Chapter 2

Presence of finger extension and shoulder abduction within 72 hours post-stroke predicts functional recovery of the upper limb: the EPOS cohort study

Rinske HM Nijland, Erwin EH van Wegen,
Barbara C Harmeling-van der Wel, Gert Kwakkel;
on behalf of the EPOS Investigators. A complete list of the EPOS Investigators is provided in the acknowledgements.

Stroke 2010 April;41:745-50

ABSTRACT

Background and purpose: The aim of the present study was to determine if outcome in terms of upper limb capacity at 6 months after stroke can be predicted at hospital stroke units using clinical parameters measured within 72 hours after stroke. In addition, the effect of the timing of post-stroke assessment on the accuracy of prediction was investigated by measurements on days 5 and 9.

Methods: Candidate determinants were measured in 188 stroke patients, within 72 hours and at 5 and 9 days post stroke. Logistic regression analysis was used for model development, to predict upper limb capacity at 6 months, measured with the Action Research Arm Test (ARAT).

Results: Patients with an upper limb motor deficit who exhibit some voluntary extension of the fingers and some abduction of the hemiplegic shoulder on day 2 have a probability of 0.98 to regain some dexterity at 6 months, whereas the probability was 0.25 for those without this voluntary motor activity. Sixty percent of patients with some early finger extension achieved full recovery at 6 months in terms of ARAT score. Retesting the model on days 5 and 9 resulted in a gradual decline in probability from 0.25 to 0.14 for those without voluntary motor activity of shoulder abduction and finger extension, whereas the probability remained 0.98 for those with this motor activity.

Conclusions: Based on two simple bedside tests, finger extension and shoulder abduction, functional recovery of the hemiplegic arm at 6 months can early be predicted at an hospital stroke unit within 72 hours after stroke onset.

INTRODUCTION

Although prospective epidemiological studies are lacking, findings of a number of prospective cohort studies suggest that 33–66%[1, 2] of the stroke patients with a paretic upper limb fail to show any recovery of upper limb function 6 months after stroke. Depending on the outcome measures used, 5–20% achieve full functional recovery of upper limb function at 6 months.[3]

Early prediction of final functional outcome for the paretic upper limb is paramount for stroke management, including discharge policies at hospital stroke units. Considering that most patients are discharged to rehabilitation centres or nursing homes within the first week post stroke to reduce health care costs, discharge planning should start within the first days after stroke.[4] Moreover, guidelines for rehabilitation management recommend starting the treatment of stroke patients as early as possible.[5] Prospective cohort studies have shown that early return of finger extension,[6, 7] shoulder shrug and abduction[8] and active range of motion[9] are important prognostic determinants of the outcome for the paretic upper limb 6 months after stroke. Additionally, results from a recent cohort study with repeated measurements in time suggest that the outcome in terms of regaining dexterity at 6 months is largely defined within the first four weeks after stroke.[10] Unfortunately, most previous studies did not investigate the time-dependency of clinical determinants in relation with spontaneous neurological recovery in the very early stages of recovery.[11, 12]

To improve early stroke management an answer is required to the question whether accurate prediction of the final outcome in terms of upper limb capacity can be achieved within the first days post stroke at the hospital stroke unit. Therefore, the first aim of the present study was to determine if outcome in terms of upper limb capacity at 6 months can be predicted within 72 hours after stroke onset. The second aim was to explore the biological relationship of the proposed clinical predictors with spontaneous neurological recovery by means of investigating the effect of the moment of assessment on the accuracy of prediction by assessing on days 5 and 9 post stroke.

MATERIALS AND METHODS

The EPOS study (an acronym of Early Prediction of functional Outcome after Stroke) is a prospective cohort study whose design involves intensive repeated-measurements within the first two weeks after stroke onset. Over a period of 24 months, 188 stroke patients were recruited from nine acute hospital stroke units in the Netherlands. All determinants were measured within 72 hours after stroke and were reassessed on days 5 and 9. Final outcome was defined at 6 months after stroke, using the Action Research Arm Test (ARAT).[13-15] Measurements were performed by trained assessors working as physical therapist or occupational therapist at the stroke units of the participating centers (including several affiliated nursing homes). All assessors were familiar with the test battery. In addition, a one day training course was given and the assessors were tested for inter-observer-reliability. All patients received treatment according to the Dutch rehabilitation guidelines, which are in agreement with current international rehabilitation guidelines.[5, 16] The research proposal was approved by ethics committees of all participating hospitals and all affiliated rehabilitation centres and nursing homes approved local feasibility.

Subjects

2

Stroke was defined according to the World Health Organization criteria (WHO).[17] Type and localization of stroke were determined using CT or MRI scans and clinical features according to the Bamford classification.[18] Patients meeting the following admission criteria were included: (1) a first-ever ischemic anterior circulation stroke; (2) a monoparesis or hemiparesis within the first 72 hours after stroke onset; (3) no disabling medical history (i.e., a premorbid Barthel Index score ≥19); (4) at least 18 years of age; (5) no severe deficits in communication, memory or understanding that impede proper measurement performance; (6) signed informed consent.

Dependent variable

The outcome in terms of hemiplegic arm capacity was assessed with the ARAT. This one-dimensional hierarchical scale consists of 19 functional tasks that are divided into four domains, i.e.: grasp, grip, pinch and gross movement, with a maximum total score of 57 points. The clinimetric properties of the ARAT are excellent.[13, 14] All ARAT measurements were performed in a standardized manner according to van der Lee and collegues.[14]

For the purpose of logistic regression analysis, ARAT scores were dichotomized into 1 for those who regained some dexterity (≥10 points on ARAT) and 0 for those who did not regain any dexterity (<10 points on ARAT).[10] A cut-off score of ≥10 points was chosen because a score of nine points or lower mainly reflects gross arm movements, whereas a score above nine points always represents some hand function.[10, 14, 15]

Independent variables

On the basis of existing literature[7-9] and a previous cohort study on predicting upper limb capacity early after stroke[10] the following candidate determinants were selected for the development of a prediction model (1) gender; (2) age; (3) hemisphere of stroke; (4) type of stroke (Bamford classification);[18] (5) days between stroke and first assessment; (6) recombinant tissue plasminogen activator (rTPA); (7) Comorbidity (Cumulative Illness Rating Scale [CIRS][19]); (8) visual inattention (National Institutes of Health Stroke Scale [NIHSS][20] item 11); (9) hemianopia (NIHSS item 3); (10) deviation conjugee (NIHSS item 2); (11) sensory loss (NIHSS item 8); (12) ADL score (Barthel Index [BI] total score[21]); (13) urinary incontinence (BI item 2); (14) severity and extent of paresis of the arm and leg according to the upper and lower extremity parts of the Motricity Index [MI],[22] and the Fugl-Meyer [FM][23] assessment; and (15) Sitting Balance (Trunk Control Test [TCT][24]).

Data analysis

The possible association between the return of some dexterity on the ARAT (i.e., ≥10 points) at 6 months and the candidate determinants (independent variables) within 72 hours was investigated using bivariate logistic regression analysis and calculating odds ratios (OR) and their 95% confidence intervals (CIs). Ordinal or ratio scaled determinants were preferably dichotomized on clinical grounds; in the other cases, the optimal cut-off point for each determinant was determined with the help of a receiver-operating characteristic curve (ROC). The optimal dichotomization was estimated separately for each candidate determinant on the basis of sensitivity/1-specificity and maximum area under the curve for each cut-off score. Based on the bivariate logistic regression analysis, significant determinants (P-value ≤0.10) were selected for the subsequent development of a multivariate logistic model predicting within 72 hours whether some (i.e., ARAT ≥10 points) or no (i.e., ARAT <10) dexterity will return after 6 months. Collinearity between the determinants included was defined if their correlation coefficient was ≥0.7. Subsequently, the determinant with the lowest OR was excluded from multivariate modelling. Because of the large number of variables relative to the number of patients involved, the maximum likelihood estimation of parameters in the multivariate model was conditional on the basis of a forward, stepwise approach. Entry and removal criteria with P-values of 0.05 and 0.10, respectively were used. The multivariate logistic model thus derived was used to calculate probabilities for developing some dexterity at 6 months, using the following equation:

$$P = 1 / (1 + (\exp^{[-(B0+B1X1+B2X2+B3X3....+BnXn)]}))$$

A 2-way contingency table was used to calculate sensitivity, specificity and negative (NPV) and positive predicted values (NPV), including their 95% CIs. The same analyses were repeated at 5 and 9 days post stroke.

All analyses used two-tailed tests and were conducted using SPSS version 15.

RESULTS

2

One hundred and eighty-eight stroke patients were recruited for the EPOS study in 24 months. Nineteen patients died during follow-up, two patients refused assessment at 6 months, three patients were excluded after admission due to recurrent stroke, two were unable to undergo the assessments and three were lost to follow-up. Finally, three patients were excluded because of incomplete data on the baseline FM assessments. Table 2.1 presents the main characteristics of the remaining 156 patients. The mean (standard deviation) moments when the candidate determinants were measured were 2.26 (1.28), 5.48 (1.40) and 9.02 (1.81) days post stroke. The median ARAT score was 1.5 points on day 2. At 6 months, some dexterity (ARAT ≥10 points) in the paretic arm was found in 70.5% of the subjects, whereas 34% showed a maximum score of 57 points on the ARAT.

Bivariate associations between dependent and independent variables

Table 2.2 shows odds ratios and their 95% CI as determined by bivariate logistic regression analysis within 72 hours after stroke. Eleven candidate determinants were significantly related to the return of some dexterity at 6 months post stroke. The highest ORs were found for finger extension according to the FM-hand score, using an optimal cut-off of 1 point, followed by shoulder abduction according to the MI-arm score, with an optimal cut-off of 9 points. Collinearity diagnostics showed a significant correlation coefficient of 0.75 between 'shoulder elevation' and 'shoulder abduction'. As a consequence, shoulder abduction, which showed a higher association with ARAT, was included in the multivariate modelling.

Multivariate modelling

Table 2.3 shows the multivariate logistic regression models for days 2, 5 and 9 after stroke. The probability to achieve some dexterity 6 months after the stroke for those patients who showed some voluntary finger extension (FE) and some shoulder abduction (SA) on day 2 was estimated at 0.98. The probability for those without voluntary motor activity of these determinants was estimated at 0.25. Two-way contingency table analysis showed a sensitivity of 0.89 (95% CI:

Table 2.1 Patient characteristics assessed within 72 hours after stroke

Patient characteristics	Total
N	156
Gender, M/F	69/87
Mean (SD) age, years	66.47 (14.43)
Hemisphere of stroke, L/R	69/87
rTPA, N/Y	117/39
Mean (SD) BMI	26 (4.62)
Mean (SD) time interval (days) between stroke and:	
first assessment, days (mean (SD))	2.26 (1.28)
second assessment, days	5.48 (1.40)
third assessment, days	9.02 (1.81)
Type of stroke (BAMFORD)	
LACI	79
PACI	50
TACI	27
NIHSS*	7 (4–14)
Cognitive disturbance	
Inattention, N/Y	93/63
Disorientation, N/Y	119/37
Impairments of vision	
Hemianopia, N/Y	114/42
Deviation conjugee, N/Y	122/34
Sensory loss, N/Y	63/93
TCT (0–100)*	74 (37–100)
MI arm (0–100)*	39 (0–76)
MI leg (0–100)*	53 (23–83)
FM arm (0–66)*	21 (4–56)
FM leg (0–34)*	21 (9–29)
FAC (0–5)*	1 (0–3)
ARAT total score (0–57)*	1.5 (0–41)
BI total score* (0–20)	8 (3–14)
BI urinary incontinence, N/Y (N=2; y≤1)	76/79

N, number of patients; M/F, male/female; SD, standard deviation; L/R, left/right; rTPA, recombinant tissue plasminogen activator; N/Y, no/yes; BMI, Body Mass Index; Type of stroke: LACI, Lacunar Anterior Cerebral Infarction; PACI, Partial Anterior Cerebral Infarction; TACI, Total Anterior Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; TCT, Trunk Control Test; MI, Motricity Index; FM, Fugl-Meyer; FAC, Functional Ambulation Categories Score; ARAT, Action Research Arm Test; BI, Barthel Index. * Median values (interquartile ranges).

Table 2.2 Candidate determinants, measured within 72 hours, associated with the return of some dexterity at 6 months after stroke, as determined by logistic regression coefficients

	N=156		
Determinant	Odds ratio	95% CI	P-value
Gender (M/F)	1.58	0.79–3.15	0.198
Age (0<70; 1≥70)	1.13	0.57–2.25	0.726
Hemisphere of stroke (L/R)	0.44	0.21–0.91	0.027
BAMFORD (0:TACI/PACI; 1:LACI)	10.56	4.31–25.85	<0.001
Days between stroke and first assessment	0.98	0.75–1.28	0.877
rTPA (N/Y)	1.73	0.81–3.73	0.158
CIRS total score (0≥1; 1=0)	1.96	0.96–3.98	0.063
Visual inattention (0≥1; 1=0)	7.91	3.62–17.32	<0.001
Hemianopia (0≥1; 1=0)	7.63	3.47–16.80	<0.001
Deviation conjugee (0≥1; 1=0)	9.00	3.84–21.05	<0.001
Sensory loss (0≥1; 1=0)	9.15	3.36–24.89	<0.001
Urinary incontinence (0<1; 1≥1)	6.41	2.81–14.59	<0.001
MI shoulder abduction (0=0; 1≥9)	32.57	12.64–83.92	<0.001
MI leg (0<25; 1≥25)[10]	15.35	6.47–36.49	<0.001
FM Shoulder elevation (0<1; 1≥1)	22.80	9.39–55.37	<0.001
FM Finger extension (FM, 0<1; 1≥1)	58.67	13.83–257.17	<0.001
Sitting balance (TCT item 3, 0<25; 1=25)[10]	20.67	8.44–50.62	<0.001

The values between the brackets represent the cut-off scores. M/F, male/female; L/R, left/right; BAMFORD:TACI, Total Anterior Cerebral Infarction; PACI, Partial Anterior Cerebral Infarction; LACI, Lacunar Anterior Cerebral Infarction; rTPA, recombinant tissue plasminogen activator; N/Y, no/yes; CIRS, Cumulative Illness Rating Scale; MI, Motricity Index; FM, Fugl-Meyer; TCT, Trunk Control Test.

0.85–0.92), a specificity of 0.83 (95% CI: 0.72–0.90), a PPV of 0.93 (95 CI%: 0.88–0.96) and an NPV of 0.76 (95% CI: 0.67–0.83). Sixty percent of the patients with some voluntary finger extension (N=82) reached the maximum ARAT score of 57 points, while 48% of the patients who were able to abduct the paretic shoulder (N=104) reached the maximum ARAT score. Thirty-four percent of all 156 patients reached a score of 57 points on the ARAT.

Retesting the multivariate model for days 5 and 9 showed that the probability remained 0.98 for those patients able to extent their fingers and abduct their shoulders and declined to 0.14 for those who failed to satisfy either of these criteria. Two-way contingency table analysis showed a sensitivity of 0.95 (95% CI: 0.91– 0.97), specificity of 0.83 (95% CI: 0.74–0.89), PPV of 0.93 (95 CI%: 0.89–0.95) and NPV 0.86 (95% CI: 0.77–0.93) for both days.

Table 2.3 Probabilities of achieving some dexterity at 6 months after stroke, N=156

	ARAT ≥10 at 6 months						
	Finger extension	Shoulder abduction	True negatives N	False negatives N	False positives N	True positives N	Probability
Model for day 2			$P = 1 / (1 + 1 * (\exp^{[-1.119+2.807*FE+2.149*SA]}))$				
	FM FE ≥1	MI SA ≥9					
	+	+	38	12	8	98	0.98
	+	-					0.89
	-	+					0.71
	-	-					0.25
Model for day 5			$P = 1 / (1 + 1 * (\exp^{[-1.874+3.070*FE+3.075*SA]}))$				
	FM FE ≥1	MI SA ≥9					
	+	+	38	6	8	104	0.98
	+	-					0.78
	-	+					0.78
	-	-					0.14
Model for day 9			$P = 1 / (1 + 1 * (\exp^{[-1.815+3.224*FE+2.449*SA]}))$				
	FM FE ≥1	MI SA ≥9					
	+	+	38	6	8	104	0.98
	+	-					0.80
	-	+					0.65
	-	-					0.14

FM, Fugl-Meyer; FE, Finger extension; MI, Motricity Index; SA, Shoulder abduction.

2

DISCUSSION

The present study is the first prospective cohort study to show that accurate prediction of upper limb capacity is possible within 72 hours after stroke by using two simple clinical tests, i.e., finger extension and shoulder abduction. Those patients with some finger extension and shoulder abduction on day 2 after stroke onset had a 98% probability of achieving some dexterity at 6 months. In contrast, patients who failed to show this voluntary motor control had a probability of 25%. It is also remarkable that 60% of the patients with some finger extension within 72 hours had regained full recovery of upper limb capacity according to the ARAT at 6 months. This finding confirms the substantial predictive value of finger extension as a positive sign for a favorable outcome for the upper paretic limb in the acute phase after stroke. Retesting the model on days 5 and 9 showed that the probability of regaining dexterity remained 98% for those with some finger extension and shoulder abduction, whereas the probability decreased from 25% to 14% for those without this voluntary control.

Although the present study did focus on the early time window of stroke recovery, our findings build on results of previous prospective studies, which started beyond the first week post stroke.[7-10] For example, Smania and colleagues showed in a sample of 48 stroke patients that active finger extension at day 7 post stroke is an early, valid indicator of a favorable prognosis in terms of upper limb outcome, measured with the Nine Hole Peg Test, the FM-arm and the MI-arm.[7] Katrak et al. reported that initial shoulder abduction, measured an average of 11 days after stroke, is an early predictor of good hand function at 1 and 2 months after stroke.[8] Our results validate the value of assessing shoulder abduction and finger extension as early favorable indicators for some return of dexterity at 6 months post stroke.

The preservation of voluntary finger extension may reflect the need for some fibres of the corticospinal tract system in the affected hemisphere to remain intact, to control distal arm and hand muscles,[25, 26] assuming that the hand lacks bilateral innervation from both hemispheres.[27] To date Transcranial Magnetic Stimulation (TMS)[25, 28] and Diffusion Tensor Imaging (DTI)[25, 29] studies further underpin this hypothesis. For example van Kuijk and colleagues showed that in patients with an initial paralysis of the upper limb the presence or absence of a motor evoked potential in the abductor digiti minimi measured with TMS at the end of the first week post stroke is highly predictive for final outcome of dexterity at 6 months.[28] However, the presence or absence of a motor evoked potential in the abductor digiti minimi has similar predictive values when compared to clinical assessment alone.[28] The present study suggests that TMS measurements should investigate the predictive validity of motor evoked potentials of finger extensors rather than finger flexors or the abductor digiti minimi alone.[30]

The presence of shoulder abduction as a determinant for upper limb capacity may reflect the intra limb neural coupling between proximal and distal segments in motor control. As early as 1916, Souques observed that elevation of the affected arm frequently caused the paralysed finger to extend.[31] A recent study has shown that distal elbow joint control is dependent on shoulder abduction.[32] Obviously, the strength of shoulder abduction affects the elbow-flexion torque and with that the reaching range of motion (work area) in patients with stroke.[30]

With respect to the second aim of the present study, to explore the biological relationship of the proposed clinical determinants with spontaneous neurological recovery, the presented findings show that the probability of regaining some dexterity after 6 months fell from 25% to 14% in the first 9 days for those without finger extension and shoulder abduction. This may reflect the gradual decline of uncertainty as a result of time-dependent spontaneous processes such as decrease of cerebral shock or diaschisis.[33, 34] In contrast, for those patients with some finger extension and shoulder abduction the probability of regaining dexterity remained 98%. This latter finding suggests that the viability of the corticospinal tract system is almost entirely defined within the first days post stroke in terms of achieving dexterity at 6 months. However, it is important to note that these findings do not suggest that no changes in upper limb capacity occur beyond 9 days, but rather that the final outcome of dexterity is almost fully defined within this critical time window in this cohort with mild to moderate impairments. In order to improve our understanding of mechanisms that may underlie recovery, future prospective studies should longitudinally combine clinical and non-invasive neurophysiologic assessments such as TMS and fMRI in an intensive early started repeated measurement design post stroke.[30]

For clinical practice, the findings of the present study might improve early stroke management decisions like discharge and multidisciplinary intervention planning at (sub)acute stroke units. As a consequence, subsequent multidisciplinary rehabilitation services may be optimized in line with the probability for regaining some dexterity, in particular acknowledging that many evidence based therapies for the upper paretic limb, including CIMT, require some return of voluntary wrist and finger extension.[6, 35] The findings of a recent study by Smania and colleagues strengthen this suggestion by also showing the predictive validity of finger extension and shoulder abduction at day 7 for daily life autonomy.

In interpreting the findings of the present study, some limitations should be noted. In accordance with the stroke guidelines,[5] we included only medically stable patients with first ever, ischemic strokes in one of the hemispheres. As a consequence patients with a mild to moderate stroke, who were able to communicate and understand were included in the present study. This might limit the generalization of the present findings to other patients with problems like dysphasia, confusion or reduced consciousness. However, having an early prognosis is most relevant for an appropriate discharge treatment policy from a hospital stroke unit for the cohort we selected.

ACKNOWLEDGEMENTS

We thank all EPOS assessors in the stroke units of the participating university centers and local hospitals (AMC Amsterdam; Erasmus MC Rotterdam; LUMC Leiden; UMC Sint Radboud; UMC Utrecht; VUmc Amsterdam; Amphia Hospital Breda; Diaconessen Hospital Leiden; Franciscus Hospital Roosendaal) and in the affiliated nursing homes (i.e. St. Jacob, Zonnehuis and Cordaan/Berkenstede in Amsterdam, Laurens Antonius Binnenweg and Reumaverpleeghuis in Rotterdam, Albert van Koningsbruggen in Utrecht and Wiekendaal in Roosendaal) for performing the measurements. We also want to thank the patients who participated in the study. Finally we thank J. de Vries and A. Jansen, students at Hogeschool Amsterdam, for their contribution to the data management.

EPOS Investigators

Executive committee: G. Kwakkel (PhD), principal investigator, department rehabilitation medicine, VU University Hospital Medical Center, Amsterdam, and *co-principal investigator* B.C. Harmeling-van der Wel, department rehabilitation medicine and physical therapy, Erasmus MC University Medical Center Rotterdam. *Steering committee and data management:* J.M. Veerbeek and R.H.M Nijland, department rehabilitation medicine, VU University Hospital Medical Centre, Amsterdam. *Revision of the manuscript:* E.E.E. van Wegen (PhD), department rehabilitation medicine, VU University Hospital Medical Centre, Amsterdam. *Monitoring board:* M.A. van der Beek, UMC Utrecht; W.A.M. Cornelissen, AMC Amsterdam; A.A.G. Goos, Franciscus Hospital, Roosendaal; C.S. Steeg, UMC Sint Radboud, Nijmegen; J.M. Timmermans, LUMC, Leiden; R. Tichelaar, Amphia Hospital, Breda.

Funding/support

This study was part of the EPOS research project funded by the 'Wetenschappelijk College Fysiotherapie' (WCF: number 33368) of the Royal Dutch Society for Physical Therapy (KNGF), the Netherlands. This part of the EPOS project is co-financed by ZON-MW (grant no: 89000001) as a part of the EXPLICIT-stroke programme (www.explicit-stroke.nl).

REFERENCES

(1) Sunderland A, Fletcher D, Bradley L, Tinson D, Hewer RL, Wade DT. Enhanced physical therapy for arm function after stroke: a one year follow up study. *J Neurol Neurosurg Psychiatry* 1994 July;57(7):856-8.

(2) Wade DT, Langton-Hewer R, Wood VA, Skilbeck CE, Ismail HM. The hemiplegic arm after stroke: measurement and recovery. *J Neurol Neurosurg Psychiatry* 1983 June;46(6):521-4.

(3) Nakayama H, Jorgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. *Arch Phys Med Rehabil* 1994 April;75(4):394-8.

(4) Summers D, Leonard A, Wentworth D, Saver JL, Simpson J, Spilker JA, Hock N, Miller E, Mitchell PH. Comprehensive Overview of Nursing and Interdisciplinary Care of the Acute Ischemic Stroke Patient. A Scientific Statement From the American Heart Association. *Stroke* 2009 August; 40(8):2911-44.

(5) Duncan PW, Zorowitz R, Bates B, Choi JY, Glasberg JJ, Graham GD, Katz RC, Lamberty K, Reker D. Management of Adult Stroke Rehabilitation Care: a clinical practice guideline. *Stroke* 2005 September;36(9):e100-e143.

(6) Fritz SL, Light KE, Patterson TS, Behrman AL, Davis SB. Active finger extension predicts outcomes after constraint-induced movement therapy for individuals with hemiparesis after stroke. *Stroke* 2005 June;36(6):1172-7.

(7) Smania N, Paolucci S, Tinazzi M, Borghero A, Manganotti P, Fiaschi A, Moretto G, Bovi P, Gambarin M. Active finger extension: a simple movement predicting recovery of arm function in patients with acute stroke. *Stroke* 2007 March;38(3):1088-90.

(8) Katrak P, Bowring G, Conroy P, Chilvers M, Poulos R, McNeil D. Predicting upper limb recovery after stroke: the place of early shoulder and hand movement. *Arch Phys Med Rehabil* 1998 July;79(7):758-61.

(9) Beebe JA, Lang CE. Active range of motion predicts upper extremity function 3 months after stroke. *Stroke* 2009 May;40(5):1772-9.

(10) Kwakkel G, Kollen BJ, van der Grond 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 September;34(9):2181-6.

(11) Kwakkel G, Kollen B. Predicting improvement in the upper paretic limb after stroke: a longitudinal prospective study. *Restor Neurol Neurosci* 2007;25(5-6):453-60.

(12) Kwakkel G, Kollen B, Twisk J. Impact of time on improvement of outcome after stroke. *Stroke* 2006 September;37(9):2348-53.

(13) Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. *Int J Rehabil Res* 1981;4(4):483-92.

(14) van der Lee JH, De G, V, Beckerman H, Wagenaar RC, Lankhorst GJ, Bouter LM. The intra- and interrater reliability of the action research arm test: a practical test of upper extremity function in patients with stroke. *Arch Phys Med Rehabil* 2001 January;82(1):14-9.

(15) Yozbatiran N, Der-Yeghiaian L, Cramer SC. A standardized approach to performing the action research arm test. *Neurorehabil Neural Repair* 2008 January;22(1):78-90.

(16) Quinn TJ, Paolucci S, Sivenius J, Walker MF, Toni D, Lees KR. Evidence-based stroke r-ehabilitation: an expanded guidance document from the european stroke organisation (ESO) guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *J Rehabil Med* 2009 February;41(2):99-111.

(17) Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ* 1976;54(5):541-53.

(18) Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991 June 22;337(8756):1521-6.

(19) de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity. a critical review of available methods. *J Clin Epidemiol* 2003 March;56(3):221-9.

(20) Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V, . Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989 July;20(7):864-70.

2

(21) Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. *Int Disabil Stud* 1988;10(2):61-3.

(22) Collin C, Wade D. Assessing motor impairment after stroke: a pilot reliability study. *J Neurol Neurosurg Psychiatry* 1990 July;53(7):576-9.

(23) Sanford J, Moreland J, Swanson LR, Stratford PW, Gowland C. Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke. *Phys Ther* 1993 July;73(7):447-54.

(24) Franchignoni FP, Tesio L, Ricupero C, Martino MT. Trunk control test as an early predictor of stroke rehabilitation outcome. *Stroke* 1997 July;28(7):1382-5.

(25) Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD. Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain* 2007 January;130(Pt 1):170-80.

(26) Ward NS, Newton JM, Swayne OB, Lee L, Thompson AJ, Greenwood RJ, Rothwell JC, Frackowiak RS. Motor system activation after subcortical stroke depends on corticospinal system integrity. *Brain* 2006 March;129(Pt 3):809-19.

(27) Morecraft RJ, Herrick JL, Stilwell-Morecraft KS, Louie JL, Schroeder CM, Ottenbacher JG, Schoolfield MW. Localization of arm representation in the corona radiata and internal capsule in the non-human primate. *Brain* 2002 January;125(Pt 1):176-98.

(28) van Kuijk AA, Pasman JW, Hendricks HT, Zwarts MJ, Geurts AC. Predicting hand motor recovery in severe stroke: the role of motor evoked potentials in relation to early clinical assessment. *Neurorehabil Neural Repair* 2009 January;23(1):45-51.

(29) Cho SH, Kim DG, Kim DS, Kim YH, Lee CH, Jang SH. Motor outcome according to the integrity of the corticospinal tract determined by diffusion tensor tractography in the early stage of corona radiata infarct. *Neurosci Lett* 2007 October 16;426(2):123-7.

(30) Kwakkel G, Meskers CG, van Wegen EE, Lankhorst GJ, Geurts AC, van Kuijk AA, Lindeman E, Visser-Meily A, de VE, Arendzen JH. Impact of early applied upper limb stimulation: the EXPLICIT-stroke programme design. *BMC Neurol* 2008;8:49.

(31) Brunnstrom S. *Movement therapy in hemiplegia: a neurophysiological approach*. New York: Harper and Row; 1970.

(32) Ellis MD, Sukal-Moulton T, Dewald JP. Progressive shoulder abduction loading is a crucial element of arm rehabilitation in chronic stroke. *Neurorehabil Neural Repair* 2009 October;23(8):862-9.

(33) Kwakkel G, Kollen B, Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. *Restor Neurol Neurosci* 2004;22(3-5):281-99.

(34) Feeney DM, Baron JC. Diaschisis. *Stroke* 1986 September;17(5):817-30.

(35) Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, Giuliani C, Light KE, Nichols-Larsen D. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *JAMA* 2006 November 1;296(17):2095-104.