Statistical Analysis Plan

Study: AHA GWTG – Stroke
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Title: **Earlier Time to Treatment Start Increases the Likelihood of Good Clinical Outcome after Endovascular Recanalization Therapy for Acute Ischemic Stroke**

Primary objectives

- Examine the association of early time from onset to puncture (OTP) and clinical outcomes amongst ischemic stroke patients undergoing endovascular therapy
- Use data on the relation of OTP to functional outcomes to indicate faster OTP time improves outcome to drive quality improvement projects.
- Examine predictors of earlier onset-to-treatment time
- Examine the association of early time from door (hospital arrival) to puncture (DTP) among non-transfer patients and clinical outcomes amongst ischemic stroke patients undergoing endovascular therapy
- Use data on the relation of DTP to functional outcomes to indicate faster DTP time improves outcome to drive quality improvement projects.
- Examine predictors of earlier door-to-treatment time

Hypotheses

- Earlier OTP is associated with good clinical and functional outcomes
- Earlier DTP is associated with good clinical and functional outcomes
- DTP times are more strongly related to outcome than are OTP times

Data sources

Data for this analysis come from Get With the Guidelines Stroke (GWTG-S) registry from Jan 2017 harvest. CSTK elements will be used.

Study population

The study population for this analysis will be based on those patients who:

- Hospitals in GWTG-S registry had at least 75% complete data on medical history
- Clinical diagnosis of Acute ischemic stroke (AIS)
- Admitted between Jan. 1, 2015 and Dec. 31, 2016
- Documented baseline NIHSS
- IA catheter based treatment at this hospital
- Site of Occlusion
    - If Site of Occlusion is documented in greater than 80% of cases, all analyses will be confined to patient WITH any of: Cervical ICA, Intracranial ICA, MCA, M1 MCA, and M2 MCA

  - If Site of Occlusion is documented in less than 80% of cases, all analyses will be confined to patients WITH any of: Cervical ICA, Intracranial ICA, MCA, M1 MCA, and M2 MCA, and Not Documented

Further exclude (apply sequentially):

- IA received in outside hospital
- Stroke occurred in this hospital
- Stroke symptoms resolved at the time of presentation
- Transfer out/discharge destination ND or missing/LAMA
- Last known well date/time missing or unknown or MM/DD/YYYY only
- Arrival date/time missing or unknown or MM/DD/YYYY only
- IA arterial puncture date/time missing or unknown or MM/DD/YYYY only
- Incorrect order of last known well, arrival and arterial puncture time
- Onset to arterial puncture time > 8 hours
- Gender missing

Outcomes

- Reperfusion
  - Substantial reperfusion TICI 2b-3 yes vs no
  - Reperfusion degree: TICI ordinal scale 0,1,2a,2b,3
- In-hospital mortality/hospice, Yes vs. No
  - Exclude transfer out and discharge destination missing or not documented/unable to determine
- Functional outcomes
  - Ambulatory status
    - Binary: able to ambulate at discharge (includes both patients able to ambulate without AND with assistance), Yes vs. No
    - Ordinal: highest->lowest able to ambulate independently->with assistance->not able to ambulate->death/hospice
    - Exclude transfer out, reported among non-missing data
  - Discharge destination
    - Binary: discharge home or acute rehabilitation, Yes vs. No
    - Ordinal: highest->lowest home->IRF ->SNF, other care facilities, like LTC, intermediate care facilities->death/hospice
    - Exclude transfer out and discharge destination missing or not documented/unable to determine
  - Discharge Modified rankin scale (mRS)
    - Binary: 0-1 vs. 2-6
    - Binary: 0-2 vs. 3-6
    - Ordinal: 0->1->2->3->4->5->6
    - Collected from 2012, among non-missing data
    - If expired or discharge to hospice at discharge, discharge mRS is set as 6
  - 3-month post discharge Modified Rankin scale
    - Binary: 0-1 vs. 2-6
    - Binary: 0-2 vs. 3-6
    - Ordinal: 0->1->2->3->4->5->6

    - Collected from 2012, among non-missing data
- sICH complication after treatment, Yes vs. No
    - Reported among all patients (all received IA tPA or MER)

All the outcomes are determined by GWTG-S registry.

(We we anticipate a high rate of missingness for 3 month mRS, so it will be an auxiliary, rather than lead outcome. Analysis for this endpoint will use IPW where propensity is defined as the probability that a patient is a complete case.)

Main variables of interest

- OTP time: Last known well to puncture time
    - Continuous: in 15 minutes increment
    - Categorical: 0-120m, 121-240m, 241-360m, 361-480m, the largest OTP time will be used as the referent group.
- DTP time: Door to puncture time
    - Continuous: in 15 minutes increment
    - Categorical: 0-30m, 31-60m, 61-90m, 91-120m, 121-150m, 151-180m, > 180m, the 151-180m DTP time will be used as the referent group.

Subgroups of interest

- Prior treated with IV tPA, Yes vs. No
- Achieved substantial reperfusion, Yes vs. NO
- Witnessed Onset, Yes vs No (Witnessed onset = "Time of Discovery Same as Last Known Well" checked Yes)

Statistical analysis

We will first describe baseline characteristics of the study population by the pre-specified categorical OTP variable, using proportions for categorical variables and median with 25^{th} and 75^{th} percentiles for continuous variables. We will test for differences on the patient and hospital variables between any of the OTP levels using Chi-square tests for categorical variables and Kruskal-Wallis test s for continuous variables.

The relation of OTP to functional outcomes will be examined. Multivariable logistic regression models will be performed to assess the relationship of OTP time and the binary outcomes, and the OTP time and the ordinal outcomes. Analyses will probably be conducted in two steps. First, the relationship between OTP time and binary outcomes will be evaluated, and presented to PIs to determine OTP target value and the categories. Then we will move to modeling. OTP will be analyzed as a continuous variable (in a 15 minutes increment) in the models. The curves will be displayed. If non-linear relationship exist, splines might be employed in that proper knots will be chosen based upon the curves.

In addition to the continuous time OTP analysis, the relation of OTP categories to outcome will be analyzed, using the OTP categories of 0-120m, 121-240m, 241-360m, and 361-480m. The largest OTP time will be used as the referent group. Multivariable regression models will be performed to assess the association of OTP and the outcomes, specifically, logistic regression for binary outcomes, and ordinal model for multinomial ordinal outcomes. Generalized estimation equations (GEE) will be used in all regression models to account for within-hospital clustering. The outcomes modified rankin scales at discharge and 90 days had slightly higher missing, analysis of these outcomes will be conducted in complete case (CS) sample and using IPW method. In IPW,

propensity will be defined as the probability that a patient is a complete case, the IPW method will up weight those who have high propensity of being missing and down weight the other patients as to compensate for those who are actually missing the outcome measure.

The relation of DTP to functional outcomes will be examined, only in EMS-arriving patients. Multivariable logistic regression models will be performed to assess the relationship of DTP time and the binary outcomes, and the DTP time and the ordinal outcomes. DTP will be analyzed as a continuous variable (in a 15 minutes increment) in the models. The curves will be displayed. If non-linear relationship exist, splines might be employed in that proper knots will be chosen based upon the curves.

As well as the continuous time DTP analysis, the relation of DTP categories to outcome will be analyzed, only in EMS-arriving patients, using the OTP categories of: 0-30m, 31-60m, 61-90m, 91-120m, 121-150m, 151-180m, > 180m. The 151-180m DTP time will be used as the referent group. Multivariable regression models will be performed to assess the association of DTP and the outcomes, specifically, logistic regression for binary outcomes, and ordinal model for multinomial ordinal outcomes.

The multivariable models will adjust for patient and hospital characteristics as follow:

- Demographics, age (continuous), female sex, race (Black, Hispanic, Asian and others vs. Caucasians, missing imputed to Caucasian;
- Insurance: Medicare, Medicaid, private insurance/VA/others, vs. no insurance, missing imputed to private/other insurance;
- Medical history: Atrial Fibrillation, Prosthetic Valve, CAD-Prior MI, Carotid Stenosis, Diabetes, PVD, Hypertension, Smoking, Dyslipidemia, Prior Stroke/TIA, HF, missing imputed to No;
- Arrival and admission information: EMS arrival vs transfer from another facility vs private transportation) (missing imputed to EMS arrival), arrived off-hours;
- NIHSS (continuous), interaction of age and NIHSS; patients with missing NIHSS will be excluded from the primary analysis
- Use of IV tPA either at this hospital or at the transferring hospital
- Prior to admission medications: antihypertensive, lipid lowering, diabetic, antiplatelet and anticoagulation, missing imputed to No;
- Ambulatory status prior to admission: Independent vs. Other, imputed to Independent if missing < 15%. If larger, we will not include;
- Site of Occlusion: Any ICA (cervical or intracranial) vs any MCA (MCA, M1 MCA, M2 MCA). If not documented are included (depending on results on page 3), impute them to MCA
- Hospital characteristics: rural vs. urban setting, number of beds (continuous), teaching hospital, regions, certified primary stroke center (PSC), certified comprehensive stroke center (CSC) and annual number of AIS discharges, annual IV tPA volume, annual IA therapy volume~~)~~, missing on rural vs. urban setting, number of beds, teaching hospitals will be excluded.
- Variables with >15% missing will not be used in the model

Primary analysis will be conducted for all outcomes using all patients in the study population. Secondary analysis will be conducted in the patients with substantial reperfusion for the in-hospital mortality/hospice, functional outcomes, and sICH complication outcomes. A sensitivity analysis subset in patients who collected at least one lab variables (BMI, diastolic and systolic BP, fasting blood glucose, INR and serum creatinine) will be conducted as well.

Subgroup analyses will be conducted by using similar multivariable logistic or ordinal models. The models will include: 1) the subgroups of interest, OTP time, and interaction of OTP and each of the abovementioned subgroup variables of interest; and 2) the subgroups of interest, DTP time, and interaction of DTP and each of the abovementioned subgroup variables of interest. The interaction p-value will be reported and a significant interaction infers that the association of OTP and DTP and outcomes is different among subgroups. The association of OTP and DTP and outcomes will be reported in each subgroup.

Tables to be produced

Table 1.a: Descriptive of Patient and hospital characteristics for patients treated with IA therapy, overall, and separately for witnessed onset vs unwitnessed onset, and by OTP time intervals 0-120m, 121-240m, 241-360m, and 361-480m.

Table 1.b: Descriptive of Patient and hospital characteristics for patients treated with IA therapy, in EMS-arriving patients only, overall and by DTP time intervals 0-30m, 31-60m, 61-90m, 91-120m, 121-150m, 151-180m, >180m.

Table 2.a: Descriptive of Outcomes for patients treated with IA therapy, overall and by OTP time intervals 0-120m, 121-240m, 241-360m, and 361-480m.

Table 2.b: Descriptive of Outcomes for patients treated with IA therapy, in EMS-arriving patients only, overall and by DTP time intervals 0-30m, 31-60m, 61-90m, 91-120m, 121-150m, 151-180m, >180m.

Table 3: Descriptive of IA therapy treatment rates among all ischemic stroke patients, all arrive by 5 hours patients and all arrive by 7 hours patients.

Table 4.a: Multivariable model for assessing the association of OTP time 0-120m, 121-240m, 241-360m, and 361-480m and binary clinical outcomes, unadjusted and adjusted, overall and in witnessed only and in unwitnessed only.

Table 4.b: Multivariable model for assessing the association of DTP time intervals 0-30m, 31-60m, 61-90m, 91-120m, 121-150m, 151-180m, >180m and binary clinical outcomes, unadjusted and adjusted, in EMS-arriving patients only.

Table 5.a: Multivariable model for assessing the association of OTP time 0-120m, 121-240m, 241-360m, and 361-480m and ordinal clinical outcomes, unadjusted and adjusted, overall and in witnessed only and in unwitnessed only.

Table 5.b: Multivariable model for assessing the association of DTP time intervals 0-30m, 31-60m, 61-90m, 91-120m, 121-150m, 151-180m, >180m and ordinal clinical outcomes, unadjusted and adjusted, in EMS-arriving patients only.

Table 6: Multivariable model for Subgroup analyses

Figure 1: Bar graph distribution of patients by last known well to puncture (OTP) in 30 minute intervals from 0 to 12 hours. A) in all patients, B) in witnessed onset patients, C) in unwitnessed onset patients.

Figure 2: Bar graph distribution of patients by door to puncture (DTP) in 15 minute intervals from 0 to 4 hours, A) in EMS-arriving patients only, B) in transfer from another facility patients only

Figure 3. Bar graph distribution of patients by last known well to hospital/ED arrival (onset to door - OTD) in 30 minute intervals from 0 to 8 hours. A) in all patients, B) in witnessed onset patients, C) in unwitnessed onset patients

Figure 4a: Curve from multivariable model illustrating the relationship of OTP time as a continuous variable and binary clinical outcomes, unadjusted and adjusted, overall and in witnessed only and in unwitnessed only.

Figure 4b. Curve from multivariable model illustrating the relationship of DTP time as a continuous variable and binary clinical outcomes, unadjusted and adjusted, in EMS-arriving patients only.

Figure 5a: Curve from multivariable model illustrating the relationship of OTP time as a continuous variable and ordinal clinical outcomes, unadjusted and adjusted, overall and in witnessed only and in unwitnessed only.

Figure 5.b: Curve from multivariable model illustrating the relationship of DTP time as a continuous variable and ordinal clinical outcomes, unadjusted and adjusted, in EMS-arriving patients only.

Additional Tables

Table 7. Treatment Time Processes among Patients with Arterial Puncture Time Documented

	Median	IQR	Mean	SD	Range
Onset to Door, all IA patients					
Onset to Door, IA patients with witnessed onset					
Onset to Door, IA patients with unwitnessed onset					
Onset to Puncture, all IA patients					
Onset to Puncture, IA patients with witnessed onset					
Onset to Puncture, IA patients with unwitnessed onset					
Door to Puncture, all IA patients					
Door to Puncture, IA patients with witnessed onset					
Door to Puncture, IA patients with unwitnessed onset					

Table 8. Procedural characteristics among patients with Arterial Puncture Time Documented

		n/N (%)
Type of Treatment	Retrievable stent Other mechanical device (not retrievable stent) Clot suction device Intracranial angioplasty +/- stent Cervical carotid angioplasty +/- stent Other	

Occlusion proximal or distal	Proximal Distal Not documented	
Site of occlusion		
	ACA	
	A1 ACA	
	Acom	
	Cervical ICA	
	Intracranial ICA	
	MCA	
	M1	
	M2	
	M3/4	
	VA	
	BA	
	PCA	
	Other cerebral artery	
	ND	