

# Rate, degree, and predictors of recovery from disability following ischemic stroke

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**ABSTRACT Objective:** To determine the rate, degree, and predictors of recovery from disabling ischemic stroke. **Methods:** Patients with ischemic stroke enrolled in the Management of Atherothrombosis With Clopidogrel in High-Risk Patients (MATCH) study underwent long-term prospective assessment of their modified Rankin Scale (mRS) score. Disability (functionally dependent state) was defined as mRS  $\geq$  3, and recovery (functionally independent state) was defined as mRS  $<$  3. The timing and the independent predictors of recovery were determined using a Cox proportional hazards multiple regression analysis. **Results:** Of 7,599 patients enrolled with ischemic stroke or TIA, 1,662 (21.8%) were disabled (mRS  $\geq$  3) at baseline (median of 14 [0 to 96] days after stroke onset). Disability was moderate (mRS 3) in 931 (56%) patients, severe (mRS 4) in 691 (42%), and very severe (mRS 5) in 40 (2%). By 18 months, 877 (52.8%, 95% CI 50% to 55%) patients had recovered, 589 (63%, 60% to 66%) with moderate disability, 281 (41%, 37% to 44%) with severe disability, and 7 (17%, 7 to 33%) with very severe disability. Median time to recovery was 3 months for patients with moderate disability and 18 months for severe disability; 82.5% of severely disabled patients remained so at 18 months. Predictors of recovery were moderate disability (mRS 3) at baseline compared with severe (mRS 4: hazard ratio [HR] 2.13, 1.86 to 2.44) or very severe disabling stroke (HR 5.88, 2.86 to 12.5); younger women (aged  $<$ 65 years, compared with  $\geq$ 75 years; HR 1.85, 1.47 to 2.33); decreasing time (days) between the qualifying event and the baseline assessment (HR 1.01, 1.01 to 1.02); and the absence of previous ischemic stroke (HR 1.61, 1.35 to 1.92), concurrent peripheral artery disease (HR 1.61, 1.23 to 2.13), or diabetes (HR 1.30, 1.10 to 1.54). **Conclusions:** Half of patients with disabling ischemic stroke recovered within 18 months, and recovery was greatest within 6 months. Significant predictors of recovery included the severity of the index stroke and no history of ischemic stroke, peripheral artery disease, or diabetes. **NEUROLOGY 2007;68:1583-1587**

After an ischemic stroke, patients (and their care planners) want to know whether they will recover from their neurologic deficit and, if so, when and by how much. It is known that most patients show some recovery of neurologic function within the first 3 months, and that between 3 months and 10 years after stroke, approximately 40% to 60% of all stroke patients regain functional independence (table E-1 on the *Neurology* Web site at [www.neurology.org](http://www.neurology.org)), as defined by a modified Rankin Scale (mRS) score of 0 to 2.<sup>1-9</sup> However, the rate of recovery and the prognostic factors that influence recovery are not well characterized. In one of the few studies to examine change in mRS over time, 58% of patients disabled by stroke (mRS 3 to 5) improved at least one grade in their mRS by 3 months after stroke.<sup>6</sup> Furthermore, 35% of disabled patients had regained functional independence (mRS  $<$  3) at this time point. Differences were seen in the proportion of patients recovering according to their initial degree of disability, but patients were not followed up regularly beyond 3 months, and no information was collected on factors associated with transition toward recovery. Prognostic factors that have been reported to be associated with dependency after acute stroke include age, dementia, stroke severity, and heart failure.<sup>9</sup>

In this study, we sought to determine the rate, degree, and predictors of recovery to a

Supplemental data  
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nondisabled state (mRS < 3) over the first 18 months after a disabling (mRS ≥ 3) ischemic stroke.

**METHODS Study design.** This was a prospective, observational, prognostic study of a cohort of patients who were enrolled in the Management of Atherothrombosis With Clopidogrel in High-Risk Patients (MATCH) study and who were functionally disabled (mRS ≥ 3) at the time of their baseline assessment. The overall design and clinical findings of the MATCH study have been reported previously.<sup>10,11</sup> Briefly, it was a randomized, double-blind, placebo-controlled trial to compare aspirin (75 mg/day) with placebo in 7,599 high-risk patients with recent ischemic stroke (n = 5,994) or TIA (n = 1,605) and at least one additional vascular risk factor who were already receiving clopidogrel 75 mg/day.

After the baseline assessment, patients were reassessed at 1, 3, 6, 12, and 18 months. The assessment included an estimate of the mRS grade, accommodating language disorders and cognitive defects compared with the original Rankin Scale.<sup>12,13</sup> Assessments were performed by trained research nurses in face-to-face interviews. If a patient was unable to complete the interview because of dementia or aphasia, a proxy interview was sought from the best available informant, usually the next of kin or, if necessary, a professional carer.

For the purposes of this study, patients randomly assigned placebo and aspirin were combined into a single cohort. Patients who had a Rankin score of 0 to 2 were classified as nondisabled, whereas those with a score of 3 to 5 were classified as disabled.

**Statistical analysis.** Kaplan–Meier survival estimates were performed to analyze the evolution of the proportion of patients switching from a disabled (functionally dependent) to a nondisabled (functionally independent) state over time. Survival curves for each covariate were compared using a log-rank test.

To evaluate the impact of all covariates on the time of change from disabled to nondisabled, a multivariate analysis using a Cox proportional hazards model was performed. Initially, 20 independent variables were screened by their individual associations with the outcome of interest after adjustment for sex and age, entered into the model. The covariates used were age, treatment, level of initial disability (3, 4, or 5), sex, race, country (region, n = 4), time between qualifying event and baseline assessment (assessed as ≤7 days, 7 days to 1 month, 1 to 2 months, 2 to 3 months), Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification of ischemic stroke etiologic subtype, and tobacco consumption. All covariates were included in the initial multivariate model with any variable with *p* > 0.05 eliminated stepwise. The point estimate of the hazard ratio (HR) associated with a reduced time to change from a disabled to a nondisabled state among those patients disabled at baseline and its two-sided 95% CI was calculated.

**RESULTS Patients disabled at baseline.** At baseline, of the 7,599 patients enrolled in the MATCH study, 5,937 (78%) patients were classed as nondisabled (mRS 0 to 2), and 1,662 were classed (22%) as disabled (mRS ≥ 3). Baseline characteristics are shown in table 1. The baseline assessment was undertaken a median of 14 (0 to 96) days after the qualifying

event. Of the disabled patients, 66 patients (4%) had experienced a TIA as their qualifying event; of these, 47 (71%) had experienced a previous stroke.

**Recovery of functional independence.** At 18 months follow-up, complete mRS follow-up data were available for 1,382 patients (83% of 1,662). Sufficient information was available for all of the 1,662 disabled patients to enable assessment of a change in their mRS score. Of the 1,662 patients, 877 (53%, 95% CI 50% to 55%) recovered, with a median time to recover of 357 days (interquartile range 36 to >600 days). Recovery was seen in 589 of 931 patients (63%, 60% to 66%) with moderate disability (mRS 3), 281 of 691 patients (41%, 37% to 44%) with severe disability (mRS 4), and 7 of 40 patients (17%, 7% to 33%) with very severe disability (mRS 5) (table 2).

Figure shows the Kaplan–Meier survival curve for the probability that disabled patients at baseline (n = 1,662) will recover functional independence (mRS < 3) during the first 18 months after stroke according to their initial mRS at the time of the disabling ischemic stroke. The median time to recovery was estimated at 96 days for moderately disabled patients, 585 days for severely disabled patients, and more than 600 days for very severely disabled patients. For moderate and severely disabled patients, the greatest improvement occurred within the first 6 months, with more gradual improvement thereafter.

**Factors associated with recovery.** The findings of the multivariate model for significant prognostic factors associated with recovery are shown in table 3. After adjustment for age and sex, the factor of greatest prognostic significance was the initial disability status. Increasing initial mRS score correlated with a longer time to return to a nondisabled state. Moderately disabled patients had a higher chance of recovering within 18 months compared with severely disabled patients (HR 2.13, 95% CI 1.86 to 2.44) and were more than five times as likely to recover compared with patients who very severely disabled (HR 5.88, 2.86 to 12.5).

Other covariates shown to have a significant influence included the absence of concurrent atherothrombotic risk factors. Patients with no previous history of ischemic stroke, diabetes, or peripheral artery disease were more likely to recover to a nondisabled state. Women aged <65 years were more likely to recover vs older women (≥75 years). No significant difference was seen for younger men.

**DISCUSSION** In this cohort of patients with predominantly moderate or severe disabling ischemic

**Table 1** Characteristics of patients disabled at baseline (n = 1,662)

Characteristic	n (%)
Age	
Mean (SD)	68.1 (9.8)
Age class	
<65 y	563 (33.9)
[65–75 y]	625 (37.6)
≥75 y	474 (28.5)
Sex	
Women	696 (41.8)
Men	966 (58.1)
Qualifying event	
TIA	66 (4.0)
Ischemic stroke	1,596 (96.0)
Region	
Asia	89 (5.4)
North America	154 (9.4)
Oceania	64 (3.8)
East Europe	371 (22.3)
West Europe	984 (59.2)
Race	
Asian/oriental	102 (6.2)
Black	49 (2.9)
White	1,475 (88.7)
Other	36 (2.2)
Time from qualifying event	
≤7 days	387 (23.5)
7 days–1 month	865 (52.6)
1–2 months	238 (14.5)
2–3 months	155 (9.4)
TOAST classification	
Cardioembolism	48 (0.8)
Large-artery atherosclerosis	637 (38.3)
Small-vessel occlusion	744 (44.8)
Stroke of other undetermined cause	19 (1.1)
Undetermined cause	148 (8.9)
Baseline clinical features	
Previous ischemic stroke	510 (30.7)
Previous TIA	200 (12.0)
Previous MI	78 (4.7)
Angina pectoris	156 (9.4)
Peripheral arterial disease	149 (9.0)
Diabetes	1,207 (72.6)
Smokers	720 (43.3)
Treatment allocation	
Placebo	832 (50.1)
Aspirin	830 (49.9)

TOAST = Trial of Org 10172 in Acute Stroke Treatment; MI = myocardial infarction.

stroke, approximately half recovered (mRS < 3) within 18 months of the index event. The rate of recovery of functional independence was greatest within the first 6 months but continued in some patients for up to 18 months. The independent, significant predictors of recovery included the severity of index stroke; no previous history of ischemic stroke, diabetes, or peripheral artery disease; decreasing time between the disabling ischemic stroke and the baseline assessment; and women aged <65 years compared with ≥75 years. The time to recovery was heavily dependent on the degree of initial disability after an event. The time frame to recovery was relatively short (3 months) for moderately disabled patients compared with severely disabled patients. As the level of mRS grade increased, the probability of returning to a nondisabled state was reduced, with only seven mRS Grade 5 patients improving to a nondisabled state over an 18-month time frame.

The main strengths of this study are the prospective assembly and uniform assessment of a large number (n = 1,662) of patients disabled at study entry soon after the onset of stroke (median 14 days); the prospective and frequent (at least 3 monthly) follow-up assessments over a long period of time (18 months) when recovery is likely to be greatest; the completeness of the follow-up assessments (83% at 18 months); the assessment of recovery by means of a uniform, valid, reliable, and widely used measure (the mRS); and the analysis of prognosis by means of actuarial (Kaplan–Meier survival technique) and prognostic factors by multiple regression (Cox model) techniques.

The potential weaknesses of the study are as follows: First, the patients enrolled were highly selected (e.g., they were hospitalized, were enrolled in a clinical trial, and had disabling ischemic stroke due to atherothrombosis, and few [2%] had very severe disabling ischemic stroke [mRS 5]), which limits the generalizability of the results to other types of patients. Second, the patients did not undergo a baseline assessment until a median of 14 days (with some up to 3 months) after their qualifying event, during which some recovery (or a recurrent stroke) may already have occurred. Third, a small group of patients (n = 19) had experienced a TIA only as their qualifying event. Fourth, patients did not undergo subsequent assessments of disability status on a more regular basis than 3 monthly (with the exception of the initial 1-month visit). Fifth, potential prognostic factors during the follow-up (e.g., duration and intensity of stroke rehabilitation therapy) were not recorded and entered into the prognostic model. Sixth, the MATCH study was not initially designed to answer the objec-

**Table 2** Recovery to mRS < 3 at 18 months after disabling ischemic stroke

Patient characteristic	mRS at time of assessment		
	3	4	5
Disabled at baseline (mRS ≥ 3)*, n (%)	931 (56)	691 (42)	40 (2)
Recovered (mRS < 3) †, n (%)	589 (63.3)	281 (40.7)	7 (17.5)
95% CI	60–66	37–44	7–33
No change in mRS‡, n (%)	342 (36.7)	410 (59.3)	33 (82.5)
Days to recover, median (interquartile range)	96 (32 to 673)	585 (97 to >600)	>600 (588 to >600)§

\*Number of patients (%) with various degrees of disability at initial baseline assessment.

†Number of patients (%) with various degrees of disability at initial assessment who subsequently recovered to a nondisabled state at the end of the study follow-up period 18 months after stroke.

‡Number of patients (%) with various degrees of disability at initial assessment who remained disabled at the end of the study follow-up period.

§Exact figure cannot be calculated because 33 of the 40 patients did not recover within 18 months follow-up.

mRS = modified Rankin Scale.

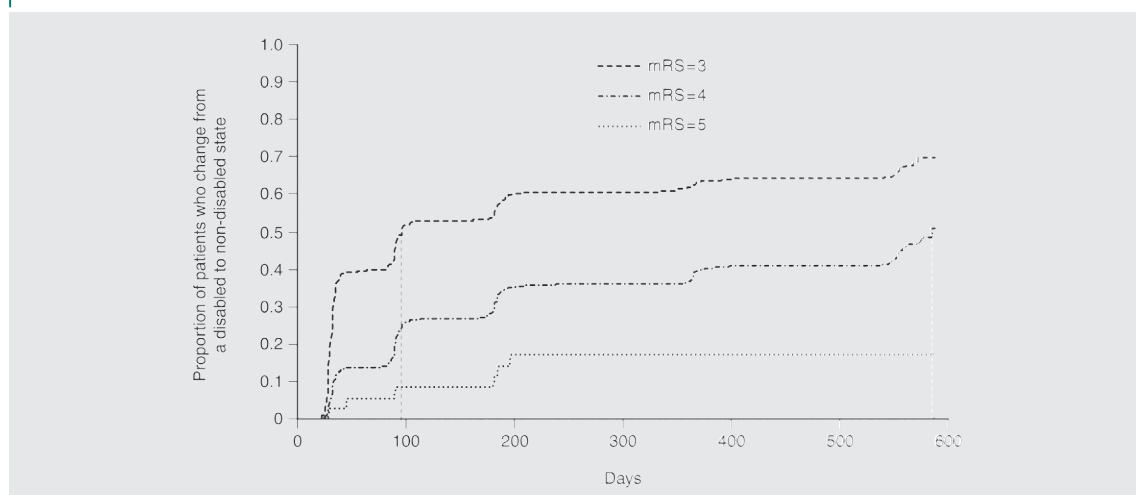
tives of this study; therefore, limitations of secondary analyses should be recognized. Seventh, our analysis only accounted for complete transition from a disabled to a nondisabled state (i.e., Grades 3–5 to Grades 0–2) rather than assessing the transition between mRS grades (i.e., Grade 4 to Grade 3). A change in mRS from Grade 4 or 5 to Grade 3 may still be considered by the patient as a clinically important and favorable improvement.<sup>14</sup>

The major predictors of recovery were similar to those identified in previous studies<sup>9,15</sup> and add weight to the notion that elderly female patients with severe disabling ischemic stroke and a background of atherothrombosis (peripheral artery disease) and atherothrombotic risk (diabetes) are those least likely to recover independently.<sup>8</sup>

The implications of our results are that identifying the prognosis and prognostic factors for recovery and using this information early in the treatment of disabled stroke patients may help to refine esti-

mates of prognosis and may have some role in appropriate streaming of patients for early rehabilitation. Information about the rate of recovery after stroke is valuable in health planning, and our findings may have value in designing studies and evaluating different therapeutic strategies. Current treatment approaches in stroke management are largely designed to improve neurologic function or reduce disability. The findings of this study suggest that mRS transition may be a useful measure of recovery and favorable outcome.

The implications of these results for health economists are that the degree of disability, as measured by mRS, can be directly related to costs of subsequent care. One study<sup>16</sup> determined that, based on a population of patients with ischemic stroke, direct care costs per patient in the 18 months after hospital discharge differed considerably according to disability levels, as measured by mRS. By 18 months, total costs per patient for those with mild disability

**Figure** Time to change from disabled to nondisabled state

Kaplan-Meier survival curve for the probability that disabled patients (n = 1,662) will recover (modified Rankin Scale score [mRS] < 3) according to their initial mRS of 3, 4, or 5. The dotted vertical lines show the time for >50% of patients within each mRS group to recover.

**Table 3** Multivariate prediction model for recovery from a disabled to a nondisabled state after stroke\*

Prognostic variable	Hazard ratio	95% CI	p Value
<b>Demographic</b>			
Female aged <65 y (vs female aged ≥75 y)	1.85	1.47-2.33	<0.0001
<b>Baseline clinical features</b>			
No peripheral artery disease	1.61	1.23-2.13	0.0006
No previous ischemic stroke	1.61	1.35-1.92	<0.0001
No history of diabetes	1.30	1.10-1.54	0.0028
Decreasing time from qualifying event to baseline assessment of functional status (per day)	1.01	1.01-1.02	<0.0001
<b>Initial disability status</b>			
mRS level 3 (vs mRS level 4)	2.13	1.86-2.44	<0.0001
mRS level 3 (vs mRS level 5)	5.88	2.86-12.50	<0.0001

\*Model based on 1,662 disabled patients at baseline who returned to independence after 18 months and experienced no further vascular events (stroke, myocardial infarction, vascular death, rehospitalization for acute ischemia) during the study. mRS = modified Rankin Scale.

(mRS 0 to 2) were €10,255, rising to €17,457 for moderate handicap (mRS 3) and €31,728 for severe handicap (mRS 4 or 5). Indeed, disability level was the major determinant of overall costs, with most costs determined within the first 6 months. Our study reflects this finding, with most recovery for mRS 3 and 4 found in the initial 6 months.

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