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 thromboloyzed (T) and nonthromboloyzed 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. (Stroke. 2011;42:1046-1050.)

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.1 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.1 Home time is being collected prospectively in acute stroke research (eg, the Membrane-Activated Chelator Stroke Intervention [MACSI] Phase III trial, ISRCTN NCT00893867).2 Pending prospective data, it is desirable to examine attributes of home time in existing data sets. The Stroke Acute Ischemic NXY Treatment (SAINT) 1³ 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 thrombolyzed and nonthrombolyzed patients. For sensitivity analysis, we repeated the comparison using as covariates any baseline variables that significantly differed between thrombolyzed 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 and with baseline NIHSS. We undertook our analyses on SAS 9.2 and Stats direct software.

**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. Cochrane 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. 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 alteplase 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.

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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**Abstract**

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**Background and Objectives:**

Home time (HT) refers to the number of days patients remain at home or with relatives after their stroke within the first 90 days, excluding hospital stays. HT is a readily accessible and objective parameter that is not subject to biased judgments, and which has potential meaning as an outcome measure in acute stroke trials. We aimed to independently validate HT and assess treatment responses.

**Methods:**

We analyzed the acute ischemic stroke NXY treatment (SAINT) trial of 1699 patients, including 28.7% treated with alteplase. HT was compared between the alteplase (T) and placebo (C) groups using HT and modified Rankin Scale (mRS) scores at 90 days. Preliminary analyses were adjusted for baseline characteristics that significantly affected HT and considered all variables in each group. Logistic regression and 95% confidence intervals were used to analyze results. We described the relationship between HT and baseline NIHSS scores, its components, and mRS and Barthel Index scores at 90 days.

**Results:**

In the SAINT I trial, 1699 patients were included, where 28.7% received alteplase. HT was significantly correlated with age, baseline NIHSS score, alteplase use, ischemic lesion location, diabetes, and country of registration. We found that alteplase-treated patients had a better adjusted outcome (HT extended OR = 1.36, 95% CI, 1.08-1.72; P = 0.009; Cochran-Mantel-Haenszel P = 0.046). HT was related to mRS scores and Barthel Index scores at 90 days. HT was significantly correlated with baseline NIHSS scores and its components (except for level of consciousness, speech disorder, and cerebellar ataxia).

**Conclusion:**

HT is a valid measure of treatment response that can be used in multi-center acute stroke trials. Including HT in outcome assessment is reasonable. Adjustments for age, baseline NIHSS score, stroke location, country of registration, and diabetes are recommended.

**Keywords:**

Alteplase, Clinical Trial, Home Time, Outcome, Stroke.