

Supplementary Online Content

Man S, Xian Y, Holmes DN, et al. Association between thrombolytic door-to-needle time and 1-year mortality and readmission in patients with acute ischemic stroke. *JAMA*. doi:10.1001/jama.2020.5697

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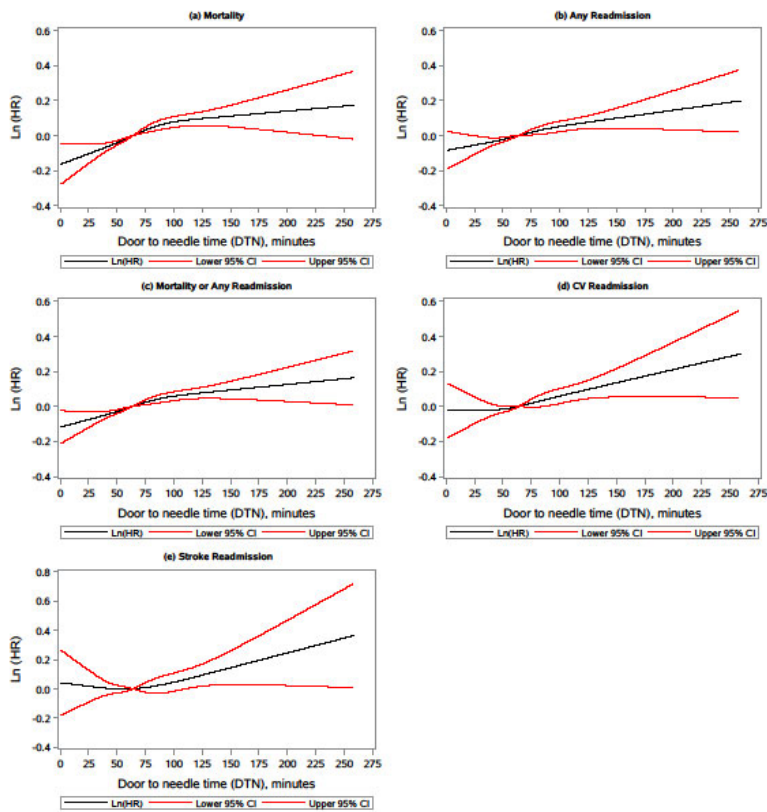
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This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Spline plots of one-year outcomes in relationship to door-to-needle times



Footnote: The spline plots provided a graphical representation of the relationship between door-to-needle times and each outcome of interest (on the natural log scale) and allowed for detection of non-linearity. When the linearity assumption was violated, pictorially, there was a change in the direction of the displayed curve. Linear splines could then be used to approximate the curve through a series of straight lines with a knot point placed where the slope of the straight lines approximating the relationship curve change. The point where the line crossed zero was when the relationship between door-to-needle times and the outcome changed from being less likely to have the outcome to being more likely to have the outcome.

(a) All-cause mortality in one year showed non-linear distribution in relation to door-to-needle times in 15-minute increments with a cut-off at 90 minutes; (b) All-cause readmission outcomes showed linear distribution in relation to door-to-needle times in 15-minute increments within 4.5 hours.; (c) All-cause mortality or any readmission showed linear distribution in relation to door-to-needle times in 15-minute increments within 4.5 hours; (d) Cardiovascular readmission showed non-linear distribution in relation to door-to-needle times in 15-minute increments with a cut-off at 60 minutes; (e) Recurrent stroke readmission showed non-linear distribution in relation to door-to-needle times in 15-minute increments with a cut-off at 60 minutes. Stroke readmission was defined as readmissions with the diagnosis of transient ischemic attack, ischemic and hemorrhagic stroke, carotid endarterectomy or stenting, but not direct complications of index stroke.

Abbreviation: Ln, natural log; CI, confidence interval; CV readmission, cardiovascular readmission.

eTable 1. Patient and hospital characteristics by door-to-needle times of 45 minutes and 60 minutes

Door-to-Needle Time	Overall	≤45 min	>45 min	Standardized Difference	≤60 min	>60 min	Standardized Difference
Number of patients (%)	61426	12760 (20.8%)	48666 (79.2%)		27059 (44.1%)	34367 (55.9%)	
Age, years, Median (IQR)	80 (73-86)	79 (72-86)	80 (73-86)	4.09	80 (73-86)	80 (73-86)	2.94
65-74	18658 (30.4%)	4095 (32.1%)	14563 (29.9%)	4.71	8491 (31.4%)	10167 (29.6%)	4.08
75-84	23331 (38.0%)	4743 (37.2%)	18588 (38.2%)		10054 (37.2%)	13277 (38.6%)	
85+	19437 (31.6%)	3922 (30.7%)	15515 (31.9%)		8514 (31.5%)	10923 (31.8%)	
Male	26715 (43.5%)	5887 (46.1%)	20828 (42.8%)	6.72	12259 (45.3%)	14456 (42.1%)	6.54
Female	34711 (56.5%)	6873 (53.9%)	27838 (57.2%)		14800 (54.7%)	19911 (57.9%)	
Race-Ethnicity, N	61340	12748	48592		27030	34310	
White, non-Hispanic	50324 (82.0%)	10460 (82.1%)	39864 (82.0%)	3.59	22119 (81.8%)	28205 (82.2%)	2.88
Black, non-Hispanic	5329 (8.7%)	1076 (8.4%)	4253 (8.8%)		2315 (8.6%)	3014 (8.8%)	
Hispanic	2452 (4.0%)	472 (3.7%)	1980 (4.1%)		1075 (4.0%)	1377 (4.0%)	
Other	3235 (5.3%)	740 (5.8%)	2495 (5.1%)		1521 (5.6%)	1714 (5.0%)	
Arrival mode, N	58652	12370	46282		26060	32592	
Emergency Medical Service	49797 (84.9%)	10670 (86.3%)	39127 (84.5%)	19.56	22360 (85.8%)	27437 (84.2%)	14.41
Private transport	7617 (13.0%)	1226 (9.9%)	6391 (13.8%)		2960 (11.4%)	4657 (14.3%)	
Transfer from other hospital	889 (1.5%)	413 (3.3%)	476 (1.0%)		606 (2.3%)	283 (0.9%)	
Unknown	349 (0.6%)	61 (0.5%)	288 (0.6%)		134 (0.5%)	215 (0.7%)	
Arrival during off hours ^a	31938 (52.0%)	5657 (44.3%)	26281 (54.0%)	19.43	12895 (47.7%)	19043 (55.4%)	15.57
Vascular Risk Factors^b, N	61006	12644	48362		26855	34151	
Atrial fibrillation/flutter	17992 (29.5%)	3429 (27.1%)	14563 (30.1%)	6.63	7450 (27.7%)	10542 (30.9%)	6.88

Door-to-Needle Time	Overall	≤45 min	>45 min	Standardized Difference	≤60 min	>60 min	Standardized Difference
Coronary artery disease /prior myocardial infarction	18205 (29.8%)	3544 (28.0%)	14661 (30.3%)	5.03	7692 (28.6%)	10513 (30.8%)	4.69
Carotid stenosis	2140 (3.5%)	428 (3.4%)	1712 (3.5%)	0.85	906 (3.4%)	1234 (3.6%)	1.31
Diabetes mellitus	16144 (26.5%)	3245 (25.7%)	12899 (26.7%)	2.29	6936 (25.8%)	9208 (27.0%)	2.58
Dyslipidemia	28223 (46.3%)	5889 (46.6%)	22334 (46.2%)	0.79	12575 (46.8%)	15648 (45.8%)	2.02
Heart Failure	6675 (10.9%)	1335 (10.6%)	5340 (11.0%)	1.56	2873 (10.7%)	3802 (11.1%)	1.39
Hypertension	48063 (78.8%)	9817 (77.6%)	38246 (79.1%)	3.50	20977 (78.1%)	27086 (79.3%)	2.93
Peripheral artery disease	2742 (4.5%)	518 (4.1%)	2224 (4.6%)	2.46	1128 (4.2%)	1614 (4.7%)	2.55
Previous stroke/transient ischemic attack	16285 (26.7%)	3057 (24.2%)	13228 (27.4%)	7.26	6681 (24.9%)	9604 (28.1%)	7.36
Smoker	5423 (8.9%)	1207 (9.5%)	4216 (8.7%)	2.88	2528 (9.4%)	2895 (8.5%)	3.28
Initial NIHSS, N	57812	12385	45427		26114	31698	
Median (IQR)	10 (6-18)	10 (6-17)	10 (6-18)	2.39	10 (6-17)	11 (5-18)	2.32
0-4	10371 (17.9%)	2081 (16.8%)	8290 (18.2%)	6.44	4439 (17.0%)	5932 (18.7%)	7.40
5-9	16242 (28.1%)	3642 (29.4%)	12600 (27.7%)		7659 (29.3%)	8583 (27.1%)	
10-14	10786 (18.7%)	2410 (19.5%)	8376 (18.4%)		4988 (19.1%)	5798 (18.3%)	
15-20	10893 (18.8%)	2358 (19.0%)	8535 (18.8%)		4962 (19.0%)	5931 (18.7%)	
>20	9520 (16.5%)	1894 (15.3%)	7626 (16.8%)		4066 (15.6%)	5454 (17.2%)	
Onset-to-Arrival Time, min, median (IQR)	60 (40-90)	66 (43-110)	58 (39-87)	31.15	65 (42-105)	56 (38-82)	34.51
Door-to-Needle Time, min, median (IQR)	65 (49-88)	37 (30-42)	74 (59-95)	221.83	46 (37-54)	85 (72-104)	234.19

Door-to-Needle Time	Overall	≤45 min	>45 min	Standardized Difference	≤60 min	>60 min	Standardized Difference
Onset-to-Needle Time, min, median (IQR)	137 (106-170)	102 (78-147)	144 (115-173)	67.05	112 (88-151)	150 (125-175)	72.57
<60	1075 (1.8%)	946 (7.4%)	129 (0.3%)	86.88	1056 (3.9%)	19 (0.1%)	92.92
60-90	7652 (12.5%)	4062 (31.8%)	3590 (7.4%)		6810 (25.2%)	842 (2.5%)	
91-120	14076 (22.9%)	2966 (23.2%)	11110 (22.8%)		7686 (28.4%)	6390 (18.6%)	
121-180	28896 (47.0%)	3383 (26.5%)	25513 (52.4%)		8354 (30.9%)	20542 (59.8%)	
181-270	9727 (15.8%)	1403 (11.0%)	8324 (17.1%)		3153 (11.7%)	6574 (19.1%)	
Reason for tPA Delay, n/N (%)							
Not documented ^c	7555/15940 (47.4%)	-	7555/15940 (47.4%)		-	7555/15940 (47.4%)	
Unable to determine eligibility ^d	3192/4650 (68.6%)	-	3192/4650 (68.6%)		-	3192/1650 (68.6%)	
Hypertension requiring aggressive control ^d	2498/3330 (75.0%)	-	2498/3330 (75.0%)		-	2498/3330 (75.0%)	
In-hospital delay ^e	1666/2608 (63.9%)	-	1666/2608 (63.9%)		-	1666/2608 (63.9%)	
Hospital Characteristics at Patient Level							
Regional Distribution^f				9.15			8.49
South	23486 (38.2%)	5165 (40.5%)	18321 (37.6%)		10611 (39.2%)	12875 (37.5%)	
Northeast	14975 (24.4%)	2884 (22.6%)	12091 (24.8%)		6345 (23.4%)	8630 (25.1%)	
Midwest	11734 (19.1%)	2211 (17.3%)	9523 (19.6%)		4827 (17.8%)	6907 (20.1%)	
West	11231 (18.3%)	2500 (19.6%)	8731 (17.9%)		5276 (19.5%)	5955 (17.3%)	
Rural Location ^g , n/N (%)	1818/61376 (3.0%)	289/12757 (2.3%)	1529/48619 (3.1%)	5.42	700/27050 (2.6%)	1118/34326 (3.3%)	3.97
Total number of beds, median (IQR)	380 (260-585)	424 (294-648)	370 (254-555)	16.18	405 (276-620)	365 (249-546)	12.83
Annual ischemic stroke volume, median (IQR)	266 (183-405)	313 (210-455)	255 (178-390)	26.97	295 (198-438)	250 (173-379)	23.20

Door-to-Needle Time	Overall	≤45 min	>45 min	Standardized Difference	≤60 min	>60 min	Standardized Difference
Annual volume of intravenous tPA	29 (18-43)	36 (22-51)	28 (17-41)	37.46	33 (21-48)	26 (16-39)	32.55
Teaching hospital ^h n/N (%)	47145/60675 (77.7%)	10215/12640 (80.8%)	36930/48034 (76.9%)	9.62	21370/26781 (79.8%)	25775/33894 (76.0%)	9.05
Primary stroke center ⁱ	44986 (73.2%)	9246 (72.5%)	35740 (73.4%)	2.20	19781 (73.1%)	25205 (73.3%)	0.54

Abbreviations: NIHSS, National Institute of Health Stroke Scale; tPA, tissue-type plasminogen activator.

Data were expressed as n (%) unless specified. For variables with missing data, the number of patients with complete data was specified in the cell of the variable.

Standardized difference was calculated as the difference in means or proportions divided by a pooled estimate of the standard deviation and multiplied by 100 to get a percentage of a variable. Standardized difference greater than 10% was considered significant imbalance.

^a Regular hour arrival was defined as arriving 7:00 Am to 6:00 Pm on any weekday. Off hour arrival was defined as presenting any other time, including evenings, nights, weekends and during national holidays.

^b Vascular risk factors were calculated among patients who responded to at least one of the variables in the medical history panel from the data report form.

^c The percentages were among patients admitted in October 2012 and after.

^d The percentages were among patients admitted in October 2012 and after with a documented eligibility or medical reason for delay. A patient may have more than one reason documented.

^e The percentages were among patients admitted in October 2012 and after without a eligibility or medical reason documented as a cause for delay. A patient may have more than one reason documented.

^f Regional distribution was defined by the US Census Bureau.

^g Rural location was defined by the US Office of Management and Budget as areas other than Metropolitan Statistical Area.

^h Teaching hospital was identified based on American Hospital Association data.

ⁱ Primary stroke centers received their certifications from the Joint Commission, state health department, Healthcare Facilities Accreditation Program or Det Norske Veritas.

eTable 2. Comparison of patient characteristics of included and excluded population

Variable	Overall n=102621	Included n=61426	Excluded ^a n=41195	Standardized Differences (%)
Total Patients				
Age, years, median (IQR)	79 (72-86)	80 (73-86)	78 (71-85)	15.87
65-74	33553 (32.7%)	18658 (30.4%)	14895 (36.2%)	15.20
75-84	39097 (38.1%)	23331 (38.0%)	15766 (38.3%)	
85+	29971 (29.2%)	19437 (31.6%)	10534 (25.6%)	
Male	45533 (44.4%)	26715 (43.5%)	18818 (45.7%)	4.41
Female	57088 (55.6%)	34711 (56.5%)	22377 (54.3%)	
Race-Ethnicity				30.86
White, non-Hispanic	79008 (77.1%)	50324 (82.0%)	28684 (69.7%)	
Black, non-Hispanic	10347 (10.1%)	5329 (8.7%)	5018 (12.2%)	
Hispanic	6430 (6.3%)	2452 (4.0%)	3978 (9.7%)	
Other	6682 (6.5%)	3235 (5.3%)	3447 (8.4%)	
Arrival Mode				3.59
Arrival by emergency medical services	82952 (84.5%)	49797 (84.9%)	33155 (83.9%)	
Private Transport	13190 (13.4%)	7617 (13.0%)	5573 (14.1%)	
Transfer from other hospital	1473 (1.5%)	889 (1.5%)	584 (1.5%)	
Unknown	539 (0.5%)	349 (0.6%)	190 (0.5%)	
Arrival During Off Hours ^b	53673 (52.3%)	31938 (52.0%)	21735 (52.8%)	1.54
Vascular Risk Factors				
Atrial Fibrillation/Flutter	28828 (28.3%)	17992 (29.5%)	10836 (26.5%)	6.61
Coronary artery disease/prior myocardial infarction	29446 (28.9%)	18205 (29.8%)	11241 (27.5%)	5.15
Carotid stenosis	3494 (3.4%)	2140 (3.5%)	1354 (3.3%)	1.07
Diabetes Mellitus	28267 (27.8%)	16144 (26.5%)	12123 (29.7%)	7.15
Dyslipidemia	47414 (46.5%)	28223 (46.3%)	19191 (47.0%)	1.43
Heart failure	10749 (10.6%)	6675 (10.9%)	4074 (10.0%)	3.17
Hypertension	80719 (79.2%)	48063 (78.8%)	32656 (79.9%)	2.84
Peripheral artery disease	4400 (4.3%)	2742 (4.5%)	1658 (4.1%)	2.16
Prior stroke/ transient ischemic attack	27334 (26.8%)	16285 (26.7%)	11049 (27.0%)	0.79
Smoker	9380 (9.2%)	5423 (8.9%)	3957 (9.7%)	2.74
NIHSS, median (IQR)	10 (6-18)	10 (6-18)	10 (5-17)	3.64
0-4	17766 (18.3%)	10371 (17.9%)	7395 (18.8%)	3.68
5-9	27552 (28.4%)	16242 (28.1%)	11310 (28.8%)	
10-14	18069 (18.6%)	10786 (18.7%)	7283 (18.6%)	

Variable	Overall n=102621	Included n=61426	Excluded ^a n=41195	Standardized Differences (%)
15-20	18022 (18.6%)	10893 (18.8%)	7129 (18.2%)	
>20	15642 (16.1%)	9520 (16.5%)	6122 (15.6%)	
Door-to-Needle Time, min, median (IQR)	64 (48-87)	65 (49-88)	63 (47-85)	7.08
≤30	6101 (5.9%)	3419 (5.6%)	2682 (6.5%)	7.65
31-45	16131 (15.7%)	9341 (15.2%)	6790 (16.5%)	
46-60	24391 (23.8%)	14299 (23.3%)	10092 (24.5%)	
61-75	18825 (18.3%)	11357 (18.5%)	7468 (18.1%)	
>75	37173 (36.2%)	23010 (37.5%)	14163 (34.4%)	
Regional Distribution^c				28.60
South	36161 (35.2%)	23486 (38.2%)	12675 (30.8%)	
Northeast	25438 (24.8%)	14975 (24.4%)	10463 (25.4%)	
Midwest	17717 (17.3%)	11734 (19.1%)	5983 (14.5%)	
West	23305 (22.7%)	11231 (18.3%)	12074 (29.3%)	
Rural location ^d	2447 (2.4%)	1818 (3.0%)	629 (1.5%)	9.65
Teaching hospital ^e	79423 (78.5%)	47145 (77.7%)	32278 (79.6%)	4.72
Total number of beds, median (IQR)	381 (260-583)	380 (260-585)	381 (260-558)	0.66
Annual ischemic stroke volume, median (IQR)	262 (184-404)	266 (183-405)	259 (186-401)	0.34
Annual volume of intravenous tPA, median (IQR)	30 (19-43)	29 (18-43)	31 (19-44)	4.31
Primary stroke center ^f	74286 (72.4%)	44986 (73.2%)	29300 (71.1%)	4.71

Abbreviations: NIHSS, National Institute of Health Stroke Scale; tPA, tissue-type plasminogen activator.

Data were expressed as n (%) unless specified. Standardized difference was calculated as the difference in means or proportions divided by a pooled estimate of the standard deviation and multiplied by 100 to get a percentage of a variable. Standardized difference greater than 10% was considered significant imbalance.

^aThe excluded population were patients aged ≥65 years who were treated with intravenous tPA within 4.5 hours of onset at Get With The Guideline-Stroke hospitals during the study time period otherwise meeting study entry criteria but not matched to the Medicare claims file.

^bRegular hour arrival was defined as arriving 7:00 Am to 6:00 Pm on any weekday. Off hour arrival was defined as presenting any other time, including evenings, nights, weekends and during national holidays.

^cRegional distribution was defined by the US Census Bureau.

^dRural location was defined by the US Office of Management and Budget as areas other than Metropolitan Statistical Area.

^eTeaching hospital was identified based on American Hospital Association data.

^fPrimary stroke centers received their certifications from the Joint Commission, state health department, Healthcare Facilities Accreditation Program or Det Norske Veritas.

eTable 3. Sensitivity analysis: outcomes at one year by door-to-needle times of 45 minutes and 60 minutes in 2015 and 2016

	Event Rate, % (95% CI)		Absolute Difference % (95% CI) ^a	Adjusted HR (95% CI) ^b	P value	Event Rate, % (CI)		Absolute Difference, % (95% CI) ^a	Adjusted HR (95% CI) ^b	P value
	≤ 45 min	>45 min	>45 min vs ≤ 45 min	>45 min vs ≤ 45 min		≤ 60 min	>60 min	>60 min vs ≤ 60 min	>60 min vs ≤ 60 min	
All-cause mortality	29.2 (27.8, 30.6)	31.8 (30.9, 32.9)	3.1 (1.9, 4.3)	1.16 (1.08, 1.25)	<.001	33.3 (32.4, 34.2)	36.8 (36.1, 37.5)	1.8 (0.7, 3.0)	1.09 (1.02, 1.17)	.002
All-cause readmission	36.8 (35.3, 38.3)	38.6 (37.5, 39.7)	3.3 (1.7, 5.0)	1.11 (1.04, 1.19)	<.001	40.5 (39.5, 41.5)	41.9 (41.1, 42.7)	2.7 (1.1, 4.3)	1.09 (1.02, 1.16)	.001
All-cause mortality or readmission	49.9 (48.4, 51.5)	52.9 (51.8, 54.1)	3.5 (2.1, 4.9)	1.12 (1.06, 1.19)	<.001	54.7 (53.7, 55.7)	57.7 (56.9, 58.5)	2.7 (1.3, 4.0)	1.09 (1.03, 1.15)	<.001
Cardiovascular readmission	16.8 (15.8, 17.8)	17.9 (17.2, 18.6)	1.6 (0.2, 3.1)	1.09 (1.01, 1.18)	.02	19.8 (19.1, 20.5)	20.8 (20.3, 21.3)	1.2 (-0.2, 2.6)	1.07 (0.99, 1.15)	.09
Recurrent stroke readmission ^c	8.4 (7.7, 9.2)	8.7 (8.2, 9.2)	0.7 (-0.4, 1.8)	1.08 (0.96, 1.20)	.19	9.2 (8.8, 9.7)	9.5 (9.2, 9.9)	0.2 (-0.9, 1.2)	1.02 (0.92, 1.13)	.74

The population informed all-cause mortality was 18242. The population informed readmission was 16860. The difference represented in-hospital death.

^a For absolute difference, a positive value indicates an increase in risk and a negative value indicates a reduction in risk.

^b Models adjusted for patient age, sex, race-ethnicity; vascular risk factors including atrial fibrillation/flutter, previous stroke/transient ischemic attack, history of coronary artery disease/myocardial infarction, heart failure, carotid stenosis, diabetes mellitus, peripheral artery disease, hypertension, dyslipidemia, smoking, arrival by Emergency Medical Services, arrival during off hours, stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS), hospital region, urban/rural location, total number of beds, annual ischemic stroke volume, academic status, stroke center certification status.

^c Recurrent stroke readmission, a post hoc outcome, was defined as readmission for transient ischemic attack, ischemic and hemorrhagic stroke, carotid endarterectomy or stenting, but not direct complications of index stroke.

eTable 4. Outcomes at one year by door-to-needle time in 60-minute increments

Door-to-Needle Time	Event Rate, % (95% CI)			Absolute Difference, % (95% CI) ^a		Adjusted Hazard Ratio (95% CI) ^b			
	≤ 60 min	61-120 min	>120 min	61-120 min	>120 min	61-120 min	P value	>120 min	P value
All-cause mortality	32.1 (31.5, 32.7)	35.7 (35.2, 36.2)	36.2 (34.8, 37.7)	2.1 (1.4, 2.8)	3.3 (2.0, 4.7)	1.10 (1.07, 1.13)	<.001	1.16 (1.09, 1.23)	<.001
All-cause readmission	39.1 (38.5, 39.7)	41.0 (40.4, 41.6)	43.2 (41.6, 44.8)	1.6 (0.7, 2.6)	5.4 (3.5, 7.2)	1.05 (1.02, 1.08)	<.001	1.18 (1.12, 1.25)	<.001
All-cause mortality or readmission	53.1 (52.5, 53.8)	56.6 (56.0, 57.2)	57.8 (56.2, 59.4)	2.0 (1.2, 2.8)	4.7 (3.1, 6.2)	1.07 (1.04, 1.10)	<.001	1.16 (1.11, 1.22)	<.001
Cardiovascular readmission	18.6 (18.1, 19.1)	19.9 (19.5, 20.4)	22.3 (21.0, 23.7)	0.8 (-0.1, 1.6)	3.9 (2.2, 5.7)	1.04 (1.00, 1.08)	.08	1.21 (1.12, 1.30)	<.001
Recurrent stroke readmission ^c	8.9 (8.6, 9.3)	9.2 (8.8, 9.5)	10.5 (9.5, 11.5)	0.1 (-0.6, 0.7)	1.8 (0.5, 3.1)	1.01 (0.95, 1.07)	.81	1.18 (1.05, 1.32)	.006

^a For absolute difference, a positive value indicates an increase in risk and a negative value indicates a reduction in risk. Door-to-Needle times ≤60 minutes was used as reference standard

^b Door-to-Needle times ≤60 minutes was used as reference standard. The models included 56870 patients for all-cause mortality and 51645 patients for the readmission outcomes after excluding 4556 and 3967 patients respectively, with missing data on hospital characteristics and National Institute of Health Stroke Scale. The difference in number of observation in the models represented in-hospital death. Models adjusted for patient age, sex, race-ethnicity; vascular risk factors including atrial fibrillation/flutter, previous stroke/transient ischemic attack, history of coronary artery disease/myocardial infarction, heart failure, carotid stenosis, diabetes mellitus, peripheral artery disease, hypertension, dyslipidemia, smoking, arrival by Emergency Medical Services, arrival during off hours, stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS), hospital region, urban/rural location, total number of beds, annual ischemic stroke volume, academic status, stroke center certification status and Target Stroke Initiative (using admission time before or after 2010).

^c Recurrent stroke readmission, a post hoc outcome, was defined as readmission for transient ischemic attack, ischemic and hemorrhagic stroke, carotid endarterectomy or stenting, but not direct complications of index stroke.

eTable 5. Outcomes at one year by door-to-needle time in 45-minute increments

Door-to-Needle Time	Event Rate, % (95% CI)			Absolute Difference, % (95% CI) ^a		Adjusted Hazard Ratio (95% CI) ^b			
	≤ 45 min	46-90 min	>90 min	46-90 min	>90 min	46-90 min	P value	>90 min	P value
All-cause mortality	30.8 (30.0, 31.6)	34.5 (34.0, 35.0)	36.3 (35.5, 37.1)	2.6 (1.7, 3.4)	3.4 (2.4, 4.4)	1.12 (1.08, 1.17)	<.001	1.17 (1.11, 1.22)	<.001
All-cause readmission	38.4 (37.5, 39.3)	40.4 (39.8, 40.9)	42.0 (41.1, 42.9)	2.2 (1.0, 3.3)	3.7 (2.4, 5.1)	1.07 (1.03, 1.11)	<.001	1.12 (1.08, 1.17)	<.001
All-cause mortality or readmission	52.1 (51.1, 53.0)	55.3 (54.7, 55.8)	57.7 (56.9, 58.6)	2.3 (1.3, 3.2)	3.8 (2.6, 5.0)	1.08 (1.04, 1.11)	<.001	1.13 (1.09, 1.17)	<.001
Cardiovascular readmission	18.4 (17.7, 19.1)	19.3 (18.9, 19.8)	20.9 (20.2, 21.7)	0.7 (-0.3, 1.7)	1.9 (0.6, 3.1)	1.04 (0.98, 1.09)	.17	1.10 (1.03, 1.17)	.003
Recurrent stroke readmission ^c	8.8 (8.3, 9.3)	9.1 (8.8, 9.4)	9.6 (9.1, 10.1)	0.3 (-0.4, 1.1)	0.8 (-0.1, 1.7)	1.03 (0.96, 1.11)	.35	1.08 (0.99, 1.18)	.08

^a For absolute difference, a positive value indicates an increase in risk and a negative value indicates a reduction in risk. Door-to-Needle time ≤45 minutes was used as reference standard

^b Door-to-Needle time ≤45 minutes was used as reference standard. The models included 56870 patients for all-cause mortality and 51645 patients for the readmission outcomes after excluding 4556 and 3967 patients respectively, with missing data on hospital characteristics and National Institute of Health Stroke Scale. The difference in number of observation in the models represented in-hospital death. Models adjusted for patient age, sex, race-ethnicity; vascular risk factors including atrial fibrillation/flutter, previous stroke/transient ischemic attack, history of coronary artery disease/myocardial infarction, heart failure, carotid stenosis, diabetes mellitus, peripheral artery disease, hypertension, dyslipidemia, smoking, arrival by Emergency Medical Services, arrival during off hours, stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS), hospital region, urban/rural location, total number of beds, annual ischemic stroke volume, academic status, stroke center certification status and Target: Stroke Initiative (using admission time before or after 2010).

^c Recurrent stroke readmission, a post hoc outcome, was defined as readmission for transient ischemic attack, ischemic and hemorrhagic stroke, carotid endarterectomy or stenting, but not direct complications of index stroke.

eTable 6. Sensitivity analysis: outcomes at one year by door-to-needle times in 15-minute increments in 2015 and 2016

Door-to-Needle Time, min	≤ 30	31–45	46–60	61–75	>75	Per 15-min Increment ^d	
All-cause mortality						Per 15-min Increment within 90 min ^d	Per 15-min Increment after 90 min ^d
Event rate, % (95% CI)	30.0 (28.2, 32.1)	28.8 (27.5, 30.2)	31.8 (30.6, 33.1)	31.6 (30.0, 33.3)	32.0 (30.7, 33.4)	-	-
Absolute difference, % (95% CI) ^a	reference	-0.4 (-2.4, 1.7)	2.7 (0.7, 4.7)	1.8 (-0.3, 4.0)	3.8 (1.7, 5.9)	-	-
Unadjusted hazard ratio (95% CI)	reference	0.95 (0.83, 1.08)	1.07 (0.94, 1.22)	1.05 (0.92, 1.21)	1.07 (0.94, 1.23)	1.03 (1.01, 1.06)	0.98 (0.94, 1.01)
P value		.33	.19	.37	.21	.006	.22
Adjusted hazard ratio (95% CI) ^b	reference	0.98 (0.88, 1.09)	1.14 (1.03, 1.26)	1.09 (0.97, 1.23)	1.20 (1.08, 1.34)	1.04 (1.02, 1.06)	1.03 (0.99, 1.07)
P value		.74	.01	.13	<.001	<.001	.17
All-cause readmission						Per 15-min Increment	
Event rate, % (95% CI)	36.5 (34.3, 39.9)	36.8 (35.4, 38.4)	37.9 (36.5, 39.3)	38.7 (36.9, 40.5)	39.3 (37.8, 40.9)	-	
Absolute difference, % (95% CI) ^a		0.1 (-2.7, 3.0)	2.7 (-0.1, 5.5)	2.9 (-0.2, 6.0)	4.8 (1.8, 7.7)	-	
Unadjusted HR (95% CI)	reference	1.01 (0.90, 1.13)	1.07 (0.95, 1.19)	1.09 (0.97, 1.23)	1.11 (0.99, 1.25)	1.02 (1.01, 1.03)	
P value		.85	.17	.07	.02	.005	
Adjusted hazard ratio (95% CI) ^b	reference	1.00 (0.91, 1.10)	1.09 (1.00, 1.20)	1.10 (1.00, 1.21)	1.17 (1.06, 1.28)	1.03 (1.02, 1.04)	
P value		.94	.06	.06	.001	<.001	
All-cause mortality or readmission						Per 15-min Increment	
Event rate, % (95% CI)	49.6 (47.2, 52.0)	50.1 (48.5, 51.6)	52.2 (50.8, 53.7)	52.9 (51.0, 54.7)	53.9 (52.3, 55.5)	-	
Absolute difference, % (95% CI) ^a	reference	0.7 (-1.7, 3.2)	3.4 (1.0, 5.8)	3.1 (0.4, 5.7)	5.7 (3.2, 8.2)	-	
Unadjusted hazard ratio (95% CI)	reference	1.01 (0.91, 1.12)	1.08 (0.98, 1.19)	1.09 (0.99, 1.22)	1.12 (1.01, 1.24)	1.02 (1.00, 1.03)	
P value		.83	.07	.04	.009	.007	
Adjusted hazard ratio (95% CI) ^b	reference	1.02 (0.94, 1.12)	1.12 (1.02, 1.22)	1.10 (1.01, 1.21)	1.20 (1.10, 1.31)	1.03 (1.01, 1.05)	
P value		.58	.01	.03	<.001	<.001	

Door-to-Needle Time, min	≤ 30	31–45	46–60	61–75	>75	Per 15-min Increment ^d	
Cardiovascular readmission						Per 15-min Increment within 60 min ^d	Per 15-min Increment after 60 min ^d
Event rate, % (95% CI)	16.8 (15.1, 18.7)	16.8 (15.6, 18.0)	17.4 (16.3, 18.5)	17.9 (16.5, 19.4)	18.4 (17.2, 19.6)	-	-
Absolute difference, % (95% CI) ^a	reference	-0.2 (-2.7, 2.3)	1.2 (-1.3, 3.7)	1.0 (-1.7, 3.7)	2.2 (-0.4, 4.8)	-	-
Unadjusted hazard ratio (95% CI)	reference	1.02 (0.88, 1.17)	1.07 (0.93, 1.23)	1.09 (0.94, 1.27)	1.15 (1.00, 1.32)	1.03 (0.98, 1.08)	1.03 (1.00, 1.06)
P value		.82	.32	.25	.05	.24	.06
Adjusted hazard ratio (95% CI) ^b	reference	0.99 (0.86, 1.14)	1.07 (0.93, 1.22)	1.06 (0.91, 1.23)	1.13 (0.98, 1.30)	1.02 (0.97, 1.07)	1.03 (1.00, 1.06)
P value		.89	.34	.46	.09	.40	.03
Recurrent stroke readmission^c						Per 15-min Increment within 60 min ^d	Per 15-min Increment after 60 min ^d
Event rate, % (95% CI)	8.5 (7.2, 9.9)	8.4 (7.6, 9.3)	8.7 (8.0, 9.6)	8.3 (7.3, 9.4)	8.9 (8.1, 9.9)	-	-
Absolute difference, % (95% CI) ^a	reference	0.1 (-1.7, 1.9)	1.0 (-0.9, 2.8)	-0.0 (-2.0, 1.9)	1.2 (-0.7, 3.1)	-	-
Unadjusted hazard ratio (95% CI)	reference	1.02 (0.84, 1.23)	1.09 (0.90, 1.32)	1.00 (0.81, 1.23)	1.12 (0.92, 1.35)	1.02 (0.95, 1.09)	1.01 (0.98, 1.05)
P value		.85	.37	1.0	.26	.67	.47
Adjusted hazard ratio (95% CI) ^b	reference	1.01 (0.84, 1.23)	1.10 (0.91, 1.34)	1.00 (0.80, 1.23)	1.13 (0.93, 1.38)	1.02 (0.95, 1.10)	1.02 (0.98, 1.06)
P value		.90	.31	.97	.22	.61	.38

The population informed all-cause mortality was 18242. The population informed readmission was 16860. The difference represented in-hospital death.

^a For absolute difference, a positive value indicates an increase in risk and a negative value indicates a reduction in risk.

^b Models adjusted for patient age, sex, race-ethnicity; vascular risk factors including atrial fibrillation/flutter, previous stroke/transient ischemic attack, history of coronary artery disease/myocardial infarction, heart failure, carotid stenosis, diabetes mellitus, peripheral artery disease, hypertension, dyslipidemia, smoking, arrival by Emergency Medical Services, arrival during off hours, stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS), hospital region, urban/rural location, total number of beds, annual ischemic stroke volume, academic status, stroke center certification status.

^c Recurrent stroke readmission, a post hoc outcome, was defined as readmission for transient ischemic attack, ischemic and hemorrhagic stroke, carotid endarterectomy or stenting, but not direct complications of index stroke.

^d The cutoff value was derived from non-linear distribution as shown in the spline plot. The absence of cut-off times for all-cause readmission and the composite of all-cause mortality or readmission was because these two outcomes showed linear distribution in relation to door-to-needle times in 15-minute increments within 4.5 hours.