Impact of time on improvement of outcome after stroke

Kwakkel, G.; Kollen, B.; Twisk, J.W.

Impact of Time on Improvement of Outcome After Stroke

Gert Kwakkel, PhD; Boudewijn Kollen, PhD; Jos Twisk, PhD

Background and Purpose—Longitudinal conducted studies show that neurologic and functional recovery show faster recovery in the first weeks poststroke. The aim of the present study was to study the effects of progress of time on observed improvements in motor strength, synergisms, and activities during the first 16 weeks poststroke.

Methods—Based on data from a previous study, 101 patients with first-ever ischemic middle cerebral artery strokes were prospectively investigated during the first 16 weeks after stroke. Progress of time was categorized into 8 biweekly time intervals and was used as the independent covariate in a first-order longitudinal regression model. The biweekly time change (progress of time) was related to improvement in upper and lower limb motor recovery assessed with Fugl-Meyer score and Motricity Index, reduction in visuospatial inattention based on the letter cancellation task, and improvement in walking ability, dexterity, and activities of daily living measured with the Functional Ambulation Categories, Action Research Arm test, and Barthel Index.

Results—Time explained a significant change of 8.4 (42%) measurement units on the Barthel Index for the first 10 weeks poststroke, 1.1 (22%) measurement units on Functional Ambulation Categories, and 19% on the Action Research Arm test for the first 6 and 8 weeks poststroke. Approximately 25% (for Fugl-Meyer–arm) to 26% (for Motricity Index–arm) of the significant change in measurements units was explained by time alone for the upper limb compared with 33% for Fugl-Meyer–leg and 39% for Motricity Index–leg of the lower limb. Time accounted for a reduction of 16% in the letter cancellation task. Observed associations did not change after controlling for covariates such as age, gender, hemisphere of stroke, type of stroke, or intervention.

Conclusion—Progress of time is an independent covariate that reflects spontaneous recovery of body functions and activities explaining ≈16% to 42% of the observed improvements in the first 6 to 10 weeks after stroke onset. (***Stroke***. 2006; 37:2348-2353.)

Key Words: activities of daily living ∎ prognosis ∎ recovery of function ∎ regression analysis ∎ spontaneous remission

Findings from a number of longitudinal studies show that, irrespective of the type and amount of therapy, the logistic pattern of recovery after stroke is determined by certain unknown underlying biologic processes.[1] Observed improvements, especially in the first weeks poststroke, most likely reflect the restitution of noninfarcted penumbral tissue surrounding the infracted area,[1] resolution of diaschisis,[2] and recovery of neurotransmission in spared tissue near and remote from the infarct.[1,2] This process, which is presumed to be mainly responsible for the nonlinear recovery pattern early poststroke, is often characterized as "spontaneous neurologic recovery."[3,4] Spontaneous "return" or "recovery" of some degree of neurologic function in the first weeks poststroke is often perceived as one of the most neglected features in stroke research.[4] In the past 35 years, studies have reported nonlinear recovery patterns of neurologic impairments for motor function[3–5] and synergism[6,7] as well as for activities of upper[5,8] and lower limb[9] and activities of daily living (ADLs) in general.[4,10] However, the mechanisms involved

as well the magnitude of this "spontaneous recovery" in the first weeks poststroke is poorly understood and insufficiently investigated.

One way of improving our understanding of the impact of spontaneous recovery on the pattern of recovery is by investigating the effects of time change (progress of time) on the recovery of neurologic functions and activities poststroke.[11] Recently, we introduced a new longitudinal first-order regression model in stroke rehabilitation research. In this study, we demonstrated that the individual change scores of balance control and lower limb function were related to improvement of walking ability.[11] By modeling only the within-subject change scores, one can investigate the duration and extent to which progress of time contributes to early observed improvements in neurologic impairments and functional abilities poststroke.[11]

The aim of the present study was to investigate the effects of progress of time on reduction in visuospatial inattention,

improvements in motor function of upper and lower paretic limb as well as recovery of dexterity, walking ability, and ADLs in the first 16 weeks poststroke. On the basis of significant regression coefficients, the extent of recovery explained by time was estimated for each variable of outcome. Finally, the regression coefficient for each time interval was controlled for the effects of age, gender, hemisphere, and type of stroke.

Materials and Methods

Design and Procedures

The data from the 101 patients in the prior study[10] were published before[10,11] and reanalyzed here. In this study, 101 patients with stroke participated with a mean age of 65 years (SD=12.0). Patients were included when they met the following criteria: (1) aged between 30 and 80 years; (2) experienced an ischemic, first-ever, stroke involving the territory of the medial or anterior cerebral artery as revealed by computerized axial tomography or magnetic resonance imaging scan; (3) displayed an inability to walk at first assessment; (4) revealed no complicating medical history such as cardiac, pulmonary, or orthopedic disorders; (5) no severe deficits in communication; (6) no severe deficits in memory and understanding; and (7) provided written or verbal informed consent and demonstrated sufficient motivation to participate. Within 14 days after stroke, patients were randomly assigned to a rehabilitation program with emphasis on (1) arm training, (2) leg training, or (3) immobilization by an inflatable pressure splint.[10]

Variables of Outcome

All variables of outcome were measured with biweekly intervals starting within the first 2 weeks and at 4, 6, 8, 10, 12, 14, and 16 weeks after stroke onset. To investigate the longitudinal impact of time on the recovery of strength, synergism, dexterity, walking ability, and ADLs, we modeled first-order change scores from eight biweekly measurements.

The Motricity Index (MI) was used to measure strength in upper and lower paretic extremity. It uses a weighted score to a maximum of 100 points for each extremity and tests six limb movements.[12] The Fugl-Meyer (FM) evaluation was used to assess motor performance of the upper and lower limb as well as control of sitting and standing balance (FM-balance).[13] The motor section of this test consists of upper limb (FM–arm) as well as lower limb (FM–leg) ordinal scaled components. Basically, it grades reliably and validly the degree to which dependence on synergic movements is present.[13] The letter cancellation task (LCT), which involved canceling Os, was applied to demonstrate the presence of neglect. Patients are requested to cross all Os on a sheet of paper containing 20 letters on the left side and 20 on the right.[10] The difference in the number of crossed letters on the paretic and nonparetic side was scored. Walking ability was assessed with the Functional Ambulation Categories (FAC).[14] The FAC is a reliable and valid assessment that includes six categories designed to provide information on the level of physical support needed by patients to ambulate safely. Recovery of dexterity was assessed with the Action Research Arm test (ARAT).[15] The ARAT is a reliable and valid assessment comprising of 19 items designed to provide information on the upper limb performance.[16] Finally, ADLs were assessed with the Barthel Index (BI). The BI represents a patient's ability to carry out 10 everyday tasks, including bladder and bowel control.[10] All assessments were performed by one observer (G.K.) who was blind to treatment assignment.[10]

Progress of Time

To investigate the impact of time on observed improvements in variables of outcome, time was categorized into eight equally spaced (biweekly) intervals from stroke onset to 16 weeks poststroke. In addition, baseline data were collected, including age, gender, type, and hemisphere of stroke according to the Bamford classification[17] and added to the regression model to verify whether generated regression coefficients for the eight categorized time intervals were subjected to more than 10% change in value.

Statistical Analysis

The longitudinal relationship of time on improvements in outcome was investigated by using random coefficient analysis (MLwiN, version 2.0).[18] The iterative generalized least squares algorithm was used to estimate the regression coefficients.[18,19] Before conducting the random coefficient analysis, we calculated the change between consecutive measurements of the time-dependent outcome variables. These change scores were then plotted to check for compliance with model assumptions.[18,19] To investigate the within-subject association between biweekly time intervals after stroke and observed improvements in strength (MI) and synergism (FM) of upper and lower limb,

TABLE 1. Biweekly Time Interval-Based Regression Coefficients for Recovery of Upper Limb Motor Function and Visuospatial Hemiinattention*

	N=101		
	MI–Arm (0 to 100)	FM–Arm‡ (0 to 66)	LC-Task (0 to 20)
Impact of time (biweekly assessments)	β value (β-error)	β value (β-error)	β value (β-error)
Adjusted time interval tested†			
Week 1 to 2 (n=97)	11.948 (1.178)‖	6.886 (0.710)‖	−1.740 (0.628)‖
Week 3 to 4 (n=98)	7.042 (1.050)‖	3.844 (0.589)‖	−0.652 (0.555)‖
Week 5 to 6 (n=97)	4.256 (1.064)‖	2.548 (0.597)‖	−1.354 (0.555)‖
Week 7 to 8 (n=94)	2.921 (1.050)‖	1.548 (0.589)‖	−0.474 (0.547)
Week 9 to 10 (n=92)	1.574 (1.088)	1.364 (0.601)§	−0.037 (0.558)
Week 11 to 12 (n=93)	0.168 (1.053)	0.793 (0.589)	−0.150 (0.546)
Week 13 to 14 (n=92)	0.164 (1.050)	0.240 (0.587)	0.226 (0.543)
Week 15 to 16 (n=89)	0.800 (1.050)	0.502 (0.587)	−0.699 (0.545)
Total units change in outcome (% of total) explained by time	26.2 units (≈26%)	16.2 units (≈25%)	3.2 units (≈16%)

Note: The negative β values for LC reflect reductions in omissions on the LC task.

*First 4 months poststroke shown only; †time intervals adjusted for age, gender, hemisphere, type of stroke, and type of intervention; ‡arm, wrist, and hand included; §$P<0.01$; ‖$P<0.001$; N indicates number of patients; n, number of complete data sets.
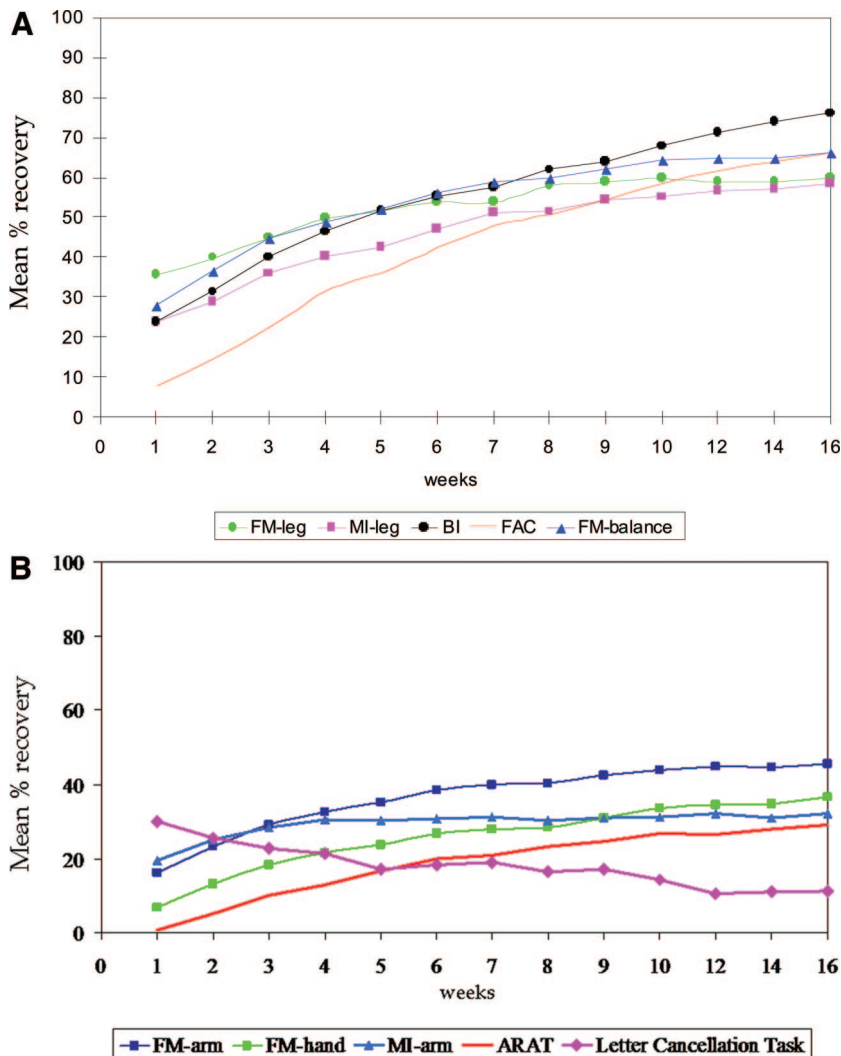
A, Mean standardized recovery patterns (percent of maximum attainable recovery) of the lower limb and ADLs as a function of time (n=101). B, Mean standardized recovery patterns of the upper limb as a function of time (n=101). Note: Reduction in LCT reflects the mean reduction in number of omissions in the cancellation of letters on the hemiplegic side.

FM-balance score, reductions in visual hemiinattention as well as recovery in FAC, ARAT, and BI, a first-order regression model for change was applied by taking the first derivative model d/dt (supplemental Appendix, available online at http://stroke.ahajournals.org).

To investigate the contribution of different time units on changes in outcome, time was categorized into eight dummy variables representing eight biweekly intervals starting from within the first 2 weeks up to 16 weeks poststroke. In addition, age, gender, hemisphere of stroke (left or right), type of stroke, and type of intervention (arm, leg, or immobilization) as well as higher-order interaction terms of the covariates with time were added to the model to investigate whether the significant regression coefficients for the eight derivatives changed as a result of these covariates by more than 10%. The likelihood ratio test was used to evaluate the necessity for allowing random regression coefficients into the model, whereas the Wald test was used to obtain a probability value for each regression coefficient.[18,19] For all tests, a 2-tailed significance level of 0.05 was used.

Results

Patient characteristics of all 101 stroke patients are presented in Table 1 of a previously published study in this journal.[11] None of the stroke patients participating in our study was able to walk unassisted during first week post-stroke onset. Mean recovery profiles for upper and lower limb motor scores (MI

arm and leg, FM arm), FM-balance, LCT, BI, ARAT, and FAC are illustrated in the Figure, A and B. On average, 752 (range=712 to 784) of the 808 change scores were available for modeling the first 16 weeks. All change scores were normally distributed based on visual plotting.

Random Coefficient Analysis

Tables 1 and 2 show the bivariate regression coefficients, their errors, and significance for the change scores of functional limitations of upper and lower limb as well as LCT. As shown, time intervals representing the first 8 (MI–arm) to 10 weeks (MI–leg, FM–arm, FM–leg) were significantly associated with change scores on the MI index and FM scores and time was significantly associated with reduced omissions on LCT for the first 6 weeks poststroke.

For the upper limb, ≈25% (FM–arm) to 26% (MI–arm) of significant change in measurements units was explained by the regression coefficients for time, whereas time explained 33% (FM–leg) to 39% (MI–leg) of change scores for the lower limb.

Table 3 illustrates the significant positive association of poststroke time intervals on improvement of BI, FAC, and ARAT. As shown, significant effects of time were found for

TABLE 2.   Biweekly Time Interval-Based Regression Coefficients for Recovery of Lower Limb Function and Balance Control for the First 4 months Poststroke

	N=101		
	MI–Leg (0 to 100)	FM–Leg (0 to 34)	FM–Balance (0 to 14)
Impact of time (biweekly assessments)	β value (β-error)	β value (β-error)	β value (β-error)
Adjusted time interval tested‡			
Week 1 to 2 (n=97)	17.509 (1.257)†	4.631 (0.389)†	2.410 (0.150)†
Week 3 to 4 (n=98)	7.063 (1.174)†	2.670 (0.335)†	0.957 (0.127)†
Week 5 to 6 (n=97)	6.447 (1.195)†	1.569 (0.340)†	0.756 (0.129)†
Week 7 to 8 (n=94)	4.988 (1.178)†	1.333 (0.335)†	0.334 (0.127)†
Week 9 to 10 (n=92)	3.919 (1.217)†	0.901 (0.348)*	0.252 (0.131)*
Week 11 to 12 (n=93)	1.304 (1.178)	0.098 (0.335)	0.091 (0.128)
Week 13 to 14 (n=92)	1.002 (1.174)	0.653 (0.334)	−0.003 (0.127)
Week 15 to 16 (n=89)	2.100 (1.178)	0.148 (0.334)	−0.034 (0.127)
Total units change in outcome (% of total) explained by time	39.4 units (≈39%)	11.1 units (≈33%)	4.7 units (≈34%)

*P<0.01; †P<0.001; ‡time intervals adjusted for age, gender, hemisphere, type of stroke and type of intervention; N indicates number of patients; n, number of complete data sets.

the first 10 weeks poststroke explaining ≈8.4 (42%) measurement units of change on the BI, whereas time was significantly associated with improvement on the FAC and ARAT for the first 6 to 8 weeks poststroke. Both time-dependent changes were responsible for 22% and 19% improvement in measurement units on FAC and ARAT, respectively.

Inclusion of the covariates age, gender, hemisphere, type of stroke according to the Bamford classification, or type of intervention did not alter the regression coefficients by more than 10% of our a priori threshold, and therefore these covariates were considered not to have a confounding effect.

Discussion

This is the first study that statistically establishes the impact of progress of time on observed improvements of body functions and activities poststroke in a repeated measurement design. The present study shows that at least 16% of the improvements in body functions and activities observed can be explained by time alone. This finding was not affected by the inclusion of other variables into the derived models such as age, gender, type or hemisphere of stroke. In addition, the first-order regression models show that the biweekly contribution of time on outcome of strength, synergism, dexterity, walking ability, and ADLs is larger in the first weeks than later on poststroke. This finding is in agreement with the general perception that the recovery after stroke displays a nonlinear, logarithmic pattern,[4] ie, the largest improvements are observed early after stroke onset and these changes subsequently gradually level off.[2,5–7,9]

The observed duration of 6 to 10 weeks, during which the process of spontaneous recovery is almost completed, is in agreement with observations of a number of other prospective

TABLE 3.   Biweekly Time Interval-Based Regression Coefficients for Recovery of BI, FAC, and ARAT for the First 4 Months Poststroke

	N=101		
	BI (0 to 20)	FAC (0 to 5)	ARAT (0 to 57)
Impact of time (biweekly assessments)	β value (β-error)	β value (β-error)	β value (β-error)
Adjusted time interval poststroke‡			
Week 1 to 2 (n=97)	3.229 (0.295)†	0.367 (0.088)†	3.779 (0.747)†
Week 3 to 4 (n=98)	2.099 (0.253)†	0.432 (0.082)†	3.180 (0.665)†
Week 5 to 6 (n=97)	1.000 (0.254)†	0.301 (0.083)†	1.953 (0.670)†
Week 7 to 8 (n=94)	0.965 (0.253)†	0.079 (0.082)	1.648 (0.665)*
Week 9 to 10 (n=92)	1.161 (0.253)†	0.158 (0.084)	0.810 (0.677)
Week 11 to 12 (n=93)	0.305 (0.251)	−0.111 (0.082)	0.434 (0.659)
Week 13 to 14 (n=92)	0.180 (0.251)	−0.098 (0.082)	0.218 (0.658)
Week 15 to 16 (n=89)	0.140 (0.251)	−0.121 (0.082)	0.139 (0.658)
Total units change in outcome (% of total) explained by time	8.4 units (≈42%)	1.1 units (≈22%)	11 units (≈19%)

*P<0.01; †P<0.001; ‡time intervals adjusted for age, gender, hemisphere, type of stroke, and type of intervention; N indicates number of patients; n, number of complete data sets.

cohort studies.[2,5–7,9] For example, Duncan and colleagues showed that between 4 and 12 weeks after stroke onset, recovery of motor function and ADLs assessed with the FM motor score and BI levels off.[6,7] Confirming their findings, observed recovery profiles in our study did highly parallel each other and no evidence was found for the clinical tenet that the recovery of the upper limb evolves less rapidly than recovery of the lower limb.[7]

In particular, the understanding that time-dependent change is a reflection of intrinsic, spontaneous recovery after stroke onset has important clinical implications. Knowledge about the extent and duration of spontaneous recovery allows clinicians to predict outcome early after stroke, enabling realistic and attainable treatment goals to be set and proper discharge planning to take place. For example, the present study shows that adding ≈8 points to the baseline BI at the end of the first week poststroke will produce a realistic estimate for the expected outcome at 12 weeks poststroke. Knowledge about the time window during which spontaneous return may be expected allows therapists to focus their therapy on either restoring existing deficits or on using adaptation strategies to achieve their functional goals.[2] Finally, the study further emphasizes the necessity for conducting appropriate randomization procedures when studying early applied therapeutic interventions poststroke and confirms the general rule that stroke outcome data should be only reported when the observations of experimental and control groups are made at the same time interval after stroke onset.[4,20]

In particular, acknowledging that recovery profiles may extend far beyond the first 3 months poststroke,[1] the present study also suggests that the observed progress in functional outcome after 3 months is strongly dependent on learning adaptation strategies to acquire certain functional tasks such as gait and ADLs.[2] The challenge will be to explore the longitudinal relationship between kinematic and neurophysiological adaptations as well as any gains in motor performance and skill acquisition. In this way, it becomes possible to investigate the way during which changes in motor control, generated by restitution and substitution of function, coincide with functional improvements. For example, we showed recently in a comparable longitudinal first-order regression model that recovery of independent gait is highly dependent on improvements in control of standing balance poststroke.[11]

Unfortunately, the present study has some limitations. First, we hypothesized that time contributes to the improvement of body functions and activities after stroke and affects the extent of spontaneous recovery. Our assumption precludes ruling out enhancement of early poststroke recovery as a result of possible interactions with therapies and differences in environment cannot be ruled out, suggesting that a "true" natural recovery pattern does not exist. In other words, the inability to study stroke recovery in a real naturalistic setting suggests that the observed time-dependent changes reflect progress over time (given variability in intervention modality, intensity, duration, environment) rather than spontaneous, intrinsic recovery alone. This suggests that the regression model is likely to overestimate the unique contribution of time to recovery in the event such an enhancement takes place. In addition, we found that age, gender, side, and type of stroke according to the Bamford classification did not affect the generated regression coefficients for the biweekly time intervals on outcome of BI, FAC, or ARAT. Second, the number of time-dependent categories investigated was restricted to the first 16 weeks poststroke. Although measurements were continued after this timeframe, the number of patients available for further modeling was too small to allow the use of more categories for time. However, we suggest that there is no evidence that extending the biweekly intervals beyond 16 weeks would add to the predictive value following the asymptotic trends of the curves in Figure, A and B.

Third, given the selection criteria and interventions administered to study participants, generalization of observed recovery patterns is limited. Fourth, we were not able to rule out possible ceiling effects of applied measurements. One may hypothesize that the gradual smaller change scores, as a function of time, are the result of a reduced range available for changes. However, the largest spontaneous improvements were found for those measurements that are known to have ceiling effects (BI and FM leg score). This finding rather suggests that modeling change scores is not affected by the scaling properties of measurements selected. Finally, we were not able to investigate the spontaneous intrinsic cerebral recovery by measuring changes in neurotransmission of spared tissue adjacent and remote to the infarcted area directly. Therefore, the establishment of a causal relationship between cerebral physiological changes on the one hand and observed improvements in neurologic functions and activities on the other hand remains inconclusive in the present study. In our opinion, future studies should identify markers that represent cerebral mechanisms of intrinsic, spontaneous recovery[1] and subsequently associate these changes as a function of time with observed patterns of neurologic and functional recovery after stroke onset. In particular, understanding the mechanisms behind this process of time-dependent spontaneous return of body functions and activities may facilitate the development of treatment programs that are more effective in maximizing the biologic drivers of neurologic recovery.

Sources of Funding

Disclosures

None.

References

1. Dobkin BH. Clinical practice. Rehabilitation after stroke. *N Engl J Med.* 2005;21:352:1677–1684.
2. Kwakkel G, Kollen B, Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. *Restor Neurol Neurosci.* 2004;22:281–299.
3. Newman M. The process of recovery after hemiplegia. *Stroke.* 1972;3: 702–710.
4. Gresham GE. Stroke outcome research. *Stroke.* 1986;17:358–362.
5. Skilbeck CE, Wade DT, Hewer RL, Wood VA. Recovery after stroke. *J Neurol Neurosurg Psychiatry.* 1983;46:5–8.

6. 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.

7. Duncan PW, Goldstein LB, Horner RD, Landsman PB, Samsa GP, Matchar DB. Similar motor recovery of upper and lower extremities after stroke. *Stroke*. 1994;25:1181–1188.

8. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. 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.

9. Jorgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Stoier M, Olsen TS. Outcome and time course of recovery in stroke. Part II: time course of recovery. The Copenhagen Stroke Study. *Arch Phys Med Rehabil*. 1995;76:406–412.

10. Kwakkel G, Wagenaar RC, Twisk JW, Lankhorst GJ, Koetsier JC. Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial. *Lancet*. 1999;354:191–196.

11. Kollen B, van de Port I, Lindeman E, Twisk J, Kwakkel G. Predicting improvement in gait after stroke. A longitudinal prospective study. *Stroke*. 2005;36:2676–2680.

12. Collen FM, Wade DT, Bradshaw CM. Mobility after stroke: reliability of measures of impairment and disability. *Int Disabil Stud*. 1990;12:6–9.

13. Duncan PW, Propst M, Nelson SG. Reliability of the Fugl-Meyer assessment of sensorimotor recovery following cerebrovascular accident. *Phys Ther*. 1983;63:1607–1610.

14. Holden MK, Gill KM, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. *Phys Ther*. 1984;64:35–40.

15. Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. *Int J Rehabil Res*. 1981;4:483–492.

16. van der Lee JH, Roorda LD, Beckerman H, Lankhorst GJ, Bouter LM. Improving the Action Research Arm test: a unidimensional hierarchical scale. *Clin Rehabil*. 2002;16:646–653.

17. Bamford J. Clinical examination in diagnosis and subclassification of stroke. *Lancet*. 1992;339:400–402.

18. Goldstein H, Browne W, Rasbash J. Multilevel modelling of medical data. *Stat Med*. 2002;21:3291–3315.

19. Twisk JWR. *Applied Longitudinal Data Analysis for Epidemiology*. Cambridge University Press; 2003.

20. Duncan PW, Lai SM, Keighley J. Defining post-stroke recovery: implications for design and interpretation of drug trials. *Neuropharmacology*. 2000;39:835–841.