July, 2014

A Simple Risk Index and Thrombolytic Treatment Response in Acute Ischemic Stroke

Gustavo Saposnik

Original Investigation

A Simple Risk Index and Thrombolytic Treatment Response in Acute Ischemic Stroke

Bruce Ovbiagele, MD, MSc, MAS; Mathew J. Reeves, BVSc, PhD; Mojdeh Nasiri, MD; S. Claiborne Johnston, MD, PhD; Philip M. Bath, MD, FRCPath, FRCP; Gustavo Saposnik, MD, MSc, FRCPC; for the VISTA-Acute Collaboration Steering Committee

IMPORTANCE The Stroke Prognostication using Age and the NIH Stroke Scale index, created by combining age in years plus a National Institutes of Health (NIH) Stroke Scale score of 100 or higher (and hereafter referred to as the SPAN-100 index), is a simple risk score for estimating clinical outcomes for patients with acute ischemic stroke (AIS). The association between this index and response to intravenous thrombolysis for AIS has not been properly evaluated.

OBJECTIVE To assess the relationship between SPAN-100 index status and outcome following treatment with intravenous thrombolysis for AIS.

DESIGN, SETTING, AND PARTICIPANTS Using the Virtual International Stroke Trials Archive (VISTA) database, an international repository of clinical trials data, we assessed the SPAN-100 index among 7093 patients with AIS who participated in 4 clinical trials from 2000 to 2006. The SPAN-100 index is considered positive if the sum of the age and the NIH Stroke Scale (a 15-item neurological examination scale with scores ranging from 0 to 42, with higher scores indicating more severe strokes) score is greater than or equal to 100. Multivariable logistic regression analyses were used to determine the independent association between SPAN-100 index status and 90-day outcomes.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of severe disability or death measured 90 days after stroke, and the secondary outcomes were death alone and a composite of no disability/modest disability.

RESULTS Of 7093 patients, 743 (10.5%) were SPAN-100 positive, and 2731 (38.5%) received intravenous thrombolysis. Compared with SPAN-100–negative patients, SPAN-100–positive patients were more likely to experience a catastrophic outcome (adjusted odds ratio [AOR], 9.03 [95% CI, 6.68-12.21]) or death alone (AOR, 5.03 [95% CI, 4.06-6.23]) and less likely to experience a favorable outcome (AOR, 0.08 [95% CI, 0.06-0.13]). However, there was an interaction between SPAN-100 index status and thrombolysis treatment ($P < .001$) revealing a reduction in the likelihood of severe disability/death with thrombolytic treatment for SPAN-100–positive (AOR, 0.46 [95% CI, 0.29-0.71]) but not SPAN-100–negative patients (AOR, 0.96 [95% CI, 0.85-1.07]). Similar interactions between SPAN-100 index status and thrombolysis treatment were observed for the 2 secondary outcomes.

CONCLUSION AND RELEVANCE Compared with the SPAN-100–negative patients with AIS, the SPAN-100–positive patients with AIS seem to have poorer 3-month outcomes but may derive greater benefit when treated with intravenous thrombolysis. The SPAN-100–positive patients are often excluded from AIS clinical trials but should probably not be denied thrombolysis treatment on the basis of such a profile alone.

JAMA Neurol. 2014;71(7):848-854. doi:10.1001/jamaneurol.2014.689
Published online May 5, 2014.

Supplemental content at jamaneurology.com

CME Quiz at jamanetworkcme.com and **CME Questions** page 932

Author Affiliations: Department of Neurosciences, Medical University of South Carolina, Charleston (Ovbiagele); Department of Epidemiology and Biostatistics, Michigan State University, East Lansing (Reeves, Nasiri); Clinical and Translational Science Institute, University of California, San Francisco (Johnston); Stroke Trials Unit, University of Nottingham, Nottingham, England (Bath); Stroke Outcomes Research Unit, Division of Neurology, University of Toronto, Toronto, Ontario, Canada (Saposnik).

Group Information: The VISTA-Acute Collaboration Steering Committee members are listed at the end of the article.

Corresponding Author: Bruce Ovbiagele, MD, MSc, MAS, Department of Neurosciences, Medical University of South Carolina, 96 Jonathan Lucas St, CSB 301, MSC 606, Charleston, SC 29425 (ovibes@musc.edu).

To facilitate the consistent use of a prognostic index by providers caring for patients with acute ischemic stroke (AIS), a simple and practical index called the Stroke Prognostication using Age and NIH Stroke Scale, created by combining age in years plus an National Institutes of Health Stroke Scale (NIHSS) score of 100 or higher (and hereafter referred to as the SPAN-100 index), was developed to be applied especially to high-risk patients (ie, elderly patients with a moderate to severe stroke).[1] When applied to a modest-sized sample of patients with AIS (n = 624), the SPAN-100 index was shown to be of value in estimating risk of intracerebral hemorrhage and clinical outcomes, at several follow-up time points, regardless of intravenous thrombolysis treatment.[1] However, the question of whether very elderly patients with very severe strokes (presumably with otherwise very poor outcomes) benefit from intravenous thrombolysis to a greater or lesser extent than other patients with AIS has not been specifically explored.[2]

In our study, we aimed to determine if the SPAN-100 index is indeed a useful practical prognostic variable/indicator for outcomes after AIS, and to assess if intravenous thrombolysis may decrease the risk of a disabling stroke or death among high-risk patients with an expected poor outcome.

Methods

The SPAN-100 index was created by combining age in years and an NIHSS score of 100 or higher. The NIHSS is a 15-item neurological examination scale with scores ranging from 0 to 42, with higher scores indicating more severe stroke.[3-5] Individuals whose combined age in years plus NIHSS score was greater than or equal to 100 were designated as SPAN-100–positive patients, whereas those whose combined age in years plus NIHSS score was less than 100 were designated as SPAN-100–negative patients. The rationale for the use of this index was that (1) age and stroke severity are the 2 most important prognostic factors for AIS,[6-9] (2) patients 80 years of age or older with a high NIHSS score (eg, ≥20) generally have poorer prognoses,[10-14] (3) a simple practical index is warranted given several factors that limit consistent use of currently available scores in routine practice,[15-19] and (4) the index performed well in a derivation cohort.[1] Ethical approval was not obtained because our study is an analysis of a repository containing de-identified participant data.

We applied the SPAN-100 index to participants with AIS whose medical records were entered into the Virtual International Stroke Trials Archive (VISTA) database; VISTA-Acute (http://www.vistacollaboration.org) is a collaborative registry that includes data from completed acute stroke clinical trials and that provides access to anonymized data for exploratory analyses. Further details of VISTA are published elsewhere.[20,21] For the purpose of this analysis, relevant data extracted from the VISTA database had to meet the following criteria: (1) a minimum data set of 100 patients; (2) a baseline assessment within 24 hours of stroke onset, including recording of neurologic deficit by use of the NIHSS; (3) confirmation of stroke diagnosis by cerebral imaging within 7 days; and (4) outcome assessed 3 months after stroke onset. The present analysis included a total of 7141 patients who participated in 4 neuroprotectant clinical trials and who met the aforementioned inclusion criteria. The identity of the 4 trials is not provided by VISTA. Onset-to-treatment duration represents the elapsed time from stroke onset to receiving the studied intervention treatment (not intravenous thrombolysis).

The modified Rankin Scale (mRS) was the primary outcome measure used in our study. The mRS is a practical clinician-reported measure of global disability, often used in large-scale multicenter studies, that defines 7 clinically discrete patient disability categories. The scale runs from 0 to 6, ranging from no symptoms of disability to death, and has been proven to be valid and reliable.[5,22] The primary outcome in this analysis was a catastrophic outcome (defined as an mRS score of 4-6 [ie, moderate to severe disability or death]) at 3 months, and the secondary 3-month outcomes were death alone or a favorable outcome (defined as an mRS score of 0-2 [ie, no disability or modest disability]).

With regard to statistical analysis, among 7141 patients with AIS, we excluded patients with missing data on age (n = 1), NIHSS score (n = 48), and mortality status (n = 47), leaving 7093 participants. Furthermore, 325 of the remaining 7093 patients (4.6%) were missing mRS data collected at 90 days. We first generated descriptive statistics comparing the characteristics of VISTA patients according to their 90-day survival status and functional level (mRS) using contingency tables. Bivariate *P* values of association were generated using χ^2 analysis for categorical variables and *t* tests for continuous variables. Primary exposure variables of interest were SPAN-100 index status (positive [≥100] or negative [<100]) and receipt of intravenous thrombolysis. Independent associations between SPAN-100 index status, intravenous thrombolysis, and outcomes were determined using multivariable logistic regression generating adjusted odds ratios (AORs) and 95% CIs. Adjustments for potentially confounding variables (sex, medical history, blood pressure on presentation, and onset-to-treatment time for the nonthrombolysis-based intervention) were evaluated using backward variable selection methods, whereby all variables with a bivariate $P < .20$ were considered candidate confounders, but variables were retained in the final model only if their *P* value for removal was less than .10. To determine if a differential effect of intravenous thrombolysis on outcomes was present according to SPAN-100 index status (≥100 vs <100), we tested the significance of a SPAN-100 × thrombolysis interaction term in the final multivariable models. If a significant interaction was present, we then generated AORs for each combination of the SPAN-100 index and thrombolysis, with the SPAN-100–negative group that did not receive thrombolysis serving as the referent group (AOR, 1.0). To further illustrate the differential effect of thrombolysis by SPAN-100 index status, we generated AORs for thrombolysis by SPAN-100–positive and –negative strata. Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc).

Results

Of 7093 patients with AIS, 3254 (45.9%) were women, 2731 (38.5%) received intravenous thrombolysis, and 743 (10.5%) were

Table 1. Baseline Demographic and Clinical Characteristics of 7093 Patients With an Acute Ischemic Stroke, Stratified by SPAN-100 Index Status

Variable	SPAN-100-Positive Patients (≥100) (n=743)	SPAN-100-Negative Patients (<100) (n = 6350)	*P* Value
Age, mean (SD), y	85.0 (4.9)	67.3 (11.9)	<.001
Sex, No. (%)			
Female	443 (59.6)	2811 (44.3)	<.001
Male	300 (40.4)	3539 (55.7)	
Medical history, No. (%)			
Stroke[a]	221 (29.7)	1515 (23.9)	.004
Transient ischemic attack	51 (6.9)	408 (6.4)	.65
Myocardial infarction	127 (17.1)	923 (14.5)	.06
Hypertension	574 (77.3)	4576 (72.1)	.002
Diabetes mellitus	148 (19.9)	1505 (23.7)	.02
Ischemic heart disease	164 (22.1)	1462 (23.0)	.56
Congestive heart failure	111 (14.9)	394 (6.2)	<.001
Atrial fibrillation	380 (51.1)	1459 (23.0)	<.001
Cerebral hemisphere, No. (%)			
Left	473 (63.7)	2924 (46.1)	<.001
Right	268 (36.1)	3424 (53.9)	
Baseline NIHSS score,[b] mean (SD)	19.9 (4.5)	12.3 (5.1)	<.001
Admission biomarker, mean (SD)			
Systolic BP, mm Hg	158 (27)	155 (26)	.002
Diastolic BP, mm Hg	79 (17)	83 (16)	<.001
Serum glucose, mg/dL	139 (51)	137 (55)	.36
Intravenous thrombolysis administered, No. (%)	286 (38.5)	2445 (38.5)	.99
OTT with nonthrombolytic study drug, mean (SD), h	4.0 (1.0)	4.0 (1.0)	.47

Abbreviations: BP, blood pressure; OTT, onset to treatment; SPAN-100, Stroke Prognostication using Age and the NIH Stroke Scale index, created by combining age in years plus a National Institutes of Health (NIH) Stroke Scale score of 100 or higher.

SI conversion factor: To convert serum glucose to millimoles per liter, multiply by 0.0555.

[a] Prior to index stroke.

[b] National Institutes of Health Stroke Scale (NIHSS) scores range from 0 to 42, with higher scores on the scale indicating worse stroke severity.

SPAN-100 positive. The median value of age plus initial NIHSS score in the entire cohort was 84 (interquartile range, 72-93) among those who received intravenous thrombolysis and 84 (interquartile range, 73-92) among those patients who did not receive intravenous thrombolysis. Patients who were SPAN-100 positive were significantly older, had more severe strokes, and had a higher prevalence of vascular risk factors, including presence of atrial fibrillation and congestive heart failure, compared with SPAN-100–negative patients (**Table 1**). Patients who received intravenous thrombolysis were younger (mean age, 68.1 vs 69.9 years; $P < .001$) and had a higher mean baseline NIHSS score (14.2 vs 12.4; $P < .001$) than those who did not.

Table 2 shows a comparison of baseline demographic and clinical variables for the 6768 participants who had data on the primary outcome (mRS score of 4-6 vs mRS score of 0-3); SPAN-100 positivity was associated with a significantly greater likelihood of death or disability at 3 months. Our **Figure** illustrates disability at 3 months across the entire range of mRS scores between patients with AIS who received intravenous thrombolysis and those who did not, stratified by the SPAN-100 index score, and indicates that there is a differential effect of intravenous thrombolysis by SPAN-100 index status.

There were significant interactions between SPAN-100 index status and intravenous thrombolysis treatment for all 3 outcomes in adjusted analyses, with thrombolysis producing more favorable differences among SPAN-100–positive patients than among SPAN-100–negative patients (**Table 3**). In **Table 4**, we present the results from the adjusted interaction model, which quantifies the effects of intravenous thrombolysis (vs no thrombolysis) on adjusted outcomes among patients with AIS according to their SPAN-100 index status. The AORs for the effect of thrombolysis on the primary and secondary outcomes indicate that thrombolysis had greater clinical benefit on improving outcomes among SPAN-100–positive patients than among SPAN-100–negative patients. For example, at 3 months, SPAN-100–positive patients who received intravenous thrombolysis were 54% less likely to have a catastrophic outcome of severe disability/death (AOR, 0.46 [95% CI, 0.29-0.71]) than were SPAN-100–positive patients who did not receive intravenous thrombolysis. In contrast, the odds of severe disability/death were not significantly different between SPAN-100–negative patients who received and those who did not receive thrombolysis (AOR, 0.96 [95% CI, 0.85-1.07]). The stratified results reflecting the interaction effect of thrombolysis are also illustrated in the eFigure in the Supplement, showing a significant reduction in the odds of severe disability or death (mRS score, 4-6) or death alone at 3 months in favor of thrombolysis among SPAN-100–positive patients, but no significant benefit of thrombolysis observed for these outcomes among SPAN-100–negative patients. There was also a trend toward a favorable outcome (mRS score, 0-2) achieved with use of thrombolysis among SPAN-100–positive patients, without a corresponding advantage of thrombolysis for this outcome among SPAN-100–negative patients.

Table 2. Baseline Demographic and Clinical Characteristics of 6768 Patients With an Acute Ischemic Stroke, Stratified by Functional Status

Variable	Severe Disability or Death (mRS score, 4-6)	No Disability or Modest Disability (mRS score, 0-3)	*P* Value
Patients, No.	2887	3881	
Age group, No. (%)			
≤65 y	587 (20.3)	1742 (44.9)	<.001
66-79 y	1386 (48.0)	1631 (42.0)	
≥80 y	914 (31.7)	508 (13.1)	
Age, mean (SD), y	73.61 (10.8)	65.77 (12.7)	<.001
Sex, No. (%)			
Female	1452 (50.3)	1649 (42.5)	<.001
Male	1435 (49.7)	2232 (57.5)	
Medical history, No. (%)			
Stroke[a]	800 (27.7)	876 (22.6)	<.001
Transient ischemic attack	178 (6.2)	253 (6.5)	.56
Myocardial infarction	454 (15.7)	538 (13.9)	.03
Hypertension	2192 (75.9)	2726 (70.2)	<.001
Diabetes mellitus	779 (27.0)	780 (20.1)	<.001
Ischemic heart disease	719 (24.9)	875 (22.6)	.02
Congestive heart failure	258 (8.9)	213 (5.5)	<.001
Atrial fibrillation	979 (33.9)	763 (19.7)	<.001
Cerebral hemisphere, No. (%)			
Left	1393 (48.3)	1843 (47.5)	.55
Right	1493 (51.7)	2035 (52.4)	
NIHSS score,[b] mean (SD)	10.6 (6.0)	2.3 (2.6)	<.001
Admission biomarker, mean (SD)			
Systolic BP, mm Hg	157.0 (27.2)	153.9 (25.4)	<.001
Diastolic BP, mm Hg	81.92 (16.7)	83.52 (15.9)	<.001
Serum glucose, mg/dL	145.2 (57.5)	130.5 (51.7)	<.001
Intravenous thrombolysis administered, No. (%)	1023 (35.4)	1534 (39.5)	.001
OTT with nonthrombolytic study drug, mean (SD), h	4.06 (1.0)	3.98 (1.1)	.003
SPAN-100 index status, No. (%)			
≥100	550 (19.1)	120 (3.1)	<.001
<100	2337 (80.9)	3761 (96.9)	

Abbreviations: BP, blood pressure; mRS, Modified Rankin Scale; OTT, onset to treatment; SPAN-100, Stroke Prognostication using Age and the NIH Stroke Scale index, created by combining age in years plus a National Institutes of Health (NIH) Stroke Scale score of 100 or higher.

SI conversion factor: To convert serum glucose to millimoles per liter, multiply by 0.0555.

[a] Prior to index stroke

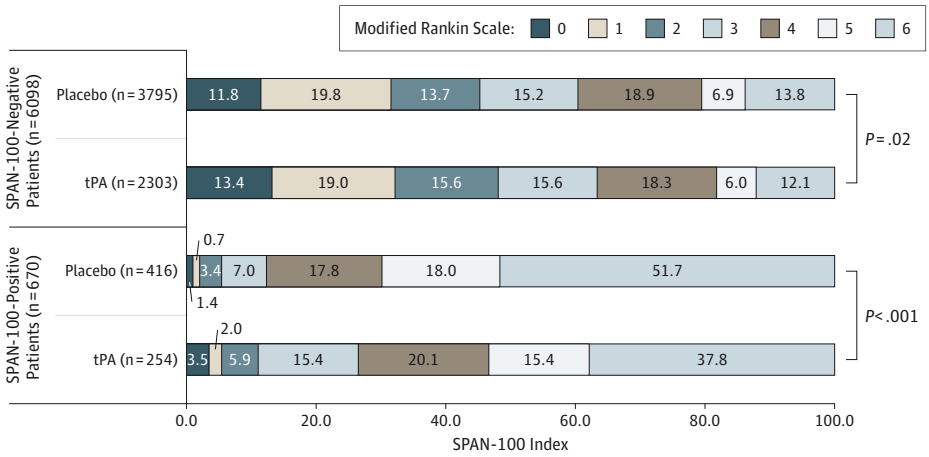
[b] National Institutes of Health Stroke Scale (NIHSS) scores range from 0 to 42, with higher scores on the scale indicating worse stroke severity.

Discussion

The true benefit of intravenous thrombolytic therapy among patients with ischemic stroke who had an expected poor outcome because of older age in combination with high stroke severity is unknown. Clinicians are more likely to face challenging medical decisions concerning this group because of the aging of the population and increasing prevalence of comorbid conditions influencing stroke severity.[23] We observed that among more than 7000 patients with AIS, a simple, practical, and readily memorable index that combines the 2 strongest predictors of outcomes after stroke—age and stroke severity—was significantly associated with various 3-month clinical end points. Specifically, when age plus NIHSS score was greater than or equal to 100, which was found in 11% of the cohort, the odds of a catastrophic outcome were 9-fold higher, and the odds of a favorable outcome were 92% lower. These results are in accord with the results of a previously published analysis of the 624 patients with AIS who participated in the National Institute of Neurological Disorders and Stroke (NINDS) tissue plasminogen activator (tPA) trials, in which it was similarly found that approximately 1 in 10 of the patients were SPAN-100 positive, and this status was related to substantially lower odds (almost 20-fold) of a 3-month composite favorable outcome, more than 6-fold higher odds of a 3-month catastrophic outcome, and more than 5-fold higher odds of death at 3 months.[1]

Age and severity of neurological deficits at the time of AIS presentation have been consistently included in previous predictive scores.[15-19] However, merits of the SPAN-100 index include: (1) the synergistic effect of its 2 components on prognosis, (2) its consistent relationship to several types of outcomes, (3) the potential for easy incorporation into risk adjustment for outcome-based measurements of hospital and provider performance, (4) use in eligibility criteria for future AIS trials, and (5) its ready applicability when counseling pa-

Figure. Unadjusted 3-Month Functional Outcomes Among Patients With Acute Ischemic Stroke



These outcomes are based on the modified Rankin Scale (from 0 [no symptoms] to 6 [death]) and stratified by the Stroke Prognostication using Age and the NIH Stroke Scale index, created by combining age in years plus a National Institutes of Health (NIH) Stroke Scale score of 100 or higher (and referred to as the SPAN-100 index), status and treatment assignment. The *P* values are for trends between patients with acute ischemic stroke receiving tissue plasminogen activator (tPA) and those not receiving tPA, within each SPAN-100 group.

Table 3. Data on Multivariable Logistic Regression Models Demonstrating the Interaction Effects Between Intravenous Thrombolysis Treatment and SPAN-100 Index Status on Primary and Secondary Outcomes for Patients With Acute Ischemic Stroke

SPAN-100 Index Status	Adjusted Odds Ratio (95% CI)					
	Death or Severe Disability (mRS Score, 4-6)[a]		Death Alone[b]		No or Modest Disability (mRS Score, 0-2)[a]	
	Thrombolysis	No Thrombolysis	Thrombolysis	No Thrombolysis	Thrombolysis	No Thrombolysis
≥100	3.70 (2.74-4.99)	9.03 (6.68-12.21)	3.10 (2.34-4.11)	5.03 (4.06-6.23)	0.18 (0.12-0.27)	0.08 (0.06-0.13)
<100	0.96 (0.85-1.08)	1 [Reference]	0.93 (0.79-1.10)	1 [Reference]	1.00 (0.90-1.12)	1 [Reference]

Abbreviations: mRS, modified Rankin Scale; SPAN-100, Stroke Prognostication using Age and the NIH Stroke Scale index, created by combining age in years plus a National Institutes of Health (NIH) Stroke Scale score of 100 or higher.

[a] Adjusted models for mRS outcomes were based on 6768 observations and also included sex; history of atrial fibrillation, diabetes, and stroke; initial systolic blood pressure; initial diastolic blood pressure; and onset-to-treatment time.

[b] Adjusted model for mortality outcome was based on 7093 observations and also included history of myocardial infarction, atrial fibrillation, ischemic heart disease, diabetes, stroke, and congestive heart failure; initial systolic blood pressure; initial diastolic blood pressure; and onset-to-treatment time (nonthrombolytic study drug).

Table 4. Effect of Intravenous Thrombolysis (vs No Thrombolysis) on Primary and Secondary Outcomes, Stratified by SPAN-100 Index Status

SPAN-100 Index Status	Death or Severe Disability (mRS Score, 4-6)[a]		Death Alone[b]		No or Modest Disability (mRS Score, 0-2)[a]	
	AOR (95% CI)	*P* Value	AOR (95% CI)	*P* Value	AOR (95% CI)	*P* Value
≥100	0.46 (0.29-0.71)	.001	0.68 (0.49-0.96)	.03	1.78 (0.96-3.31)	.07
<100	0.96 (0.85-1.07)	.44	0.91 (0.77-1.08)	.29	1.00 (0.90-1.13)	.93

Abbreviations: AOR, adjusted odds ratio; mRS, Modified Rankin Scale; SPAN-100, Stroke Prognostication using Age and the NIH Stroke Scale index, created by combining age in years plus a National Institutes of Health (NIH) Stroke Scale score of 100 or higher.

[a] Adjusted models for mRS outcomes were based on 6768 observations and also included sex; history of atrial fibrillation, diabetes, and stroke; initial systolic blood pressure; initial diastolic blood pressure; and onset-to-treatment time.

[b] Adjusted model for mortality outcome was based on 7093 observations and also included history of myocardial infarction, atrial fibrillation, ischemic heart disease, diabetes, stroke, and congestive heart failure; initial systolic blood pressure; initial diastolic blood pressure; and onset-to-treatment time (nonthrombolytic study drug).

tients and families in virtually all clinical settings (especially the time-pressured setting of an AIS) by several provider types (emergency physicians, internists, and nonstroke neurologists).[2] To the last point, although more detailed stroke scores include several additional variables that can add to their predictive power, this is likely at the expense of becoming much less practical and, therefore, being less often used.

The aforementioned findings underscore the importance of using validated risk tools vs single physician clinical experience.[24] However, perhaps the most unique contribution of the SPAN-100 index, based on the results from our study, is the novel information about the potential benefit of thrombolysis for patients who are frequently not offered thrombolysis because they are considered too high of a risk in the real world and in most randomized clinical trials.

A major distinction between the results of our study and the results of the aforementioned NINDS tPA trial analysis[1] is that we found that treatment with intravenous thrombolysis appears to greatly and differentially modify the outcome for SPAN-100–positive patients. So, even though the overall prog-

noses for SPAN-100–positive patients remained much poorer than those for SPAN-100–negative patients, treatment with intravenous thrombolysis greatly reduced this disparity across all the end points studied. Indeed, administration of intravenous thrombolysis reduced by 54% the likelihood of a SPAN-100–positive patient experiencing a catastrophic 3-month outcome, diminished by 32% the odds of a SPAN-100–positive patient being dead at 3 months, and showed a trend toward a 78% higher likelihood of a SPAN-100–positive patient experiencing a favorable 3-month outcome. As such, based on these observational data, the answer to the question posed about what to do regarding very elderly patients with very severe strokes (who are often excluded from acute stroke clinical trials)[2] seems to be to treat them with intravenous thrombolysis (rather than skipping this treatment to pursue just comfort care) if they are SPAN-100 positive. Although the application of the SPAN-100 index to the NINDS tPA trial data set did not reveal a differential effect of intravenous thrombolysis on SPAN-100–positive patients, this is very likely due to the small sample of 62 SPAN-100–positive patients, of whom only 36 received thrombolysis.[1] Supporting the notion that much older patients with severe strokes may benefit more from intravenous thrombolysis, Sandercock et al[25] suggested, in their analyses of the Third International Stroke Trial, that patients older than 80 years may benefit more than younger patients from thrombolysis. The Third International Stroke Trial[25] also showed significant trends toward greater beneficial effects of thrombolytic treatment among patients with more severe strokes.

Our study has several limitations. First, despite its great practical appeal, the SPAN-100 index was artificially created, and its use of only 2 variables in the SPAN-100 index score may be overly simplistic. Although derivation of a more continuous scoring system based on analysis of receiver operating characteristic curves may be a more precise approach, it would also likely introduce an additional level of complexity to a clinician's ability to actually use the score. Second, thrombolysis effects observed in these data are based on nonrandomized comparisons; thus, residual confounding or selection bias effects might explain some or all of the results. Third, these data are from a series of undefined neuroprotectant trials that require careful selection of patients with AIS, and thus the generalizability is unknown. Fourth, the SPAN-100 index is only a binary score that applies to approximately 10% of patients with ischemic stroke, and risk is likely to be continuously distributed rather than truncated at 100. Fifth, it would have been helpful if data on symptomatic intracerebral hemorrhages secondary to thrombolysis were available, so we could properly quantify the overall risk to benefit ratio of treatment for these high-risk patients. Finally, the VISTA data set did not have complete data on the NIHSS scores of 48 patients or on mortality for 47 patients, which, although relatively modest numbers in the context of the more than 7000 patients we studied, underscores the challenges of relying on registry-derived data.

Conclusions

In summary, with a projected increase in the occurrence of strokes over the next 2 decades, especially among the elderly,[26] clinicians will be increasingly faced with the issue of administering intravenous thrombolysis to very elderly patients with severe strokes and discussing expectations of different outcome types with their family members. In fact, older age (>70 years) has already been shown to be a factor in modifying the effect of revascularization procedures for stroke prevention.[27] The SPAN-100 index is a simple, practical, and memorable (and validated) tool that can be used to facilitate this discussion by any provider caring for patients with AIS in virtually any setting. It is especially noteworthy that SPAN-100–positive patients, although at risk for substantially worse outcomes than SPAN-100–negative patients, derived a greater benefit from intravenous thrombolysis use than younger and less severe patients. At the very least, our data indicate that even though SPAN-100–positive patients have often been excluded from AIS clinical trials, they should probably not be denied on these grounds.

ARTICLE INFORMATION

Accepted for Publication: March 12, 2014.

Published Online: May 5, 2014. doi:10.1001/jamaneurol.2014.689.

Author Contributions: Drs Nasiri and Reeves had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Ovbiagele, Reeves, Saposnik.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Ovbiagele, Saposnik.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Reeves, Nasiri.
Obtained funding: Ovbiagele, Reeves, Saposnik.
Administrative, technical, or material support: Ovbiagele, Reeves, Saposnik.
Study supervision: Ovbiagele, Reeves, Johnston, Bath, Saposnik.

Conflict of Interest Disclosures: None reported.

Funding/Support: Dr Ovbiagele is supported by Award U01 NS079179 from the NINDS. Dr Saposnik is supported by the Clinician-Scientist Award from the Heart and Stroke Foundation of Canada and the Canadian Institute for Health Research.

Role of the Sponsor: The funding agencies had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The VISTA-Acute Collaboration Steering Committee members are K. R. Lees (Chair), Institutes of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, Scotland; A. Alexandrov, University of Alabama Hospital, Birmingham; P. M. Bath, Institute of Neuroscience, University of Nottingham, Nottingham, England; E. Bluhmki, Boehringer Ingelheim, Biberach, Baden-Württemberg, Germany; N. Bornstein, Stroke Unit, Department of Neurology, Tel Aviv University Medical Center, Tel Aviv, Israel; L. Claesson, AstraZeneca LLP, Södertälje, Sweden; S. M. Davis, Department of Neurology, Royal Melbourne Hospital, University of Melbourne, Melbourne, Victoria, Australia; G. Donnan, Department Neurology, University of Melbourne, Melbourne, Victoria, Australia; H. C. Diener, Department of Neurology, University of Duisburg-Essen, Germany; M. Fisher, Department of Neurology, University of Massachusetts Medical School, Worcester; B. Gregson, Department of Neurosurgery, Newcastle University, Newcastle General Hospital, Newcastle, England; J. Grotta, Department of Neurology, University of Texas, Houston Medical School, Houston; W. Hacke and M. G. Hennerici, Department of Neurology, University of Heidelberg, Heidelberg, Germany; M. Hommel, Joseph Fourier University, Grenoble, France; M. Kaste, Department of Neurology, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland; P. Lyden, Cedars-Sinai Medical Center, Los Angeles, California; J. Marler, US Food and Drug Administration, Silver Spring, Maryland; K. Muir, Division of Clinical Neurosciences,

University of Glasgow, Glasgow, Scotland; R. Sacco, Miller School of Medicine, University of Miami, Miami, Florida; A. Shuaib, Stroke Program, University of Alberta, Edmonton, Alberta, Canada; P. Teal, University of British Columbia, Vancouver, British Columbia, Canada; N. G. Wahlgren, Karolinska Hospital, Stockholm, Sweden; S. Warach, Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Austin; and C. Weimar, Department of Neurology, University Hospital Essen, University of Duisburg-Essen, Germany.

REFERENCES

1. Saposnik G, Guzik AK, Reeves M, Ovbiagele B, Johnston SC. Stroke Prognostication using Age and NIH Stroke Scale: SPAN-100. *Neurology*. 2013;80(1):21-28.

2. Rabinstein A, Rundek T. Prediction of outcome after ischemic stroke: the value of clinical scores. *Neurology*. 2013;80(1):15-16.

3. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20(7):864-870.

4. Goldstein LB, Bertels C, Davis JN. Interrater reliability of the NIH Stroke Scale. *Arch Neurol*. 1989;46(6):660-662.

5. Kasner SE. Clinical interpretation and use of stroke scales. *Lancet Neurol*. 2006;5(7):603-612.

6. Gray LJ, Bath PM, Collier T; Optimising the Analysis of Stroke Trials (OAST) Collaboration. Should stroke trials adjust functional outcome for baseline prognostic factors? *Stroke*. 2009;40(3):888-894.

7. Weimar C, König IR, Kraywinkel K, Ziegler A, Diener HC; German Stroke Study Collaboration. Age and National Institutes of Health Stroke Scale Score within 6 hours after onset are accurate predictors of outcome after cerebral ischemia: development and external validation of prognostic models. *Stroke*. 2004;35(1):158-162.

8. König IR, Ziegler A, Bluhmki E, et al; Virtual International Stroke Trials Archive (VISTA) Investigators. Predicting long-term outcome after acute ischemic stroke: a simple index works in patients from controlled clinical trials. *Stroke*. 2008;39(6):1821-1826.

9. German Stroke Study Collaboration. Predicting outcome after acute ischemic stroke: an external validation of prognostic models. *Neurology*. 2004;62(4):581-585.

10. Mishra NK, Ahmed N, Andersen G, et al; VISTA collaborators; SITS collaborators. Thrombolysis in very elderly people: controlled comparison of sits international stroke thrombolysis registry and virtual international stroke trials archive. *BMJ*. 2010;341:c6046.

11. Sarikaya H, Arnold M, Engelter ST, et al. Intravenous thrombolysis in nonagenarians with ischemic stroke. *Stroke*. 2011;42(7):1967-1970.

12. Ford GA, Ahmed N, Azevedo E, et al. Intravenous alteplase for stroke in those older than 80 years old. *Stroke*. 2010;41(11):2568-2574.

13. Mateen FJ, Buchan AM, Hill MD; CASES Investigators. Outcomes of thrombolysis for acute ischemic stroke in octogenarians versus nonagenarians. *Stroke*. 2010;41(8):1833-1835.

14. Sylaja PN, Cote R, Buchan AM, Hill MD; Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators. Thrombolysis in patients older than 80 years with acute ischaemic stroke: Canadian Alteplase for Stroke Effectiveness Study. *J Neurol Neurosurg Psychiatry*. 2006;77(7):826-829.

15. Kent DM, Selker HP, Ruthazer R, Bluhmki E, Hacke W. The stroke-thrombolytic predictive instrument: a predictive instrument for intravenous thrombolysis in acute ischemic stroke. *Stroke*. 2006;37(12):2957-2962.

16. Saposnik G, Kapral MK, Liu Y, et al; Investigators of the Registry of the Canadian Stroke Network; Stroke Outcomes Research Canada (SORCan) Working Group. IScore: a risk score to predict death early after hospitalization for an acute ischemic stroke. *Circulation*. 2011;123(7):739-749.

17. Strbian D, Meretoja A, Ahlhelm FJ, et al. Predicting outcome of IV thrombolysis-treated ischemic stroke patients: the DRAGON score. *Neurology*. 2012;78(6):427-432.

18. Ntaios G, Faouzi M, Ferrari J, Lang W, Vemmos K, Michel P. An integer-based score to predict functional outcome in acute ischemic stroke: the ASTRAL score. *Neurology*. 2012;78(24):1916-1922.

19. Saposnik G, Fang J, Kapral MK, et al; Investigators of the Registry of the Canadian Stroke Network (RCSN); Stroke Outcomes Research Canada (SORCan) Working Group. The iScore predicts effectiveness of thrombolytic therapy for acute ischemic stroke. *Stroke*. 2012;43(5):1315-1322.

20. Ali M, Bath PM, Curram J, et al. The virtual international stroke trials archive. *Stroke*. 2007;38(6):1905-1910.

21. Mishra NK, Lyden P, Grotta JC, Lees KR; VISTA Collaborators. Thrombolysis is associated with consistent functional improvement across baseline stroke severity: a comparison of outcomes in patients from the Virtual International Stroke Trials Archive (VISTA). *Stroke*. 2010;41(11):2612-2617.

22. Rankin J. Cerebral vascular accidents in patients over the age of 60: II, prognosis. *Scott Med J*. 1957;2(5):200-215.

23. Lee M, Ovbiagele B. Navigating the gray zones of stroke management for a graying population. *Cerebrovasc Dis*. 2010;29(6):523-527.

24. Saposnik G, Cote R, Mamdani M, et al. JURaSSiC: accuracy of clinician vs risk score prediction of ischemic stroke outcomes. *Neurology*. 2013;81(5):448-455.

25. Sandercock P, Wardlaw JM, Lindley RI, et al; IST-3 collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet*. 2012;379(9834):2352-2363.

26. Ovbiagele B, Goldstein LB, Higashida RT, et al; American Heart Association Advocacy Coordinating Committee and Stroke Council. Forecasting the future of stroke in the united states: a policy statement from the American heart association and American stroke association. *Stroke*. 2013;44(8):2361-2375.

27. Bonati LH, Fraedrich G; Carotid Stenting Trialists' Collaboration. Age modifies the relative risk of stenting versus endarterectomy for symptomatic carotid stenosis—a pooled analysis of EVA-3S, SPACE and ICSS. *Eur J Vasc Endovasc Surg*. 2011;41(2):153-158.