicting results are found in the literature regarding the optimal moment to start intensive exercise therapy. For instance, Shallert and colleagues suggested on the basis of a number of experiments with rats that the region surrounding an infarction may be vulnerable “to behavioural pressure” in the early days to weeks post stroke.

The optimal intensity for upper limb exercise therapy is still under debate as well. A number of systematic reviews have shown that intensity of training, in terms of hours spent on therapy, is one of the main determinants of functional improvement after stroke. It is therefore widely accepted that increased intensity of training improves outcome. But again conflicting results have been reported in the literature, mainly in patients in the (sub)acute phase after stroke. An example of a study that did not find positive effects of increased intensity is the VECTORS study. The VECTORS study investigated the effectiveness of Constraint Induced Movement Therapy (CIMT) for the paretic upper limb in the acute phase after stroke. CIMT is currently one of the most promising interventions for the paretic upper limb. In the next paragraph, the rationale behind CIMT will be explained in more detail and conflicting theories and findings regarding the influence of intensity will be discussed as well.

What is (modified) Constraint Induced Movement Therapy?

CIMT is a neurorehabilitation intervention developed by behavioural neuroscientist Dr. Edward Taub and colleagues. Dr. Taub showed that chronic lack of use of a paretic upper limb in monkeys could be (partly) reversed with a physical restraint applied to the unaffected upper limb. These observations led to formulating the concept of learned nonuse. The learned
nonuse phenomenon is predicated on the fact that monkeys with an affected upper limb are confronted with inefficient results when they use their affected upper limb for food gathering, locomotion etc. The movement failure of the affected upper limb transfers responsibility to the unaffected upper limb, which is more successful and is therefore rewarded. Recovery of the affected limb may occur spontaneously over the first several months. However, because the monkey does not employ the affected limb for functional tasks, the latent motor ability is not expressed, but is instead held in a powerful conditioned inhibition. Interestingly, the latent potential can be unmasked by a restraint to the unaffected upper limb. It has been shown that the monkey does re-use the affected upper limb also in unrestrained conditions after 3 days of restraining. The experiments with monkeys led Taub to propose that analogous behavior might also occur in humans after neurological injury. In the nineteen-eighties, Wolf and colleagues conducted one of the first forced use studies in chronically hemiparetic stroke and traumatic brain injury patients (N=22). In this study, patients wore a sling on the less-affected arm for two weeks while requiring the more-affected arm to conduct routine daily living activities. The patients did not perform specific training of the more-affected arm. The results indicated significant improvements in movement time and force on laboratory measures of motor performance of the affected arm. Movement quality, however, did not improve. Taub and colleagues employed in 1993 at the University of Alabama at Birmingham a full treatment program. The current treatment protocol for original CIMT contains three main elements: (I) Repetitive, task-oriented training of the more-affected arm for 6 hours a day, on 10 consecutive weekdays; (II) A Transfer Package of adherence-enhancing behavioural methods designed to transfer the gains made in the clinical setting to the patient’s real world environment and; (III) Constraining the less-affected arm to promote the use of the more impaired upper limb during 90% of the waking hours. In addition to the original treatment protocol for CIMT, numerous modified forms of CIMT (mCIMT) have been described in the literature as well, most often to improve the feasibility of (m)CIMT in clinical practice. These mCIMT interventions are often characterized by a less intensive treatment protocol in terms of hours spent on repetitive training and constraining.

Although CIMT is one of the most promising interventions for the upper limb after stroke, the effectiveness of CIMT in the acute phase after stroke is still controversial because of previously mentioned conflicting results regarding the optimal timing to start intensive exercise therapy. In addition, the before mentioned VECTORS study investigated the effectiveness of mCIMT, started within 2 weeks after stroke onset. They compared two intensities of mCIMT. The high intensity mCIMT group received 3 hours of repetitive training on every workday in combination with constraining the less affected limb for 90% of the waking hours. The low
intensity mCIMT group received 2 hours of repetitive training and 6 hours of constraining per day. The results of this study suggest a negative dose-response relationship for mCIMT, when started within 2 weeks after stroke.

Conflicting theories and results about the application of (m) CIMT and the influence of intensity makes further research about (m)CIMT in the acute phase after stroke very relevant. Hence, a systematic review is presented on the effectiveness of CIMT in the acute or subacute phase after stroke is presented in chapter 5 of this thesis. In this study, separate quantitative analyses were performed to investigate the impact of intensity. The results of this systematic review can be seen as a starting point to design future studies.

(Modified) CIMT in the EXPLICIT stroke programme.

The EXPLICIT-stroke (EXplaining PLasticity after stroke) programme is a single blind randomized controlled trial, which runs from 2008 till 2013 in the Netherlands and is funded by ZonMw (grant no: 89000001) The programme aims to investigate the effectiveness of early applied intensive exercise therapy of the paretic upper limb after stroke. Intensive exercise therapy is started within the first 2 weeks after stroke and is applied in the form of EMG triggered neuromuscular stimulation for patients with a poor prognosis for functional recovery, which is expressed in the inability to extend the wrist and fingers. For patients with a favorable prognosis for outcome of the paretic upper limb, expressed in the presence of at least some voluntary extension of the wrist and fingers, intensive exercise therapy is applied in the form of mCIMT. In this thesis, the focus will be on the mCIMT intervention for patients with a favorable prognosis for functional outcome in the first two weeks post stroke. An important obstacle in comparing the few published studies on the effectiveness of (m)CIMT in the acute phase is the indistinctness about the content of (m)CIMT because of the lack of a published treatment protocol. Transparency regarding the treatment protocol applied is also essential to allow clinicians to implement the protocol in practice and to allow other researchers to replicate the claimed findings of published clinical trials, which is essential in evidence-based medicine. Therefore, we described in more detail the elements of the EXPLICIT-stroke mCIMT protocol in chapter 6 of this thesis.

How to assess the effectiveness of stroke rehabilitation?

For the motor performance of the paretic upper limb only, more than 30 measurement tools have been described in the literature. Due to the high number of available instruments and the lack of a golden standard, the selection of an appropriate instrument to measure upper limb
recovery is challenging. Although the multitude of measurements tools, only a few valid and reliable clinical measurement tools are available to quantify upper limb capacity. The Action Research Arm Test (ARAT) and the Wolf Motor Function Test (WMFT) are most commonly used in clinical trials. The clinimetric properties of both measurement tools have been well established in the literature. However, both instruments were only rarely compared in the same sample of patients. Therefore, in chapter 7 of this thesis, the concurrent validity of ARAT and WMFT was studied, and the reproducibility, internal consistency and floor and ceiling effects of both measurement tools were compared in the same group of stroke patients.

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**List of ICF terminology**

**Health condition** is an umbrella term for disease, disorder, injury, or trauma. Stroke will be the health conditions to be discussed in this thesis.

**Body structures** are the structural or anatomical parts of the body, such as the brain, the upper limb and its components.

**Body functions** are the physiological functions of body systems, such as brain circulation, muscle tone and movements and sensory perception.

**Impairment** is a loss or abnormality in body structure or function, such as muscle weakness, joint contractures or impairments in balance and movement coordination.

**Activity** is the execution of a task or action by an individual, such as manipulating objects, walking and self-care activities.

**Activity limitations** are difficulties an individual may have in executing activities.

**Capacity** is a construct that indicates the highest probable level of functioning that a person may reach in the Activities and Participation level.

**Performance** is a construct that describes what individuals do in their current environment, and so brings in the aspect of a person’s involvement in life situations.

**Participation** is a person’s involvement in a life situation. It represents the societal perspective of functioning.
REFERENCES


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