Original Contribution

To Treat or Not to Treat?

Exploring Factors Influencing Intravenous Thrombolysis Treatment Decisions for Minor Stroke

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Background and Purpose—The 2015 updated US Food and Drug Administration alteplase package insert altered several contraindications. We thus explored clinical factors influencing alteplase treatment decisions for patients with minor stroke.

Methods—An expert panel selected 7 factors to build a series of survey vignettes: National Institutes of Health Stroke Scale (NIHSS), NIHSS area of primary deficit, baseline functional status, previous ischemic stroke, previous intracerebral hemorrhage, recent anticoagulation, and temporal pattern of symptoms in first hour of care. We used a fractional factorial design (150 vignettes) to provide unconfounded estimates of the effect of all 7 main factors, plus first-order interactions for NIHSS. Surveys were emailed to national organizations of neurologists, emergency physicians, and colleagues. Physicians were randomized to 1 of 10 sets of 15 vignettes, presented randomly. Physicians reported the subjective likelihood of giving alteplase on a 0 to 5 scale; scale categories were anchored to 6 probabilities from 0% to 100%. A conjoint statistical analysis was applied.

Results—Responses from 194 US physicians yielded 156 with complete vignette data: 74% male, mean age 46, 80% neurologists. Treatment mean probabilities for individual vignettes ranged from 6% to 95%. Treatment probability increased from 24% for NIHSS score =1 to 41% for NIHSS score =5. The conjoint model accounted for 25% of total observed response variance. In contrast, a model accounting for all possible interactions accounted for 30% variance. Four of the 7 factors accounted jointly for 58% of total relative importance within the conjoint model: previous intracerebral hemorrhage (18%), recent anticoagulation (17%), NIHSS (13%), and previous ischemic stroke (10%).

Conclusions—Four main variables jointly account for only a small fraction (<15%) of the total variance related to deciding to treat with intravenous alteplase, reflecting high variability and complexity. Future studies should consider other variables, including physician characteristics. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.118.020971.)**

Key Words: contraindications ■ decision making ■ physicians ■ probability ■ stroke ■ tissue plasminogen activator

The activase/alteplase package insert from the Food and Drug Administration was updated in February 2015.[1] Several previous contraindications were modified. However, the new wording has not precisely defined specific criteria for a decision to treat or not with intravenous alteplase. Limited data exist on alteplase use with prior contraindications (based on exclusions from the National Institute for Neurological Disorders r-tPA [recombinant tissue-type plasminogen activator] Stroke Trials).[2] We thus explored factors that may influence a physician's decision to use intravenous alteplase,

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focusing on the more controversial area of treating minor stroke, defined as National Institutes of Health Stroke Scale (NIHSS) score 1 to 5, through a survey targeting physicians that commonly treat acute stroke patients.[3,4]

Methods

In compliance with the American Heart Association Journals' implementation of the Transparency and Openness Promotion Guidelines, the data that support the findings of this study are available from the corresponding author on reasonable request.

Selection of Treatment Decision Factors

A Study Steering Committee (SSC; Appendix I in the online-only Data Supplement) composed of national stroke experts (including both vascular neurologists and emergency medicine physicians) who participated in the TREAT (Reexamining Acute Eligibility for Thrombolysis) Task Force focusing on minor/rapidly improving stroke[5] identified key factors in decision-making about alteplase use. The SSC initially suggested 52 patient-specific factors (Appendix II in the online-only Data Supplement) as well as 16 physician/hospital factors. The 52 patient factor list was reviewed and reduced to 20 factors using Delphi consensus-building methodology[6–8]; the physician/hospital factor list was reduced to 12 in a similar manner (Appendix III in the online-only Data Supplement). The SSC prioritized what they considered the most salient patient factors. An NIHSS score of 1 to 5, stroke features (primary sphere of neurological deficit), and temporal course would be included to mimic the original design of the pilot survey on alteplase decision-making for minor stroke.[9]

Based on statistical considerations and sample size, and to prevent respondent fatigue, it was determined that 4 additional patient factors could be explored. These were identified from those most commonly selected by the SSC in the second round of Delphi voting: anticoagulation use (9/10 SSC members in favor); recent intracerebral hemorrhage (ICH; 9/10); recent ischemic stroke (IS; 9/10); and baseline functional status (BFS; 5/10). Two additional factors, intravenous alteplase treatment window time 0 to 3 versus 3 to 4.5 hours and patient's preference about disability, also had 5 of 10 members in favor of inclusion, but were ultimately excluded for statistical reasons, similarity to other factors (baseline status versus preference), or because they were outside the scope of practice (intravenous alteplase beyond 3 hours from symptom onset is currently off-label in the United States). Physician respondent characteristics were pared down similarly.

Selected Factors

The 7 selected factors in the final survey were NIHSS score (5 levels: 1–5), NIHSS area of deficit (3 levels: visual/language/weakness), BFS (2 levels: fully independent/mild-moderate disability), previous IS (3 levels: yes, <6 weeks ago/yes, ≥6 weeks ago/no), previous ICH (3 levels: yes, <6 months ago/yes, ≥6 months ago/no), recent use of anticoagulation (3 levels: yes, <48 hours ago/yes, ≥48 hours ago/no), and temporal pattern of symptoms in first hour of emergency department (ED) care (2 levels: stable/improving). The survey was prepared on the Qualtrics platform.[10]

Survey Construction

A total of 150 vignettes were constructed, with variation in each of the 7 factors from vignette to vignette (Appendix IV in the online-only Data Supplement). Each survey participant was randomized to 1 of 10 parallel forms, each comprised of 15 vignettes, plus nonvignette questions common to all forms (total of 35 questions). The sequence of presentation of vignettes within each form was randomized for each survey participant.

For each vignette, participants were asked to supply a subjective likelihood of giving intravenous alteplase: never; rarely (10% to 30%); some of the time (30% to 50%); a good bit of the time (50% to 70%); most of the time (70% to 90%); always. Responses were rated 0 to 5 with categories anchored to probabilities of 0 (never), 0.2, 0.4, 0.6, 0.8, and 1.0 (always), respectively. For each vignette, participants were told to assume the patient is admitted to the ED within 60 minutes from stroke symptoms onset.

Statistical Design and Analysis

We used a fractional factorial design for 7 factors.[11] Alias structure allows the 150 vignettes used (sampled from a total of $5^1 \times 3^4 \times 2^2 = 1620$ possible vignettes) to provide mutually unconfounded estimates of all 7 main effects, plus first-order interactions of the NIHSS score factor with the 6 other factors SAS procedures PLAN[12] and OPTEX[13] were used to generate the design matrix, reported to have 97% D-efficiency relative to a fully crossed design.

Simple descriptive statistics for probability of treatment are reported, broken down by each of the unconfounded patient effects in the fractional design. With probability of treatment as the dependent variable, a metric conjoint analysis[14] of those unconfounded patient effects was conducted:

Parameterizing an ordinary least-squares model such that parameter values sum to zero for each effect, a utility range statistic u_j was calculated for the jth effect, being the numeric difference between the largest and smallest of parameter estimates associated with that effect. The relative importance statistic I_j for that effect was then calculated as $100u_j$ divided by the sum of u_j values across all effects; these I_j values sum to 100% over patient effects.

In an attempt to assign valid P values for tests of patient effects, and to study intersubject variability, a generalized mixed linear model was constructed to predict probability of treatment, using a logit link function. Fixed effects were as for the conjoint analysis, but this model introduced a random effect corresponding to subject ID. The necessity of a form ID effect was tested. There were 10 different parallel forms to insure random distribution of these sets of vignettes across the participants. To investigate whether results were consistent across all of these forms, a variable coded 0 to 9 was added as a form ID fixed factor; tests of interactions of that factor with other factors were conducted. Kenward-Roger adjustments to SEs and denominator degrees of freedom were applied; model residuals were inspected for outliers. R^2 was calculated.[15]

A secondary analysis included several physician characteristics as either fixed factors or as scored covariates: age, years of practice, gender, and area of training. These predictors (unlike subject ID) cannot reasonably be construed as random effects.

Selection of Survey Participants

Surveys were sent to email lists for investigators in StrokeNET (Regional Coordinating Center Principal Investigators [N=29] and then to their spoke investigators),[16] the Neurological Emergencies Treatment Trial Network (N=269, Principal Investigators/coordinators; from them to their spokes),[17] MaRISS (Mild and Rapidly Improving Stroke Study),[18] INSTINCT (A Multilevel Intervention to Increase Community Hospital Use of Alteplase for Acute Stroke),[19] the National Stroke Association database of physicians (N=1577; 1073 Neurologists, 504 ED physicians), AHA/NorthEast Cerebrovascular Consortium (N=9821), local ED faculty (N=45), and the office email list of vascular neurology/ED colleagues (Dr Levine; N=55). Only US physicians were included. Physicians were instructed to complete the survey only once.

The study was deemed exempt by the SUNY Downstate Institutional Review Board. Written informed consent was not required; however, a study information sheet was available to potential subjects. This was designed to allow a potential participant to decide whether they were interested in completing the survey. There was no compensation for participation.

Results

Data Return and Completion Rates

Surveys were completed between February 17, 2017, and May 30, 2017. Final data download occurred on May 30,

2017. Responses were returned from 194 subjects satisfying inclusion criteria. Of the 194, 13 completed no vignettes, 25 completed only portions of the survey, and 156 who returned complete vignette data were analyzed.

Demographics

Of the complete survey responders, 116 were male (74%); mean age 46 (range, 27–76); 5 declined to answer. There were 125 trained in neurology (80%) and 31 (20%) in emergency medicine. There were 116 practicing in an urban (74%), 32 suburban (21%), and 8 (5%) rural setting. Twenty-nine (19%) practice in a community hospital, 85 (55%) in an academic institution, and 42 (27%) in a combination of both. Ninety-one (58%) practice in a comprehensive stroke center, 60 (38%) in a primary stroke center, and 5 (3%) in a facility without certification. Telestroke access was available to 105 (67%).

Intravenous Alteplase Treatment Decisions

The probability of intravenous alteplase treatment ranged across all the vignettes from 6% to 95%. The vignette most likely to be treated (95%) was a patient with an NIHSS score of 5, weakness as the area of primary deficit, fully independent BFS, and no previous IS or ICH or recent anticoagulation. The temporal pattern of symptoms was stable.

The 2 vignettes that were least likely (6%) to be treated were (1) NIHSS score of 2, visual as the area of primary deficit and mild-moderate disability at baseline, a prior IS <6 weeks ago, a previous ICH <6 months ago, and recent anticoagulation <48 hours from index stroke onset, with an improving temporal pattern of symptoms and (2) NIHSS score of 1 with weakness as the area of primary deficit, mild-moderate disability at baseline, a prior IS <6 weeks ago, a previous ICH <6 months ago, and anticoagulation <48 hours from index stroke onset, with an improving temporal pattern of symptoms. Table 1 shows the top 10 and lowest 10 vignettes by probability of treatment.

Of the 10 vignettes most likely to be treated (probabilities ranged from 0.69–0.95), 60% had NIHSS score =5 and 20% had NIHSS score =2, 50% had primarily weakness, 40% primarily language, and 10% primarily visual. Thirty percent had mild-moderate baseline disability, 70% had no prior cerebral infarcts, and 30% had an IS >6 weeks before the index stroke. None had a prior ICH, and 30% had received anticoagulation ≥48 hours before the index stroke. Forty percent had an improving course.

Of the 10 vignettes least likely to be treated (probabilities ranged from 0.06–0.10), 60% had an NIHSS score =1, and 30% had an NIHSS score =2. Fifty percent had primarily weakness, 30% had primarily visual, and 20% had primarily language. Eighty percent had a preexisting mild-moderate disability. Seventy percent had a previous IS within 6 weeks of the index stroke, and 90% had a previous ICH (50% within 6 months of the index stroke and 40% beyond 6 months). All 10 had prior

Table 1. Highest- and Lowest-Rated 10 Vignettes

Rank	NIHSS Score	Primary Deficit	Baseline Functional Status	Previous Ischemic Stroke	Previous ICH	Recent AC	Temporal Course	Mean Probability of Treatment
1	5	W	I	N	N	N	S	0.95
2	3	W	D	N	N	N	S	0.81
3	4	L	I	N	N	N	IM	0.81
4	2	W	I	N	N	N	S	0.77
5	5	V	I	≥6 wk	N	N	IM	0.75
6	5	W	D	≥6 wk	N	N	S	0.73
7	5	W	I	N	N	≥48 h	S	0.71
8	5	L	I	≥6 wk	N	N	IM	0.71
9	2	L	D	N	N	≥48 h	S	0.70
10	5	L	I	N	N	≥48 h	IM	0.69
139	1	W	D	<6 wk	≥6 mo	≥48 h	S	0.10
140	2	W	D	<6 wk	<6 mo	≥48 h	IM	0.09
141	1	V	D	<6 wk	N	<48 h	S	0.09
142	1	L	D	N	≥6 mo	<48 h	S	0.09
143	3	W	D	N	<6 mo	<48 h	IM	0.09
144	1	V	I	<6 wk	≥6 mo	≥48 h	IM	0.08
145	1	L	D	<6 wk	≥6 mo	<48 h	S	0.08
146	2	W	I	<6 wk	<6 mo	<48 h	S	0.06
147	1	W	D	≥6 wk	<6 mo	<48 h	IM	0.06
148	2	V	D	<6 wk	<6 mo	<48 h	IM	0.06

AC indicates anticoagulation; D, mild-moderate disability; I, independent; ICH, intracerebral hemorrhage; IM, improving; L, language; N, no/none; NIHSS, National Institutes of Health Stroke Scale; S, stable; V, visual; and W, weakness.

Table 2. Relative Importance of the Individual Factors Studied for an Intravenous Alteplase Treatment Decision

Effect	Relative Importance, %	Cumulative, %	*P* Value
Previous intracerebral hemorrhage	17.5	17.5	<0.001
Prior use of anticoagulation	16.6	34.1	<0.001
NIHSS	13.4	47.4	<0.001
Previous ischemic stroke	9.8	57.2	<0.001
NIHSS×previous intracerebral hemorrhage	7.1	64.3	0.074
NIHSS×baseline functional status	7.0	71.3	0.058
NIHSS×previous ischemic stroke	6.9	78.1	0.049
NIHSS×primary area of deficit	6.4	84.6	0.016
NIHSS×prior use of anticoagulation	4.1	88.7	0.878
Baseline functional status	3.7	92.4	<0.001
NIHSS×temporal course	2.8	95.2	0.393
Primary area of deficit	2.6	97.9	0.001
Temporal course	2.1	100.0	0.001

Tests of main effects have more statistical power than tests of interaction, which is why *P* values, which are derived from the mixed linear model, do not increase monotonically from top to bottom of the table. NIHSS indicates National Institutes of Health Stroke Scale.

anticoagulation (70% within 48 hours and 30% beyond 48 hours of the index stroke). Half had an improving course.

Influence of Individual Factors

The relative importance of each of the 7 factors potentially influencing alteplase treatment, in descending order of importance, are presented in Table 2. Four of the 7 main effects account jointly for ≈57% of total importance, with the top 3 (prior ICH, recent anticoagulation, and NIHSS) all of a similar magnitude. The conjoint model accounted for 25% of the total observed response variance (R^2=0.25); in contrast, a fully crossed model accounted for 30% of the variance.

The probabilities of treatment with alteplase for the conditions in each of the top 4 factors are shown in Table 3. The probability of alteplase treatment was much higher if no prior ICH is reported. It ranked first in relative importance of the individual factors studied. The probability of treating with intravenous alteplase was higher if there was no recent anticoagulant use or prior IS. The probability of treatment also increased monotonically with the total NIHSS score, whereas the probabilities of treatment based on a history of a prior IS were similar.

Other Main Factors' Effects on Probability of Treatment

The other 3 main effects (BFS, temporal course of symptoms, and primary sphere of deficit) were all similar in probability of treatment and made very little contribution to the analysis as shown in Table 3.

Table 3. Probability of Intravenous Alteplase Treatment for the Conditions of the 7 Factors Studied

Factor	Mean	SD
Previous intracerebral hemorrhage		
Within 6 mo	0.23	0.28
≥6 mo	0.30	0.32
None	0.47	0.35
Recent anticoagulation use		
Within 48 h	0.21	0.27
≥48 h ago	0.36	0.33
None	0.44	0.36
National Institutes of Health Stroke Scale		
1	0.24	0.30
2	0.31	0.32
3	0.34	0.33
4	0.37	0.35
5	0.41	0.35
Previous ischemic stroke		
within 6 wk	0.25	0.29
≥6 wk ago	0.35	0.34
None	0.39	0.35
Baseline functional status		
Independent	0.36	0.34
Mild-moderate disability	0.31	0.32
Temporal course		
Stable	0.35	0.34
Improving	0.32	0.33
Primary deficit		
Visual	0.32	0.32
Language	0.35	0.34
Weakness	0.33	0.34

Factor First-Order Interactions

There were several factor interactions with NIHSS of marginal value (Table I in the online-only Data Supplement). As an example of the nature of the interaction (NIHSS×previous ICH): if the NIHSS score =1, with a history of prior ICH, then the decision to treat seems little affected by whether the ICH occurred within 6 months or beyond 6 months as both scenarios had half the probability of treatment compared with no ICH. For higher NIHSS scores,[2–5] the timing of the ICH was more impactful on treatment probability, ranging from 6% to 10% more likely to treat with a remote history of ICH versus recent history.

Specific Physician Characteristics

The mixed linear model was augmented to include the following physician characteristics of those surveyed: age, years of practice (continuous), gender, and area of training (neurology/emergency medicine). Quadratic terms in continuous predictors were included if at least marginally significant. Two

subjects with training area listed as other were excluded; 147 subjects were included in this model which showed that none of these 4 physician characteristics independently significantly ($P<0.05$) predict probability of treatment.

The introduction of quadratic terms was used as a device to detect deviation from linear association of scored covariates with the dependent variable. In no case was any quadratic effect found; therefore these terms did not seem in the final model.

Discussion

Greater physician judgment about several prior intravenous alteplase contraindications may lead to greater uncertainty in which patients to treat. Therefore, we systematically surveyed a sample of US physicians who treat acute IS to help understand how specific factors may influence treatment decisions, focusing on minor stroke. The factors presented to the physicians were decided by SSC consensus to be important key variables. The predictive power of the conjoint model was modest; only ≈25% of variance was explained. The model including all possible interactions was not much better (30%). Further, the 3 main effects jointly account for a little less than half the explained variance, that is, less than half of one-quarter of the total variance (≈1/8 of the variance). The data suggest major factors involved in the decision-making process were not included in the study vignettes or there are many factors (none major), each with limited impact. The dependent variable was probability of treatment; although this is not a continuous variable, it was treated as a score rather than as a series of 6 categories, which would have made reporting and interpretation of results very complex. Despite utilizing expert opinion, we were unable to identify the majority of what determines treatment decisions for minor stroke. We cannot exclude that the factors studied would be more important in the treatment decision of more severe strokes where risk-benefit would more likely favor intravenous alteplase with moderate to severe strokes[20–23] among some of the factors studied (recent anticoagulation/ICH/IS). The patient's perceived level of stroke disability is one potential factor, given the recent guidelines referring to disabling versus nondisabling stroke.[22] Our approach, using the fractional factorial design, suggests that we did not identify all of the factors involved in a treatment decision.

Physician knowledge/beliefs about alteplase effectiveness for minor stroke, risk-benefit perception, risk tolerance, and degree of uncertainty are known to affect physician decision-making; errors in risky decision-making do occur.[24–26] Groups with higher domain-specific knowledge, when deciding on hypothetical cardiac patients of varying risk, rely on fewer dimensions of information than did lower knowledge groups.[24] Patient factors, such as their treatment preference,[3] were not addressed but could be important, especially for minor stroke.

The Delphi method of developing expert consensus has been used often in medicine, including assessing limits/ranges/degree of variability of the original National Institute for Neurological Disorders r-tPA Stroke Trial's exclusion criteria[8] and comparing/contrasting treatment decisions for carotid artery stenosis.[27]

Most of our surveyed physicians were male, trained in neurology, practicing in an urban setting—over half academically, within a comprehensive stroke center, and with telestroke available. We were not powered to adequately address how the latter 3 factors may influence treatment decisions. Our cohort's demographics may have led to biases in determining treatment decision probabilities.

This study was designed and characterized as one of the salience of patient characteristics, rather than physician characteristics; that was the primary analysis. However, because some physician information was collected to adequately describe the sample, a post hoc decision was made to add these in a secondary analysis. Because none of those effects approached statistical significance, it is implausible that they would constitute meaningful confounders of the patient effects.

Although training, experience, and guidelines may facilitate treatment decisions,[28] we did not find that years of experience was significant. Neurology versus EM did not make a difference. Guidelines on alteplase for minor stroke are available but are not definitive, hence the need for the recently completed randomized, placebo-controlled trial of intravenous alteplase for minor stroke.[23]

Concerning individual factors, a prior history of ICH, recent anticoagulation, and actual NIHSS score reduces the probability of giving intravenous alteplase, and appeared more important than a history of recent IS, BFS, primary sphere of deficit, and temporal course. It is more difficult to draw definitive conclusions on the first-order interactions than on individual main effects because of reduced power. Our short vignettes focused on select potential factors may have led to greater uncertainty about treatment decision because of incomplete clinical/neurological examination. As the SSC identified almost 50 factors that may influence treatment decision, a large number of unstudied potential factors remain.

No statistical power analysis was performed because the primary analysis was not inferential—no P values were generated. The conjoint analysis is essentially a descriptive method.

Limitations

We were unable to establish the denominator of all physicians receiving the survey to calculate the percent completion rate, limiting our ability to generalize without bias. We were unable to identify factors and combinations that could explain the majority of the basis for a treatment decision; we could explain ≈25%. It is possible that the use of nonpurposive sampling for the original Delphi (only including stroke experts) contributed to the fact that potentially major factors involved in the decision-making process were not included in the study vignettes. Further, it is possible that the use of a different approach to survey analysis, for example, discrete choice methodology, may have addressed our question better or lead to different results.

As over half of our surveyed physicians practiced at comprehensive stroke centers, they may be more likely to treat than those at other sites. We did not vary size/severity of the ICH or prior IS and did not detail anticoagulation (eg, warfarin with various international normalized ratios, a target-specific oral anticoagulant, or heparin). We also studied only 3 spheres of deficits, so we cannot draw conclusions about ataxia, sensory, or other spheres. We also did not study varying levels of severity, and degrees to which specific deficits may cause disability, within those studied spheres of disability. Further,

we did not include any early vascular imaging or perfusion data in the vignettes, though these have become increasingly commonly used for acute treatment decision-making. We also told respondents to assume that patients presented within 60 minutes of symptom onset so that this could have biased the responses toward treating with alteplase. We had to balance the number of factors we could study with how many vignettes would be required to test for their independent effects, sample size, and the duration physicians would spend on an emailed survey. Understanding the physician decision-making process is complex. Attempts to better understand the process may come from quantitative methods adapted from mathematics and economics as well as qualitative approaches using historical, philosophical, and psychological principles.[28]

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SUPPLEMENTAL MATERIAL

To Treat or Not to Treat? Exploring Factors Influencing rt-PA Treatment Decisions for Minor Stroke

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Supplemental Table I: First order interactions with NIHSS

Analysis Variable : Prob(treat)

NIHSS	Previous Intracerebral Hemorrhage	N	Mean	Std Dev
1	w/in 6 mos	158	0.18	0.26
	≥6mos	154	0.18	0.26
	none	171	0.35	0.33
2	w/in 6 mos	156	0.20	0.26
	≥6mos	170	0.28	0.30
	none	160	0.44	0.34
3	w/in 6 mos	158	0.25	0.29
	≥6mos	156	0.31	0.32
	none	142	0.48	0.34
4	w/in 6 mos	138	0.27	0.31
	≥6mos	167	0.34	0.34
	none	139	0.51	0.35
5	w/in 6 mos	141	0.26	0.29
	≥6mos	156	0.36	0.33
	none	174	0.57	0.36

Analysis Variable : Prob(treat)

NIHSS	Baseline Functional Status	N	Mean	Std Dev
1	independent	249	0.26	0.30
	mild-mod disability	234	0.22	0.29
2	independent	249	0.34	0.33
	mild-mod disability	237	0.27	0.30
3	independent	252	0.32	0.32
	mild-mod disability	204	0.37	0.34
4	independent	215	0.40	0.36
	mild-mod disability	229	0.35	0.34
5	independent	236	0.47	0.39

Analysis Variable : Prob(treat)

NIHSS	Baseline Functional Status	N	Mean	Std Dev
	mild-mod disability	235	0.34	0.30

Analysis Variable : Prob(treat)

NIHSS	Previous Ischemic Stroke	N	Mean	Std Dev
1	w/in 6 wks	156	0.20	0.27
	≥6 wks ago	156	0.23	0.28
	none	171	0.29	0.32
2	w/in 6 wks	142	0.26	0.30
	≥6 wks ago	189	0.29	0.29
	none	155	0.37	0.35
3	w/in 6 wks	146	0.26	0.28
	≥6 wks ago	154	0.36	0.33
	none	156	0.40	0.36
4	w/in 6 wks	154	0.25	0.29
	≥6 wks ago	138	0.44	0.36
	none	152	0.43	0.35
5	w/in 6 wks	170	0.29	0.30
	≥6 wks ago	141	0.48	0.37
	none	160	0.47	0.36

Analysis Variable : Prob(treat)

NIHSS	Primary Deficit	N	Mean	Std Dev
1	visual	156	0.24	0.29
	language	184	0.28	0.31
	weakness	143	0.20	0.27
2	visual	156	0.29	0.31
	language	154	0.32	0.31
	weakness	176	0.31	0.33
3	visual	158	0.35	0.33

Analysis Variable : Prob(treat)

NIHSS	Primary Deficit	N	Mean	Std Dev
	language	142	0.35	0.32
	weakness	156	0.33	0.33
4	visual	136	0.32	0.33
	language	154	0.41	0.36
	weakness	154	0.38	0.34
5	visual	141	0.38	0.32
	language	173	0.40	0.36
	weakness	157	0.43	0.38

Analysis Variable : Prob(treat)

NIHSS	Recent Anticoagulation Use	N	Mean	Std Dev
1	w/in 48 hs	171	0.15	0.23
	≥48 hrs ago	156	0.26	0.29
	none	156	0.32	0.33
2	w/in 48 hs	186	0.20	0.25
	≥48 hrs ago	140	0.34	0.31
	none	160	0.40	0.35
3	w/in 48 hs	172	0.22	0.26
	≥48 hrs ago	142	0.37	0.32
	none	142	0.47	0.36
4	w/in 48 hs	155	0.24	0.28
	≥48 hrs ago	134	0.39	0.34
	none	155	0.49	0.37
5	w/in 48 hs	171	0.28	0.29
	≥48 hrs ago	141	0.44	0.34
	none	159	0.51	0.38

Analysis Variable : Prob(treat)

NIHSS	Temporal Course	N	Mean	Std Dev

Analysis Variable : Prob(treat)

NIHSS	Temporal Course	N	Mean	Std Dev
1	stable	262	0.25	0.30
	improving	221	0.23	0.29
2	stable	235	0.34	0.34
	improving	251	0.28	0.29
3	stable	232	0.34	0.32
	improving	224	0.34	0.34
4	stable	213	0.41	0.34
	improving	231	0.34	0.35
5	stable	250	0.41	0.36
	improving	221	0.40	0.35

Supplemental Appendix I: List of steering committee members

Joseph Broderick
Edward Feldmann
James Grotta
Scott Kasner
Pooja Khatri
Doojin Kim
Brett Meyer
Peter Panagos
Jose Romano
Phillip Scott

Supplemental Appendix II: Proposed factors for Delphi first round

NIHSS score, NIHSS area of deficit, and temporal course are not included in the Delphi lists below because the SSC decided that they would be included as part of the goal of the study. They were agreed upon before the SSC added the extra factors.

Patient Factors

Gender
Age
Occupation
Employment
Education
Diabetes
Dialysis
Relative alteplase contraindication
Other vascular disease
Known carotid stenosis
Migraines
Seizures
Psychiatric conditions
Baseline functional status/independence
Hypertension
Intracranial tumor
Recent stroke
Previous hemorrhage
Borderline coagulopathy
Amyloid
CHF
Previous MI
Active cancer
Atrial fibrillation
Life-limiting diagnosis
Antiplatelet use
Suspected/known vessel occlusion
Suspected/known stroke etiology
Anticoagulant use in past 48 hours
Sub-therapeutic on anticoagulation
Prior stroke
Anterior vs. posterior circulation
Tobacco
Drug use/abuse
Race
English as second language
Patient's preference regarding disability
Arrival Time 0-3 vs 3-4.5 hours
Initial stroke severity
Temporal course
NIHSS <5
NIHSS grouped by clinical syndromes
NIHSS <3
Rapid improvement
Total NIHSS
Individual NIHSS
Total NIHSS + domains
Combine NIHSS into spheres of deficits
NIHSS 0-2
Neglect/visual deficits
Deficit type
Cortical vs. elemental items

Hospital/Physician Factors

Physician training
Location of training (vascular center or not)
Physician certification
Physician experience with IV alteplase
Extent of shared decision making with specialist
Stroke center certification type
Specialist access
Knowledge of probability of success from literature
Practice environment
Hospital setting (urban/rural)
Hospital size
Geographic region
Telestroke availability
Community/academic hospital
Drip & keep/drip & ship
Clinician's perception of legal risk

Supplemental Appendix III: Second Delphi round

20 Patient Factor List

Gender
Employment status/occupation
Diabetes
Renal disease
Known carotid stenosis
Baseline functional status/independence *
Hypertension
Recent stroke *
Previous hemorrhage *
Borderline coagulopathy
Active cancer or other life-limiting diagnosis
Atrial fibrillation
Patient's preference regarding disability
Recent use of anticoagulation *
Tobacco
Drug use/abuse
Arrival time 0-3 vs 3-4.5 hours
Suspected/known vessel occlusion
Dominant vs. non-dominant side deficit
Age

12 Physician/Hospital Factor List

Physician training *
Physician certification *
Physician experience with IV alteplase *
Extent of shared decision making
Stroke center certification type *
Specialist access
Knowledge of probability of success from literature *
Hospital setting (urban/rural) *
Geographic region *
Telestroke availability *
Community/academic hospital *
Drip & keep/drip & ship **

***** = Included in final survey

Supplemental Appendix IV: Sample vignette

Text provided to introduce the survey:
Thank you for taking this survey to help understand the role of specific factors that may influence a physician's treatment decision for IV rt-PA. Please answer each vignette with your single best answer for the individual scenario. The factors presented were decided by consensus of the HAMLET Steering Committee of stroke experts to be important key variables for consideration.

For each vignette, assume the patient is admitted to the Emergency Department (ED) within 60 minutes from stroke symptoms onset.

At 60 minutes after arrival you are asked to provide your IV tPA treatment decision.

SAMPLE VIGNETTE

NIHSS Score at time of treatment decision
2
NIHSS area of primary deficit
Language
Baseline functional status/independence
Mild-moderate disability
Previous ischemic stroke
Yes, 6 or more weeks ago
Previous cerebral hemorrhage
Yes, 6 or more months ago
Recent use of anticoagulation
Yes, less than 48 hours ago
Temporal pattern of symptoms in the first hour of ED care
Stable

For cases having this profile, how often would you prescribe tPA?

Response variable
0 never
1 rarely (10%-30%)
2 some of the time (30%-50%)
3 a good bit of the time (50%-70%)
4 most of the time (70%-90%)
5 always
6 I do not know