Supplementary Online Content

Jahan R, Saver JL, Schwamm LH, et al. Association between time to treatment with endovascular reperfusion therapy and outcomes in patients with acute ischemic stroke treated in clinical practice. *JAMA*. doi:10.1001/jama.2019.8286

Supplement – Table of Contents

eMethods 1

The two time intervals evaluated for relation to outcomes were onset (last known well) to arterial puncture and hospital arrival to arterial puncture (door to puncture).

Onset to puncture time was analyzed in all patients and separately in patients with and without witnessed symptom onset, both as a continuous variable and as a categorical variable with equal spaced timed periods of 30-120 minutes, 121-240 minutes, 241-360 minutes, and 361-480 minutes.

Door to puncture time was analyzed in patients who arrived directly by emergency medical services transport from the field to the emergency department of the treating hospital. Interfacility transfer patients were not included in the main door to puncture time-benefit analysis, as times for their first presentation at the outside facility were not recorded in the dataset. In addition, for several reasons, the door to puncture times of interfacility transfer and direct-arriving patients are not assimilable. First, interfacility transfer patients typically have brief door to puncture times at the endovascular treatment facility, due to having already completed some diagnostic and management processes at the first hospital and due to pre-transfer notification enabling team and equipment readiness at the endovascular treatment hospital. Concomitantly, interfacility transfer patients have distinctively long onset to puncture time, due to the time required for transfer. Door to puncture times were analyzed both as a continuous variable and as a categorical variable with equal spaced timed periods of 31-60, 61-90, 91-120, 121-150, and 151-180 minutes.

eMethods 2

As noted, generalized estimating equations were used in all regression models to account for within-hospital clustering. Patients treated at a given hospital share some commonalities that differ from patients treated at a different hospital, related to their physical environment, local sociocultural practices, hospital resources and care policies, and other location-related factors. Therefore, to account for such commonalities, models were adjusted for both patient-level and hospital-level characteristics. Since the outcomes of patients may be also affected by these commonalities (similarities in outcomes among patients within the same hospital), generalized estimating equations (GEE) technique were used in the regression models to account for such a clustering of patients within a hospital, while adjusting for both patient-level and hospital-level characteristics. The multivariable models adjusted for 28 patient-level and 9 hospital-level characteristics (listed in eTable 2) simultaneously, and non-significant variables were included. The logistic regression model assumes that independent variables have a linear relationship with respect to the prevalence of the dependent variable (i.e., the outcome) on the logit scale. All the continuous variables included for adjustment were evaluated for non-linearity with the outcome, and linear splines were used for those that violated the linearity assumption. By using restricted cubic splines for OTP and DTP, any non-linearity between these measures and the outcome of interest is accounted for in the regression model.

From the initial linear section of the time-benefit curves, before the occurrence of the first deviation from linearity and spline placement, increased number of beneficial outcomes among 1000 treated patients associated with a 15 minute faster speed of onset to puncture and of door to puncture was calculated. These benefit per thousand (BPT, also known as natural frequency) values were derived from the slope of the initial linear segment of the time-benefit graph. First the risk difference (RD) per 15 minutes was calculated by multiplying the slope, expressed in units of outcomes per minute, by 15 minutes. From the risk difference, the BPT was calculated as: BPT = RD x 1000.

Analyses of discharge and 3 month modified Rankin Scale (mRS) outcomes were conducted in complete case sample and inverse probability weighting (IPW) method was employed. The analyses were conducted in two steps. First, the propensity, defined as the probability that a patient had complete data on mRS, was calculated using a logistic regression model (propensity model). Then, the multivariable model of outcomes (IPW model) were conducted in the outcome complete cases and used the inverse of the propensity as weight to increase the weighting of patients with a high estimated propensity of outcome being missing, and to decrease the weighting of patients with a low estimated propensity of outcome being missing, so as to compensate for patients who were actually missing the outcome measure. The propensity model for discharge mRS included the baseline covariates used in the multivariable models for other outcomes and also the discharge destination and discharge ambulatory status. The propensity model for 90 day mRS included the baseline covariates and also discharge destination, discharge ambulatory status, and discharge mRS. The IPW model adjusted for the baseline covariates used in the multivariable models for other outcomes in addition to the weighting.

eResults 1

For patient-level baseline variables, among analyzed patients, complete data were available for: age, sex, race-ethnicity, arrived off-hours, National Institutes of Health Stroke Scale (NIHSS), intravenous (IV) recombinant tissue plasminogen (rtPA) use, and arterial site of occlusion. Rates of missingness were low to moderate for: past medical history 0.03%, arrival mode 0.2%, insurance status 2.7%, medications at time of index stroke - anticoagulant/antiplatelet 0.2%. cholesterol reducer 0.04%, antihypertensive 9.4%, diabetes medications 11.6%. For these missing patient-level baseline variables, missing values were imputed to the mode or median. One patient-level baseline variable had a high rate of missingness: ambulatory status prior to admission, missing in 22%. Among patients with this variable documented, the preponderance, 95%, were able to ambulate independently. Because of the high rate of missingness, this variable was not included in multivariable models.

For hospital-level variables, complete data were available for: annual ischemic stroke volume, annual IV rtPA volume, annual endovascular reperfusion therapy volume, Joint Commission stroke center certification, and geographic region. Rates of missingness for other hospital-level variables were: number of beds 2.2%, and teaching hospital status 1.8%. For these hospital-level variables with any missingness, the variables were not included in multivariable models.

For outcome variables, complete data were available for mortality. Rates of missingness were low to moderate for discharge destination 0.3%, sICH 0.9%, substantial reperfusion 6.4%, and ambulatory status at discharge 14.4%. Rates of missingness were higher for discharge mRS 21.1%, and substantial for 3 month mRS 44.1%. For 3 month mRS, across centers, the distribution of missingness was median 43% (IQR 21%,78%).

eResults 2

The Types of mechanical interventions employed were stent retrievers in 64.2% of patients, clot suction devices in 36.1%, other retriever devices in 9.1%, other mechanical techniques in 4.1%, intracranial angioplasty (with or without permanent stenting) in 2.8%, intraarterial fibrinolysis in 9.9%, and cervical carotid angioplasty (with or without permanent stenting) in 2.5%. The most common combination approach was serial or simultaneous use of stent retrievers and suction devices in 17.1% of patients. The most common solo technique approaches were stent retrievers in 37.3% of patients, suction devices in 12.4%, and other mechanical clot retriever device (not retrievable stent) in 5.6%. A single type of endovascular reperfusion therapy was used in 59.3% of patients, multiple types in 32.8%, with 7.9% unspecified.

eResults 3

Symptom onset was witnessed (last known well time same as symptom discovery time) in 67.7% of patients and unwitnessed (last known well time earlier than symptom discovery time) in 32.3%, and onset to puncture time times were shorter in witnessed than unwitnessed onset patients, median 216 minutes (IQR 161-286) vs 262 minutes (IQR 200-340), $p<0.001$. Patients with witnessed onset were younger, had mildly less severe presenting deficits and mildly lower initial serum glucose levels, were more likely to have received IV rtPA, and were more likely to arrive by interfacility transfer. Hospital-level characteristics associated with witnessed onset included: fewer annual endovascular reperfusion therapy cases, fewer annual IV rtPA cases, lack of Comprehensive Stroke Center certification, and location in the South (eTable 4, Supplement). Onset (last known well) to door times markedly differed between witnessed versus unwitnessed patients, 125 (IQR 54-201) versus 173 (IQR 92-255) minutes, $p< 0.001$, with a pronounced early 30-90 minute peak with witnessed onset but a wide 30-300 minute plateau with unwitnessed onset (eFigure 2, Supplement).

eTable 1. Patient baseline characteristics and outcomes analyzed from the comprehensive stroke center module of the GWTG-Stroke program.

Patient Characteristics
Demographics
Medical history
Last known well time
Mode and time of hospital arrival
In-hospital diagnostic studies
NIHSS
Recombinant tissue plasminogen activator treatment initiation time
Arterial site of large vessel occlusion
Arterial puncture time
Other treatments and procedures
Discharge treatments and counseling
Outcomes - Main
Technical endpoint
Substantial reperfusion, defined as mTICI score 2b-3 (50-100% reperfusion)
Functional endpoints assessed at discharge
Discharge to home (versus acute rehabilitation, skilled nursing facility, hospice, death, other)
Ambulatory without assistance
Freedom from disability (mRS, 0-1)
Functional independence (mRS 0-2)
Adverse event outcomes
In-hospital mortality/discharge to hospice
sICH within 36 hours
Outcomes - Other
Functional endpoints assessed at discharge
Discharge to home or acute rehabilitation (versus skilled nursing facility, hospice, death, other)
Ambulatory with or without assistance
Functional endpoints assessed at 3 months
Freedom from disability (mRS 0-1)
Functional independence (mRS 0-2)
Adverse event outcomes
In-hospital mortality

GWTG-Stroke, Get with the Guidelines-Stroke; NIHSS, National Institute of Health Stroke Scale; mTICI, modified Thrombolysis in Cerebral Ischemia; mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage

eTable 2. Baseline patient and hospital characteristics adjusted in the multivariable models.

Patient Characteristics
Demographics
Age
Female sex
Race (Black, Hispanic, Asian, other vs. Caucasian)
Insurance (Medicare, Medicaid, other (including private insurance, VA), vs. no insurance)
Medical History
Atrial fibrillation/flutter
Prosthetic Valve
CAD/ Prior MI
Carotid Stenosis
Diabetes
PVD
Hypertension
Smoking
Dyslipidemia
Prior Stroke / TIA
Heart Failure
Renal Insufficiency
Sleep Apnea
Depression
Arrival and Admission Information
EMS arrival vs transfer from another facility vs private transportation
Arrival off-hours
NIHSS
Interaction of age and NIHSS
Use of IV rtPA at this hospital or at the transferring hospital or prior to intraarterial use
Medications prior to admission
Antihypertensive
Lipid lowering
Antiplatelet and anticoagulation
Diabetic
Site of Occlusion
ICA (cervical or intracranial) vs MCA (MCA, M1 MCA, M2 MCA)
Hospital characteristics
Rural vs urban setting
Number of beds
Teaching hospital
Regions
West
South
Midwest
Northeast
Certified PSC
Certified CSC
Annual number of AIS discharges
Annual IV rtPA volume
Annual intraarterial therapy volume

CAD, coronary artery disease; MI, myocardial infarction; PVD, peripheral vascular disease; TIA, transient ischemic attack; EMS, emergency medical services, NIHSS, National Institute of Health Stroke Scale; IV, intravenous; rtPA, recombinant tissue plasminogen activator; ICA, internal carotid artery; MCA, middle cerebral artery; PSC, primary stroke center; CSC, comprehensive stroke center; AIS, acute ischemic stroke

eTable 3. Patient- and hospital-level characteristics for included patients compared with patients excluded for missing documentation of 1 or more key baseline covariates

	Excluded	Included	Standardized difference (%)*
N	288	6756	
Age, mean (SD), years	68.69 (14.8)	69.49 (14.8)	5.4
Female, sex (%)	119 (41.3)	3460 (51.2)	19.1
Race/ethnicity (%)			19.7
White, non-Hispanic	183 (63.5)	4667 (69.1)	
Black	40 (13.9)	1049 (15.5)	
Hispanic	25 (8.7)	433 (6.4)	
Asian	10 (3.5)	178 (2.6)	
Other	29 (10.1)	429 (6.4)	
Arrival at off hours^ (%)	145 (50.4)	3427 (50.7)	0.8
Arrival by EMS	114 (39.6)	3454 (51.1)	20.8
LKW to arrival, median (IQR), min	150 (52-225)	141 (62-218)	22.6
Received IV rtPA (at ERT or outside hospital)	208 (72.2)	4610 (68.2)	8.7
Door to rtPA (at the ERT hospital), median (IQR), m	42 (32-54)	41 (30-55)	113.1
NIHSS, median (IQR)	17 (12-22)	17 (12-22)	3.5
Ambulatory status prior to index stroke	37 (12.9)	495 (7.3)	25.9
Severe stroke, NIHSS >16 (%)	130 (60.5)	4020 (59.5)	2.0
Medical History (%)			
Atrial fibrillation/flutter	95 (33.5)	2393 (35.4)	4.2
CAD/prior MI	67 (23.6)	1665 (24.7)	2.5
Carotid stenosis	3 (1.1)	186 (2.8)	12.4
Diabetes mellitus	73 (25.7)	1645 (24.4)	3.1
Dyslipidemia	111 (39.1)	2856 (42.3)	6.5
Hypertension	203 (71.5)	4850 (71.8)	0.7
Prosthetic heart valve	9 (3.2)	144 (2.1)	6.5
Peripheral vascular disease	15 (5.3)	251 (3.7)	7.6
Heart failure	40 (14.1)	944 (14.0)	0.3
Smoker	41 (14.4)	1224 (18.1)	10.0
Previous stroke/TIA	56 (19.7)	1517 (22.5)	6.7
Obesity	68 (23.9)	1652 (24.5)	1.2
Drug/alcohol abuse	16 (5.6)	465 (6.9)	5.2
Renal insufficiency	17 (6.0)	393 (5.8)	0.7
Sleep apnea	14 (4.9)	263 (3.9)	5.0
Depression	18 (6.3)	582 (8.6)	8.7
Medication before admission (%)			
Anticoagulants/ Antiplatelets	145 (50.4)	3498 (51.8)	1.3
Antihypertensive	144 (50.0)	3952 (58.5)	16.1
Cholesterol reducer	113 (39.2)	2803 (41.5)	2.9
Antidiabetic	49 (17.0)	976 (14.5)	8.7
Hospital size, median no. of beds (IQR)	469 (349-635)	572 (425-762)	35.3
Hospital region (%)			76.4
West	127 (44.1)	843 (12.5)	
South	77 (26.7)	2943 (43.6)	

Midwest	44 (15.3)	1526 (22.6)	
Northeast	40 (13.9)	1444 (21.4)	
	Excluded	**Included**	**Standardized difference (%)***
Academic hospital (%)	251 (87.2)	5922 (87.7)	6.4
Primary stroke center (%)	206 (71.5)	4714 (70.0)	3.9
Comprehensive stroke center (%)	114 (39.6)	3334 (49.4)	19.8
Urban location (versus rural location) (%)	288 (100)	6756 (100)	0.0
Annual volume of ischemic stroke discharges, median (IQR)	283(222-413)	407 (288-494)	58.6
Annual volume of rtPA administration, median (IQR)	31 (26-46)	36 (27-50)	21.0
Annual volume of ERT cases, median (IQR)	36 (24-48)	41 (27-62)	28.3

^Off hours are holiday or before 7AM and after 6PM on Monday-Friday
N, number; SD, standard deviation; EMS, Emergency Medical Service; IQR, interquartile range; LKW, last known well; rtPA, recombinant tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; CAD, coronary artery disease; MI, myocardial infarction; TIA, transient ischemic attack; ERT, endovascular reperfusion therapy
*Calculated as the difference in means or proportions divided by a pooled estimate of the standard deviation. A standardized difference greater than 25 is typically considered meaningful and a standardized difference between >10 and ≤25 is considered potentially meaningful.

eTable 4. Patient- and hospital-level characteristics for patients with witnessed versus unwitnessed stroke onset.

	Witnessed	Unwitnessed	p-value*
N	4572	2184	
Age, mean (SD), years	69.2 (14.7)	70.1 (14.8)	0.008
Female, sex (%)	2358 (51.6)	1102 (50.5)	0.39
Race/ethnicity (%)			0.82
White, non-Hispanic	3166 (69.2)	1501 (68.7)	
Black	704 (15.4)	345 (15.8)	
Hispanic	298 (6.5)	135 (6.2)	
Asian	114 (2.5)	64 (2.9)	
Other	290 (6.3)	139 (6.4)	
Arrival at off hours^	2313 (50.6)	1114 (51.0)	0.75
Arrival by EMS	2279 (49.8)	1175 (53.8)	0.01
LKW to arrival, median (IQR), min	125 (54-201)	173 (92-255)	<0.001
Received IV rtPA (at ERT or outside hospital)	3240 (70.9)	1370 (62.7)	<0.001
Door to rtPA, median (IQR), min	41 (30-54)	41 (31-56)	0.12
NIHSS, median (IQR)	17 (12-22)	18 (13-22)	0.002
Severe stroke, NIHSS > 16 (%)	2660 (58.2)	1360 (62.3)	0.001
Medical History (%)			
Atrial fibrillation/flutter	1600 (35)	793 (36.3)	0.29
CAD/prior MI	1118 (24.5)	547 (25.1)	0.59
Carotid stenosis	116 (2.5)	70 (3.2)	0.12
Diabetes mellitus	1118 (24.5)	527 (24.1)	0.78
Dyslipidemia	1930 (42.2)	926 (42.4)	0.88
Hypertension	3281 (71.8)	1569 (71.9)	0.94
Prosthetic heart valve	102 (2.2)	42 (1.9)	0.41
Peripheral vascular disease	171 (3.7)	80 (3.7)	0.88
Heart failure	630 (13.8)	314 (14.4)	0.51
Smoker	811 (17.7)	413 (18.9)	0.24
Previous stroke/TIA	1007 (22.0)	510 (23.4)	0.22
Obesity	1138 (24.9)	514 (23.5)	0.23
Drug/alcohol abuse	327 (7.1)	138 (6.3)	0.21
Renal insufficiency	264 (5.8)	129 (5.9)	0.83
Sleep apnea	181 (4.0)	82 (3.8)	0.69
Depression	377 (8.2)	205 (9.4)	0.12
Medical history panel missing	1 (0.02)	1 (0.05)	0.59
Medication before admission			
Anticoagulants/ Antiplatelets	2361 (51.6)	1137 (52.1)	0.73
antihypertensive	2702 (59.1)	1250 (57.2)	0.30
Cholesterol reducer	1886 (41.2)	917 (42.0)	0.55
Antidiabetic	662 (14.5)	314 (14.4)	0.93
Hospital size, median no. of beds (IQR)	572 (424-747)	579 (427-826)	0.08
Hospital region			<0.001
West	548 (12.0)	295 (13.5)	
South	2090 (45.7)	853 (39.1)	
Midwest	1041 (22.8)	485 (22.2)	
Northeast	893 (19.5)	551 (25.2)	
Academic hospital	3991 (87.3)	1931 (88.4)	0.91
Primary stroke center	3166 (69.3)	1548 (70.9)	0.17
Comprehensive stroke center	2171 (47.5)	1163 (53.3)	<0.001

	Witnessed	Unwitnessed	p-value*
Urban location (versus rural location)	4572 (100)	2184 (100)	
Annual volume of ischemic stroke discharges, median (IQR)	407 (288-486)	410 (284-510)	0.10
Annual volume of rtPA administration, median (IQR)	36 (27-50)	37 (27-56)	<0.001
Annual volume of ERT cases, median (IQR)	40 (27-62)	43 (28-62)	<0.001

^Off hours are holiday or before 7AM and after 6PM on Monday-Friday
N, number; SD, standard deviation; EMS, Emergency Medical Service; IQR, interquartile range; LKW, last known well; rtPA, recombinant tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; CAD, coronary artery disease; MI, myocardial infarction; TIA, transient ischemic attack; ERT, endovascular reperfusion therapy
*P-values are based on Pearson chi-square tests for categorical variables, and chi-square rank based group means score statistics (Kruskal-Wallis tests).for continuous/ordinal variables

eTable 5. Patient- and hospital-level characteristics of EMS-arriving patients treated with endovascular reperfusion therapy, overall and in different door to puncture time windows.

	Door to Puncture Interval						
	Overall	**31-60 m**	**61-90 m**	**91-120 m**	**121-150 m**	**151-180 m**	**P value***
N	3097	283	915	960	622	317	
Age, mean (SD), years	70.3 (14.8)	69.8 (15.0)	69.8 (14.9)	70.6 (14.6)	70.8 (14.8)	70.3 (15.4)	0.74
Female, sex (%)	1603 (51.8)	130 (45.9)	463 (50.6)	500 (52.1)	340 (54.7)	170 (53.6)	0.14
Race/ethnicity							0.005
White, non-Hispanic	2097 (67.7)	198 (70.0)	645 (70.5)	668 (69.6)	395 (63.5)	191 (60.2)	
Black	520 (16.8)	38 (13.4)	135 (14.7)	161 (16.8)	115 (18.5)	71 (22.4)	
Hispanic	231 (7.5)	16 (5.6)	66 (7.2)	73 (7.6)	50 (8.0)	26 (8.2)	
Asian	77 (2.5)	10 (3.5)	15 (1.6)	20 (2.1)	22 (3.5)	10 (3.1)	
Other	172 (5.5)	21 (7.4)	54 (5.9)	38 (4.0)	40 (6.4)	19 (6.0)	
Arrival at off hours^	1451 (46.8)	45 (15.9)	308 (33.7)	505 (52.6)	391 (62.9)	202 (63.7)	<0.001
Arrival by EMS	3097 (100)	283 (100)	915 (100)	960 (100)	622 (100)	317 (100)	0.02
LKW to arrival, median (IQR), min	69 (44-121)	65 (40-128)	70 (45-119)	69 (45-130)	67 (43-117)	69 (44-119)	0.62
Received IV rtPA (at ERT or outside hospital)	2158 (69.7)	192 (67.8)	641 (70.1)	657 (68.4)	436 (70.1)	232 (73.2)	0.54
Door to rtPA, median (IQR), min	40 (30-52)	27 (19-33)	34 (26-44)	41 (33-54)	47 (36-61)	52 (35-70)	<0.001
NIHSS, median (IQR)	17 (13-22)	18 (14-24)	17 (13-22)	17 (13-22)	17 (12-22)	16 (11-22)	<0.001
Severe stroke, NIHSS > 16 (%)	1873 (60.5)	197 (69.6)	564 (61.6)	569 (59.3)	369 (59.3)	174 (54.9)	0.004
Absence of limb weakness (%)	147 (4.8)	6 (2.1)	34 (3.7)	53 (5.5)	34 (5.5)	20 (6.3)	0.02
Medical History (%)							
Atrial fibrillation/flutter	1103 (35.6)	101 (35.7)	317 (34.7)	346 (36.0)	219 (35.3)	120 (37.9)	0.89
CAD/prior MI	767 (24.8)	63 (22.3)	217 (23.7)	242 (25.2)	156 (25.1)	89 (28.1)	0.48
Carotid stenosis	85 (2.7)	11 (3.9)	16 (1.7)	29 (3.0)	18 (2.9)	11 (3.5)	0.22
Diabetes mellitus	705 (22.8)	61 (21.5)	198 (21.7)	221 (23.0)	145 (23.3)	80 (25.2)	0.71
Dyslipidemia	1338 (43.2)	124 (43.8)	386 (42.2)	414 (43.1)	258 (41.5)	156 (49.2)	0.22
Hypertension	2223 (71.8)	200 (70.7)	626 (68.5)	692 (72.1)	472 (76.0)	233 (73.5)	0.03
Prosthetic heart valve	72 (2.3)	5 (1.8)	23 (2.5)	25 (2.6)	14 (2.2)	5 (1.6)	0.80
Peripheral vascular disease	126 (4.1)	9 (3.2)	36 (3.9)	33 (3.4)	26 (4.2)	22 (6.9)	0.08
Heart failure	444 (14.3)	36 (12.7)	125 (13.7)	128 (13.3)	111 (17.9)	44 (13.9)	0.09
Smoker	543 (17.5)	50 (17.7)	147 (16.1)	184 (19.2)	103 (16.6)	59 (18.6)	0.44
Previous stroke/TIA	736 (23.8)	58 (20.5)	190 (20.8)	234 (24.4)	167 (26.9)	87 (27.4)	0.02

	Door to Puncture Interval						
	Overall	**31-60 m**	**61-90 m**	**91-120 m**	**121-150 m**	**151-180 m**	**P value***
Medical History (%)							
Obesity	713 (23.0)	61 (21.5)	201 (22.0)	227 (23.6)	143 (23.0)	81 (25.5)	0.69
Drug/alcohol abuse	212 (6.8)	17 (6.0)	53 (5.8)	76 (7.9)	46 (7.4)	20 (6.3)	0.40
Renal insufficiency	191 (6.2)	16 (5.6)	55 (6.0)	62 (6.5)	37 (6.0)	21 (6.6)	0.98
Sleep apnea	111 (3.6)	2 (0.7)	36 (3.9)	36 (3.7)	24 (3.9)	13 (4.1)	0.11
Depression	284 (9.2)	21 (7.4)	87 (9.5)	90 (9.4)	59 (9.5)	27 (8.5)	0.83
Medical history panel missing	2 (0.06)	0 (0)	1 (0.11)	0 (0)	1 (0.16)	0 (0)	0.70
Medication before admission							
Anticoagulants/ Antiplatelets	1605 (51.8)	139 (49.1)	457 (49.9)	519 (54.1)	323 (51.9)	167 (52.7)	0.39
antihypertensive	1808 (58.4)	141 (49.8)	492 (53.8)	599 (62.4)	378 (60.8)	198 (62.5)	<0.001
Cholesterol reducer	1305 (42.1)	114 (40.3)	388 (42.4)	394 (41.0)	270 (43.4)	139 (43.8)	0.80
Antidiabetic	408 (13.2)	37 (13.1)	110 (12.0)	139 (14.5)	85 (13.7)	37 (11.7)	0.45
Hospital size, median no. of beds (IQR)	561 (416-739)	601 (472-759)	572 (424-759)	560 (404-711)	551 (404-777)	510 (391-733)	<0.001
Hospital region							<0.001
West	355 (11.5)	23 (8.1)	99 (10.8)	115 (12.0)	69 (11.1)	49 (15.5)	
South	1526 (49.2)	157 (55.5)	507 (55.4)	446 (46.5)	277 (44.5)	139 (43.8)	
Midwest	579 (18.7)	43 (15.2)	145 (15.8)	182 (19.0)	145 (23.3)	64 (20.2)	
Northeast	637 (20.6)	60 (21.2)	164 (17.9)	217 (22.6)	131 (21.1)	65 (20.5)	
Academic hospital	2594 (83.8)	235 (83.0)	758 (82.8)	813 (84.7)	526 (84.6)	262 (82.6)	0.78
Primary stroke center	2021 (65.3)	188 (66.4)	622 (68.0)	605 (63.0)	403 (64.8)	203 (64.0)	0.24
Comprehensive stroke center	1352 (43.7)	139 (49.1)	402 (44.0)	429 (44.7)	260 (41.8)	122 (38.5)	0.08
Urban location (versus rural location)	3097 (100)	283 (100)	915 (100)	960 (100)	622 (100)	317 (100)	
Annual volume of ischemic stroke discharges, median (IQR)	407 (289-510)	462 (346-555)	418 (295-518)	405 (288-492)	393 (288-510)	349 (259-460)	<0.001
Annual volume of rtPA administration, median (IQR)	39 (29-59)	43 (29-64)	39 (29-60)	39 (29-59)	38 (28-57)	38 (27-55)	0.01
Annual volume of ERT cases, median (IQR)	40 (26-61)	51 (37-90)	45 (28-69)	38 (26-61)	33 (23-55)	29 (19-41)	<0.001

^Off hours are holiday or before 7AM and after 6PM on Monday-Friday
N, number; SD, standard deviation; EMS, Emergency Medical Service; m, minutes; IQR, interquartile range; LKW, last known well; rtPA, recombinant tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; CAD, coronary artery disease; MI, myocardial infarction; TIA, transient ischemic attack; ERT, endovascular reperfusion therapy
*P-values are based on Pearson chi-square tests for categorical variables, and chi-square rank based group means score statistics (Kruskal-Wallis tests).for continuous/ordinal variables

eTable 6. Additional effectiveness outcomes of patients treated with endovascular reperfusion therapy, overall, and in different onset to puncture time windows.

Category	Outcome	Unadjusted						Adjusted Odds Ratios^^		
		Overall	OTP 0-120m	OTP 121-240m	OTP 241-360m	OTP 361-480m	P value*	0-120m vs 361-480m	121-240m vs 361-480m	241-360m vs 361-480m
Clinical	Discharge to Home or ARF	61.3% (4143/6756)	71.9% (333/463)	61.2% (1963/3207)	59.2% (1323/2235)	61.6% (524/851)	<0.001	2.08 (1.52-2.85)	1.10 (0.90-1.34)	0.90 (0.75-1.09)
	Ambulatory (w/ or w/o assist) at DC	74.0% (4278/5783)	82.0% (341/416)	73.8% (2017/2735)	73.0% (1384/1897)	72.9% (536/735)	<0.001	NP^^^	NP^^^	NP^^^
	Disability-Free at 3months**	28.7% (1086/3780)	40.1% (113/282)	29.8% (549/1842)	26.6% (323/1216)	23.0% (101/440)	<0.001	3.44 (2.23- 5.30)	1.81 (1.31-2.50)	1.35 (0.97-1.87)
	Functional Independence at 3months^	39.8% (1505/3780)	49.6% (140/282)	40.8% (751/1842)	38.1% (463/1216)	34.3% (151/440)	<0.001	2.88 (1.88-4.41)	1.61 (1.21-2.14)	1.22 (0.92-1.62)
Adverse Event	In-Hospital Mortality	12.1% (814/6756)	7.6% (35/463)	12.4% (397/3207)	12.8% (285/2235)	11.4% (97/851)	0.01	NP^^^	NP^^^	NP^^^

OTP, Onset (last known well) to puncture time; ARF, acute rehabilitation facility; w/ or w/o, with or without; mRS, modified Rankin Scale; ICH, intracranial hemorrhage; DC, discharge; m, minutes; NP, not performed
*P values from Pearson chi-square test
**Disability-Free – modified Rankin Scale 0-1
^Functional Independence – modified Rankin Scale 0-2
^^Adjustment variables listed in eTable 2
^^^ Some auxiliary outcomes did not have statistical analysis performed due to funding constraints

eTable 7. Clinical and adverse event outcomes of EMS-arriving patients treated with endovascular reperfusion therapy, overall and in different door to puncture time intervals.

Category	Outcome	Unadjusted							Adjusted Odds Ratios^^^			
		Overall (n=3097)	DTP 31-60 m (n=283)	DTP 61-90 m (n=915)	DTP 91-120m (n=960)	DTP 121-150m (n=622)	DTP 151-180m (n=317)	P value*	31-60m vs 151-180m	61-90m vs 151-180m	91-120m vs 151-180m	121-150m vs 151-180m
Clinical	**Discharge to Home**	30.5% (944/3097)	35.0% (99/283)	35.5% (325/915)	29.4% (282/960)	25.1% (156/622)	25.9% (82/317)	<0.001	2.08 (1.37-3.13)	1.81 (1.28-2.57)	1.28 (0.93-1.77)	0.99 (0.71-1.40)
	Ambulatory (unassisted) at DC	38.6% (1023/2651)	40.6% (102/251)	43.1% (345/801)	37.6% (308/819)	34.1% (176/516)	34.8% (92/264)	0.009	1.87 (1.21-2.87)	1.76 (1.24-2.49)	1.31 (0.94-1.82)	1.11 (0.78-1.59)
	Disability-Free at DC**	17.7% (433/2444)	16.7% (35/209)	22.5% (167/743)	16.8% (130/772)	14.3% (69/482)	13.4%(32/238)	<0.001	2.74 (1.50-5.00)	3.17 (1.95-5.17)	1.93 (1.15-3.23)	1.35 (0.82-2.22)
	Functional Independence^ at DC	24.1% (589/2444)	22.0% (46/209)	30.6% (227/743)	23.1% (178/772)	19.1% (92/482)	19.3% (46/238)	<0.001	2.18 (1.28-3.72)	2.77 (1.80-4.26)	1.64 (1.01-2.66)	1.09 (0.70-1.68)
Technical	**Substantial reperfusion^^**	86.0% (2482/2885)	85.6% (226/264)	88.1% (766/869)	87.1% (785/901)	82.3% (466/566)	83.9% (239/285)	0.02	0.88 (0.53-1.45)	1.14 (0.76-1.70)	1.13 (0.79-1.61)	0.87 (0.59-1.29)
Adverse Events	**Symptomatic ICH**	5.9% (182/3078)	5.7% (16/280)	4.8% (44/911)	4.9% (47/957)	7.8% (48/614)	8.5% (27/316)	0.02	0.72 (0.34-1.53)	0.63 (0.33-1.18)	0.56 (0.34-0.94)	0.89 (0.52-1.52)
	In hospital mortality/hospice	20.2% (624/3097)	18.0% (51/283)	17.2% (157/915)	19.3% (185/960)	23.5% (146/622)	26.8% (85/317)	<0.001	0.43 (0.26-0.71)	0.47 (0.30-0.72)	0.53 (0.37-0.77)	0.73 (0.50-1.05)

EMS, emergency medical services; DTP, door to puncture time; DC, discharge; ICH, intracranial hemorrhage; m, minutes
*P values from Pearson chi-square test
**Disability-Free – modified Rankin Scale 0-1
^Functional Independence – modified Rankin Scale 0-2
^^Substantial reperfusion – modified thrombolysis in cerebral ischemia 2b-3
^^^Adjustment variables listed in eTable 2

eTable 8. Additional clinical outcomes of EMS-arriving patients treated with endovascular reperfusion therapy, overall and in different door to puncture time intervals.

Category	Outcome	Unadjusted							Adjusted Odds Ratios^^			
		Overall (n=3097)	DTP 31-60m (n=283)	DTP 61-90m (n=915)	DTP 91-120m (n=960)	DTP 121-150m (n=622)	DTP 151-180m (n=317)	P value*	31-60 vs 151-180	61-90 vs 151-180	91-120 vs 151-180	121-150 vs 151-180
Clinical	**Discharge to Home or ARF**	61.1% (1891/3097)	64.7% (183/283)	66.3% (607/915)	62.5% (600/960)	54.3% (338/622)	51.4% (163/317)	<0.001	2.45 (1.61, 3.72)	2.36 (1.68, 3.32)	1.90 (1.39, 2.61)	1.26 (0.91, 1.75)
	Ambulatory w/ or w/o assist at DC	73.9% (1958/2651)	74.9% (188/251)	76.2% (610/801)	76.1% (623/819)	69.8% (360/516)	67.1% (177/264)	0.003	NP^^^	NP^^^	NP^^^	NP^^^
	Disability-Free at 3 months**	27.7%(531/1916)	29.2% (54/185)	32.2 (191/593)	27.8% (165/593)	21.8 (81/372)	23.1 (40/173)	0.006	1.87 (0.99, 3.55)	1.81 (1.09, 3.02)	1.42 (0.86, 2.34)	0.94 (0.59, 1.51)
	Functional Independence^ at 3 months	36.5 (700/1916)	40% (74/185)	41.3% (245/593)	36.8% (218/593)	31.2% (116/372)	27.2% (47/173)	0.001	2.51 (1.29, 4.91)	2.07 (1.17, 3.66)	1.67 (0.93, 3.00)	1.20 (0.70, 2.06)

EMS, emergency medical services; DTP, door to puncture time; ARF, acute rehabilitation facility; w/ or w/o, with or without; DC, discharge; m, minutes; NP, not performed
*P values from Pearson chi-square test
**Disability-Free – modified Rankin Scale 0-1
^Functional Independence – modified Rankin Scale 0-2
^^Adjustment variables listed in eTable 2
^^^ Some auxiliary outcomes did not have statistical analysis performed due to funding constraints

eTable 9A. Comparison of time-benefit relationships in all patients in the 30-270 minute onset-to-puncture time window versus the 271-480 minute onset-to-puncture window, in relation to onset-to-puncture time as a continuous curve, adjusted analysis.

Category	Outcome^^	P value for Non-linearity*	OTP 30-270 Minutes		OTP 271-480 Minutes	
			Odds Ratio (per 15m decrease OTP)	P Value	Odds Ratio (per 15m decrease OTP)	P Value
Clinical	**Discharge to Home**	<0.001	1.08 (1.05-1.10)	<0.001	1.01 (0.98-1.03)	0.62
	Ambulatory (unassisted)	0.006	1.05 (1.04-1.08)	<0.001	1.01 (0.99-1.03)	0.43
	Disability-Free at DC* **	<0.001	1.10 (1.05-1.14)	<0.001	1.02 (0.99-1.05)	0.25
	Functional Independence at DC^	<0.001	1.06 (1.03-1.10)	<0.001	1.03 (1.01-1.06)	0.009
Technical	**Substantial reperfusion**	0.27	1.01 (0.99-1.04)	0.23	1.00 (0.98-1.02)	0.84
Adverse Events	**Symptomatic ICH**	0.12	0.96 (0.93-0.99)	0.03	0.97 (0.94-1.01)	0.13
	In-Hospital Mortality/Hospice	<0.001	0.94 (0.93-0.97)	<0.001	1.02 (0.99-1.04)	0.14

OTP, Onset (last known well) to puncture time; ICH, intracranial hemorrhage; m, minutes; DC, discharge
*Results of test for non-linearity on the logit scale over the time period 30-480 minutes. When non-linearity was present over the entire time window, splines were placed at a cutpoint of 270 minutes, whereupon the 0-270m and 271-480m segments could be modeled using linear relationships.
***Disability-Free – modified Rankin Scale 0-1 / ^Functional Independence – modified Rankin Scale 0-2 / ^^Adjustment variables listed in eTable 2

eTable 9B. Absolute change in clinical and adverse event outcomes of all patients treated with endovascular reperfusion therapy in relation to onset-to-puncture time as a continuous curve, adjusted analysis, in the 30-270 minute onset-to-puncture window.

Category	Outcome^^^	Within OTP 0-270 Minute Time Period – All Patients			
		Odds Ratio (per 15m decrease OTP)	P Value	Absolute Change (per 15m decrease OTP)	Minutes Needed to Treat^^
Clinical	**Discharge to Home**	1.08 (1.05-1.10)	<0.001	1.15% (0.78,1.52)	13.0
	Ambulatory (unassisted)	1.05 (1.04-1.08)	<0.001	1.14% (0.75,1.53)	13.2
	Disability-Free at DC* **	1.10 (1.05-1.14)	<0.001	0.98% (0.57,1.39)	15.3
	Functional Independence at DC^	1.06 (1.03-1.10)	<0.001	0.91% (0.45,1.36)	16.5
Technical	**Substantial reperfusion**	1.01 (0.99-1.04)	0.23	0.17% (-0.12,0.47)	NS
Adverse Events	**Symptomatic ICH**	0.96 (0.93-0.99)	0.03	-0.22% (-0.40,-0.03)	68.2
	In-Hospital Mortality/Hospice	0.94 (0.93-0.97)	<0.001	-0.77% (-1.07,-0.47)	19.5

OTP, Onset (last known well) to puncture time; ICH, intracranial hemorrhage; m, minutes; DC, discharge; NS, not significant
***Disability-Free – modified Rankin Scale 0-1
^Functional Independence – modified Rankin Scale 0-2
^^Minutes faster needed to treat for 1 patient of every 100 to have a different outcome
^^^Adjustment variables listed in eTable 2

eTable 10. Comparison of time-benefit relationships in the 30-270 minute onset-to-puncture time window in witnessed versus unwitnessed onset patients, in relation to onset-to-puncture time as a continuous curve, adjusted analysis.

Category	Outcome^^	Witnessed onset OTP 30-270 Minutes		Unwitnessed onset OTP 30-270 Minutes	
		Odds Ratio (per 15m decrease OTP)	P Value	Odds Ratio (per 15m decrease OTP)	P Value
Clinical	**Discharge to Home**	1.09 (1.06, 1.12)	<0.001	1.04 (1.01, 1.08)	0.01
	Ambulatory (unassisted)	1.08 (1.05, 1.11)	<0.001	1.01 (0.98, 1.05)	0.46
	Disability-Free at DC* **	1.10 (1.05, 1.15)	<0.001	1.08 (1.01, 1.14)	0.02
	Functional Independence at DC^	1.08 (1.04, 1.12)	<0.001	1.02 (0.97, 1.07)	0.37
Technical	**Substantial reperfusion**	1.03 (1.00, 1.06)	0.05	0.97 (0.92, 1.03)	0.33
Adverse Events	**Symptomatic ICH**	0.96 (0.92, 1.00)	0.05	0.95 (0.88, 1.03)	0.23
	In-Hospital Mortality/Hospice	0.94 (0.91, 0.97)	<0.001	0.96 (0.92, 0.99)	0.02

OTP, Onset (last known well) to puncture time; ICH, intracranial hemorrhage; m, minutes; DC, discharge; NS, not significant
***Disability-Free – modified Rankin Scale 0-1 / ^Functional Independence – modified Rankin Scale 0-2 / ^^Adjustment variables listed in eTable 2

eTable 11A. Comparison of time-benefit relationships in EMS-arriving patients in the 30-120 minute door-to-puncture time window versus the 121-180 minute onset-to-puncture window, in relation to door-to-puncture time as a continuous curve, adjusted analysis

Category	Outcome^^	P value for Non-linearity*	DTP 30-120 Minutes		DTP 121-180 Minutes	
			Odds Ratio (per 15m decrease DTP)	P Value	Odds Ratio (per 15m decrease DTP)	P Value
Clinical	Discharge to Home	0.03	1.12 (1.05-1.22)	0.002	1.09 (0.97,1.20)	0.15
	Ambulatory (unassisted)	0.006	1.09 (1.00-1.18)	0.04	1.10 (0.97-1.25)	0.12
	Disability-Free at DC***	0.07	1.16 (1.05-1.30)	0.005	1.22 (1.02-1.43)	0.03
	Functional Independence at DC^	0.01	1.16 (1.06-1.28)	0.002	1.18 (1.00-1.37)	0.06
Technical	Substantial reperfusion	0.08	1.01 (0.93-1.09)	0.89	1.04 (0.93-1.16)	0.54
Adverse Events	Symptomatic ICH	0.15	1.01 (0.89-1.14)	0.92	0.85 (0.73-1.01)	0.06
	In-Hospital Mortality/Hospice	0.08	0.91 (0.83-0.98)	0.02	0.87 (0.78-0.98)	0.03

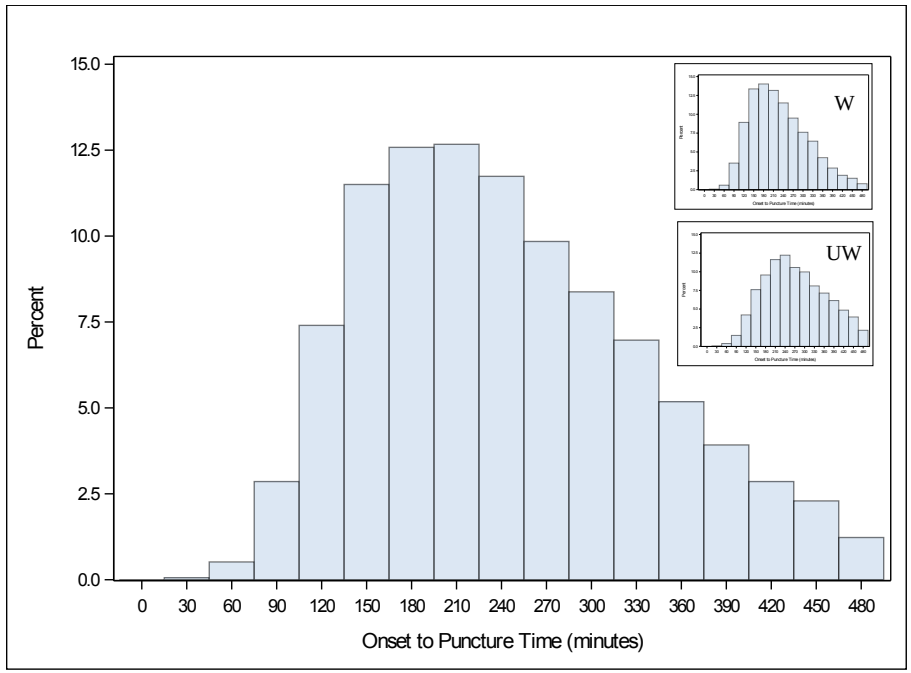
DTP, Door (ED arrival) to puncture time; ICH, intracranial hemorrhage; m, minutes; DC, discharge; NS, not significant
*Results of test for non-linearity on the logit scale over the time period 30-180 minutes. When non-linearity was present over the entire time window, splines were placed at a cutpoint of 120minutes, whereupon the 0-120m and 121-180m segments could be modeled using linear relationships.
***Disability-Free – modified Rankin Scale 0-1 / ^Functional Independence – modified Rankin Scale 0-2 / ^^Adjustment variables listed in eTable 2

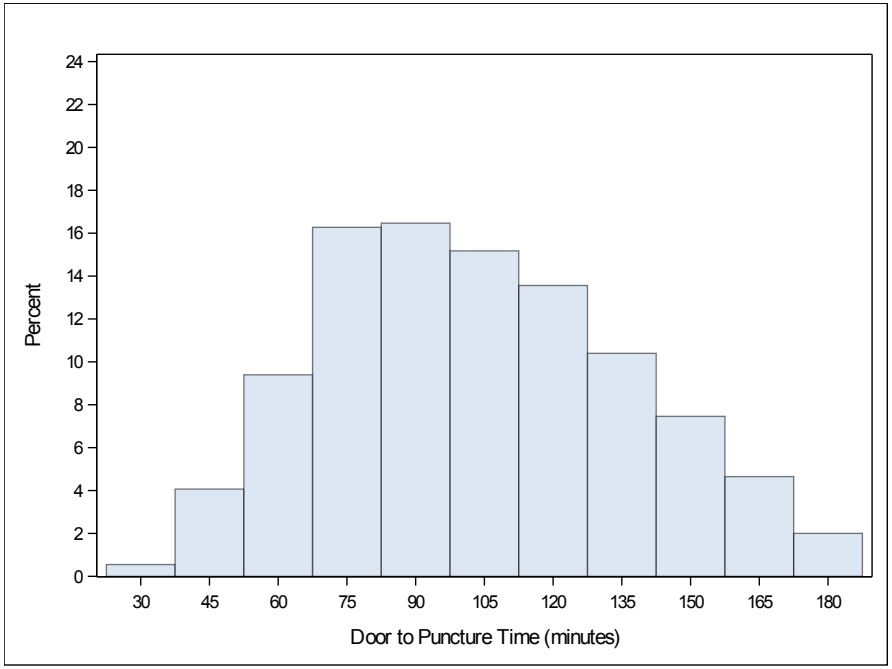
eTable 11B. Clinical and adverse event outcomes of EMS-arriving patients treated with endovascular reperfusion therapy in relation to door-to-puncture as a continuous curve, in adjusted analysis, in the 30-120 minute window.

Category	Outcome	Within DTP 31-120 Minute Time Period – All Patients^^^			
		Odds Ratio (per 15 m decrease DTP)	P Value	Absolute Change (per 15 min decrease DTP)	Minutes Needed to Treat^^
Clinical	**Discharge to Home**	1.12 (1.05-1.22)	0.002	2.13% (0.81-3.44)	7.0
	Ambulatory (unassisted)	1.09 (1.00-1.18)	0.04	1.72% (0.08-3.37)	8.7
	Disability-Free at D/C* **	1.16 (1.05-1.30)	0.005	1.78% (0.43-3.14)	8.4
	Functional Independence at D/C^	1.16 (1.06-1.28)	0.002	2.19% (0.71-3.66)	6.8
Technical	**Substantial reperfusion**	1.01 (0.93-1.09)	0.89	0.07% (-0.80,0.94)	NS
Adverse Events	**Symptomatic ICH**	1.01 (0.89-1.14)	0.92	-0.01% (-0.60,0.57)	NS
	In-Hospital Mortality/Hospice	0.91 (0.83-0.98)	0.02	-1.48% (-2.60,-0.36)	10.1

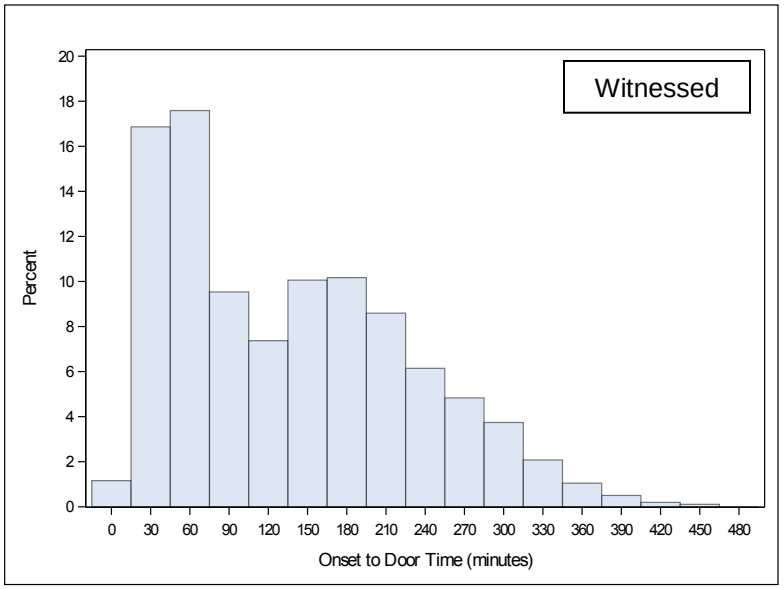
EMS, emergency medical services; DTP, door to puncture time; ICH, intracranial hemorrhage; m, minutes; NS, not significant
***Disability-Free – modified Rankin Scale 0-1 / ^Functional Independence – modified Rankin Scale 0-2
^^Minutes faster needed to treat for 1 patient of every 100 to have a different outcome
^^^Adjustment variables listed in eTable 2

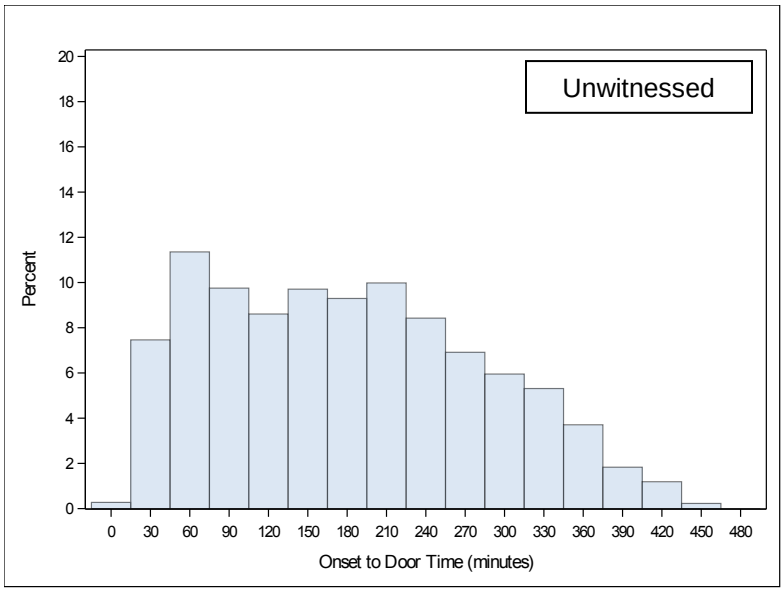
eFigure 1. Distribution of time intervals in endovascular reperfusion therapy patients. A) Onset (last known well) to arterial puncture times, in all patients (main display), patients with witnessed onset (W, upper inset), and patients with unwitnessed onset (UW, lower inset); B) Door (ED arrival time) to arterial puncture times in EMS arriving patients.





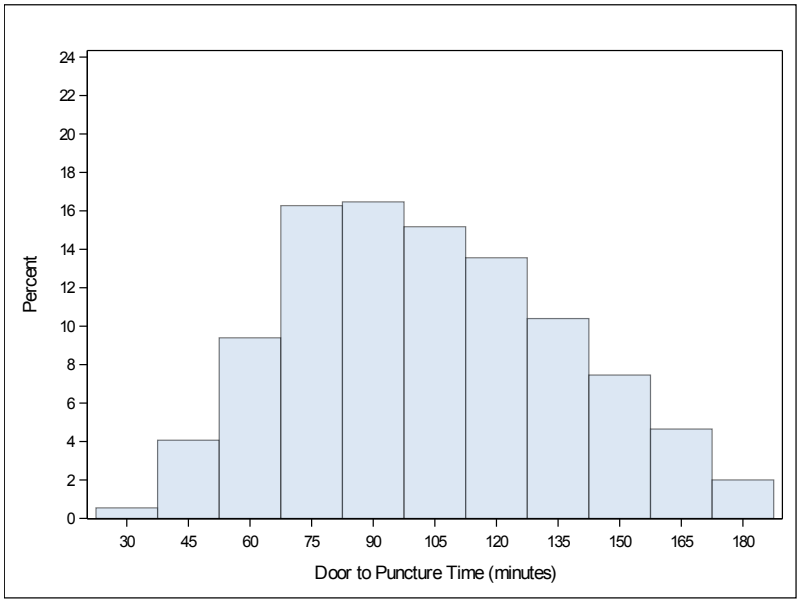
eFigure 2. Onset to Door Times (OTD) among patients with: Top) Witnessed stroke onset, and Bottom) Unwitnessed stroke onset. Histograms show differing patterns, with a pronounced early 30-90 minute OTD peak with witnessed onset versus a wide 30-300 minute OTD plateau with unwitnessed onset.



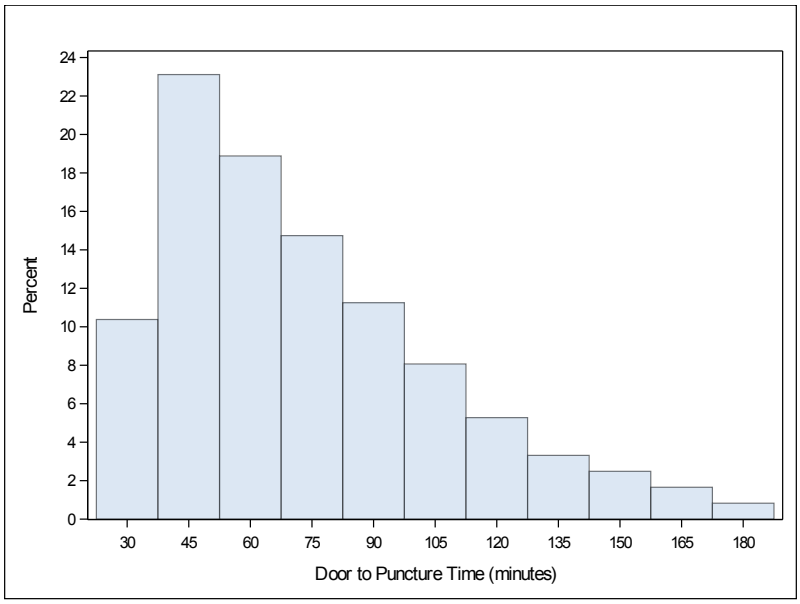


eFigure 3. Door to puncture times up to 180 minutes among: A) patients arriving directly via EMS to the endovascular reperfusion therapy hospital, and B) patients arriving by interfacility transfer to the endovascular reperfusion therapy hospital. The distribution of door to puncture times is left-shifted (compressed toward shorter intervals) in interfacility transfer patients, reflecting pre-completion of several initial diagnostic and therapeutic management activities at the outside hospital and prenotification of transfer, giving opportunity to have neurodiagnostic evaluation and neuroendovascular intervention teams already in place.

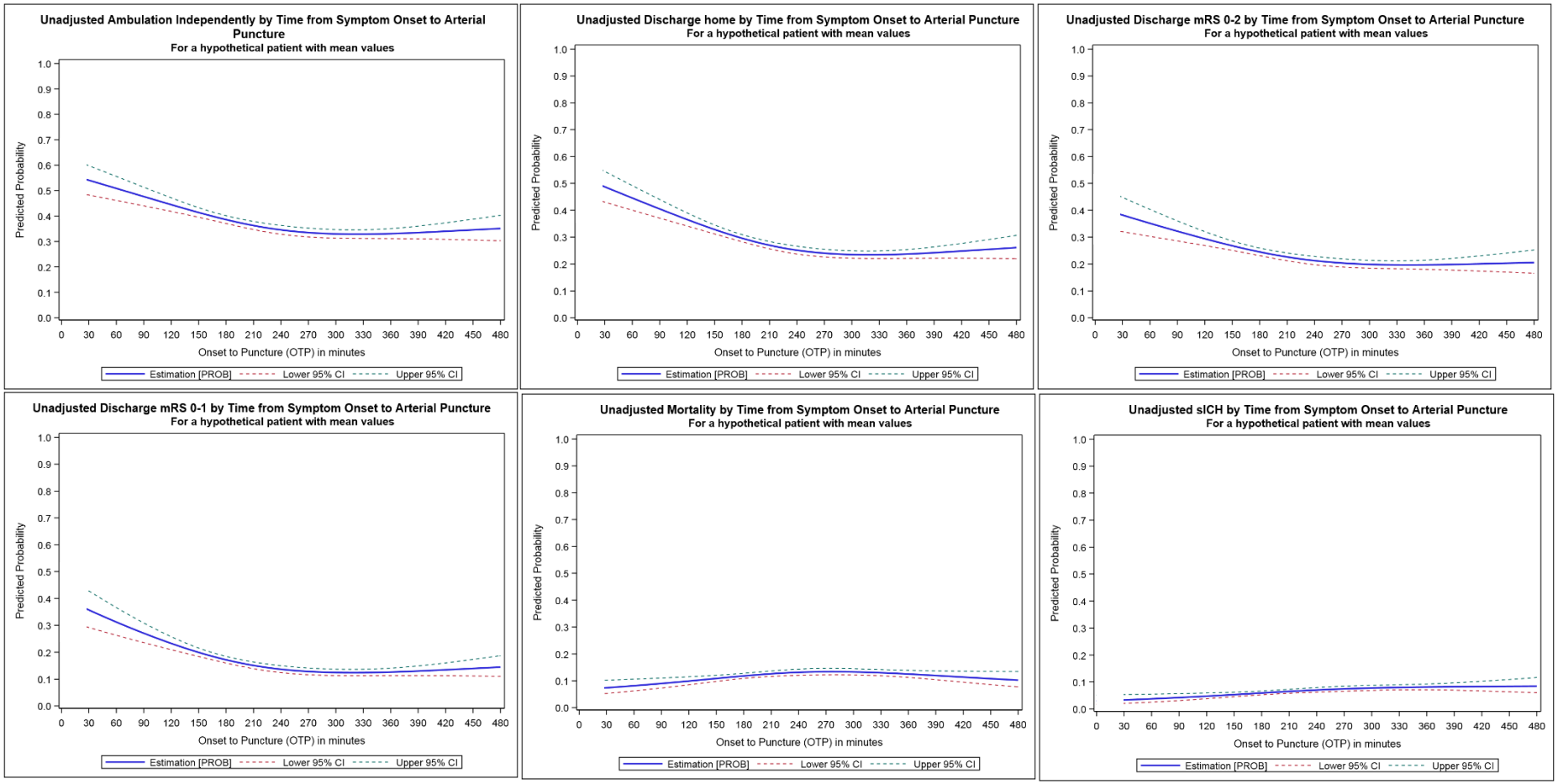
A



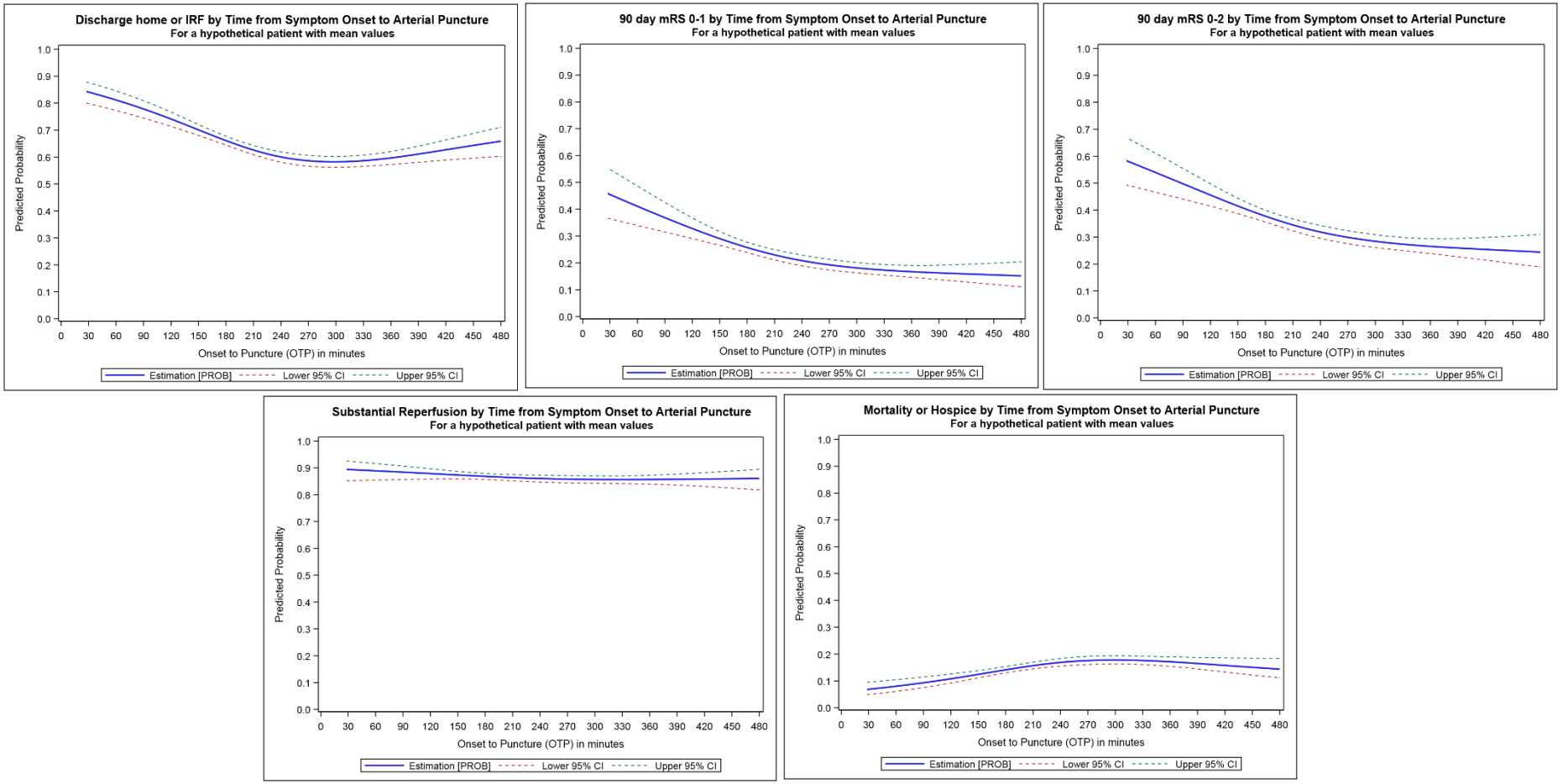
B



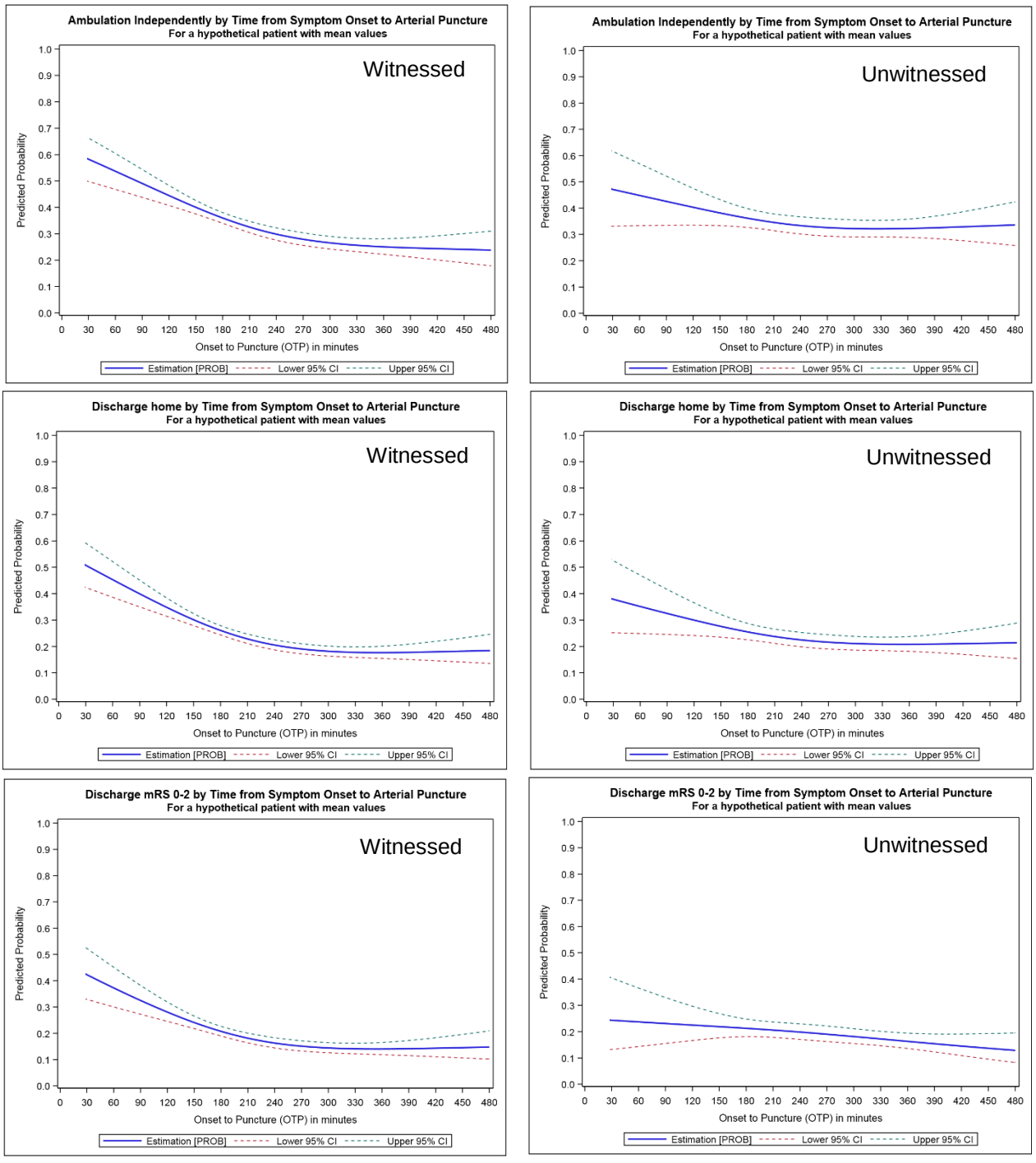
eFigure 4. Changes in main clinical and adverse event outcomes with continuous variation in onset-to-puncture time, unadjusted analysis. Relationships between onset to puncture and the binary outcomes were assessed using logistic regression models with restricted cubic splines with knots at the 5th, 35th, 65th, 95th percentiles. Curves show the unadjusted predicted outcome rate for a hypothetical patient with mean values for baseline characteristics, for onset to puncture and: Top row: Left-independent ambulation at discharge; Middle-discharge to home; Right-functional independence (mRS 0-2) at discharge; Bottom row: Left-disability-free (mRS 0-1) at discharge; Middle-in-hospital mortality; Right-symptomatic intracranial hemorrhage.



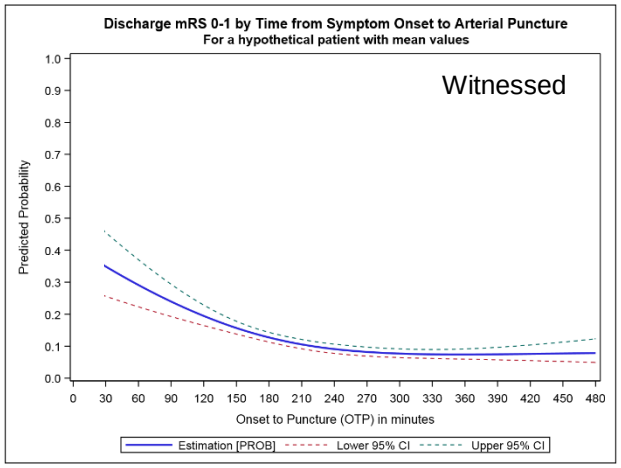
eFigure 5. Changes in additional clinical and adverse event outcomes with continuous variation in onset-to-puncture time, adjusted analysis. Curves show the adjusted predicted outcome rate for a hypothetical patient with mean values for baseline characteristics, for Onset to Puncture and: Top row: Left) discharge to home or acute rehabilitation facility (IRF, inpatient rehabilitation facility) ; Middle) disability-free (mRS 0-1) at 3 months; Right) functional independence (mRS 0-2) at 3 months; Bottom row: Left) substantial reperfusion (mTICI 2b-3); Right) in-hospital mortality or discharge to hospice.

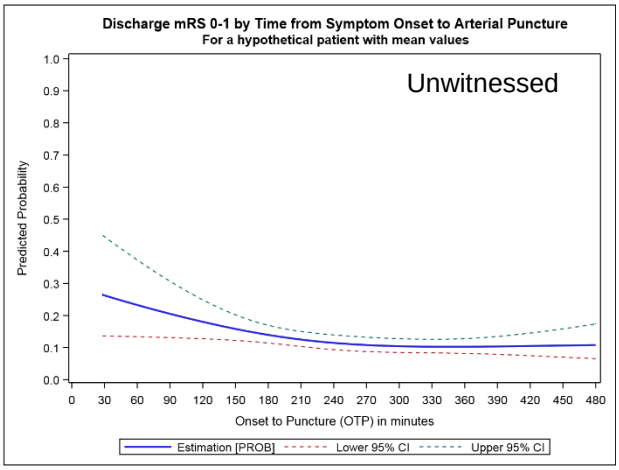


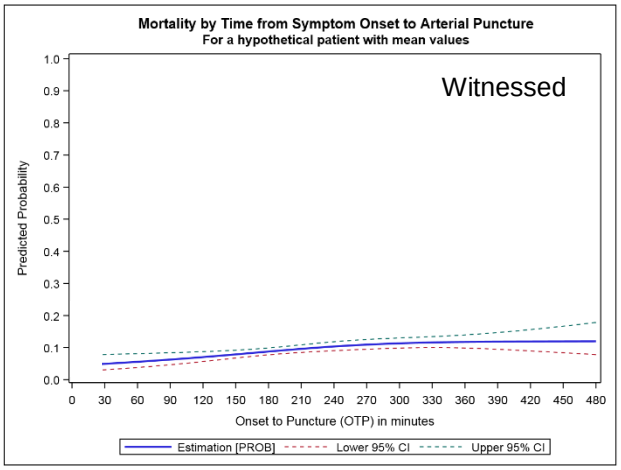
eFigure 6. Changes in main clinical and adverse event outcomes with continuous variation in onset-to-puncture time, in witnessed and unwitnessed onset patients, adjusted analysis. Relationships between onset to puncture and the binary outcomes were assessed with restricted cubic splines with knots at the 5th, 35th, 65th, 95th percentiles. Curves show the predicted outcome rate for a hypothetical patient with mean values for baseline characteristics, for onset to puncture and: First row: independent ambulation at discharge; Second row: discharge to home; Third row: functional independence (mRS 0-2) at discharge; Fourth row: disability-free (mRS 0-1) at discharge; Fifth row: in-hospital mortality; Sixth row: symptomatic intracranial hemorrhage.

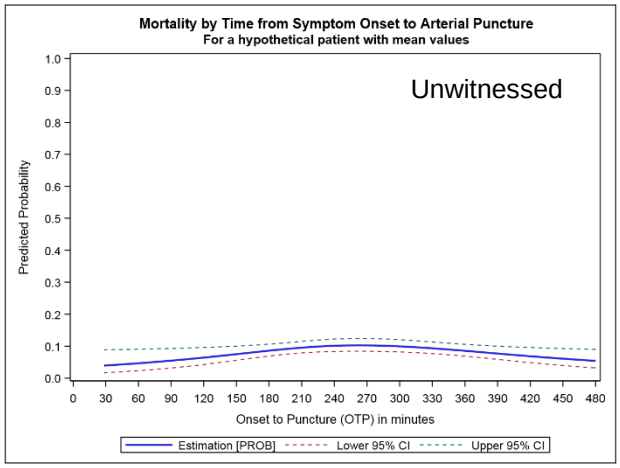


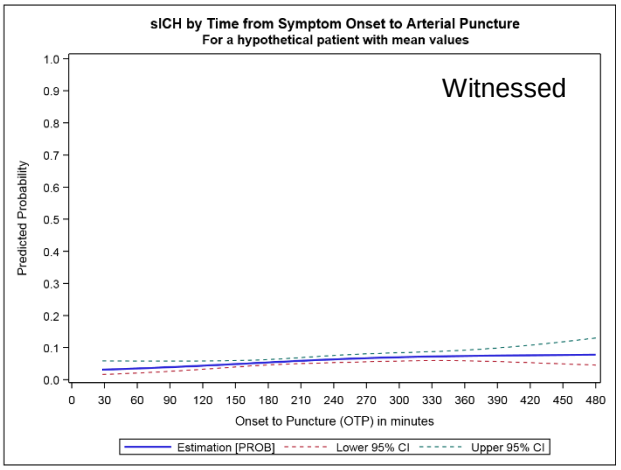
eFigure 6. (continued from previous page)

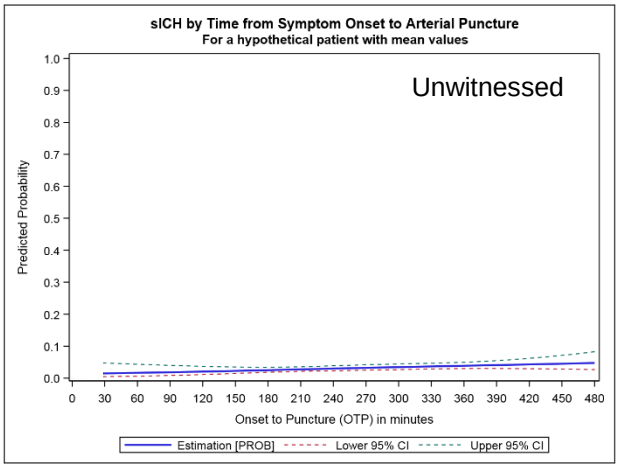




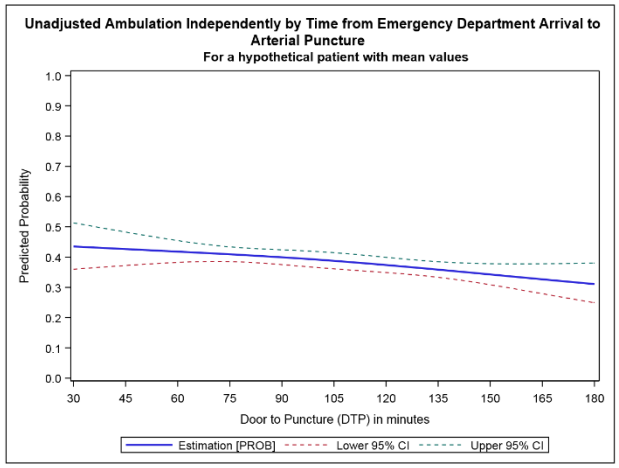


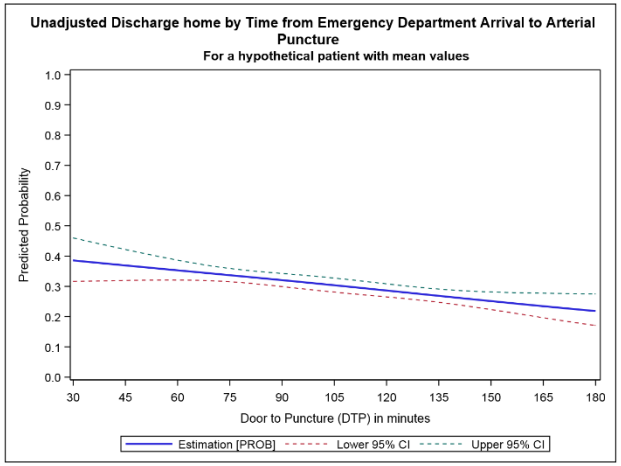


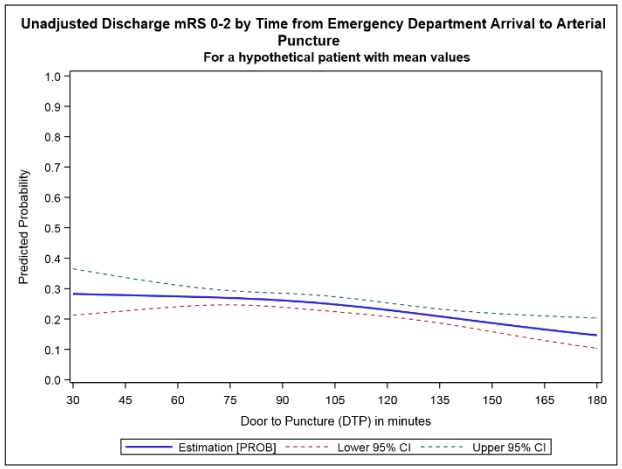


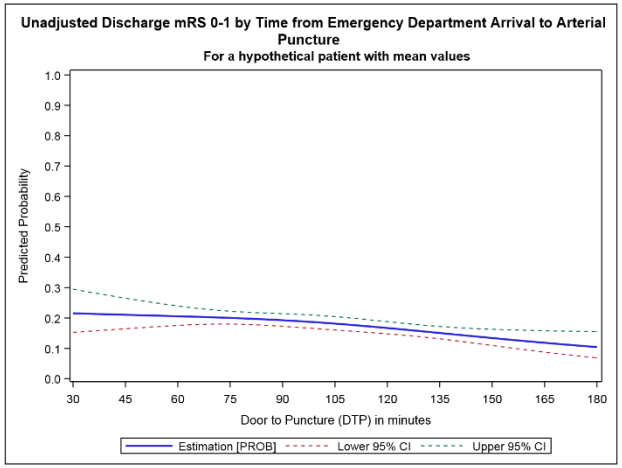


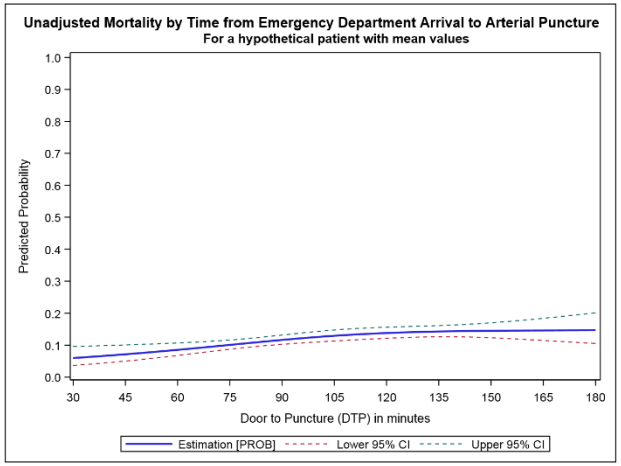
eFigure 7. Changes in clinical and adverse event outcomes with continuous variation in door-to-puncture time, unadjusted analysis. Relationships between onset to puncture and the binary outcomes were assessed using logistic regression models with restricted cubic splines with knots at the 5th, 35th, 65th, 95th percentiles. Curves show the unadjusted predicted outcome rate for onset to puncture and: Top row: Left-independent ambulation at discharge; Middle-discharge to home; Right-functional independence (mRS 0-2) at discharge; Bottom row: Left-disability-free (mRS 0-1) at discharge; Middle-in-hospital mortality; Right-symptomatic intracranial hemorrhage.

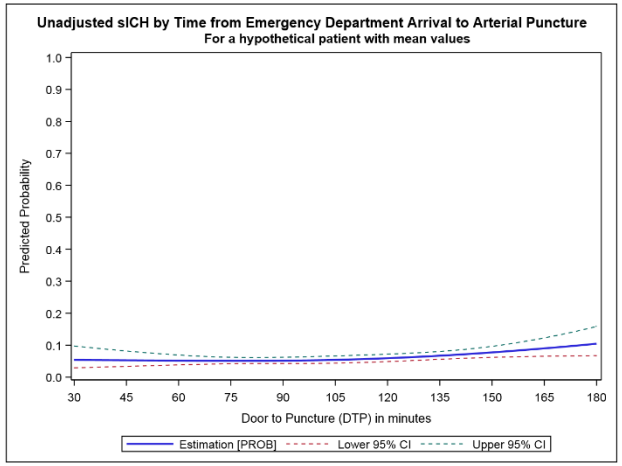












eFigure 8. Changes in additional clinical and adverse event outcomes with continuous variation in door-to-puncture time, adjusted analysis. Curves show the adjusted predicted outcome rate for a hypothetical patient with median/mode values for baseline characteristics, for door to puncture and: Top row: Left) discharge to home or acute rehabilitation facility (IRF, inpatient rehabilitation facility); Middle) disability-free (mRS 0-1) at 3 months; Right) functional independence (mRS 0-2) at 3 months; Bottom row: Left) substantial reperfusion (mTICI 2b-3); Right) in-hospital mortality or discharge to hospice.