SUPPLEMENTAL MATERIAL

Supplemental Table I. Patient and Hospital Characteristics

	Intervention Hospitals n = 287 (56.2%)	Control Hospitals n = 224 (43.8%)
Age, mean (SD)	70.6 (14.0)	68.1 (16.0)
Male (%)	48.1%	58.0%
Race, %(n)		
White non-Hispanic	77.0% (221)	74.6% (167)
Black	10.1% (29)	6.3% (14)
Hispanic	2.4% (7)	1.3% (3)
Other	1.1% (3)	0.9% (2)
Unknown	9.4% (27)	17.0% (38)
NIHSS pre-treatment		
Mean, SD	12.0, +/- 6.0	12.4, +/- 5.7
Median	11	12
IQR	7-17	8-16
Range	2-29	1-29
Co-morbidities/risk factors:		
Prior stroke	19.5% (56)	17.9% (40)
Prior TIA	12.5% (36)	11.6% (26)

Diabetes mellitus	25.4% (74)	22.3% (50)
Hypertension	76.7% (220)	73.2% (164)
Hyperlipidemia	55.1% (158)	46.9% (105)
Coronary artery disease	34.2% (98)	29.0% (65)
Congestive heart failure	14.3% (41)	12.1% (27)
Atrial fibrillation	24.4% (70)	19.6% (44)
Valvular heart disease	6.6% (19)	5.8% (13)
Smoking	25.4% (73)	19.2% (43)
Antiplatelet therapy	51.6% (148)	47.3% (106)
Beta-blocker therapy	46.0% (132)	38.8% (87)
Possible tPA contraindications:		
History of significant head trauma	0%	0.5% (1)
History of intracranial hemorrhage	0%	0%
Uncontrolled hypertension at treatment	6.6% (20)	7.5% (19)
Seizure at onset	0%	0.9% (2)
Active internal bleeding	0.4% (1)	0.9% (2)
Oral anticoagulant with INR>1.7	0%	0%
Heparin with 48h, elevated PTT	0%	0%
Platelets<100,000	0.7% (2)	0.5% (1)
Location at onset %(n)		
Home	57.5% (165)	61.2% (137)
Work	8.0% (23)	8.0% (18)
Car	6.6% (19)	3.6% (8)

Nursing home/assisted living	5.9% (17)	9.8% (22)
Other/unknown	22.0% (63)	17.4% (39)
Ground or air ambulance arrival %(n)	82.2% (236)	84.4% (189)
Weekend presentation, %(n)	26.1% (75)	28.1% (63)
BP>=185/110 on arrival, %(n)	7.6% (22)	7.6% (17)
tPA within180 minutes of onset, %(n)	84.7% (243)	84.8% (190)
Door-to-imaging time, min (SD)	20.7 min (13.7)	19.7 min (13.2)
Hospital Characteristics		
Stroke center status	33.3% (4)	33.3% (4)
Mean study period stroke volume, mean+/-SD, range	1,027 +/- 693.1 (139-2536)	1,119.5 +/- 938.1 (280-3363)
Trauma Center status	25.0% (3)	33.3% (4)

SD: standard deviation; IQR: interquartile range; TIA: transient ischemic attack

II. Additional Detail of the INSTINCT Intervention[1]

The INSTINCT trial was a cluster-randomized, controlled trial that matched 12 intervention with 12 control hospitals. Eligible hospitals were non-specialty, acute-care community hospitals in Michigan's Lower Peninsula, and were excluded if they: had fewer than 100 stroke discharges per year, greater than 100,000 ED visits per year, were an academic comprehensive stroke center, or a direct affiliation with the University of Michigan coordinating site. A computer-generated randomization sequence adaptively balanced urban-rural status, race, and age between groups. All hospitals had uninterrupted CT availability. One-third were designated Joint

Commission stroke centers (indicating certification for high level of compliance with performance standards, 4 per group).

The aim of the trial was to increase thrombolytic use in Michigan community hospitals. The intervention design was based on behavior change theory, and focused on change in the ED setting with the aim of altering systems and behavior at the institutional and individual level. A multi-level barrier assessment and interactive educational program was delivered to intervention hospitals. Barriers to thrombolytic use were assessed quantitatively and qualitatively. The intervention also included clinical practice guideline promotion, development of local stroke champions, continuing education, telephone decision-making support, academic detailing, and audit and feedback mechanisms. The intervention was delivered from January-December 2007 with recurrent activities throughout the trial period.

Supplemental Table II: Barrier assessment-interactive educational intervention components[1]

	Targets	Description	Content	Purpose
Beginning Stroke champions meeting	Physicians, nurses, pharmacists, administration teams	1-day meeting of teams from all intervention hospitals	6 hours of educational content, and focus groups to explore local barriers to stroke treatment.	Networking between sites, understanding barriers and solutions, and developing local stroke content experts.
3 Months Local barrier assessment	Physicians, nurses, pharmacists, administration teams	Coordinating center team meeting with individual hospital staff at each intervention hospital.	Focus group discussions with emergency physicians and nurses. Structured interviews with neurology, radiology, and hospital administration teams. Complete checklist assessment of physical hospital resources for acute stroke treatment.	Identification and understanding of environmental and organizational barriers to stroke treatment. Further promotion of local stroke content experts.
6 Months First on-site educational intervention	Physicians, nurses, pharmacists, EMS, administration teams	On-site mock stroke codes and lectures delivered by coordinating center personnel.	Mock stroke codes test the response and decision making of the stroke chain of survival (EMS pick-up through	Self-assessments of performance and identification of areas for improvement. Further enhancement of local knowledge and identification of

			tPA delivery) using prewritten, common scenarios.	specific local barriers.
Audit and feedback	Physicians, nurses, pharmacists, administration teams	Monthly email about tPA success at each intervention hospital.	-	Anonymous comparison promoting competition with other sites.
6 months to study conclusion				
Academic detailing	Physicians	After identification of index event, critical incident diffusing with physicians at coordinating center.	Abbreviated critical incident stress debriefing completed for all guideline deviations and treatment complications.	Review of the event to resolve the emotional content of an event and provide professional support.
Decision support	Physicians	Continuing telephone access to university-based stroke specialist at any time.	-	Real-time assistance with decision making for tPA treatment.
Web-based instruments	Physicians, nurses, pharmacists, administration teams.	Web access to previously provided educational materials, checklists, and protocols.	-	Reference resource and continued access to educational content.
9 Months				
Second on-site	Physicians, nurses,	On-site mock stroke codes	As at 6 months	As at 6 months

educational intervention	pharmacists, EMS, administration teams	and educational lectures delivered by coordinating center personnel.		
12 Months to study conclusion Follow-up interventions	Physicians, nurses, pharmacists, others	Stroke champions meeting (one per year for two years) with updated content; mock stroke code (four times per year for 1-5 years).	As at beginning and 6 months	Reinforcement of knowledge and understand of tPA use in stroke.

EMS: Emergency Medical Services

III. Additional Details of Statistical Analysis

Determining Intervention Effect on DIT

In addition to the described intention-to-treat analysis, we also performed a target-population analysis, excluding one hospital and its matched pair, because after randomization a control hospital became an academic comprehensive stroke center with a neurovascular stroke fellowship (ie, study exclusion criterion). In target population analysis (22 hospitals, n=367), the mean overall DIT was 20.4 minutes (SD 13.5 min), and intervention hospitals had similar improvement (22.5 to 19.2 minutes) as control hospitals (25.6 to 20.1 minutes) from pre- to post-intervention (p=0.42).

Candidate variables for the adjusted analysis were based on literature review and clinical observation. Patient-level variables previously associated with DIT or door-to-needle time were age, sex, race, diabetes, valvular heart disease, stroke severity, ambulance arrival, weekend presentation, and onset-to-arrival time.[2,3] We also included location at onset, and elevated arrival blood pressure, hypothesizing that these could affect DIT. Hospital variables were stroke volume (number of stroke admissions during study period) and stroke center status.

Examining Variation in DIT and Predictors of DIT

A two-level linear mixed-effect regression model was built to examine the proportion of variation in DIT explained by patient- and hospital-level factors. First, an empty model without

explanatory variables decomposed the unadjusted patient- and hospital-level variation. The intraclass correlation (ICC) evaluated the proportion of unadjusted variation attributable to hospitals.

Patient-level explanatory variables were added to the model to evaluate differences between hospitals after accounting for patient-level differences. In addition to above patient-level variables, we also evaluated for an interaction between ambulance arrival and stroke severity, hypothesizing that they may have varying influence on DIT between hospitals. Continuous variables were mean-centered; patient-level variables were entered as fixed effects. Hospitals were included as a random effect, allowing intercepts to vary between hospitals. The proportional change in hospital variance between the empty model and the model including patient factors was used to calculate the proportion of hospital variance explained by patient-level variables included in the model. The ICC evaluated the proportion of variation in DIT attributable to hospitals after adjusting for patient-level factors.

Next, hospital-level variables of stroke volume and stroke center status were added as fixed effects to estimate the effects of these attributes on hospitals' DIT performance. The ICC evaluated the proportion of variation in DIT attributable to hospitals after adjusting for patient-level and hospital-level factors. We then evaluated the proportion of hospital variance explained by the hospital-level variables by calculating proportional change of variance between the model including patient factors and the model with patient and hospital-level factors. Regression coefficients described the covariates' effect size on DIT. Finally, onset-to-arrival time,

9

ambulance arrival, and treatment time were included as random effects, given that these factors' effects on DIT may differ across hospitals.

Because DIT distribution was right-skewed, we explored analyses after log-transformation of DIT. However, as both models had relatively normally distributed residuals and similar mean squared error, we used the untransformed model for ease of interpretability.

Finally, we made posterior predictions of the average marginal effects of ambulance arrival and stroke severity by NIHSS on predicted DIT, holding other variables constant. Predicted DITs are reported with 95% confidence intervals (95%CI).

References:

1.   Scott PA, Meurer WJ, Frederiksen SM, Kalbfleisch JD, Xu Z, Haan MN, et al. A multilevel intervention to increase community hospital use of alteplase for acute stroke (instinct): A cluster-randomised controlled trial. *Lancet neurology*. 2013;12:139-148

2.   Jauch EC, Saver JL, Adams HP, Jr., Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke; a journal of cerebral circulation*. 2013;44:870-947

3.   Abdullah AR, Smith EE, Biddinger PD, Kalenderian D, Schwamm LH. Advance hospital notification by ems in acute stroke is associated with shorter door-to-computed tomography time and increased likelihood of administration of tissue-plasminogen activator. *Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors*. 2008;12:426-431