

Expanding Eligibility in Stroke Prevention Trials to Patients with Early Disability

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Background and Purpose: Early disability after stroke is common, though many patients improve. Stroke secondary prevention trials often prohibit the recruitment of nonambulatory patients, limiting their access to potential treatment options and impeding trial enrollment. We aimed to determine outcomes after early dependence around the time of transition from acute care to recovery. *Methods:* Data were obtained from a composite of patients enrolled in acute stroke clinical trials within the Virtual International Stroke Trials Archive (VISTA-Acute). Early disability was defined by the modified Rankin Scale (mRS) of 4 or 5 between days 3-10 after onset, representing the time of discharge or transition to a rehabilitation-focused care setting. We developed multivariable models to identify factors associated with recovery to independent ambulatory function and recurrent stroke during the 90 days after stroke. *Results:* 4965 patients were included, with 2905 (59%) having early disability. Patients with early dependence were older, more likely to be women, had higher baseline NIHSS scores, and had more atrial fibrillation and diabetes mellitus, compared with those who were initially ambulatory. Recovery to ambulatory function occurred in 58% with early mRS = 4, compared to only 16% with early mRS = 5. Of those with early mRS = 4, return to independent ambulatory status by 90 days was associated in multivariable analysis with age, diabetes, prior stroke, NIH motor and gaze subscores, and thrombolysis. Recurrent ischemic stroke through day 90 was reported in 126 of 2905 (4.3%) subjects with early dependence compared to 63 of 2060 (3.1%), which was not different after adjustment for age, sex, and risk factors (odds ratio 1.27; 95% confidence interval 0.92-1.73). *Conclusions:* Favorable outcomes are common among ischemic stroke patients previously enrolled in acute clinical trials despite early dependence (mRS = 4) after initial acute hospital care. Further, their risk of recurrent stroke is high in the short term. These patients likely benefit from aggressive poststroke care and should be actively recruited into secondary prevention trials.

Key Words: Clinical trial—prevention—disability—recovery
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Stroke is far more often disabling than fatal, and the majority (50%-70%) of stroke survivors requires ongoing support at inpatient rehabilitation or nursing facilities after their acute hospital care.¹⁻³ Ultimately, many of these

patients regain their ability to ambulate independently and return home over the ensuing months.^{1,4,5} While early intervention facilitates recovery and reduces subsequent stroke risk,^{6,7} unfortunately, many stroke prevention trials

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Received March 21, 2019; revision received May 6, 2019; accepted May 14, 2019.

Funding: Drs. Kasner and Siegler were supported by NIH grant U10 NS086474.

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1052-3057/\$ - see front matter

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<https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.05.016>

prohibit the enrollment of patients with early disability. Such trials often have specific exclusion criteria for patients with a threshold modified Rankin Scale (mRS) more than 3 or otherwise described as nonambulatory.⁸⁻¹¹ However, the mRS was created for assessment of late stroke disability and has a known floor effect making it suboptimal in the acute setting.¹² Potential arguments for the exclusion of early disability include both a nihilistic perspective on outcome (e.g., "what is the public health impact of a recurrent stroke in someone who is already disabled?") as well as practical or operational considerations (e.g., "if they are that impaired, would we be able to detect a new stroke?" or "will this dependent patient be able to return for follow-up visits?"). However, these patients comprise a large group of otherwise potentially eligible trial subjects. Their exclusion limits their options as individuals, slows the pace of enrollment in prevention trials, and may restrict the options for future stroke patients who could otherwise benefit from novel secondary prevention strategies.

We aimed to determine outcomes after early dependence (mRS 4-5) around the time of hospital discharge, specifically the proportion of such patients who would ultimately improve to independent ambulatory function (mRS 0-3) by 90 days poststroke. We hypothesized that a substantial proportion of patients with early dependence would improve to ambulatory function by 90 days, and that key baseline features could be used to predict outcomes in this population. We also compared the risk of stroke recurrence between patients with major early dependence (mRS 4-5) and early ambulatory function (mRS 0-3) during the 90 days poststroke, and hypothesized that the risks would be similar. If both hypotheses could be supported by data, then inclusion of such patients could provide enhanced opportunities for both patients and research.

Methods

Data were obtained from a composite of patients enrolled in acute stroke clinical trials within the Virtual International Stroke Trials Archive (VISTA-Acute) database. Briefly, VISTA collects standardized and monitored prospective data from stroke clinical trials into a single database housed at the University of Glasgow, which is overseen by an international committee of academic stroke researchers.^{13,14} Available data elements vary by trial and trial sources remain anonymous in accord with VISTA policy. This analysis used data accumulated from acute trials performed between 1997 and 2012, and was limited to those with neutral results to minimize potential treatment effects. All but one of these studies explicitly excluded patients who were disabled prior to enrollment. For this study, we further applied the following criteria for eligibility and requirements for data availability: age more than equal to 18 years, diagnosis of acute ischemic stroke, medical history related to major vascular risk factors

(hypertension, diabetes, current smoking, atrial fibrillation, and prior stroke), measurement of baseline stroke severity using the NIH Stroke Scale (NIHSS), assessment of the mRS between days 3-10 after onset and alive at that time point, another mRS assessment at day 90 poststroke, and serious adverse events and/or recurrent strokes through day 90. The time point of day 3-10 was selected to represent early disability around the time of discharge, as this is the typical length of initial acute stroke hospitalization in many countries prior to the transition to a rehabilitation-focused care setting. It also serves as a critical time point at which patients are likely to be screened for—and may be disqualified from—secondary prevention trials. If there was more than one assessment of mRS during the day 3-10 period, we used the last one.

For the analysis of outcomes, we limited our population to those subjects with early disability (mRS 4 or 5) on day 3-10. We dichotomized the 90-day mRS as less than equal to 3 (ambulatory without assistance or supervision, or better) or greater than 3 (nonambulatory). We compared baseline demographic, historical, and clinical features between these 2 outcome groups. The baseline NIHSS was divided into separate motor and nonmotor components for this analysis. We then developed multivariable models associated with 90-day outcome, using a stepwise approach that removed variables associated with *P* values more than .05.

For the analysis of risk, we compared the incidence of recurrent stroke through approximately day 90 between subjects with early mRS 4 and 5 to those with early mRS 0-3. We used the cumulative risk through day 90 rather than time-to-stroke survival analysis because recurrent strokes were not necessarily adjudicated in these trials and the exact timing of reported events could not be verified, but all were reported within 90 ± 30 days. We compared baseline demographic, historical, and clinical features based on these 2 baseline groups. We then created a multivariable model to estimate the association between baseline dependence and recurrent stroke risk.

The available sample from VISTA included 4965 subjects with mRS available at an early time point (day 3-10) and at 90 days. Assuming that about half of subjects had early disability and half of those would eventually become ambulatory by 90 days, then our model to predict outcome would have sufficient power to explore the role of all of our proposed candidate variables in this model.¹⁵ Further, this sample provided 80% power to detect a difference in absolute recurrence risks of 1.5% between subjects with and without early disability with $\alpha = 0.05$.

Results

A total of 4965 patients met all eligibility criteria, with 2905 (59%) having early disability, including 1498 (30% of

Table 1. Baseline characteristics and early disability status

	Early mRS 0-3 (n = 2060)	Early mRS 4-5 (n = 2905)	P value
Age, years	65.6 ± 12.8	70.9 ± 11.9	<.001
Female sex	41%	48%	<.001
Past medical history			
Hypertension	72%	74%	.19
Diabetes mellitus	20%	25%	.001
Atrial fibrillation	20%	29%	<.001
Prior stroke	20%	18%	.028
Left hemispheric infarction	48%	47%	.64
Baseline total NIHSS, median (IQR)	9 (7, 12)	14 (10,18)	<.001
Treated with thrombolytics	40%	41%	.40

Continuous data are presented as mean ± standard deviation or median (interquartile range).

all patients) with initial mRS 4 and 1407 (28% of all patients) with mRS 5. Patients with early disability were older, more likely to be women, had higher baseline NIHSS scores, and had more atrial fibrillation and diabetes mellitus, compared with those who were ambulatory at the early time point (Table 1). Outcomes in the 2 initially dependent mRS groups were markedly different: 58% of those with early mRS 4 were ambulatory by day 90, compared to only 16% of those with early mRS 5 ($P < .001$, Fig 1). Based on this observation, further modeling related to outcome was limited to those with early mRS 4. In this group with early mRS 4, return to independent ambulatory status by 90 days was associated in multivariable analysis with younger age and thrombolytic therapy, while diabetes, prior stroke, and NIH motor and best gaze subscores were associated with a lower odds of long-term independent ambulatory status (Table 2).

Recurrent ischemic stroke through day 90 was reported in 126 of 2905 (4.3%) subjects with early dependence compared to 63 of 2060 (3.1%) who were initially ambulatory ($P = .020$). In multivariable analysis, recurrent stroke risk was not significantly different between groups after adjustment for age, sex, and risk factors (odds ratio 1.27, 95% confidence interval 0.92-1.73; Table 3).

Discussion

In this large cohort of patients with acute ischemic stroke who were followed closely in clinical trials, more than half were nonambulatory around the time that they transitioned to postacute care, yet many of these patients subsequently improved to ambulatory status by 90 days. Inclusion of such patients may increase the absolute yield of secondary stroke trial enrollment by more than 20%, and at the same time allow us to explore the benefits of novel treatment strategies in this population. Improvement to independent ambulatory status was observed predominantly in those whose early mRS score was 4 rather than 5, and among those who were younger and had a lower burden of risk factors or comorbidities. Initial neurological deficits were also indicators of subsequent ambulatory status, and those with less motor impairment or gaze deviation (likely representing brainstem involvement or very large hemispheric strokes) were more likely to regain ambulatory function. While the relationships between baseline clinical features and outcome are expected, the delayed relationship with thrombolytic therapy deserves some explanation. At the initial time point 3-10 days after stroke onset, there was no association

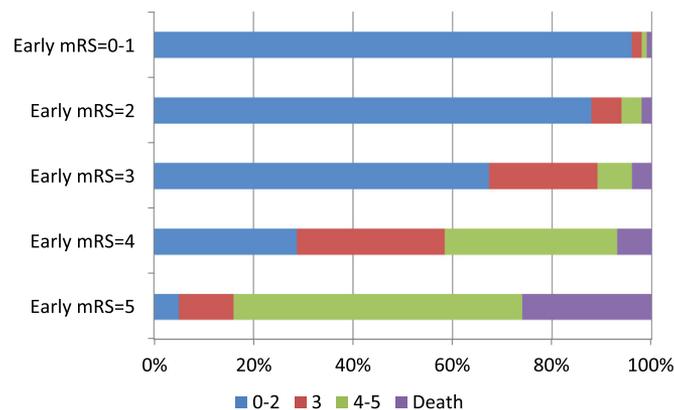


Figure 1. Distribution of modified Rankin Scale (mRS) scores at 90 days based on mRS scores obtained early (day 3-10) after onset.

Table 2. Characteristics and 90-day outcomes of stroke survivors with early mRS 4

	90-day mRS 0-3 (n = 875)	90 day mRS 4-6 (n = 623)	P value (univariable)	OR of ambulatory outcome (95% CI) (multivariable)
Age, years	66.9 ± 12.6	72.8 ± 10.7	<.001	.96 (.95-.97)/year
Female sex	45%	50%	.040	—
Past medical history				
Hypertension	71%	78%	.005	—
Diabetes mellitus	21%	29%	<.001	.60 (.46-.77)
Atrial fibrillation	21%	30%	<.001	—
Prior stroke	15%	22%	<.001	0.69 (0.52-0.92)
Left hemispheric infarction	47%	44%	.13	—
Treated with thrombolytics	65%	35%	<.001	1.66 (1.32-2.09)
Median baseline NIHSS, total	11 (8, 15)	13 (10, 17)	<.001	—
Median baseline NIHSS motor items	5 (3, 7)	6 (4, 7)	<.001	0.84 (.80-.89)/point
Left arm	1 (0, 3)	2 (0, 4)	.005	—
Right arm	0 (0, 3)	0 (0, 3)	.38	—
Left leg	1 (0, 2)	1 (0, 3)	.002	—
Right leg	0 (0, 2)	0 (0, 3)	.92	—
Median baseline NIHSS nonmotor	6 (4, 9)	7 (5, 10)	<.001	—
Level of Consciousness (LOC a)	0 (0, 0)	0 (0, 0)	.62	—
Questions (LOC b)	0 (0, 1)	0 (0, 1)	.82	—
Commands (LOC c)	0 (0, 0)	0 (0, 0)	.098	—
Gaze	0 (0, 1)	1 (0, 1)	<.001	.71 (.61-.84)/point
Visual fields	0 (0, 2)	1 (1, 2)	.002	—
Facial strength	2 (1, 2)	2 (1, 2)	.18	—
Limb ataxia	0 (0, 0)	0 (0, 0)	.14	—
Sensory	1 (0, 1)	1 (0, 1)	.016	—
Language	0 (0, 1)	0 (0, 1)	.31	—
Dysarthria	1 (0, 1)	1 (0, 1)	.31	—
Extinction	0 (0, 1)	0 (0, 1)	.003	—

Continuous data are presented as mean ± standard deviation or median (interquartile range). Goodness of fit $P = .79$. C-statistic 0.70.

between dependence and thrombolysis. However, during the ensuing weeks to months, those who were acutely treated with thrombolysis fared better, suggesting an ongoing effect of treatment. Such an effect, attributed to an initially “stunned brain,” has been proposed

previously to explain the apparent discrepancy between the effects of thrombolysis at 24 hours and those at 90 days.¹⁶⁻¹⁸

Moreover, the finding that 30% of all patients had an early mRS score of 4 and that the majority of them became

Table 3. Relationship between baseline characteristics and recurrent ischemic stroke

	Recurrent stroke (n = 189)	No recurrent stroke (n = 4776)	P value (univariable)	OR (95% CI) (multivariable)
Age, years	71.8 ± 10.9	68.5 ± 12.5	<.001	1.02 (1.01-1.04)/year
Female sex	48%	45%	.53	—
Past medical history				
Hypertension	80%	73%	.028	—
Diabetes mellitus	32%	22%	.001	1.63 (1.19-2.23)
Atrial fibrillation	33%	25%	.009	—
Prior stroke	24%	19%	.047	—
Left hemispheric infarction	45%	48%	.46	—
Baseline NIHSS, total	11 (8-16)	12 (8-16)	.71	—
Early dependence (mRS 4-5)	67%	58%	.020	—

Continuous data are presented as mean ± standard deviation or median (interquartile range).

ambulatory suggests that early mRS is not a reliable discriminator of outcome and that this group should be offered all opportunities for both recovery and prevention promptly after onset. This extends beyond clinical care into trials, and these patients should not be categorically excluded from enrollment. Unfortunately, it has been common for stroke prevention trials to limit enrollment to patients with mRS less than equal to 3,⁸⁻¹¹ requiring those with early dependence to have to wait until they improve before they might become eligible to participate. Patients are most likely to be enthusiastic about trial participation and face the greatest risk recurrent stroke in the first few days to weeks their stroke.^{6,7} While expanding the inclusion criteria to mRS less than equal to 4 would increase the absolute yield of ambulatory patient enrollment in secondary prevention trials, this would potentially double the pool of potentially eligible patients. Such inclusion may also further diversify these trials by increasing the recruitment of women. Additionally, those with early dependence had a 4.3% risk of recurrent stroke within 90 days suggesting that they would be highly informative for prevention trials. The combined volume of such patients and their high risk profile could substantially improve trial accrual and efficiency.

Major strengths of this analysis include the standardized approach to prospective clinical assessments through 90 days after stroke in the trial context and the large sample size. Limitations include the challenges of generalizability from trials to clinical practice; the long time epoch from which these trials are drawn including possible changes in management over that time; inability to account for socioeconomic factors, other comorbidities, stroke etiological mechanisms, or frequency and intensity of postacute care interventions; potential misclassification of outcomes with the mRS as a result of inter-rater variability¹⁹ or non-neurological factors that might impact scoring; and the lack of adjudication of recurrent stroke events in acute treatment trials. Notably, the mRS was not designed for use in the acute setting despite its common application in this context. We also cannot directly address how inclusion of patients with early disability would affect other aspects of trial conduct, such as retention of patients with early disability.

We conclude that favorable outcomes are common among ischemic stroke patients previously enrolled in acute clinical trials despite early dependence based on a mRS score of 4 after initial acute hospital care. Further, their risk of recurrent stroke is high in the short term. These patients likely benefit from aggressive poststroke care and should be actively recruited into secondary prevention trials.

Conflicts of Interest

None.

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