Proposal for a Scientific Manuscript using the GWTG AHA Databases

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Project Liason/ GWTG Committee Approval:	
Target: ❑ **Scientific Conference: International Stroke Conference** ❑ **Manuscript (Target Journal)**: Stroke	
Database: ❑ CAD **XStroke** ❑ Heart Failure	
Working Title: Earlier Time to Reperfusion Increases the Likelihood of Good Clinical Outcome after Endovascular Recanalization Therapy for Acute Ischemic Stroke: Evidence from Routine Clinical Practice	
Goals/Objectives/ Research Question: Time to treatment with IV TPA has been shown to be a key determinant of improved outcome, as demonstrated with analyses of pooled randomized controlled trials and of the Get with the Guidelines – Stroke database. A similar association of onset to treatment time and outcome has been demonstrated in randomized controlled trials (RCTs) of endovascular intervention in acute ischemic stroke and in small practice registries. For example, in a post-hoc analysis of pooled data from the IMS pilot trials (IMS I and II), increased time to reperfusion was associated with a decreased likelihood of good clinical outcome. Similarly, in the phase 3 IMS III trial, it was shown that every 30-min delay in angiographic reperfusion reduces the relative likelihood of a good clinical outcome by 15%. An understanding of how the time interval from symptom onset to angiographic reperfusion influences clinical outcome is critical to clinical decision-making in the setting of intraarterial (IA) revascularization therapies. Information from very large cohorts of patients can complement and extend RCT observations, permitting better characterization of the shape and inflection points of the treatment time – benefit curve. In addition, evidence of association between time to treatment and outcome in routine clinical practice, in addition to formal RCTs, would provide support for implementation of National guidelines in this regard, including the specification of target door to reperfusion times to drive national quality improvement programs (similar to the national door to needle targets of 60 minutes for Target: Stroke I and 45 minutes for Target: Stroke 2). Univariate and multivariate stepwise logistic regression modeling will be employed to evaluate the independent impact of onset to revascularization (OTR = time of first deployment of treatment device). The predictor models will be developed in the population of the first 10,000 patients with documented baseline NIHSS undergoing endovascular therapy after January 1, 2015, when the release of the GWTG-Stroke PMT form capturing OTR was released. The 10,000 patient sample is chosen as a natural milestone that will provide at least 4 times the sample size of pooled patients enrolled in all randomized trials of second generation thrombectomy devices.	
Hypothesis/Rationale:	

Hypothesis 1. Earlier OTR is associated with increased rates of dichotomized good functional outcomes at discharge (ambulatory status, discharge destination, discharge modified Rankin Scale).

Hypothesis 2. Earlier OTR is associated with improved functional outcomes over entire outcome range at discharge (ambulatory status, discharge destination, discharge modified Rankin Scale).

Hypothesis 3. Earlier OTRT is associated with increased rates of dichotomized good functional outcomes at 3 months (modified Rankin Scale).

Hypothesis 4. Earlier OTR is associated with improved disability outcomes over entire outcome range at 3 months (modified Rankin Scale).

Hypothesis 5. Earlier OTR is associated with reduced mortality, at discharge and at 3 months.

Hypothesis 6. Earlier OTR is associated with reduced rates of symptomatic intracranial hemorrhage.

Hypothesis 7. Data on the relation of OTR to functional outcomes can be employed to identify OTR target times to drive quality improvement projects.

Study Population (*specify admission diagnosis of interest, including inclusion and exclusion criteria*):
The main study population will be patients with ischemic stroke with a documented baseline NIHSS treated with with IA therapy. For certain analyses, in addition to the overall IA-treated population, separate analyses will be undertaken in the subgroups of patients pretreated with IV TPA and patients not pre-treated with IV TPA. In addition, for certain analyses, in addition to the overall IA-treated population, separate analyses will be undertaken in the subgroup of patients with achieved substantial reperfusion (TICI 2b-3).

Prognostic Variables Utilized for Project:

Patient level
Age, race/ethnicity, sex, medical history (including atrial fibrillation, prosthetic heart valve, previous stroke or TIA, coronary heart disease or prior myocardial infarction, history of congestive heart failure, patient location when stroke discovered (chronic health facility vs other), ambulatory status prior to current event, ambulatory status on admission, initial exam findings (weakness, LOC, aphasia), carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, diabetes, and current smoking), stroke severity (NIHSS), an age-by-NIHSS interaction term, arrival time during regular work hours (7 AM-PM Monday-Friday), arrival mode (ambulance, private vehicle), and select classes of vascular risk prevention medications prior to admission.

Hospital level
Hospital size
Region
Teaching status
Rural location
Certified primary stroke center status
Average number of patients treated with tPA annually
Average number of patients treated with IA therapy annually
Average number of annual stroke discharges.

The following additional variables will also be analyzed if they do not have a high rate of missingness. (If they do, they will be included in a sensitivity analysis):

Baseline diastolic blood pressure (mm Hg)
Baseline systolic blood pressure (mm Hg)
Blood glucose concentration at baseline (mg/L)
INR
Creatinine

Primary Outcome/Endpoint:
Please see above

Secondary Outcomes/ Endpoints:
Please see above

Brief Description of Proposed Analyses :
Table 1: Patient characteristics and hospital characteristics for patients treated with IA therapy, overall and in the intervals 0-2h, 2-4h. 4-6h, 6-8h, >8h.
Table 2: Treatment rates among all ischemic stroke patients, all arrive by 2h patients, all arrive by 3.5h patients, all arrive by 6.5h patients.
Figure 1: Bar graph distribution of patients by onset to reperfusion (OTR) in 30 minute intervals from 0 to 12 hours.
Table 3: Patient- and Hospital-Level Characteristics Independently Associated With Earlier Onset-to-Treatment Time Within the 0—8h Time Period (Multivariable Analysis)
Table 4: Binary clinical outcomes, adjusted and unadjusted, in the time windows 0-2h, 2-4h. 4-6h, 6-8h, >8h
Table 5: Ordinal outcomes, adjusted and unadjusted, in the time windows 0-2h, 2-4h. 4-6h, 6-8h >8h

Sample Tables (*please provide examples of the tables as you plan to present them in the space below)*
Similar to tables in: Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV, Pan W, Olson DM, Hernandez AF, Peterson ED, Schwamm LH. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. JAMA. 2013 Jun 19;309(23):2480-8.

Key References:

Hacke W, Donnan G, Fieschi C, et al, ATLANTIS Trials Investigators, ECASS Trials Investigators, NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;363:768–774.

Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. Neurology 2000;55:1649 –1655.

NINDS rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581–1587.

Khatri P, Abruzzo T, Yeatts SD, Nichols C, Broderick JP, Tomsick TA, for the IMS I and II Investigators. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. Neurology 2009; 73: 1066–72.

P Khatri, SD Yeatts, M Mazighi, for the IMS III Trialists, et al. Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke: an analysis of data from the Interventional Management of Stroke (IMS III) phase 3 trial Lancet Neurol (2014) published online April 28. http://dx.doi.org/10.1016/S1474-4422(14)70066-3.