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Predicting Improvement in Gait After Stroke
A Longitudinal Prospective Study

Boudewijn Kollen; Ingrid van de Port, MS; Eline Lindeman, MD, PhD; Jos Twisk, PhD; Gert Kwakkel, PhD

Background and Purpose—To study the longitudinal relationship of functional change in walking ability and change in time-dependent covariates and to develop a multivariate regression model to predict longitudinal change of walking ability.

Methods—A total of 101 acute stroke patients with first-ever ischemic middle cerebral artery strokes was used as the population. Prospective cohort study based on 18 repeated measurements over time during the first poststroke year. Baseline characteristics as well as longitudinal information from functional ambulation categories (FAC), Fugl–Meyer leg score (FM-leg), Motricity index leg score (MI-leg), letter cancellation task (LCT), Fugl-Meyer balance (FM-balance), and timed balance test (TBT) were obtained. Intervention consisted of a basic rehabilitation program with additional arm, leg, or air splint therapy. Main outcome measure constituted change scores on FAC over time.

Results—In total, 1532 of the 1717 change scores were available for regression analysis. The regression model showed that TBT change scores were the most important factor in predicting improvement on FAC \((\beta=0.094; P<0.001)\) followed by changes scores on FM-leg \((\beta=0.014; P<0.001)\) and reduction in LCT omissions \((\beta=-0.010; P<0.001)\) and MI leg test \((\beta=0.001; P<0.001)\). In addition, time itself was significantly negatively associated with improvement \((\beta=-0.002; P<0.001)\).

Conclusion—Improvement in standing balance control is more important than improvement in leg strength or synergism to achieve improvement in walking ability, whereas reduction in visuospatial inattention is independently related to improvement of gait. Finally, time itself is an independent covariate that is negatively associated with change on FAC, suggesting that most pronounced improvements occur earlier after stroke. (Stroke. 2005;36:2676-2680.)

Key Words: cerebrovascular accident ■ gait ■ longitudinal studies ■ prognosis ■ recovery of function

In the last 2 decades, there is growing interest in conducting longitudinal studies after stroke.\(^{1-4}\) In these studies, the variables of interest are measured on the same individuals at several mostly fixed occasions. Findings from longitudinal studies with repeated measurements over time indicate that recovery of neurological impairments and disabilities show nonlinear recovery patterns over time.\(^{3-5}\) According to Gre-sham, time itself appears to be one of the most important, although neglected, factors in our understanding of functional recovery after stroke.\(^{6}\) To date, no study has been published that investigated the longitudinal time-dependent relationship between recovery of impairments, such as strength, synergism, visuospatial inattention, and recovery of disabilities such as gait after stroke. As a consequence, the impact of these changes as a function of time on regaining independent gait after stroke is not well understood. Moreover, knowledge about the relationship between specific impairments and limitations, such as balance control, would be useful in selecting optimal treatment strategies for improving gait after stroke.

Within the last 2 decades, new statistical techniques such as random coefficient modeling (multilevel modeling or hierarchical modeling) have been developed that correct for the dependency of repeated measurements within each individual.\(^{7-9}\) The use of this technique allows for analysis of the cross-sectional and longitudinal relationship between covariates simultaneously while taking the dependency of repeated measurements of individuals into account.\(^9\) In standard multilevel hierarchical regression modeling, the regression coefficients presented collectively reflect the cross-sectional (ie, so-called between-subjects variation) as well as the longitudinal relationship (ie, so-called within-subject variation) between determinant(s) and outcome. This constitutes a limitation in the event the absolute differences between subjects exceed the changes over time. Consequently, the longitudinal within-subject relationships will be more or less overruled by...
the cross-sectional relationships. This is likely to occur in particular when the time periods between repeated measure-
ments are relatively short and the within-subject correlation high, which is often the case in stroke. Because of this
limitation, we elected to use a model in which the cross-
sectional component is more or less “removed” from the
analysis by modeling only change scores. By modeling
longitudinal change scores, one can develop a rationale for
the impact of improvements of underlying functions, such as
strength, synergism, and balance control on changes in
walking ability (ie, quasi-causal relationships).

In the present study, we initially investigated the bivariate
longitudinal relationship of improvements in walking ability
and patient characteristics at baseline and improvements in
impairments and functional limitations during the first year
after stroke using the following time-dependent covariates:
leg strength, leg synergism, visual hemi-inattention, and
balance control. Subsequently, we developed a multivariate
multilevel regression model for the prediction of functional
improvements in gait as a function of time.

Materials and Methods
Design and Procedures
This prospective cohort study was part of a randomized clinical trial
conducted to study the effects of intensity of rehabilitation on stroke
outcome. In this study, 101 stroke patients participated with a mean
age of 65 years (SD 12.0). Patients were included when they met the
following criteria: (1) they were between 30 and 80 years of age; (2)
they experienced an ischemic, first-ever stroke involving the territory
of the middle or anterior cerebral artery as revealed by computed
tomography or MRI scan; (3) they displayed inability to walk at first
assessment; (4) they revealed no complicating medical history such as
cardiac, pulmonary, or orthopedic disorders; (5) they had no severe
deficits in communication, (6) they had no severe deficits in
memory and understanding, and (7) they had provided written or
verbal informed consent and demonstrated sufficient motivation to
participate. Details about design and outcome are published previously.

Measurements
To investigate the longitudinal impact of recovery from impairments
on gait, we modeled first-order change scores from 18 repeated
measurements of different impairments to fit the change scores
observed in walking ability. All time-dependent measurements
were taken weekly, starting from within 14 days after stroke onset. From
week 10 to week 20, biweekly measurements were obtained, whereas
follow-up measurements were performed at 26, 38, and 52 weeks
after stroke. All assessments were done by 1 observer (G.K) who was
blinded for treatment assignment. Walking ability was assessed with the
functional ambulation categories (FAC). The FAC is a reliable and
valid assessment comprising of 6 categories designed to provide
information on the level of physical support needed by patients to
ambulate. Walking devices were allowed to be used during the
measurements with the exception of a rollator or walker. Age,
gender, hemisphere of stroke, and social support were used as
time-independent covariates and severity of paresis, stage of syner-
gism, control for standing balance, and severity of visuospatial
inattention as time-dependent covariates in the multilevel
regression model.

Motricity index (MI) was used to measure strength in upper and
lower extremities. This instrument reliably assesses the presence of
a paresis in stroke patients. It uses a weighted score to a maximum
of 100 points for each extremity and is derived from the Medical
Research Council grades. It tests 6 limb movements. Balance was
measured with the timed balance test (TBT). This instrument
consists of 5 components on an ordinal scale and involves timed
balance (ie, 60 seconds) on progressively diminishing support
surfaces. The Fugl–Meyer evaluation was used to assess motor
performance. The motor section of this extensive test consists of
upper limb, wrist, hand, as well as lower limb ordinal scaled
components. Basically, it grades the degree to which dependence on
synergic movements is present. Finally, the letter cancellation task
(LCT) was applied to demonstrate the presence of neglect. Patients
are requested to cross certain letters among many letters of the
alphabet on a sheet of paper containing 5 lines of letters (34 per line).
The difference in the number of crossed letters on the parietic and
nonparietic side is scored.

Statistical Analysis
The random coefficient analysis was performed with MLwiN. The
iterative generalized least-squares algorithm was used to estimate the
regression coefficients. Before conducting the random coefficient
analysis, we calculated the change between subsequent measure-
ments of the time-dependent covariates. These change scores were
then plotted to check for compliance with model assumptions.
Because time constitutes an independent covariate, random coeffi-
cient analysis enables longitudinal analysis of unequally spaced time
points of measurement.

To investigate the possible longitudinal association between walk-
ing ability on FAC and covariates, initially bivaria longitudinal
regression analysis was conducted with FAC change scores and
time-independent covariates at baseline, such as age, gender, and
lateralization of stroke, as well as with t = 1 change scores of the
time-dependent covariates MI-leg, Fugl–Meyer leg score (FM-leg),
Fugl-Meyer balance (FM-balance), TBT, and LCT (see Appendix,
models 1 and 2). Subsequently, standardized regression coefficients
were calculated, and a multivariate regression model for predicting
functional recovery of gait based on FAC scores was developed (see
Appendix, model 3).

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 P value for a particular regression
coefficient. 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. None of the stroke patients participating in our
study were able to walk unassisted during the first week after
stroke onset. Mean recovery profiles for MI leg, FM-leg,
FM-balance, LCT, and TBT for all 18 measurements are
illustrated in the Figure. In total, 1530 of the 1717 change
scores were available for modeling. All change scores were
normally distributed based on visual plotting.

Bivariate Random Coefficient Analysis of
Change Scores
Table 2 shows the bivariate regression coefficients, their
errors, and significance for time-independent covariates and
change scores of time-dependent covariates. Except for age
(P=0.046) none of the time-independent covariates was
significantly associated with the change scores of FAC. However,
all time-dependent covariates were statistically
significantly associated with the change scores on FAC. The
highest regression coefficient was observed for improve-
ments on the TBT followed by the FM-balance, FM-leg,
LCT, time, and MI-leg. Time after onset and LCT showed to
be negatively associated with change on FAC.

Multivariate Random Coefficient Modeling of
Significant Time-Dependent Covariates
Table 3 presents the significant covariates of the multivariate
random coefficient model. This model includes change scores
of the covariates TBT, FM-leg, LCT, MI leg, as well as time itself. This model predicted 18% of the variance of outcome on change of FAC.

Discussion
To the best of our knowledge, this is the first longitudinal study that investigated the functional impact of observed changes of time-dependent covariates such as balance, synergism, leg strength, visuospatial inattention, and time on the recovery of gait after acute stroke. The significant bivariate random coefficients found in the present study confirm the assumption that larger improvements in impairments and gait-related functional limitations, including control of standing balance, are highly associated with improvements in gait. The present study further shows that improvement in standing balance, as measured with the TBT test or FM-balance test, is the most important determinant for regaining gait based on the FAC, whereas changes in synergism and muscle strength of the paretic leg are less associated with recovery of walking ability. This finding is in agreement with the literature suggesting that recovery in postural control of standing is more important for regaining gait than the restoration of support functions and voluntary control of the paretic leg itself. This finding also suggests that the use of compensatory strategies in the standing position (eg, shifting the weight to the nonparetic side) is more important than muscle strength in the lower paretic limb for regaining gait.

Interestingly, the present findings also show that visuospatial inattention was weakly but significantly and negatively related to recovery of gait, suggesting that more reductions in visuospatial inattention, as expressed by the difference in the number of omissions in the LCT, are associated with better improvements in gait. This latter finding is in agreement with the studies that show that patients with visuospatial neglect experience more difficulty in negotiating obstacles and walking appropriate trajectories than controls. Finally, time itself is an independent fixed determinant in the multivariate model that is significantly negatively associated with recovery of gait, suggesting that most improvements take place sooner after stroke. This finding is in agreement with the general assumption about the speed of neurological (and with that, functional) recovery after stroke (ie, the largest improvements are observed early after stroke onset and these changes subsequently gradually level off). However, in part, gradual smaller change scores over time may have been the result of the availability of a reduced range for changes (ceiling effect).

The major advantage of a repeated measurement design compared with a traditional prognostic design is that it represents reality far better than just 2 measurements over time. Instead of observing 2 images of the patients’ functional

TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>101</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>43/58</td>
</tr>
<tr>
<td>Age, years (±SD)</td>
<td>65.4 (10.5)</td>
</tr>
<tr>
<td>MMSE (±SD)</td>
<td>26.4 (2.5)</td>
</tr>
<tr>
<td>Hemispheric of stroke (left/right)</td>
<td>41/61</td>
</tr>
<tr>
<td>Type of stroke (OCSP)</td>
<td></td>
</tr>
<tr>
<td>TACI</td>
<td>55</td>
</tr>
<tr>
<td>PACI</td>
<td>33</td>
</tr>
<tr>
<td>LACI</td>
<td>14</td>
</tr>
<tr>
<td>OPS (±SD)</td>
<td>4.4 (0.8)</td>
</tr>
<tr>
<td>GCS (±SD)</td>
<td>14.8 (0.8)</td>
</tr>
<tr>
<td>Cognitive disturbances (%)</td>
<td></td>
</tr>
<tr>
<td>Aphasia (0/1)†</td>
<td>27.5</td>
</tr>
<tr>
<td>Inattention (0/1)</td>
<td>49.0</td>
</tr>
<tr>
<td>Impairments of vision (%)</td>
<td></td>
</tr>
<tr>
<td>Hemianopia (0/1)</td>
<td>31.4</td>
</tr>
<tr>
<td>Visual gaze deficit (0/1)</td>
<td>23.5</td>
</tr>
<tr>
<td>Days between stroke onset and first assessment (±SD)</td>
<td>7.3 (2.8)</td>
</tr>
<tr>
<td>MI-arm (±SD)</td>
<td>13.5 (23.3)</td>
</tr>
<tr>
<td>MI-leg (±SD)</td>
<td>21.7 (24.4)</td>
</tr>
<tr>
<td>Sitting balance (0/1)</td>
<td>26/76</td>
</tr>
<tr>
<td>BI (%) (±SD)</td>
<td>28.5 (17.2)</td>
</tr>
<tr>
<td>FAC score (±SD)</td>
<td>0.8 (1.0)</td>
</tr>
<tr>
<td>ARA score (±SD)</td>
<td>3.9 (9.7)</td>
</tr>
<tr>
<td>Risk factors (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension (160/95) (0/1)</td>
<td>45.1</td>
</tr>
<tr>
<td>Smoking habit (0/1)</td>
<td>36.3</td>
</tr>
<tr>
<td>Family hereditary (0/1)</td>
<td>31.3</td>
</tr>
<tr>
<td>Cardiac disease (0/1)</td>
<td>28.4</td>
</tr>
<tr>
<td>Diabetes mellitus (0/1)</td>
<td>14.7</td>
</tr>
<tr>
<td>Hyperlipidemia (0/1)</td>
<td>9.8</td>
</tr>
</tbody>
</table>

†Based on the Dutch Foundation Aphasia test (ie, SAN).
To understand the impact of time after stroke on recovery, future research should focus on the impact of individual neurological changes of impairments on functional recovery and the significance of using compensatory strategies to improve gait.3,14,20,23 This information can than be used to determine the relationship between recovery of impairments and disabilities, such as gait.1 Recovery of disabilities reflects the intrinsic recovery of impairments as well as applied compensation.3 Understanding the different mechanisms involved as well as the optimal time windows for functional recovery allows clinicians to develop treatment programs that are more effective in maximizing underlying mechanisms responsible for neurological and adaptive (ie, compensatory) recovery.3,5,24

The relatively low regression coefficients observed for the covariates and the low explained variance of ≈18% for included determinants suggest that most progress cannot be explained by restitution of function. Most likely this progress is facilitated by the use of compensation strategies that involve the participation and adaptation of the nonparetic side to enable gait. This latter finding suggests that recovery after stroke occurs to a large extent through behavioral compensation rather than via processes of “true recovery” alone.5 Future studies may explore the relationship between observed behavioral adaptations and improved skills after stroke by addressing the issue of which changes in motor control coincide with functional improvements. This knowledge may contribute to determining the best way to subject stroke patients to therapeutic exercises.

Finally, modeling change scores in a repeated measurement design (whereby the measures are nested within the subjects) offers also opportunities for the exploration of the longitudinal relationship between, on the one hand, macroscopic neuroplastic changes observed (eg, functional MRI and TMS), and, on the other hand, found changes in neurological and kinematical examination.

### Appendix

For the bivariate longitudinal regression analysis of time-dependent variables, we used the following regression model: (\(Y_{it} - \bar{Y}_{it}\)) = \(\beta_0 + \sum \Delta \beta_j (X_{ij} - \bar{X}_{ij}) + \epsilon_i (model 1)\), where \(Y_i\) are the observations for subject \(i\) at time \(t\) and \(Y_{it}\) the observations for subject \(i\) at time \(t−1\), reflecting the change score for the dependent variable “walking

![Image](https://via.placeholder.com/150)

**TABLE 2.** Bivariate Regression Coefficients With Random and Fixed Slopes (standard errors (SEs) in parenthesis) for Time-Independent and Time-Dependent Covariates for Recovery of Gait During the First Year After Stroke

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Fixed Slope</th>
<th>Random Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>Fixed Slope</td>
<td></td>
</tr>
<tr>
<td>Age (range 30–80 years)</td>
<td>–0.002 (0.001)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hemisphere of stroke (left/right)</td>
<td>–0.006 (0.025)</td>
<td>0.60</td>
</tr>
<tr>
<td>Type of stroke (OCS)</td>
<td>–0.023 (0.020)</td>
<td>0.25</td>
</tr>
<tr>
<td>Days between stroke onset and first assessment</td>
<td>–0.002 (0.004)</td>
<td>0.62</td>
</tr>
<tr>
<td>MMSE</td>
<td>0.008 (0.005)</td>
<td>0.11</td>
</tr>
<tr>
<td>Visual gaze deficit (0/1)</td>
<td>–0.011 (0.029)</td>
<td>0.70</td>
</tr>
<tr>
<td>Homonymous hemianopia (0/1)</td>
<td>–0.018 (0.027)</td>
<td>0.51</td>
</tr>
<tr>
<td>Baseline visual inattention (0/1)</td>
<td>–0.027 (0.025)</td>
<td>0.28</td>
</tr>
<tr>
<td>Baseline TFT score (0–3)</td>
<td>–0.014 (0.013)</td>
<td>0.28</td>
</tr>
<tr>
<td>Baseline OPS (1.6–6.8)</td>
<td>0.013 (0.013)</td>
<td>0.32</td>
</tr>
<tr>
<td>Baseline sitting balance (O/1)</td>
<td>0.050 (0.028)</td>
<td>0.07</td>
</tr>
<tr>
<td>Urinary incontinence (0/1)</td>
<td>–0.013 (0.025)</td>
<td>0.60</td>
</tr>
<tr>
<td>Baseline MI-leg</td>
<td>0.000 (0.000)</td>
<td>–0</td>
</tr>
<tr>
<td>Baseline FM-leg</td>
<td>0.001 (0.002)</td>
<td>0.62</td>
</tr>
<tr>
<td>Baseline TCT</td>
<td>0.001 (0.000)</td>
<td>0.32</td>
</tr>
<tr>
<td>Baseline FM-balance</td>
<td>0.008 (0.005)</td>
<td>0.11</td>
</tr>
<tr>
<td>Baseline TBT</td>
<td>0.007 (0.015)</td>
<td>0.64</td>
</tr>
<tr>
<td>Baseline FAC</td>
<td>0.007 (0.013)</td>
<td>0.59</td>
</tr>
<tr>
<td>Baseline Barthel index</td>
<td>0.004 (0.003)</td>
<td>0.18</td>
</tr>
<tr>
<td>Social support (0/1)</td>
<td>–0.021 (0.026)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time-dependent Covariates</th>
<th>Fixed Slope</th>
<th>Random Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\Delta)MI-leg</td>
<td>0.014 (0.002)</td>
<td>0.00***</td>
</tr>
<tr>
<td>(\Delta)FM-leg</td>
<td>0.053 (0.005)</td>
<td>0.00***</td>
</tr>
<tr>
<td>(\Delta)FM-balance</td>
<td>0.091 (0.015)</td>
<td>0.00***</td>
</tr>
<tr>
<td>(\Delta)LCT</td>
<td>–0.025 (0.007)</td>
<td>0.00***</td>
</tr>
<tr>
<td>(\Delta)TBT</td>
<td>0.116 (0.019)</td>
<td>0.00***</td>
</tr>
<tr>
<td>Time of measurement after stroke</td>
<td>–0.018 (0.003)</td>
<td>0.00***</td>
</tr>
</tbody>
</table>

(0/1) indicates no/yes; \(\Delta\), change score of 1 time lag (ie, from \(t\) to \(t−1\)); \(n\), No. of patients; \(\beta\) value, regression coefficient; OCS, Oxford Community Stroke Project; MMSE, mini-mental state examination (range 23–30); TFT, thumb finding test (range 0–3); OPS, Orpington prognostic score (range 1.6–6.8); LCT, letter cancellation task (range 0–20); TBT, timed balance test.

status frozen in time, it becomes feasible to analyze several closely sequential images over time, providing insight into the dynamics of recovery. This, in turn, allows for a more valid interpretation of the factors that modulate the process of spontaneous neurological recovery.

More research is needed for the development of prognostic models based on the within-subject variability of covariates as a function of time for the accuracy of functional change.
ability” based on FAC registration. Regression coefficient $\beta_{0m}$ reflects the random intercept and $\beta_{ij}$ the random selected regression coefficient for the time-dependent covariate $j$ and $X_{ij}$ the time-dependent variable $j$ for subject $I$ at time $t$ and $X_{i(t-1)}$ at time $t-1$.

For the bivariate longitudinal regression analysis of time-independent variables, we used the following model: $(Y_{it} - Y_{i(t-1)}) = \beta_{0m} + \Sigma \beta_{im} X_{im} + \epsilon_{it}$ (model 2), where $Y_{i}$ are the observations for subject $I$ at time $t$ and $Y_{i(t-1)}$ the observations for subject $I$ at time $t-1$. reflecting the change score for the dependent variable “walking ability” measured with the FAC. Regression coefficient $\beta_{0m}$ is a random intercept and $\beta_{im}$ the regression coefficient of the time-independent covariate $m$ and $X_{im}$ the time-independent covariate for subject $I$. $\epsilon_{it}$ represents the error for subject $I$ at time $t$.

To develop a multivariate regression model for predicting functional recovery of gait based on FAC scores, the following statistical model was used: $(Y_{it} - Y_{i(t-1)}) = \beta_{0m} + \Sigma \beta_{im} (X_{im} - X_{i(t-1)m}) + \beta_{1t} + \Sigma \beta_{in} X_{in} + \epsilon_{it}$ (model 3), where $Y_{i}$ are the observations for subject $I$ at time $t$ and $Y_{i(t-1)}$ the observations for subject $I$ at time $t-1$. reflecting the change scores for the dependent variable “walking ability” measured with the FAC. Regression coefficient $\beta_{0m}$ is a random intercept and $\beta_{ij}$ the random selected regression coefficient for time-dependent variable $j$ and $X_{ij}$ the time-dependent variable $j$ for subject $I$ at time $t$ and $X_{i(t-1)j}$ at time $t-1$. $\beta_{1j}$ is the regression coefficient for time $t$ and $\beta_{in}$ the regression coefficient for time-independent covariate $m$ and $X_{in}$ the time-independent covariate. Finally, $\epsilon_{it}$ represents the error for subject $I$ at time $t$.

**Acknowledgments**

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**References**