Functional Recovery After Stroke: A Review of Current Developments in Stroke Rehabilitation Research

Boudewijn Kollen[1]*, Gert Kwakkel[2,3] and Eline Lindeman[2]

[1] *Research Bureau, Isala klinieken, Zwolle, The Netherlands*

[2] *Rehabilitation Centre "De Hoogstraat", Rudolf Magnus Institute of Neuroscience, UMC, Utrecht, The Netherlands*

[3] *Department of Rehabilitation of Vrije Universiteit Medical Centre, Amsterdam, The Netherlands*

Abstract: This review article discusses current research developments in functional recovery after stroke. With the institutionalization of stroke services across health care facilities, a reduction in mortality rates, length of inpatient stay and improved independence in activities of daily living has been reported. Several systematic reviews show that traditional treatment approaches induce improvements that are confined to impairment level only and do not generalize to a functional improvement level. More recently developed treatment strategies that incorporate compensation strategies with a strong emphasis on functional training, may hold the key to optimal stroke rehabilitation. Intensity and task-specific exercise therapy are important components of such an approach. Guidelines may assist the clinician in this responsibility. However, due to marked heterogeneity of the stroke population and poor methodological quality of many studies, results are uncertain. Several options are discussed to overcome the problem of stroke heterogeneity in research designs.

Longitudinal repeated measurements designs are required to study the effects of non-linearity and time dependency of functional recovery in stroke. Furthermore, prognostic research based on sound clinimetric data generates relevant information that may guide the clinician in clinical decision making and in determining optimal treatment strategies.

INTRODUCTION

Stroke is a disease of developed nations. Worldwide it is increasing along with modernization. In the United States (US), stroke is the third leading cause of death and leading cause of serious, long-term disability [1]. While stroke mortality rates have declined, the number of total stroke deaths has increased in the US in the 1990s. This trend may continue as the percentage of older individuals grows. It is estimated that there are over 750,000 first-ever or recurrent cases of stroke in the US each year [2]. Strokes occur at any age but are much more common in the elderly, with the death rate doubling every ten years between 55 and 85 [1]. Both life expectancy and incidence of stroke is increasing in the United States [3].

It is anticipated that by 2020, stroke will have moved from the 6th leading cause of lost disability adjusted life years (DALY's) to 4th [4]. The expected increase in stroke survivors potentially living with disabilities will place a burden on the survivor's family, the community, and the healthcare system. Because of the substantial costs and their impact on society, much attention is paid to the prevention of stroke. Major preventable risk factors include hypertension, atrial fibrillation, diabetes, and tobacco consumption, as well as hypercholesterolemia and obesity. Moreover, a meta-analysis has demonstrated that moderate to high levels of physical activity are associated with reduced risk of total, ischemic, and hemorrhagic strokes [5].

New developments in stroke treatment induced changes in stroke care and the necessity to concentrate this care in specialized, well organized and coordinated medical facilities, hence creating stroke services. The scientific evidence for the benefits of these stroke services is mounting. As a consequence, many health care facilities and institutions proceeded to incorporate such a service. A stroke unit is part of a stroke service. At present, stroke units can be found within a large number of hospitals. A reduction of mortality rates, length of inpatient stay and improved independence in activities of daily living (ADL) have been demonstrated for patients who are admitted to a stroke unit [6,7,8]. These benefits have been attributed to an integrated approach in which acute care is linked with early mobilization and rehabilitation, as well as the prevention of post-stroke complications, comprehensive assessment of medical problems, impairments and disabilities, active physiological management, skilled nursing care, early setting of rehabilitation plans involving carers and early assessment and planning for discharge needs [9,10,11]. Stroke units employ a team of experts on stroke care. Such a team incorporates a neurologist, specialized registered nurses, physiatrist, physiotherapist, occupational therapist, speech pathologist, social worker, and a transfer nurse. In addition, a neuropsychologist, geriatrician, psychiatrist, dietician,

*Address correspondence to this author at the Research Bureau, Isala klinieken, P.O. Box 10400, 8000 GK Zwolle, The Netherlands; Tel: +(31)-38-424 5027; Fax: +(31)-38-424 7687; E-mail: b.j.kollen@isala.nl

cardiologist, internist, neurosurgeon and Ear, Nose and Throat physician may be consulted if required. In a systematic review, Langhorne and Duncan showed that there can be substantial benefit from organized inpatient multidisciplinary rehabilitation in the postacute period [12]. Based on a heterogeneous group of 9 trials totaling 1,437 patients, they found a reduced odds of death (OR: 0.66 CI: 0.49 to 0.88; *p* = 0.01), death or institutionalization (OR: 0.70 CI: 0.56 to 0.88; *p* = 0.001), and death or dependency (OR: 0.65 CI: 0.50 to 0.85; *p* = 0.001), which was consistent across a variety of trial subgroups.

Based on this information, the following questions with regard to stroke rehabilitation will be addressed:

1. Is stroke rehabilitation efficacious?

2. Is methodological quality of studies sufficient in stroke rehabilitation research?

3. What is the significance of repeated measurements for the prediction of stroke recovery?

Efficacy of Stroke Rehabilitation

The importance of evidence-based medicine and practice as a guide to the clinical decision-making process is increasingly recognized by health care professionals. In the absence of any curative therapy, rehabilitation constitutes the main mode of therapy to improve quality of life following stroke [13] and is considered a corner stone of multidisciplinary stroke care [14]. However, to date, the choice of applied therapeutic interventions is still subject to empiricism, and demonstration of their efficacy is often based on methodologically low quality research. One way of assessing the quality of randomized controlled trials (RCT) is with the Physiotherapy Evidence Database (PEDro) scale [15]. This rating allows for distinguishing between methodological sound and poor trails. This instrument has been used in a systemic review for determining the evidence for the impact of physical therapy on functional outcomes after stroke [16]. For this review, from the 735 publications identified as clinical trials in stroke rehabilitation, 151 studies were selected including 123 randomized controlled trials (RCT) and 28 controlled clinical trials (CCT). Methodological quality of all RCTs constituted 5 median points on a 10 point PEDro scale. The effects generated by different neurological treatment approaches, including Bobath or Neurodevelopmental treatment (NDT), Brunn-strom, Rood, Johnstone, Proprioceptive Neuromuscular Facilitation (PNF), Motor Relearning Program (MRP), Ayres or combinations of these methods, were investigated [16]. Best-evidence synthesis showed moderate evidence for a reduced length of hospital stay in favor of MRP or traditional care compared with an impairment-focused neuromuscular treatment approach such as Bobath. [17,18,19]. No evidence was found for applying a specific neurological treatment programme in terms of muscle strength [20,21], synergism [22], muscle tone [23], walking ability [23], dexterity [17,24,25] or ADL [17,26,20,21,27,25,23,18]. Hafsteinsdottir reported a similar finding for nursing care in hospitalized stroke patients. The NDT-approach was not found to be an effective method and therefore she encouraged health care

professionals to reconsider the use of the NDT-approach [28].

Impairment-focused programs fail to generate functional improvements. These programs include biofeed-back, neuromuscular or transcutaneous nerve stimulation, cardio-vascular fitness training and muscle strengthening [16]. Moreover, this review indicates that the rationale for different treatment approaches is still weak. However, strong evidence was found for therapies that administered functional training, such as constraint-induced movement therapy, treadmill training with or without body weight support, aerobics, external auditory rhythms during gait and neuromuscular stimulation for glenohumeral subluxation [16].

Another systematic review investigated the outcomes of progressive resistance strength training following stroke [29]. From the 350 publications initially identified, eight met the inclusion criteria of the review. Only three were randomized trials and the remainder were single-case time-series analyses or pre-experimental trials. The authors concluded that there is preliminary evidence that progressive resistance strength training reduces musculoskeletal impairment after stroke, but they were unable to demonstrate effects on enhancing performance of functional activities or participation in societal roles [29]. Yet another systematic review of exercise trials after stroke identified insufficient evidence to establish a positive effect of cardiovascular exercise on disability, impairment, extended ADL, quality of life and case fatality [30]. From the 18,934 potential relevant trials identified, 16 trials were found to meet the inclusion criteria. Ultimately, information from only three trials, all with different outcome measures, was used for the review, as poor methodological quality necessitated to disregard the other studies.

A meta-analysis subsequently provided evidence for the use of increased intensity of task-specific exercise therapy as a means of achieving faster motor recovery after stroke [31]. A random effects model adjusted for the difference in treatment intensity in each study was used. Twenty of the 31 candidate studies, involving 2,686 stroke patients, were included in the synthesis. Small but statistically significant weighted mean differences (WMD) were found for ADL measured at the end of the intervention phase. Further analysis showed a significant homogeneous WMD for the effects of increased exercise intensity, i.e. augmented therapy for at least 16 hours within the initial 6 post-stroke months, on instrumental ADL and gait speed. The authors concluded that there is strong evidence that patients benefit from exercise programs in which functional tasks are directly and intensively trained [31].

Following discharge from stroke service treatments are often continued albeit less frequently. According to a Cochrane review, outpatient rehabilitation may prevent deterioration in seven of every 100 patients residing in the community [32]. This rehabilitation is directed to the restoration of motor control in gait and gait-related activities, improvement of upper extremity function, teaching the patient to cope with existing deficits in ADL and enhancement of participation in general.

Based on multidisciplinary consensus, guidelines have been developed in many countries for overall stroke care [e.g. 33] and stroke rehabilitation [e.g. 34]. Adherence to these guidelines has been shown to be related to functional recovery. Greater levels of adherence to postacute stroke rehabilitation guidelines are associated with improved patient outcomes [35] and patient satisfaction [36]. Compliance with guidelines may be viewed as a quality-of-care indicator with which to evaluate new organizational and funding changes involving postacute stroke rehabilitation.

Methodological Quality of Stroke Rehabilitation Research

What these systematic reviews also demonstrate is the poor methodological quality of many intervention studies. These studies either failed to meet the inclusion criteria by design and thus were not included in the analysis or lacked statistical and internal validity. Ottenbacher and Jannell found that standardized mean differences (i.e. effect sizes) of poorly designed trials were twice as large (i.e. 0.73 versus 0.38 standard deviation units) when compared to those of well designed intervention trials [37]. Quite often, the observer was not independent of treatment assignment [38]. In addition, it has been claimed that insensitivity of most ordinal scaled measurement instruments jeopardizes the detection of relatively small effects of stroke rehabilitation. Matyas and Ottenbacher also noticed a lack of power of intervention studies in the detection of differences in efficacy [39].

When there are large differences in patient characteristics and individual recovery patterns within both the experimental and control groups, it becomes difficult to demonstrate differences between groups, in particular, when these effects of treatment are small compared to the extent and heterogeneous nature of developing spontaneous recovery. For this reason, a number of researchers advocate the inclusion of a large number of patients in stroke rehabilitation trials, whereas others prefer controlled single subject experimental designs or interrupted time series experiments [40,41,42]. A major advantage to this latter design is its control for subject homogeneity. However, it should be noted that there are also some inherent disadvantages to controlled single subject experimental designs in that systematic variance may be induced by initial patient selection, carry over effects of treatment conditions from preceding phases onto ensuing phases, training effects of repeated measurements, contamination by differences in circumstances during the study, and confounding effects generated by non-specific parts of the treatment [40,43]. In addition, single subject experimental designs may suffer from the unknown natural history of individual subjects [44]. To overcome the problem of heterogeneity within the stroke population, several authors have suggested that the implementation of well-defined criteria for patient selection may improve statistical power and concomitant conclusion validity in stroke rehabilitation trials conducted to detect differences in efficacy [45,46,47,48].

Alternative methods of experimental control accomplish efficient treatment comparisons at the individual patient level. To control for spontaneous recovery after the subacute phase, multiple baseline design studies are useful in demonstrating immediate short lasting effects [49]. In cross-over and single subject designs, patients act as their own control thus reducing attrition from patients randomized to the control group. Another advantage of these designs is that they require fewer participants. Although by definition, single subject designs have low generalizability, if done well, they are controlled and can provide very specific answers. This information can then be used for further scientific scrutiny in clinical randomized trials [50].

Measurement and Prediction in Stroke

When based on high quality studies systematic reviews and meta-analyses provide the ultimate evidence upon which evidence based practice is built. This evidence is based upon the (pooled) weighted mean differences of several RCTs and CCTs designed to study the effects of specific therapeutic interventions. The goal of these trials is to elucidate the benefits generated by specific interventions, which eventually may lead to the development of efficient and effective rehabilitation programs for acute and chronic stroke patients. These training programs are likely to produce better results if they comply with the principles of motor learning. Motor learning is defined as a relatively permanent change in the capability for responding associated with practice or experience [51]. Task-specificity, practice, goal-setting, feedback and motivation are considered important elements in motor learning [51]. In practice, it appears that repetition alone is less effective than repetition with variable practice. Many rehabilitation studies report immediate post-training gains, particularly if they used physical conditioning principles. Therefore, immediate post-training changes are considered 'performance gains' that can only be assessed as re-learned if sufficient time has elapsed to allow the gains to become permanent [52]. This implies that stroke patients require long term follow-up and assessment in order to demonstrate rehabilitation induced effects. Moreover, this approach also allows for revealing any time-course related effects. To date, many time dependent variables are yet to be determined. However, time itself appears to be one of the most important, although neglected determinants in relation to spontaneous functional recovery [53].

Findings from longitudinal studies with repeated measurements over time indicate that recovery of neurological impairment and disability shows a non-linear pattern as a function of time [54,55,56,57,58,59]. Such research employs a dynamic model which reflects reality more accurately and validly, as time is likely to confound reported predictive relationships in cross-sectional research. It may even address important issues such as elucidating the critical time window for therapy in stroke recovery. Moreover, predicting outcome at an early post-stroke stage allows for the development of optimal individual tailored treatments and early discharge planning. For instance, in a paper describing the probability of regaining dexterity in the flaccid upper limb, it was reported that optimal arm function at 6 months could be predicted within 4 weeks after onset based on Fugl-Meyer scores of the flaccid arm [60]. Furthermore, it was found that lack of voluntary motor control of the leg in the first week with no emergence of arm synergies at 4 weeks was associated with poor outcome at 6

months [60]. The outcome of prediction models assists the practitioner in making a proper prognosis and treatment plan for an individual stroke patient. This process, known as clinical reasoning or clinical decision making, is characterized by the gathering and interpretation of information obtained from a patient, the estimation of expected treatment effects and subsequently, the formulation of predictions regarding functional outcome. Unfortunately, studies describing adequate prediction models for recovery of gait after stroke are relatively scarce and of poor quality. A systematic review on prognostic factors for ambulation and ADL in the subacute phase after stroke involving 26 studies with 7,850 patients found only one prognostic factor (incontinence for urine) identified in three level A studies (i.e. good level of scientific evidence according to the methodological score). However, they concluded that at present, insufficient methodological quality of selected publications did not allow for an evidence-based prediction of ADL and ambulation in the subacute stage of stroke [61].

Ideally, the development of a new prediction model should be based on established guidelines, and the accuracy of a model's predictions must be externally validated in at least one independent cohort of stroke patients that was not used to generate the model [62]. Predictor variables must be easy to collect, clinically relevant and reliable. Basically, such a newly developed prediction model could suffer from three types of error: overfitting, i.e. too many variables in the model, results in the erroneous inclusion of false positive predictors (type I error); underfitting, i.e. too few variables in the model, is responsible for the omission of important variables (type II error) and paradoxical fitting. This represents a reported negative association with outcome when in fact, this association is positive (type III error). The risk of these problems increases as the ratio of outcome events to the number of predictor variables becomes smaller. The risk of error is especially high with an events per variable (EPV) ratio of <10 for binary outcomes [62].

The use of clinimetrics is of vital importance in this process [63]. The systematic assessment of longitudinal changes based upon clinimetric sound measurement instruments improves objectivity and facilitates communication among and between professionals and caregivers. In stroke research, with its large clinimetric 95% error thresholds and its dominating dynamics in recovery profiles as a result of underlying mechanisms of spontaneous recovery, longitudinal applied clinimetric measures will create a valid representation of any post-stroke changes that may have occurred. The information based on these measurements will generate a recovery profile of individual patients, which allows for an estimation of the relationship between impairments, activities and participation levels and contributes to the identification of risk factors that can be used in the discrimination between stroke patients with good and poor prognosis. It can guide patient management by providing a foundation on which realistic and attainable short and long-term therapeutic goal setting and discharge planning can be implemented. Retrospectively, it allows for a reflection on the impact of treatment decisions made during the course of recovery. A learning process is thus created that may benefit the care of future stroke patients [64].

Discussion

The objective of stroke rehabilitation is to enable individual patients to achieve their full potential and to maximize the benefits from training, in order to attain the highest possible degree of physical and psychological performance. The ultimate goals for many stroke patients is to achieve a level of functional independence necessary for returning home and to integrate as fully as possible into community life. For this reason, clinicians are challenged to reliably predict at an early post-stroke stage, the degree of disability the patient will ultimately experience in order to facilitate optimal stroke rehabilitation and appropriate discharge planning and implementation of resources. Still, a gap remains between prognostic research and rehabilitation practice. Therapists and physicians need to formulate their functional goals as precisely as possible. This requires adequate knowledge of the patient and disease characteristics that determine functional outcome. Making a proper prognosis is far more complex than just applying a suitable prediction model and incorporates clinical decision making or clinical reasoning based on recovery milestones, such as sitting balance, standing upright and the ability to walk [65]. Although adherence to major methodological principles in prognostic research is a prerequisite for achieving internal and statistical validity, the heterogeneity of the stroke population remains a major threat to the external validity of prediction models. Therefore, stratification of patients based on demographic and diagnostic data has been recommended in order to increase precision of prediction models. The aim of applying prediction models in more specific subpopulations of stroke patients is to strike a balance between precision and generalizability. In order to achieve the most efficient use of stroke services, it is important to identify predictors that discriminate between stroke patients with good and poor prognosis. Differences within and between studies in post-stroke timing of measurements taken for prediction decrease external validity of existing prediction models. The strict adherence to adequate study designs, restrictive selection criteria and repeated measurements over time, based on clinimetric sound instruments, can contribute to a better understanding of stroke recovery in general and patient characteristics that allow for an early reliable prediction of the final outcome. Only than individually tailored optimal treatment programs can be implemented.

Traditionally, cross-sectional stroke research is conducted. However, the variability in timing of the assessment of final outcome has made comparisons between prognostic studies difficult. This presents a problem in systematic reviews as the lack of uniformity limits mutual comparison let alone the pooling of results for meta-analysis. In stroke research, the non-linear functional recovery pattern presents challenges to overcome, and calls for an inception cohort with repeated measurements taken at fixed times post-stroke. A major advantage of frequently repeated measurements over time is that it represents reality far better than one or two measurements. Instead of relying on one or two images of the patients' functional status frozen in time for analysis, several closely sequential images over time can be observed and analyzed, thus providing insight into the dynamics of recovery. This in turn allows for a more valid interpretation of reality as it enables observing changes in actual recovery

processes that take place over time. More research is needed for the development of prognostic models based on the within-subject variability of covariates and uniform timing of prediction and assessment of final outcome. Future research should also focus on identifying time dependent determinants. This information can then be used to determine critical time windows for specific therapeutic interventions, but may also assist in identifying hierarchy in recovery patterns [53]. The use of mixed modeling statistical techniques allows for analyzing cross-sectional and longitudinal treatment and time effects simultaneously, while correcting for the correlated observations within subjects over time and allowing for regression coefficients to differ between subjects. As time constitutes an independent covariate in such a model, these statistical methods enable longitudinal analysis of unequally spaced time points of measurement. Moreover, in random coefficient analysis, missing data are presumed to be missing at random [66]. Finally, there are strong indications that motor recovery after stroke occurs to a large extent through behavioral compensation, rather than *via* processes of 'true recovery' alone [67]. Future studies may explore the relationship between behavioral adaptations and improved skills after stroke i.e. addressing the issue of which changes in motor control coincide with functional improvements. This knowledge may contribute to determining the best way in which to subject stroke patients to therapeutic exercises.

ACKNOWLEDGEMENT

REFERENCES

[1]   Association AH. Heart disease and stroke statistics-2003 update. Dallas, TX: American Heart Association; 2002.

[2]   Broderick J, Brott T, Kothari R, *et al.* The greater Cincinnati / Northern Kentucky stroke study. Stroke 1998; 29:415-421.

[3]   Elkins JS, Johnston SC. Thirty-year projections for deaths from ischemic stroke in the United States. Stroke 2003; 34: 2109-12.

[4]   Murray JL, Lopez AD, ed. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020, Cambridge, Mass: Harvard University Press, 1996.

[5]   Lee CD, Folsom AR, Blair SN. Physical activity and stroke risk. A meta-analysis. Stroke 2003; 34: 2475-2482.

[6]   Stroke Unit Trialists Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev 2002; 1: CD000197.

[7]   Hankey GJ, Warlow CP. Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations. Lancet 1999; 354: 1457-63.

[8]   Langhorne P, Duncan P. Does the organization of postacute stroke care really matter? Stroke 2001; 32: 268-74.

[9]   Stroke Unit Trialists Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev 2002; 1: CD000197.

[10]   Hankey GJ, Warlow CP. Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations. Lancet 1999; 354: 1457-63.

[11]   Langhorne P, Pollock A. What are the components of effective stroke unit care? Age Ageing 2002; 31: 365-71.

[12]   Langhorne P, Duncan P. Does the organization of postacute stroke care really matter? Stroke 2001; 32: 268-74.

[13]   Gresham GE, Duncan PW, Statson WB. 'Priorities for future research'. Clinical practice guidelines number 16, US department of health and human services, Agency for health care policy and research, Rockwell, Maryland, AHCPR publication 1995; no. 95-0662.

[14]   Langhorne P, Duncan P. Does the organization of postacute stroke care really matter? Stroke 2001; 32: 268 –274.

[15]   Sherrington C, Herbert RD, Maher CG, Moseley AM. PEDro. A database of randomized trials and systematic reviews in physiotherapy. Man Ther 2000; 5: 223-26.

[16]   Peppen van RPS, Kwakkel G, Wood-Dauphinee S, Hendriks HJM, Van der Wees PhJ, Dekker J. The impact of physical therapy on functional outcome after stroke: What's the evidence? Clin Rehabil 2004; 18: 833-862.

[17]   Langhammer B, Stanghelle JK. Bobath or motor relearning programme? A comparison of two different approaches of physiotherapy in stroke rehabilitation: a randomized controlled study. Clin Rehabil 2000; 14: 361-69.

[18]   Lord JP, Hall K. Neuromuscular re-education versus traditional programmes for stroke rehabilitation. Arch Phys Med Rehabil 1986; 67: 88-91.

[19]   Patel M, Potter J, Perez I, *et al.* The process of rehabilitation and discharge planning in stroke: a controlled comparison between stroke units. Stroke 1998; 29: 2484-87.

[20]   Logigian MK, Samuels MA, Falconer J, *et al.* Clinical exercise trial for stroke patients. Arch Phys Med Rehabil 1983; 64: 364-67.

[21]   Stern PH, McDowell F, Miller JM, *et al.* Effects of facilitation exercise techniques in stroke rehabilitation. Arch Phys Med Rehabil 1970; 51: 526-31.

[22]   Poole JL, Whitney SL, Hangeland N, *et al.* The effectiveness of inflatable pressure splints on motor function in stroke patients. Occup Ther J Res 1990; 10: 360-66.

[23]   Dickstein R, Hocherman S, Pillar T, *et al.* Stroke rehabilitation. Three exercise therapy approaches. Phys Ther 1986; 66: 1233-38.

[24]   Basmajian JV, Gowland CA, Finlayson MA, *et al.* Stroke treatment: comparison of integrated behavioral-physical therapy vs traditional physical therapy programmes. Arch Phys Med Rehabil 1987; 68: 267-72.

[25]   Gelber DA, Josefczyk PB, Herrman D, *et al.* Comparison of two therapy approaches in the Impact of physical therapy after stroke 855 rehabilitation of the pure motor hemiparetic stroke patients. J Neuro Rehab 1995; 9: 191-96.

[26]   Jongbloed L, Stacey S, Brighton C. Stroke rehabilitation: sensorimotor integrative treatment versus functional treatment. Am J Occup Ther 1989; 43: 391-97.

[27]   Mudie MH, Winzeler-Mercay U, Radwan S, *et al.* Training symmetry of weight distribution after stroke: a randomized controlled pilot study comparing task-related reach, Bobath and feedback training approaches. Clin Rehabil 2002; 16: 582-92.

[28]   Hafsteinsdottir TB, Algra A, Kappelle LJ, Grypdonck MH; Dutch NDT Study Group. Neurodevelopmental treatment after stroke: a comparative study. J Neurol Neurosurg Psychiatry 2005; 76: 788-92.

[29]   Morris SL, Dodd KJ, Morris ME. Outcomes of progressive resistance strength training following stroke: a systematic review. Clin Rehabil 2004; 18: 27-39.

[30]   Meek C, Langhorne P. A systematic review of exercise trials post stroke. Clin Rehabil 2003; 17: 6-13.

[31]   Kwakkel G, Peppen van R, Wagenaar RC, *et al.* Effects of augmented exercise therapy time after stroke A meta-analysis. Stroke 2004; 35: 2529-2536.

[32]   Outpatient Service Trialists. Therapy-based rehabilitation services for stroke patients at home. Cochrane Database Syst Rev 2003; 1: CD002925.

[33]   Adams HP, Adams RJ, Brott T, *et al.* Guidelines for the early management of patients with ischemic stroke. A Scientific Statement from the Stroke Council of the American Stroke Association. Stroke 2003; 34: 1056 –1083.

[34]   Scottish Intercollegiate Guidelines Network. Management of patients with stroke: rehabilitation, prevention and management of complications, and discharge planning. A national clinical guideline. 2002.

[35]   Duncan PW, Horner RD, Reker DM, *et al.* Adherence to postacute rehabilitation guidelines is associated with functional recovery in stroke. Stroke 2002; 33: 167-178.

[36]   Reker DM, Duncan PW, Horner RD, *et al.* Postacute stroke guideline compliance is associated with greater patient satisfaction. Arch Phys Med Rehabil 2002; 83 (6): 750-756.

[37] Ottenbacher KJ, Jannell S. The results of clinical trials in stroke rehabilitation research. Arch Neurol 1993; 50: 37-44.

[38] Schultz KF, Calmers I, Hayes RJ, Altman DG. Empirical evidence of bias. JAMA 1995; 273: 408-412.

[39] Matyas TA, Ottenbacher KJ. Confounds of insensitivity and blind luck: Statistical conclusion validity in stroke rehabilitation clinical trials. Arch Phys Med Rehabil 1993; 74: 559-565.

[40] Wagenaar RC. Functional recovery after stroke. VU university press Amsterdam 1990.

[41] Gonella C. Designs for clinical research. Phys Ther 1973; 53: 1276-1283.

[42] Hayes SC. Single subject research strategies in occupational clinical practice. J Consult Clin Psychol 1981; 50: 193-211.

[43] Wagenaar RC, Meyer OG, Van Wieringen PCW, *et al.* The functional recovery of stroke. A comparison between neurodevelopmental treatment and the Brunnstrom method. Scand J Rehabil Med 1990; 22: 1-8.

[44] Basmajian JV, Gowland CA. The many hidden faces of stroke: A call for action. Arch Phys Med Rehabil 1987; 68: 319.

[45] Jongbloed L. Prediction of function after stroke: a critical review. Stroke 1986; 17: 765-776.

[46] Gresham GE. Past achievement and new directions in stroke outcome research. Stroke 1990; 21 (II supplement), 1S-3S.

[47] Gladman JRF, Harwood DMJ, Barer DH. Predicting the outcome of acute stroke.: prospective evaluation of five multivariate models and comparison with single methods. J Neurol Neurosurg Psychiatry 1992; 55: 347-351.

[48] Hier DB, Edelstein G. Deriving clinical prediction rules from stroke outcome research. Stroke 1991; 22: 1431-36.

[49] Kazdin AE. Single-Case Research Designs. Oxford University Press. 1982.

[50] Zhan S, Ottenbacher KJ. Single subject research designs for disability research. Disabil Rehabil 2001; 23: 1-8.

[51] Schmidt RA, Lee T. Motor control and learning. Champaign, IL. Human kinetics. 1999.

[52] Winstein CJ. Knowledge of results and motor learning – implications for physical therapy. Phys Ther 1991; 71: 140-9.

[53] Kwakkel G. Dynamics in functional recovery after stroke. Ponsen & Looijen BV, The Netherlands. 1998.

[54] Heller A, Wade DT, Wood VA, Sunderland A, Langton Hewer RL. Arm function after stroke: measurement and recovery over the first three months. J Neurol Neurosurg Psychiatry 1987; 50: 714–719.

[55] Wade DT, Langton Hewer RL, Wood VA, Skilbeck CE, Ismail HM. The hemiplegic arm and recovery. J Neurol Neurosurg Psychiatry 1983; 46: 521–524.

[56] Sunderland A, Tinson DJ, Bradley L, Langton Hewer RL. Arm function after stroke: an evaluation of grip strength as a measure of recovery and prognostic indicator. J Neurol Neurosurg Psychiatry 1989; 52: 1267–1272.

[57] Nakayama H, Jørgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil 1995; 76: 27–32.

[58] Loewen SC, Anderson BA. Predictors of stroke outcome using objective measurement scales. Stroke 1990; 21: 78–81.

[59] Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J. Measurement of motor recovery after stroke: outcome assessment and sample size requirements. Stroke 1992; 23: 1084–1089.

[60] Kwakkel G, Kollen BJ, Grond van der J, Prevo AJH. Probability of regaining dexterity in the flaccid upper limb: Impact of severity of paresis and time since onset in acute stroke. Stroke 2003; 34: 2181-2186.

[61] Meijer R, Ihnenfeldt DS, de Groot IJ, van Limbeek J, Vermeulen M, de Haan RJ. Prognostic factors for ambulation and activities of daily living in the subacute phase after stroke. A systematic review of the literature. Clin Rehabil 2003; 17(2): 119-129.

[62] Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute and subacute stroke. Development and validation of new prognostic models. Stroke 2002; 33: 1041-1047.

[63] Feinstein AR. Clinimetrics. Yale University Press. New Haven. 1987.

[64] Koolstra M, Burgers-Bots IAL, Lemmens CJ, Smeets CJ, Kwakkel G. Klinimetrie na een beroerte. Een praktische handleiding. VU medisch centrum 2001.

[65] Kwakkel G, Kollen BJ, Wagenaar RC. Therapy impact on functional recovery in stroke rehabilitation - A critical review of the literature. Physiotherapy 1999; 85 (7): 377-391.

[66] Twisk JWR. Applied Longitudinal Data Analysis for Epidemiology. Cambridge University Press 2003.

[67] Kwakkel G, Kollen BJ, Lindeman E. Understanding the pattern of functional recovery after stroke: Facts and theories. Restorative Neurolo Neurosci 2004; 22: 281-299.