Home Time Is Extended in Patients With Ischemic Stroke Who Receive Thrombolytic Therapy
A Validation Study of Home Time as an Outcome Measure

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Background and Purpose—“Home time” (HT) refers to the number of days over the first 90 after stroke onset that a patient spends residing in their own home or a relative’s home versus any institutional care. It is an accessible and objective parameter, free from subjective bias, with potential as an outcome measure in acute stroke trials. We sought to validate HT and assess treatment responsiveness using independent data.

Methods—We estimated HT in the Stroke Acute Ischemic NXY Treatment (SAINT) I neuroprotection trial. We compared outcomes between thrombolysed (T) and nonthrombolysed comparators (C) using HT and the modified Rankin Scale. For our primary analysis, we adjusted for baseline covariates that significantly influence HT and in sensitivity analyses considered all variables that differed between groups at baseline. We report ordinal logistic regression and analysis of covariance with 95% CIs. We describe the relationship of HT with baseline National Institutes of Health Stroke Scale and its components and with Day 90 modified Rankin Scale and Barthel Index.

Results—SAINT I included 1699 patients from 23 countries, of whom 28.7% received alteplase. HT correlated with age, baseline severity, alteplase use, side of ischemic lesion, presence of diabetes, and country of patient enrolment (each \(P<0.05\)). We found an association between use of alteplase with better adjusted outcomes by either measure (OR for extended HT, 1.36; 95% CI, 1.08 to 1.72; \(P=0.009\); analysis of covariance \(P=0.007\) with a 5.5-day advantage; OR for more favorable modified Rankin Scale, 1.6; 95% CI, 1.28 to 2.00; \(P<0.0001\); Cochran-Mantel-Haenszel \(P=0.046\)). HT was significantly associated with baseline National Institutes of Health Stroke Scale and each component of the National Institutes of Health Stroke Scale except level of consciousness, dysarthria, and ataxia. HT was significantly associated with Day 90 modified Rankin Scale and Barthel Index.

Conclusions—HT is a responsive measure for use in multinational acute stroke trials. Its inclusion as a complementary outcome is reasonable. We propose treatment effects are adjusted for age, baseline National Institutes of Health Stroke Scale, side of stroke lesion, country of enrollment, and the presence of diabetes. 

Key Words: alteplase ■ clinical trial ■ home time ■ outcomes ■ stroke ■ thrombolysis

Home time” has been defined as the number of days over the first 90 after stroke onset that a patient spends residing in their own home or in that of a relative as opposed to within institutional care of any sort. Thus, it provides a graded objective outcome measure for stroke trials and correlates closely with modified Rankin Scale (mRS) score but has not yet been validated in independent data sets. Home time is being collected prospectively in acute stroke research (eg, the Membrane-Activated Chelator Stroke Intervention [MACSI] Phase III trial, ISRCTN NCT00893867). Pending prospective data, it is desirable to examine attributes of home time in existing data sets. The Stroke Acute Ischemic NXY Treatment (SAINT) I trial collected data on discharge setting, date of discharge, and on adverse event duration associated with hospitalization sufficient to estimate home time. The SAINT trials examined the role of neuroprotection...
with NYX-059 in patients with ischemic stroke, finally concluding it ineffective, but recorded data on use of alteplase.3 Because alteplase has an established treatment effect,4–6 we planned to examine outcomes from alteplase use among SAINT patients. We wished to examine home time as our primary outcome and to validate this against mRS scores at Day 90, which is conventionally used for outcome assessment in acute thrombolysis trials.7

Methods

Data
We collated data on patients enrolled in the SAINT I trial, including age, baseline severity, risk factors, demography, use of recombinant tissue plasminogen activator, and outcome measures like mRS, National Institutes of Health Stroke Scale (NIHSS), and Barthel Index. The SAINT trial recorded dates of admissions to institutions and residence at home across the first 90 days from ischemic stroke. From these we calculated home time (HT).

Statistical Analyses
We modeled HT for all variables available at baseline. Age and baseline NIHSS are known to influence outcomes in patients with stroke.8,9 However, we chose to identify any additional predictors based on a regression analysis. For this, we undertook a logistic regression analysis in which HT was considered an ordinal variable and identified significant predictors in the model. We likewise modeled HT using linear regression analysis. For our primary analysis we retained predictors that were significant at \( P=0.05 \) within adjusted analyses when comparing for outcomes between thrombolysed and nonthrombolysed patients. For sensitivity analysis, we repeated the comparison using as covariates any baseline variables that significantly differed between thrombolysed patients and comparators.

We analyzed the treatment effect of thrombolytic therapy on HT both by ordinal logistic regression analysis and by analysis of covariance. With 91 possible HT categories across a sample of 1699 patients, the Cochran-Mantel-Haenszel (CMH) test with simultaneous stratification for all relevant covariates was found unreliable. However, the large number of categories led the ordinal HT data to approximate closely enough to a continuous distribution to satisfy the assumptions of analysis of covariance.

For comparison against Rankin scores as the standard measure of outcome, we performed CMH test and ordinal logistic regression analysis as before.3 Where incomplete cells in the stratified analysis precluded CMH testing, we provide probability values from ordinal regression. The CMH probability value is considered more reliable because it invokes fewer assumptions.

We used logistic regression to examine the relationship of HT with Rankin scores at Day 90, which is conventionally used for outcome assessment. For comparison against Rankin scores as the standard measure of outcome, we performed CMH test and ordinal logistic regression analysis as before.3 Where incomplete cells in the stratified analysis precluded CMH testing, we provide probability values from ordinal regression. The CMH probability value is considered more reliable because it invokes fewer assumptions.

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Results

Baseline Characteristics and Unadjusted Outcomes
There were important differences in baseline characteristics between groups, as shown in the Table, and neither HT nor mRS score was better in the thrombolysis group based on unadjusted analyses. Unadjusted mean HT in thrombolysed patients was 43.9±39.1 days compared with 51.5±38.1 days in untreated control subjects (n=1699). The unadjusted OR for more favorable distribution of mRS scores among thrombolysed patients was 1.02 (95% CI, 0.8 to 1.2; CMH \( P=0.9 \)).

In both logistic and linear regression analysis, we found age, side of lesion, baseline severity, country of patient enrollment, known diabetes, and use of alteplase to be significant predictors (\( P<0.05 \)) of HT.

In the univariate linear regression model, these factors, respectively, contributed 3.4%, 0.4%, 20.8%, 0.15%, 0.4%, and 0.75% to variation in HT. From multivariate regression they together accounted for 25.6% of the variation. We adjusted for these variables in our primary analysis. In a sensitivity analysis, we adjusted for the variables that differed between groups at baseline as shown in the Table.

Outcomes After Use of Alteplase

Home Time

Primary Analysis
When controlled for age, side of lesion, baseline severity, country of patient enrollment, and known diabetes, the odds for longer HT over the first 90 days after thrombolysis was 1.36 (95% CI, 1.08 to 1.72; \( P=0.009 \)). From analysis of covariance applying age, side of lesion, baseline severity, country of patient enrollment, and known diabetes as covariates, we estimated that HT was extended by 5.5 days (\( P=0.007 \)) in patients who received alteplase.
Sensitivity Analysis
Logistic regression analysis adjusted for variables that differed at baseline (Table) confirmed significant odds for longer HT among patients who received alteplase (OR, 1.38; 95% CI, 1.09 to 1.74; \( P = 0.007 \)). From analysis of covariance that included country of enrollment and all variables listed in the Table, we estimated that HT was extended by 4.6 days \(( P = 0.03)\) in patients who received alteplase.

mRS at 90 Days
Primary Analysis
When adjusted for variables that influence the HT, namely age, side of lesion, baseline severity, country of patient enrollment, and known diabetes, the OR for more favorable distribution of mRS after thrombolysis was 1.6 (95% CI, 1.28 to 2.00; \( P < 0.0001; \) CMH \( P = 0.046 \)).

Sensitivity Analyses
When adjusted for variables that differed at baseline (Table), the OR for more favorable distribution of mRS after thrombolysis was 1.53 (95% CI, 1.23 to 1.92; \( P = 0.0002 \)).

We show the OR for more favorable HT (left) and mRS scores (right) for each stratum of baseline severity in the Figure. Here, the combined odds were derived from random effects meta-analysis of odds across all strata. Cochran’s Q and \( I^2 \) values refer to variability among strata of NIHSS levels.

Relationship of HT With Baseline Severity or With Other Measures of Outcome

Relationship of HT With Baseline NIHSS Score and Its Components
In an analysis of covariance model that controlled for age, side of lesion, country of trial center, and diabetes, HT correlated significantly with baseline NIHSS \(( P < 0.05)\). The NIHSS components that significantly associated with HT were: best gaze \(( P = 0.0004)\), vision \(( P = 0.0076)\), facial palsy \(( P = 0.0016)\), motor weakness (left arm \( P = 0.013\); right arm \( P = 0.0256\); left leg \( P < 0.0001\); right leg \( P = 0.0015)\), language \(( P = 0.0004)\), and extinction \(( P = 0.0137)\). Limb ataxia, sensory disturbance, dysarthria, and level of consciousness were not associated with HT (each \( P > 0.05 \)).

Relationship of HT Time With 90-Day Rankin Scores
In a logistic regression analysis, longer HT correlated significantly with more favorable Rankin scores. This occurred both independently and also when other predictors of HT, including alteplase use, were considered in the model. Analysis of covariance resulted in a significant model \(( P < 0.0001, R^2 57.5\% )\): HT = 2.76 + 81.6 (Rankin 0) + 76.4 (Rankin 1) + 65.05 (Rankin 2) + 48.5 (Rankin 3) + 28.8 (Rankin 4) + 17.2 (Rankin 5) + 0 (Rankin 6).

Relationship of HT With 90-Day Barthel Index
In logistic regression analysis, longer HT correlated significantly with better Barthel Index \(( P < 0.0001)\). This occurred independently and also when other predictors of HT, including alteplase use, were considered in the model. Analysis of covariance also resulted in a significant model \(( P < 0.0001)\) for HT.

Alteplase Use and the Trial Center
Alteplase use varied across countries that contributed to the SAINT trial \(( P < 0.0001)\). Country accounted for 19.1% of center variation in alteplase use.

Discussion
A desirable outcome measure for use in acute stroke needs to be simple to measure; open to confirmation; resistant to subjective bias; comprehensible to clinicians, patients, and regulatory authorities; responsive to treatment effects; robust to confounding factors such as withdrawal of consent; robust to cultural variation; and statistically convenient. \(^{10}\) HT offers features that suggest its suitability but has yet to be validated. In a trial population, we have now shown better outcomes among patients who received alteplase not only on Rankin
scale, which is a widely used measure of outcome assessment in stroke trials, but also on HT. This suggests responsiveness of HT to treatment effects. We found an association of paresis, visual disturbance, aphasia, and extinction at baseline with shorter HT in patients with stroke. This implies that intervention to lessen stroke severity will extend HT. We confirmed a relationship of HT with Rankin scores on Day 90 and with Barthel Index.

Prospectively collected HT data have not been reported for any trial. In analyzing SAINT I, we are exposed to 2 constraints: we could only estimate HT from admission and discharge records and this will have weakened the relation with treatment effects and our treatment was applied in a nonrandom manner to <30% of our cohort. This treatment bias is illustrated by substantial differences in baseline characteristics between our groups and by the absence of more favorable outcomes on mRS before adjustment for these factors. The reversal of the HT disadvantage in the thrombolysis group into a highly significant advantage after covariate adjustment may represent confirmation of the sensitivity of HT as an outcome measure but we must interpret this cautiously until it can be confirmed.

There is international variation in stroke care systems that will affect HT. Our data take account of admissions to rehabilitation facilities when estimating HT; only the time spent at home unassisted, with or without limited care services, is counted. The variation in use of inpatient rehabilitation facilities should not confound interpretation of randomized trials, in which treatment and control group patients are balanced within countries. There is potential for a confounding effect in the present study with regard to alateplase use, however, and its direction is unpredictable. If alteplase is widely used in healthcare systems that also offer extensive inpatient rehabilitation, then we would see shorter HT despite alteplase use. To control for any influence, we included “country of patient enrollment” as a variable in our analysis. Country was a significant predictor of HT and was therefore retained as a covariate in our adjusted analyses.

At present, we cannot claim HT to be a better outcome measure compared with others that are routinely used (eg, mRS, NIHSS, Barthel Index, etc), but it deserves a complementary role.10

There are underlying reasons why HT may be more sensitive to early treatment effects than 90-day mRS or Barthel Index. HT reflects the status of the patient across each of the 90 days after stroke rather than a snapshot view; it incorporates medical, nursing, social, and rehabilitation needs with patient and family preferences; and it places more emphasis on early outcome than the Day 90 measures.

Sensitivity of outcome measures to baseline variables is not a disadvantage; it is desirable that the outcome should be influenced by stroke severity. It is more difficult to assess whether it is appropriate for the outcome to be affected by a treatment equally at all levels of the baseline factor or show disproportionate effects. Our finding that ORs for HT are greater at higher levels of baseline severity may reflect a greater influence of alteplase in larger strokes, a disadvantage of HT as an outcome measure, or a consequence of the statistical presentation; a constant absolute increase in HT will become proportionately smaller as it is expressed as a function of the longer HTs achieved by patients with mild stroke.

Fewer than 30% of patients received thrombolytic therapy in the SAINT I trial and alteplase use varied across the participating countries. Cultural differences in stroke care could profoundly influence HT and in our study could interact with the decision to treat with intravenous alteplase. Adjustment for regional variation may be essential. In a prospective randomized trial, cultural variations will remain but should not interact with the decision to treat. It is reassuring that despite involvement of 23 countries, we still observed an apparent treatment effect of alteplase in our sample.

HT is a continuous variable that was recorded as an ordinal measurement. Hence, we present both regression analysis in which HT was treated as an ordinal variable and analysis of covariance in which HT was regarded as a continuous variable. We propose that handling HT as a continuous variable will offer greater statistical power and flexibility in analysis.

In conclusion, we find HT to be a responsive measure of outcome for use in acute stroke trials. We conclude that its inclusion as a complementary outcome is reasonable and propose that treatment effects should be adjusted for age, baseline NIHSS, side of stroke lesion, country of enrollment, and the presence of diabetes.

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**References**


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Abstract

经溶栓治疗的缺血性卒中患者居家时间延长
一项关于居家时间作为预后评估指标的验证研究

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背景与目的：居家时间（HT）是指患者发生卒中的首个90天内在自己家里或者亲戚家里的居住而非任何医疗机构居住的天数。这是一个可获得且客观的参数，不受主观偏倚的干扰，具有评估急性卒中试验中结局指标的潜在意义。我们试图使用独立数据来验证HT的作用并评估治疗的效果。

方法：我们分析急性缺血性卒中NXY治疗（Stroke Acute Ischemic NXY Treatment, SAINT）I期神经保护试验中HT，采用HT及改良Rankin量表（mRS）对经溶栓治疗（T）及未经溶栓治疗的对照组（C）的结局进行比较。初步分析中，校正了会显著影响HT的基线协变量，并在敏感性分析中考虑了所有的变量在不同组之间的基线水平。用有序logistic回归及95%置信区间的协方差分析来分析结果。描述HT与基线NIHSS评分及其组成部分、90天的mRS评分和Barthel指数间的关系。

结果：SAINT I试验纳入来自23个国家的1699例患者，其中28.7%的患者应用阿替普酶溶栓。HT与年龄、基线病情的严重性、阿替普酶的应用、缺血性损伤的部位、糖尿病及纳入患者所登记的国家相关（每一项P<0.05）。我们发现无论采取何种评估方式，应用阿替普酶的患者校正后的预后都较好（HT延长的OR为1.36，95%CI, 1.08-1.72；P=0.009；协方差分析P=0.007，有5.5天的优势；更良好的mRS评分的OR为1.6，95%CI, 1.28-2.00；P<0.0001；Cochran-Mantel-HaenszelP=0.046）。HT与基线NIHSS评分及其各组成部分（除外意识水平、构音障碍及共济失调外）显著相关，HT与90天的mRS评分及Barthel指数显著相关。

结论：HT是一个治疗反应的测量指标，可用于多国参与的急性卒中试验。将其列入补充的结局评估是合理的，我们建议对治疗效果要根据年龄、基线NIHSS评分、卒中损伤部位、患者所登记的国家及糖尿病进行调整。

关键词：阿替普酶，临床试验，居家时间，结局，卒中，溶栓

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