8

General discussion

Stroke rehabilitation is a cyclic process consisting of (1) assessment of the patient's needs; (2) realistic goal setting, taking into account the functional prognosis; (3) selection and application of relevant intervention(s); (4) reassessment of clinical status to monitor the clinical course, improvement, and stated goals; and finally (5) completion of the treatment.[1,2] The present thesis focuses on two key aspects of stroke rehabilitation, namely: *early prediction of functional outcome after stroke* (**chapters 2**, **3**, and **4**) and *evidence for physical therapy interventions after stroke* (**chapters 5**, **6**, and **7**).

In this general discussion, the main findings are summarized and critically appraised. Subsequently, directions for clinical practice are given. In the concluding part, future developments and avenues for optimal prediction of functional outcome after stroke and evidence-based physical therapy interventions in stroke rehabilitation are addressed.

PREDICTION OF FUNCTIONAL OUTCOME AFTER STROKE

Main findings

In the light of two important functional outcomes in stroke rehabilitation, namely walking ability and basic activities of daily living (ADL), **chapters 2**, **3**, and **4** of this thesis address early prediction of these two outcomes. **Chapter 2** aimed to increase our knowledge about robust and unbiased factors that predict or, conversely, do not predict outcome of ADL 3 months or later after stroke. First, a risk of bias assessment scale for prognostic studies was developed to distinguish between studies with a "low risk of bias" and "high risk of bias." Best-evidence synthesis of 48 cohort studies showed strong evidence for baseline neurological status including upper limb paresis, and age as significant predictors for outcome of basic ADL. In addition, strong evidence was found that gender and risk factors for cardiovasculaur diseases such as arterial fibrillation are likely not to be related to outcome in terms of basic ADL. In addition, synthesizing the results from the cohort studies in this systematic review showed that the prognostic value of ADL-score at baseline for final outcome at 3 or 6 months poststroke remains unclear. The Barthel Index (BI) was the most frequently investigated outcome measure for basic ADL in the studies included in this review.

From this perspective, **chapter 3** investigated the optimal moment for assessment of the BI early poststroke to predict independency in basic ADL at 6 months. For this purpose, nine different hospital stroke units did participate in the Early Prediction of Outcome after Stroke (EPOS) study. Comparing the accuracy between assessment at days 2, 5, and 9, suggested that day 5 was the most

optimal moment for an early prediction of ADL-independency on the BI at 6 months poststroke, whereas assessment of the BI at day 2 was significantly less accurate in its predictive value.

From the literature, it is obvious that outcome of BI at 6 months is heavily dependent on items such as transfers, toilet use, and mobility and with that, dependent on patients ability to control balance and have motor function of the paretic lower limb. Contrastingly, outcome of BI is less dependent on the paretic upper limb, acknowledging that upper limb capacity is easily compensated by the non-affected arm. In order to investigate outcome of independent gait at 6 months, a multivariable model was developed in **chapter 4**. In this model, only patients who were unable to walk at hospital stroke units within the first 3 days were investigated. Based on the derived model, it was shown that patients who were able to sit unsupported for 30 seconds and had some voluntary movement in the paretic leg measured within 72 hours after onset had a high probability of 98% to regain independent gait at 6 months. Patients who did not meet these two criteria had a probability of only 27% to achieve independent gait a 6 months. Reassessment in patients with an initially poor prognosis, however, showed a decreased probability for independent gait when the scores on the two determinants remained negative, with probabilities dropping from 23% at day 5 to 10% at day 9. This indicates that early and accurate prediction is possible with simple clinical bedside tests, and that repeated assessment in the first two weeks after onset improves accuracy of prediction of walking ability at 6 months. In fact, this finding suggests that these non-walkers at stroke units should be monitored repeatedly in the first days poststroke for change in these key determinants of independent gait.

Below the main concerns for prognostic research will be discussed and practical implications for further treatment and research will be given.

8

ISSUES TO CONSIDER

Synthesizing prognosis research

Chapter 2 shows that a number of factors affect the validity of prognostic research poststroke.[3] First, the reporting of cohort studies is poor and most publications suffer from bias by poor methodology and selective reporting.[3-6] In addition, large variations exist in the use of different cut-off scores in dichotomized predictor variables and in the type of estimates reported. This hampers aggregated data meta-analysis in prognosis research.[7] Therefore, the applied best-evidence synthesis in **chapter 2** for factors being predictive or not predictive for outcome in basic ADL poststroke seems to be an optimal solution to summarize the evidence in prognosis research, next to individual patient

data meta-analysis. Nevertheless, the degree of importance of each predictor variable within the context of other variables is difficult to assess with this best-evidence synthesis.

Model development

Prognosis in stroke rehabilitation is still underexposed. Ideally, prognostic model research in general consists of three phases: (1) development of the model; (2) external validation of the model; and (3) investigation of the clinical impact of the model.[8] By far the majority of prognostic studies in stroke focuses on development of prognostic models, including the EPOS study in **chapters 3** and **4**.[9,10] External validation is infrequent, while improving models through iteration and investigating the impact on daily practice are hardly ever done.[8,11,12]

Outcome selection

The Functional Ambulation Categories (FAC) was selected as outcome measure for independent gait at 6 months after stroke in **chapter 4**. Although the ability to walk without human assistance or supervision is important, this does not automatically mean that patients are able to walk independently in the community. Community walking, defined as "the ability to integrate walking with other tasks in a complex environment," also makes requirements regarding gait speed, obstacle avoidance, multi task attention, endurance, and fatigue.[13-15] However, models including these factors are scarce.[16]

Bias

In prognostic studies, six major potential sources of bias are (1) study design; (2) study attrition; (3) predictor measurement; (4) outcome measurement; (5) statistical analysis; and (6) clinical performance and validity.[3,17-19] Unfortunately, universally accepted criteria to assess the risk of bias of prognosis studies are lacking. The review presented in **chapter 2** assessed the risk of bias of cohort studies aiming to predict basic ADL poststroke, using a newly developed assessment scale. The items related to bias that were poorly addressed in the included cohort studies were in line with various other reviews that all used different risk of bias assessment scales.[11,12,18,20,21] However, sometimes it is unclear whether methodological issues simply were not addressed in the study, or whether the methodological issue was addressed but the reporting inadequate. Adherence to the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) Statement, containing recommendations for reporting on observational studies should prevent occurrence of the latter.[22,23]

Study design and statistical analysis in cohort studies

Chapters 3 and **4** are derived from the EPOS study, which has a different design than other prospective cohort studies published so far by an early start within the first 72 hours poststroke and serial assessments in time during the first weeks poststroke. However, there are some aspects that need consideration in **chapters 3** and **4**. The first issue relates to the *statistical analysis*. The candidate predictors were objectified with reliable and valid outcome measures and dichotomized for the statistical modeling. From a statistical perspective, dichotomizing candidate predictors is not preferred, because it is accompanied with, for example, a reduction of statistical power, an inability to detect a possible non-linear relationship, and the application of data driven techniques to determine cut-off points.[24,25] However, the advantage of dichotomizing candidate predictors is that cut-off points are easy to apply in clinical practice.

The second issue concerns the *clinical performance and validity* of the prediction model for independent gait and the predictive value of the BI for outcome of basic ADL. Both were investigated in a sample of mild to moderately affected stroke patients without severe cognitive impairments and in whom comorbidities hampering independency before stroke were absent. The clinical usefulness of the model in this subgroup was reflected in the positive predictive value (PPV) and negative predictive value (NPV). However, we did not perform external validation.[8,26] In addition, the clinical impact of the application of the model on the clinicians' practice and patients' outcomes are unclear and needs further investigation.[8]

IMPLICATIONS

Knowledge of early measured clinical predictors for functional outcome poststroke is essential for an optimal rehabilitation triage at hospital stroke units.[27,28] Accurate prognosis does not only guide clinical decisions about the most suitable rehabilitation environment and rehabilitation content for the patient to optimize outcomes (i.e. stroke management). It also facilitates properly informing patients and their families in order to improve their understanding, help them in the shared-decision making, and optimize psychological adjustment.[29-31] Besides, knowledge about prognosis is also important for other stakeholders in stroke rehabilitation. Researchers could use the currently available knowledge of prognosis to further refine clinical prediction models for functional outcomes. Accurate time-dependent, dynamic recovery patterns for individual patients should also be developed on the impairment level of the International Classification Functioning, disability and health (ICF), like motor function of the paretic arm[32] and leg, or neglect.[33] These impairment-focused models could provide insight in the abilities to regain body functions, as a

8

reflection of spontaneous neurological recovery. Accurate prognostic models could subsequently serve as a basis for tailoring interventions or developing new interventions for specific subgroups of patients by, for example, bioengineers who develop robotic devices for rehabilitation purposes. Last but not least, health care insurance companies could benefit from accurate dynamic prediction models for the course of recovery, and the identification of patients who do not fit these models, for targeted health care purchasing after stroke. Although "efficiency" in stroke rehabilitation is often interpreted as decreasing costs accompanying rehabilitation interventions like exercising in groups instead of on a one-to-one basis, prognosis could also be seen as a way to enhance "efficient" care by delivering interventions only to those patients who benefit most.

As shown in **chapters 2 to 4**, functional outcomes in terms of walking ability and basic ADL can be accurately predicted early after stroke. At least the first chapters suggest that knowledge about the patients' future is paramount for making clinical decisions including selecting therapies. As a consequence, this knowledge about clinical determinants for outcome and the timing of measurements should preferably an integral part of evidence-based guidelines for clinicians. Therefore, the above described knowledge about prognostic determinants are incorporated in the revision of the Dutch national Clinical Practice Guideline for physical therapy in patients with stroke (*KNGF-Guideline Stroke*) of the Royal Dutch Society for Physical Therapy (KNGF).[34]

When predicting final outcome in terms of basic ADL, factors such as initial neurological functions including paresis of the arm, and age should be taken into account. People with less impairments in neurological functions and a younger age have a favorable prognosis for independency in basic ADL. On the other hand, gender nor the presence of cardiovascular risk factors do contribute to a functional prognosis for basic ADL and should therefore not be used.

When the BI is used for prediction of final outcome of ADL 6 months after stroke onset, this measurement should be performed on day 5 for each stroke patient instead of the in daily practice frequently used earlier time moments.[35-37] Earlier assessment than 5 day of the BI for prognostic purpose is discouraged, because the BI reflects the actual performance of the patient during the previous 24–48 hours as patients with acute stroke admitted to a hospital do often not perform all activities that they may well be able to, like climbing stairs. Importantly, improvement of neurological impairments from day 2 to day 9 in the same cohort was quite invariant over time,[9] suggesting that spontaneous neurological recovery is not likely to be a valid explanation of better performance of derived prediction model from day 2 to 5. Therefore, early assessment of activities may result in an underestimation of the patients' abilities, emphasizing the difference between what patients actually can and do early poststroke.[38]

When aiming to make a prognosis for independent gait 6 months after onset in patients who are unable to walk independently poststroke, in the *KNGF-guideline Stroke* it is recommended to assess the sitting balance and motor function of the paretic leg with respectively the sitting balance item of the Trunk Control Test and the leg subscale of the Motricity Index as soon as possible, but preferably on day 2 after stroke. Second, it is recommended to reassess patients who have an initial unfavorable prognosis for return of these determinants as long as the prognosis remains unfavorable. The recommended measurement intervals are: weekly during the first 4 weeks and subsequently monthly till 6 months after onset.

However, due to the fact that there is a certain percentage of people who are misclassified, as expressed by the PPV and NPV, frequent reassessment (every few days) during the first weeks is necessary to improve accuracy of prediction. Nevertheless, still a certain percentage of patients does not fit the model, and therefore making a prognosis for an individual patient solely based on computational models has limitations. In the interpretation of the prognosis as indicated by the computational model including easily measured clinical variables, professionals should also take into account their clinical experience, knowledge about underlying mechanisms of recovery, predictive factors known from systematically reviewing the literature, and concomitant comorbidities with related pre-existent disabilities.

EVIDENCE FOR NEUROREHABILITATION INTERVENTIONS AFTER STROKE

Main findings

In **chapters 5**, **6**, and **7**, the evidence for stroke rehabilitation interventions in the domain of physical therapy is summarized based on randomized controlled trials (RCTs). These RCTs were retrieved from systematic searches in the literature and were analyzed in meta-analyses.

Chapter 5 summarizes the evidence for stroke rehabilitation interventions in the domain of physical therapy. This review showed that the number of published RCTs in the field of physical therapy in stroke rehabilitation has been growing tremendously, with 123 RCTs published up till January 2003 and 467 up till August 2011. The results presented in **chapter 5** are aggregated for the intervention section of the updated *KNGF-guideline Stroke*. It was shown that the number of physical therapy interventions that was assigned "strong evidence" has been increased since 2003.[39] Now, there are 30 out of 53 interventions for which significant summary effect sizes (SESs) were found in favor of one or more clinical outcomes, with the majority of interventions relating

to the categories (1) interventions related to gait and mobility-related functions and activities; (2) interventions related to arm-hand activities; and (3) interventions related to physical fitness. From the analyses, it can be concluded that exercise therapy mainly speeds up the recovery, but not the maximal level that could be achieved, or prevents deterioration. In addition, strong evidence was demonstrated for "intensity of practice" regardless of timing poststroke, while the best-evidence synthesis for "neurological treatment approaches" in terms of Bobath/Neurodevelopmental Treatment showed equal or unfavorable effects when compared to other exercise interventions.

Chapter 6 described the effects of intensity of poststroke exercise therapy focused on the lower limb and applied within the first 6 months poststroke.[40] It was suggested that patients poststroke benefit from an increased dose of practice in terms of therapy time. The significant positive small (<0.02[41]) to moderate (range 0.2–0.8[41]) SESs were related to walking speed, walking ability, and extended activities of daily living.

For the upper limb, constraint-induced movement therapy (CIMT) is an intervention that explicitly incorporates the aspect of intensity of practice. The evidence for the original form of CIMT, it's modified versions (mCIMT), and forced use was reviewed in **chapter 7**. Significant positive SESs in favor of both original CIMT and mCIMT post intervention and at follow-up were found for the outcomes arm-hand activities and self-reported arm-hand functioning. Motor function directly post intervention and at follow-up was significantly better in patients who received mCIMT when compared to another intervention or no intervention at all, while the immediate post intervention effects of mCIMT on muscle tone and basic ADL were not sustained. As for quality of life, post intervention scores were not significantly better for mCIMT when compared to a control intervention. Interestingly, a significant positive effect on quality of life in favor of original CIMT was shown about 4 months after termination of the intervention.

ISSUES TO CONSIDER

Intervention

The present thesis reflects the massive flight of RCTs in rehabilitation medicine poststroke. More interventions and outcomes have been investigated over the past 10 years than before. The magnitude of the differential effects of these interventions varied from about 5% to 15%,[42] while prognostic research suggests that 80% to 90% of the observed improvements relative to the actual outcome could be explained by the progress of time alone after correcting for covariates such as age, type of intervention and type of stroke.[43] This could raise the question

what stroke rehabilitation interventions add to the natural course of recovery of functions and activities poststroke. Acknowledging that there are strong indications that recovery poststroke seems to be mainly driven by "spontaneous" neurophysiological processes, an additional improvement of 5% to 15% can still be clinically meaningful for patients and can also be relevant from epidemiological and economical perspectives. For trialists', the relatively small contribution of rehabilitation interventions implies the need for better patient stratification, larger samples, and more precise measurements to determine the pattern of recovery. Within this perspective, innovative technologies such as wireless systems allowing monitoring real world activity may be promising and may have an added value to solely clinical assessments.[44]

The update of the evidence for stroke rehabilitation interventions in the domain of physical therapy also showed that there is instability in effects over time. Virtually all RCTs are single-center (or: "proof of concept" [POC]) trials, while only recently a few large multi-center randomized trials have been published.[45-47] Only one of these large trials showed significant positive effects.[46] The other large multi-center randomized trials (i.e. phase III trials) showed neutral results, whilst small POC trials for these interventions initially were promising.[48-51] These changes in direction of the evidence could be explained by broader inclusion criteria as applied in larger phase III trials suffering from no or less optimal stratification, the presence of more bias in POC trials,[49,51] or the presence of publication bias in which only POC trials with positive results are published while small trials with neutral or negative results are not. On the other hand, it could be suggested that the commitment of professionals is larger in small studies, and that therefore significant positive effect sizes have been found in the literature.

In the last decade, a number of new stroke rehabilitation interventions in the domain of physical therapy have emerged. The introduction of these interventions seems mainly driven by technological developments like virtual reality and robotic devices,[52-54] whereas differences in outcome are small and often clinically meaningless.[55] However, one should be vigilant for "novelty effects." Placing new, costly technologies on the market without thoroughly testing their effectiveness, and not taking into account the accompanying high financial investments, could be a threat to existing evidence-based interventions. These technological novelties should only be considered for implementation in clinical practice, after an added value has been determined in multiple, independent trials with a low risk of bias, which are subsequently analyzed in a meta-analysis. However, reality tells us that these innovations are often implemented before the added value has been demonstrated.

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Common characteristics of efficacious interventions

Repetition, task-specificity, and intensity have shown to be important elements that drive effectiveness of stroke rehabilitation interventions in the domain of physical therapy. Repetition and task-specificity probably reflect (anti-)Hebbian learning processes, in which synaptic strength is improved by coincident, repetitive activation of presynaptic and postsynaptic neurons (use-dependent strengthening of synaptic connections).[56-58] Although core ingredients of efficacious interventions seem to be clear, closer examination of individual RCTs shows that the exact content of therapies provided in RCTs remains somewhat indistinct. There is a very limited number of published treatment protocols[59,60] and also reporting of the actual intensity of exercise therapy in scientific publications is often lacking.

In stroke neurorehabilitation, intensity of practice is often expressed as time spent in exercise therapy.[40,42,61-65] Dose-response trials in stroke rehabilitation are rare.[66,67] In fact, dose-matched trials with a significant effect in favor of the experimental intervention are scarce.[68-70] The intensity difference of ≈17 hours between experimental and control groups found in meta-analyses of non-dose-matched trials[40,42,61] reflects about 1 point (or 5%) change on the BI in favor of higher intensities of practice. By lack of any estimate how intensive patients should practice in the first months poststroke, this surrogate estimate is often used in clinical (interdisciplinary) guidelines in, for example, the United Kingdom[71] and the Netherlands,[27,34] with the intensity indicator being that stroke patients should practice minimally 40 to 60 minutes per working day as long as there are rehabilitation goals. However, a recent survey revealed that adherence to these recommended intensities is difficult.[72] In the Netherlands, patients admitted to a hospital stroke unit receive a mean of 22 minutes physical therapy per working day.[72] In addition, due to the lack of ambulatory activity monitoring, it is unclear whether patients who are assumed to train intensively, compensate for their efforts made by reducing their activity levels outside therapy hours.

Timing of intervention

The presented reviews in **chapters 5**, **6**, and **7** about stroke rehabilitation interventions in the domain of physical therapy showed that many of these interventions have differential effects on the body function level, the activities, and – to a far lesser extent – participation level. In general, a moderator effect of timing poststroke was not demonstrated, except for CIMT. In this case, only significant effects on motor function of the paretic upper limb were found within the first 3 months but not beyond 3 months poststroke. However, most of the trials included in **chapters 5 to 7** started beyond the first 30 days after onset,[42,73] while animal studies have shown that

reduction of impairments mainly occurs within the first month poststroke.[58] This so called "critical time window" is characterized by several non-learning dependent mechanisms that contribute to spontaneous neurological recovery, like recovery of the penumbral tissue, elevation of diaschisis, and homeostatic mechanisms, which induce brain reorganization.[58,74-76] Furthermore, it is assumed that also behavioral experience influences plasticity of the brain,[76-78] but that this is task-specific.[79] The available evidence from both human and animal studies suggests that behavioral experience in terms of training may be more beneficial when applied early after onset instead of delayed.[75] However, the intensity of training should be carefully looked at. There are indications that a very early start of highly *intensive* training may have detrimental effects on early brain damage[80,81] and functional recovery.[82] It could be hypothesized that rehabilitation should be started within the first days to weeks poststroke to optimize recovery, and should be intensified after the vulnerable period of the first few days has elapsed.[80,83] Nevertheless, the optimal timing of start as well as intensity of rehabilitation remain unclear in humans with stroke.

Significant positive intervention effects are also found in the chronic phase poststroke. This could be explained by the fact that even though patients have already finished their rehabilitation, they often show deterioration caused by for example a sedentary, inactive life style, or learned non-use.[84] Therapy-induced improvements of for example CIMT in this phase are, however, at the activities level, but not at the impairment level,[85] suggesting that this is more about compensation (i.e. learning to cope with existing deficits) rather than "true neurological recovery."

Bias affecting effect estimates

In the present thesis, a trend was observed that the risk of bias scores of RCTs in the field of stroke rehabilitation is decreasing in the last decade. The median PEDro score for RCTs increased with one point from 5 (interquartile range [IQR] 4-6) for RCTs published till 2004, to 6 (IQR 5-7) for RCTs published from 2004 till 2011.[42] Apparently, authors and editors are increasingly aware of the importance of conducting studies with little bias and obtaining valid results, and disseminate their resulting clinical messages. It is assumed that this trend to improve transparency and methodology of studies is partly the result of the obligation to adhere to guidelines for reporting primary studies (i.e. "'original research' in which data are collected"[86]), to register trials, and to publish study protocols.[87,88] However, there is still room for improvement in decreasing bias, like sequence generation, allocation concealment, blinding of assessors, and the application of an intention-to-treat analysis.[42,88]

8

Statistical and ethical issues to combine results of individual RCTs

In the meta-analyses presented in **chapters 5 to 7**, SESs were calculated to quantify the magnitude, direction, and consistency of the difference between groups for various interventions and outcomes.[6] A summary effect size, as an expression of the "signal-to-noise ratio," could for example be influenced by the contrast with the comparator. Nowadays, it is not accepted and ethically not allowed to exclude patients from stroke services. As a consequence, all recent trials have an active comparator, instead of a "no therapy" control group. Hereby, an experimental intervention is compared to a specific control intervention or usual care. One can statistically address a possible moderating effect of the type of comparator, by applying subgroup analyses. However, this also increases the number of analyses and thus the risk of incurring a type I error.[6,89] Often, performing subgroup analyses is not possible because there are too few RCTs in each subgroup. Additionally, there may be difficulties with adequate categorization of the comparator, as it reflects a wide variety of interventions with differences in content and dosage.[91] Also, usual care changes over time and might vary between countries, sites, and even clinicians. For example, a decade ago usual care was often provided according to Bobath principles. However, after the lack of added value of this approach was demonstrated,[92-94] usual care now consists mainly of task-oriented training which is in line with the evidence-based guidelines. This shift might have contributed to a decreasing therapy contrast between experimental and usual care control groups in contemporary RCTs.

Research design

The reviews presented in this thesis exclusively included trials in which patients with stroke were allocated to the groups "at random."[94] This is the only way to investigate causality, assuming that – known and unknown – confounding factors are equally affecting the arms in a trial. Nevertheless, for those interventions described in **chapters 5 to 7** that are demonstrated to be efficacious upon meta-analysis, the real world effectiveness remains unclear. Observational cohort designs[95-97] are suitable for this purpose, but are currently not commonly applied in stroke rehabilitation.

Identifying subgroups

It is hypothesized that effects of interventions can be improved by identifying subgroups of patients that respond best to that particular intervention.[98] For this so called "stratified medicine,"[99] knowledge of predictors for outcomes poststroke is important to select subgroups of patients who are most likely to benefit from a certain stroke rehabilitation intervention. While reviewing the

literature for stroke rehabilitation interventions in the domain of physical therapy, there is hardly any report of predictors to response (i.e. treatment effect modifiers). Although inclusion criteria are defined in trials in order to target a subgroup or specific type of patients, the inclusion might still be broad, especially in larger trials. For example, there are indications that massed practice of walking with robotic assistance might be beneficial for patients with a low motor function and thus a poor prognosis for independent gait, but not for those patients who have an initial high level of motor function and good prognosis.[100-102]

Outcome measures and timing of measurement

One problem in synthesizing the evidence in the presented systematic reviews in **chapters 5 to 7**, is the use of different outcome measures and the underlying constructs they are supposed to measure.[103] Also, selective outcome reporting hampered an unbiased synthesis of the evidence. This could be due to the fact that a global compiled standardized set of outcome measures in stroke rehabilitation interventions is lacking.[104] Another striking observation is that up till now, ambulatory activity monitoring[44,105,106] is hardly applied in clinical research, while it could provide valuable information about the level and pattern of physical activity of the patient outside therapy hours and helps to gain insight in the actual performed movements and number of repetitions during supervised exercise therapy as a more appropriate measure of "intensity." As an additional advantage, this longitudinal continuous profiling allows investigators to explore the longitudinal relationship with the amount of functional recovery poststroke. Another salient fact is that patient-reported outcome measures (PROMs), as a reflection of subjective qualifications of for example the multidimensional health-related quality of life (HRQOL) as indicated by the patient,[6,107] are increasingly used in stroke research, but hardly any significant effects have been found.[42] This could due to, for example, low responsiveness of the used outcome measures when compared to the introduced therapy-induced improvements.[6,108,109] In addition, it should be questioned whether a specific, one dimensional intervention can influence such a multidimensional construct as HRQOL.

The sustainability of differential effects in the long term is relevant to stroke rehabilitation and patients. For that purpose, but also because of the non-linear recovery pattern after stroke (see section "*Looking forward, Prognostic research in stroke*"), follow-up assessments and their timing are important aspects in the design of RCTs. As can be seen from the different reviews in this thesis, follow-up measurements were often lacking in RCTs, and when they were carried out, the timing of assessment was highly variable.[42,61,85]

CLINICAL IMPLICATIONS

The clinical effectiveness of several specific interventions in the domain of physical therapy is clear from various reviews in this thesis.[42,61,85] As intervention effects seem to be task or function specific, exercise therapy should be focused on those impairments in functions and/or limitations in activities that the patient experiences as being disabling. In addition, timing of interventions in the domain of physical therapy poststroke does not seem to modify reported differential effects. However, this does not mean that timing of intervention is not important. The goal of rehabilitative interventions may vary between the first 6 months and the phase beyond 6 months after stroke. The focus in the first 6 months after onset is on reducing impairments in body functions and improving activities and participation.[2] Early started exercise therapy, with an increasing intensity remains recommended. The phase beyond 6 months is mainly directed at prevention of functional deterioration and inactivity, or targeting learned non-use secondary to the stroke.[73]

Selection of evidence-based interventions should be based on the patient's functional prognosis with corresponding treatment goals. Physical therapists have a wide variety of interventions to choose from, although there are more interventions with strong evidence and outcomes with significant positive differential effects for the lower limb than for the upper limb. When making decisions about an appropriate evidence-based intervention, the inclusion criteria as applied in RCTs should be considered. Unfortunately, only about 10% of the total number of screened patients are included in RCTs and often have a limited number of concomitant diseases. Therefore, meta-analyses typically reflect the effects of an intervention in an optimal research population, based on which recommendations in guidelines are formulated. In fact, the far majority of patients in daily clinical practice does not fit the criteria as applied in RCTs, because on average stroke patients have four[110] different comorbidities. In contrast, most patients recruited for trials do not suffer from concomitant diseases.

The aforementioned implies that physical therapists should be able to combine existing evidence concerning interventions with, for instance, knowledge about (neuro)physiology, (neuro)pathology, and prognosis for recovery in order to determine whether the found evidence is also applicable to an individual patient. This requires post bachelor training and continuing education in neurorehabilitation after stroke. In addition, continued experience is needed in treating stroke patients and therefore, in the *KNGF-guideline Stroke* the minimal number of patients that physical therapists have to treat to remain skilled is five per year. The *KNGF-guideline Stroke* is one of the ingredients of clinical decision making, next to clinical experiences, and patient's values. It helps directing physical therapists in making their clinical decisions. An issue that is probably getting less

attention, is that one of the strengths of guidelines is that they also recommend which interventions should *not* be applied. The latter allows discouragement of non-effective interventions or methods like Neurodevelopmental Treatment from use in clinical practice.

LOOKING FORWARD

The present thesis showed that a first functional prognosis for ADL and walking in patients with stroke can be made within the first few days after onset and that specific stroke rehabilitation interventions in the domain of physical therapy are effective in improving rehabilitation outcomes. However, as previously mentioned, the differential effects of these interventions amount 5% to 15%, while prognostic research suggests that 80% to 90% of the observed change in the first 6 to 10 weeks poststroke can be explained by time alone (i.e. "spontaneous neurological recovery").[43] This highlights the need for further knowledge about (1) mechanisms that drive (spontaneous) recovery poststroke; (2) sophisticated and externally validated (dynamic) prognostic models for functional outcomes in individuals poststroke and their influence on clinical practice and outcomes; and subsequently (3) evidence for the added value of novel techniques to collect clinical information for improving existing clinical prognostic models, such as activity monitoring and other portable recording techniques of brain activity; and (4) the merits of innovative techniques that may enhance experience-dependent neuroplasticity in stroke rehabilitation, such as exercise therapy combined with noninvasive brain stimulation[111,112] by means of transcranial Direct Current Stimulation (tDCS)[113] and repetitive Transcranial Magnetic Stimulation (rTMS),[114,115] or exercise therapy combined with pharmacological interventions like fluoxetine.[116]

PROGNOSTIC RESEARCH IN STROKE

Computational prognostic models for outcome after stroke are hardly being improved, while this is assumed to be an important ingredient of prognostic model development.[8] Considering the fact that walking is a priority in stroke rehabilitation, prediction models for independent gait should be refined[8] with additional sophisticated measurements in those patients with an initial poor prognosis,[117-119] in order to reduce the amount of false negative predictions. The NPV of the prediction model for independent gait at 6 months poststroke in **chapter 4** was relatively low and increased from 0.63 (95% CI, 0.57–0.82) on day 5 to 0.75 (95% CI, 0.56–0.88) on day 9. When updating the presented prognostic model for independent gait after stroke to decrease misclassification, the first clinical measures of sitting balance and strength of the paretic leg should

8

be performed early poststroke, though at least within 2 days. Acknowledging the time-dependency of prediction, these predictors should be reassessed at fixed, preferably, weekly time-points, during the first month. In parallel, more sophisticated neurophysiological measures of the central nervous system (i.e. to determine intactness of corticospinal projections) should be performed.[119] These additional determinants could be derived from for example Transcranial Magnetic Stimulation (TMS) techniques and functional magnetic resonance imaging. However, the added value of these variables[120] to the accuracy of the computational model solely containing simple bedside tests should be studied carefully, as they are complex and burdensome to obtain. Also, I assume that implementation of prognostic models is partly dependent on the feasibility in daily practice.

Future prognostic studies should not only focus on independency in gait and basic ADLs. Another important outcome is community walking, distinguishing between for example physiological walkers, who walk for exercise only either at home or in parallel bars during physical therapy, and various levels of household and community walkers.[13,16] For clinical practice, it would be worthwhile to be able to accurately predict discharge to home in an independent state. Acknowledging that the prognosis for outcome of basic ADL is an important factor that should be taken into account in predicting living at home independently, it is necessary to gain more insight in which contextual factors play a role in determining whether a patient is being able to live at home independently or not.[20,121,122] This also fits within the aim of the Dutch government (as stated in the roadmap Homecare, self-management & ICT of the Topsector Life Sciences & Health) to enable people to stay healthy at an older age, to help them remain independent and active, prevent a sedentary life style, and to support them to participate in society and live in their own home as long as possible, despite disease and disability. With its increasing incidence and prevalence, stroke remains a major threat to self-dependence. Therefore, improvement of rehabilitation strategies, including accurate prognosis for living at home, is urgently required.

Prediction of functional outcomes is important for patients, family, and health care provision. In addition, prognostic models at the level of impairments, like motor function of the paretic arm[32] and leg, kinematics such as smoothness,[123] or neglect,[33] could give insight in the abilities to regain body functions, as a reflection of spontaneous neurological recovery. This prognostic information on the impairment level (i.e. maximal recovery potential)[32] could be used for (1) goal setting in stroke rehabilitation; (2) developing interventions focused on restoring impairments; and (3) investigate their efficacy in specific subgroups of patients. Although the prediction studies presented in this thesis are focused on outcomes 6 months after stroke onset, there is also need for models predicting which patients are at risk of deterioration in the chronic phase. This information could be useful for stratified long term stroke care.

To be really valuable for clinical practice, prediction models should not only be able to accurately predict final outcomes for the individual patient, but should also predict the time course of recovery. Dynamic time series modeling for curved, non-linear relationships[124] allows prediction of a future value of a time series based on the current and past values of the same series, and error terms.[125-127] Also possible confounding variables like timing poststroke, premorbid situation, health care decisions made, and resource use should be taken into account in these dynamic models. Knowledge about the predicted recovery pattern of the individual patient and the natural sequences of recovery[128,129] could guide setting realistic (sub)goals in stroke rehabilitation and the selection of relevant interventions. This will be further exemplified in the "*Research of rehabilitation interventions in stroke*" section below.

In order to achieve the above described (i.e. refinement of prognostic models; additional models for community walking, discharge destination, outcome at the impairment level, deterioration in the chronic phase; dynamic models), prognostic model research in stroke – with the ultimate goal to improve the patient's outcome[130] – should take into account the following aspects:[99,130-132] (1) the quality of prognostic studies should be high in design, analysis, and reporting; (2) a research protocol should be available a priori; (3) electronic patient records which include a core set of variables should be used to serve as a basis for large "big data" cohorts; (4) patients with stroke should be engaged in setting goals and valuing prognosis research by including responsive PROMs and it should be checked that predicted outcomes are relevant to the patients' needs; (5) suitable statistical methods should be used; and (6) multiple replication studies should be performed, starting already early after development of the model, to determine the robustness of found prognostic factors (i.e. external validation). In addition, when models are found to be adequate in multiple studies, it should be investigated how application of these prognostic models in daily practice affects clinical decision making, patients' outcomes, and costs. For that purpose, physical therapists should be trained in application of evidence from stroke prognosis research in daily practice.

Furthermore, prognostic model research should be available through one electronic source, being easily accessible and frequently updated, for example by guidelines, cohort study registers, or review databases analogue to the Cochrane Library. Finally, findings in primary studies should be accumulated in meta-analyses on prognosis poststroke. Ideally, meta-analysis should be based on individual patient data and adhere to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.[4]

8

RESEARCH OF REHABILITATION INTERVENTIONS IN STROKE

Based on the findings reported in the present thesis, high-quality[42,133] multi-center trials, investigating the efficacy of an intervention for most stroke rehabilitation interventions in the domain of physical therapy, are needed due to lack of power in both primary studies and meta-analyses. Single-center trials appear to be suitable for initial testing of interventions that address gaps in research. Examples of interventions for which there is hardly any research available are falls prevention programs, the use of telerehabilitation, and exercise therapy combined with the application of neuromodulation techniques, like pharmacological approaches, tDCS, and rTMS. A neglected topic in stroke research is secondary prevention in patients with a transient ischemic attack and stroke by lifestyle changes including physical fitness training.[134-136] As these patients are at risk for new cardiovascular diseases, evidence for prevention analogous to heart rehabilitation programs is highly needed. These programs have the potential to modify risk factors for cardiovascular diseases like low physical activity, high blood pressure, and overweight. For transparency and to allow replication, the intervention protocols for these but also other interventions tested in RCTs should be published.

Additionally, the efficiency of stroke rehabilitation should be further improved by avoiding the "one size fits all"-principle,[100] in which the study sample is heterogeneous. Instead, those patients should be targeted who are likely to benefit most from a certain intervention. For this purpose, insight is needed in appropriate selection of specific subgroups of patients, not only based on the initial level of motor impairments and functional prognosis, but also on the presence or absence of for example sensory impairments, a pusher syndrome, or neglect. It is hypothesized the patients' motor potential or ability is masked by the presence of these impairments.[137] Therefore, it is necessary to increase knowledge about the natural course of these impairments and their association with, for example, motor impairments and activities.

Although intensive exercise therapy is favored, more insight is needed into the optimal intensity of training. Also cost-effectiveness of interventions aimed at high-intensive practice like circuit class training[138] and caregiver-mediated exercises[139] combined with telerehabilitation facilities should be further investigated. In addition, future dose-response trials should apply ambulatory activity monitoring, both during exercise therapy and outside therapy hours, to gain insight in the real world performance of physical activity.

Insight is also needed in the identification of those patients who should be targeted for intensive rehabilitation. Who does need an intensive rehabilitation program after stroke, and who does not? In a similar way: who can be discharged early to home with support and who cannot? The

currently available evidence is insufficient to answer these questions. It might be hypothesized that patients with a favorable functional prognosis for full recovery do not need intensive supervised exercise therapy. In these patients, less intensive rehabilitation programs should be investigated, like customized home exercises – including principles of repetition, task-specificity, and intensity – combined with low-frequent consultation with a physical therapist using telerehabilitation facilities. The same might apply to patients who have an unfavorable prognosis and will remain largely dependent. In those patients, monitoring is indicated and a less intensive rehabilitation trajectory, especially focused on compensation during ADLs and leisure activities, prevention of secondary complications, and adaptations of the environment. In general, monitoring remains important to detect those patients who do not fit the model. When they deviate from the predicted pattern, changes in treatment goals and plans should be made accordingly.

Another important topic for future research in stroke rehabilitation in the domain of physical therapy is the timing of intervention. Knowing that poststroke recovery mainly occurs within the first 6 months after onset and is assumed to be fixed, trials should be performed within this first half year. Only then the value of interventions in the domain of physical therapy for poststroke "recovery" could be determined. Beyond this time frame, interventions target learned non-use or sedentary life style more than recovery of body functions and activities lost due to stroke. Zooming in on the first 6 months, the first month is considered to be the "critical time window" for neuroplasticity after stroke.[58] During this time window, the changes in recovery are most pronounced.[58] It is assumed that this is caused by a temporarily elevation of growth-promoting factors and down regulation of growth-inhibiting factors, allowing structural and functional changes in the brain.[58] Hebbian learning is assumed to strengthen these changes.[58] As up till now most interventions are investigated in patients beyond the first month poststroke, efficacy testing of interventions starting within this time window is urgently needed.[73] Within this time frame, it should also be investigated whether impairment-focused interventions, especially targeting those body functions that are predictive for functional outcomes (e.g. finger extension for outcome in terms of arm-hand activities)[15,60] and preventing the development of compensation strategies, show better results when compared to interventions in which only activities are trained.

To improve comparability of studies, a globally accepted standardized set of outcome measurements should be used in evaluating the efficacy of stroke rehabilitation interventions in the domain of physical therapy.[104] This set of outcome measures should also include activity monitoring[44,105,106] and PROMs. Outcome measures of which the clinimetric properties like the minimal clinical important difference are known would increase the clinical interpretation of published findings. Parallel to measurements of clinical outcomes, measurements of neurophysiological "recovery"

8

mechanisms are needed, to provide insight in a possible effect of rehabilitation interventions on these mechanisms.[140] For this purpose, knowledge about neurophysiological mechanisms related to improvement in functions and activities poststroke is crucial.

To improve comparability of experimental data regarding stroke interventions, global consensus is also needed on timing of assessments in the long term.[6,141,142] Especially for interventions initiated early poststroke, patients should be measured at fixed time points; weekly in the first weeks after inception, and subsequently followed-up 3 and 6 months after stroke, taking into account the recovery pattern of functions and/or activities after stroke.[73,141] This repeated-measurement design in the early phases poststroke allows investigating whether the experimental intervention induces an earlier occurrence of improvements while the scores are equal at follow-up,[73] or that exercise therapy also induces long term effects.

Finally, there is need for large cohorts of stroke patients in regular health care worldwide. In these research groups, "big data" should be collected systematically for all patients with a stroke, starting at admission to a hospital stoke unit. Data collection should include standardized clinical assessments according to a predetermined schedule, but also information regarding content and process of the delivered poststroke care. These data are invaluable for (1) prognosis research and (2) determining "real world" effectiveness of stroke rehabilitation interventions. In addition, analyses and interpretation of these data could serve as an input for testing new hypothesis in RCTs.[95]

GUIDELINE DEVELOPMENT AND UPDATING – AIMING TOWARDS WORLDWIDE UNIFORMITY

It should be emphasized that the *KNGF-guideline Stroke* is complementary to existing interdisciplinary guidelines for stroke. However, these interdisciplinary guidelines do not describe the evidence for the entire physical therapy process. At the same time, the evidence described in the *KNGF-guideline Stroke* is not solely reserved to physical therapists. Some evidence applies to domains which also belong to, for example, occupational therapists or neurorehabilitation nurses.

The revision of *KNGF-guideline Stroke*, ten years after the first edition saw it's light,[39] showed that there is a vast increase in the number of scientific publications in the field of physical therapy in stroke rehabilitation.[42] Unfortunately, reviews are not frequently updated and therefore it is difficult for clinicians to treat patients according to the most recent evidence, especially because the most RCTs are POC trials which are prone to bias. This indicates the necessity of continuous updating of the evidence, preferably using an easily accessible online database. These so called "live" guidelines

should be supported by an international collaboration between stroke and neurorehabilitation platforms, like the World Federation for NeuroRehabilitation (WFNR) and World Confederation for Physical Therapy (WCPT) with their affiliated national platforms. Another important partner is the Virtual International Stroke Trials Archive (VISTA) group which collects data from completed clinical trials,[143] allowing individual patient data meta-analyses to improve power and perform subgroup analysis. International collaboration does not only contribute to uniformity of guidelines worldwide, but also reduces resources and costs by centralized development and updating of guidelines.[144] Due to variations in health care systems, subsequent cross-cultural validation of these global recommendations remains necessary.

When and how to update guidelines, including the systematic reviews they are (partly) based on, is still unclear. In the United States, it has been shown that the half-life of guidelines is only 3 to 5 years,[145] while the Cochrane Collaboration has the policy that systematic reviews need an update every 2 years.[6] Even though the update of stroke rehabilitation interventions in the domain of physical therapy in the present thesis resulted in an increased number of "strong evidence" interventions and outcomes,[42] the assumed robustness of this so called level 1 evidence[146] is not a matter of course. For example, the "strong evidence" label assigned in 2004 to speed dependent treadmill training in favor of walking ability was changed to equivalent effects when nine newly published RCTs were added. On the other hand, the Cochrane Library found that although concerns were expressed when reviews were not updated, only a small amount of reviews changed their conclusion based on the update.[147] Since there is little known about the timing and methodology of updating systematic reviews and guidelines,[148,149] it should probably be recommended that for physical therapy in stroke rehabilitation, every 4 years a check has to be performed whether a (partial) update of recommendations is necessary. This check should be performed in consultation with all international partners involved and should include a targeted screening of the literature with the previously used electronic search string in one major database like Embase or PubMed, or use a search engine based on artificial intelligence technologies allowing textual and semantic analysis.[150] In addition, international experts should be asked about the actual validity of the guideline, the relevance of key questions, and recent developments in the field. Existing tools like the AGREE II instrument[151] could guide future updating of the *KNGF-guideline Stroke*. However, to date there is no global consensus about criteria for updating stroke guidelines. Therefore, more knowledge should be acquired about a cost-effective and efficient methodology to determine if and how guidelines need to be updated and how to reduce the time lag from start of the update to completion.

8

GUIDELINE IMPLEMENTATION

Although it has been shown that acting in accordance with guidelines is beneficial for patients,[152-155] adherence is not common practice.[156,157] There are many factors that can either facilitate or hamper implementation of guidelines and with that quality of care (outcomes).[156,158] Only disseminating guidelines has been shown to be an ineffective method to improve clinicians' adherence to these guidelines.[159] Even though the best implementation strategy is unknown, and evidence on implementation strategies inconclusive, it is suggested that a mix of strategies is preferred in which interaction and tailoring are core elements.[158-162]

To be able to critically appraise the *KNGF-guideline Stroke* and translate the evidence to the individual patient, physical therapists treating patients with stroke need post bachelor education. This group-based course should include theoretical knowledge about all parts of the guideline, pathology, neurophysiology, assumed recovery mechanisms poststroke, and motor learning. In addition, clinical reasoning and practice should be an integral part of the education. With the *KNGF-guideline Stroke* serving as a template for a European guideline, this neurorehabilitation after stroke education should be made available for all participating countries, including education materials and clinical decision tools such as Apps.[140] These specialized physical therapists should participate in networks aiming for high-quality, transparent physical therapy poststroke. Finally, electronic patient records could be useful for evaluating physical therapy stroke care according to the guideline by comparison of outcomes, PROMs, and content of care including its processes.[140]

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