

Even Faster Door-to-Alteplase Times and Associated Outcomes in Acute Ischemic Stroke

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Background and Purpose: The timely administration of thrombolytic therapy for acute ischemic stroke has been associated with good functional outcomes. Current guidelines recommend alteplase administration within 60 minutes in 75% of eligible patients and within 45 minutes in 50% of patients. There is limited evidence guiding these measures and their effect on outcomes. We report a single-center, retrospective assessment of the safety and efficacy of alteplase treatment within 45 minutes. *Methods:* Five hundred and eighty-six patients were treated with alteplase in our emergency departments (EDs) between January 2014 and October 2016; 368 patients were included for analysis. Multivariate regression analysis was used to assess the association between door-to-alteplase (DTA) times and 90-day modified Rankin scale (mRS) scores. Incidence of intracerebral hemorrhage (ICH) was also documented. *Results:* The median DTA time was 29 minutes versus 64 minutes in the DTA less than or equal to 45 minutes arm and more than 45 minutes arm, respectively. The primary outcome of 90-day mRS 0-1 was achieved in 56% of patients in the less than or equal to 45 minutes group versus 58% in more than 45 minutes group ($P = .67$). Odds of achieving mRS 0-1 were not significantly impacted by DTA times. In the multivariate regression analysis, patient characteristics associated with achieving mRS 0-1 were: younger age, male sex, not requiring intubation in the ED, and without prior history of hypertension, atrial fibrillation, or stroke. There was no significant difference in rates of ICH for patients less than or equal to 45 minutes versus more than 45 minutes. *Conclusions:* Rapid administration of alteplase was not associated with significantly better outcomes nor increased risk of ICH. Conclusions about efficacy are limited due to the retrospective nature of the study, small sample size, and incomplete data points.

Key Words: Ischemic stroke—tissue plasminogen activator—thrombolysis—stroke outcomes—door-to-needle

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Background and Purpose

The use of alteplase (tissue plasminogen activator, tPA) in patients with acute ischemic stroke (AIS) has shown improved functional outcomes when administered within 4.5 hours of symptom onset.¹⁻² Since the rate of neuronal loss is strongly correlated with rate of infarct size expansion, the timely administration of thrombolytic therapy is essential to good outcomes.³⁻⁴

In 2015, the American Heart Association/American Stroke Association instituted new target goals in the Get With the Guidelines (GWTG) TargetL Stroke Phase II program. According to GWTG, hospitals have the opportunity to be recognized as Honor Roll, Honor Roll Elite, or Honor Roll Elite Plus status depending on the percentage of

patients achieving thrombolytic therapy within a defined time period. To achieve Target: Stroke Phase II Elite Plus recognition, alteplase must be given within 60 minutes of arrival in at least 75% of eligible patients as well as within 45 minutes in 50% of patients.⁵⁻⁷ Despite the benefits of timely administration of alteplase in stroke patients, there is limited evidence guiding these explicit measures and the effect on outcomes. Our study was aimed at assessing outcomes of early administration of alteplase under 45 minutes.

Methods

This was a retrospective cohort study of ischemic stroke patients that received alteplase in the emergency departments (ED) of a large academic healthcare system. The hospital system is comprised of a Joint Commission-designated Comprehensive Stroke Center, Primary Stroke Center, and a nondesignated free-standing ED. Altogether, the hospital system has an annual volume of 180,000+ ED visits and 1100+ inpatient beds.

Data from all ED stroke patients are collected within an internal stroke database that is managed by trained hospital abstractors as part of the stroke program. Follow-up evaluations performed by the clinical team are collected by the same data abstraction team, and these data are shared with GWTG-Stroke for metric reporting purposes. Both internal stroke database and GWTG-Stroke databases were used to identify patients consecutively admitted to the hospital with the principle diagnosis of ischemic stroke. Confirmation of admission was done via *International Classification of Disease*, ninth and tenth editions, billing codes, and chart review. Patient data—such as demographics, past medical history, stroke presentation and history of present illness, timing of alteplase administration, mortality, and disposition—were also collected. Stroke severity was indexed by the National Institutes of Health Stroke Scale (NIHSS). The study was approved by the institutional review board. The authors declare that all supporting data are available within the article.

Patients were enrolled if treated for AIS with intravenous (IV) alteplase (.9 mg/kg of actual body weight; maximum dose of 90mg) at any of our 3 EDs from January 2014 to October 2016. Other inclusion criteria were: age more than or equal to 18 years and documented 90-day modified Rankin scale (mRS) score. Patients were excluded if: alteplase was given for indication other than AIS, alteplase was received outside of ED, thrombectomy in addition to IV alteplase was performed, or door-to-alteplase (DTA)-time more than 120 minutes.

Patients were stratified based upon DTA times: patients treated within 45 minutes or patients treated after 45 minutes. The primary outcome measured was 90-day mRS 0-1, which represented a favorable outcome. Secondary outcomes included the rate of intracranial hemorrhage (ICH) after alteplase administration, rate of achieving mRS 0-1 if alteplase was given within 30 minutes versus

after 30 minutes, rate of achieving mRS 0-1 if alteplase was given within 60 minutes versus after 60 minutes, and in-hospital mortality rate.

Acute Stroke Process

When a patient with suspected AIS arrives, the stroke team is alerted, which consists of a multidisciplinary team including ED physicians, stroke neurologists, neuroradiologists, nurses, pharmacists, and radiology technicians. On arrival, the patient is evaluated by the stroke team with a focus on collecting pertinent medical history and previous medication exposure. The patient then obtains a noncontrast computed tomography of the head. Stroke neurologists are routinely available at bedside at the Comprehensive Stroke Center on Monday through Friday from 07:00 to 19:00; at the other sites, the neurologist is available via video consultation. Outside of normal hours, they are available via phone and/or video consultation. After evaluation of imaging and discussion with the patient, alteplase is administered if appropriate and the patient is admitted to the neurocritical care unit at the Comprehensive Stroke Center campus.

Statistical Methods

Demographic and clinical characteristics were summarized by medians and interquartile range (25th-75th percentiles) for continuous variables; the median test was used to compare DTA groups. Categorical variables were summarized by percentages and number of total patients/visits; groups were compared with a chi-square test. The relationship between DTA times and mortality and categorized mRS scores were analyzed by logistic regression. Continuous outcomes (eg, hospital and ICU length of stay) were analyzed by linear regression. DTA was analyzed as a categorical (%) and as a continuous variable (means, medians).

Results

There were a total of 586 patients who received alteplase for AIS during the approximate 2.5 year study time frame. After applying prespecified exclusions, 490 patients remained. Of those, 122 were further excluded due to lack of documented 90-day mRS scores. Three hundred and sixty-eight patients were included for final analysis. There were 191 patients that received alteplase less than or equal to 45 minutes from arrival and 177 patients that received alteplase more than 45 minutes from arrival (Fig 1).

Baseline characteristics of patients are depicted in Table 1. The median age of study patients was 72 years, with 53.8% female and median BMI 28.7 kg/m²(25-33). The most common comorbidities were hypertension and coronary artery disease, with 51% of patients being active or former smokers. Ten patients (2.7%) required emergent intubation in the ED. Patients were more likely to have alteplase

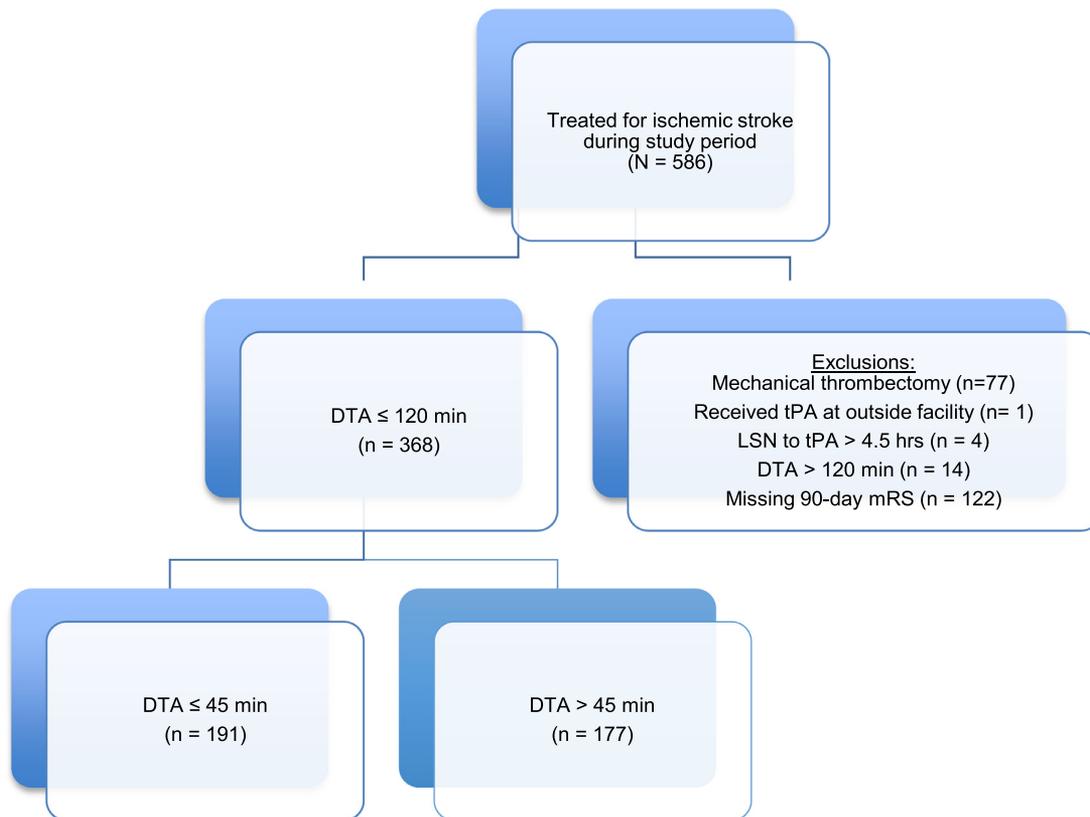


Figure 1. Enrollment diagram. Abbreviations: DTA, door-to-alteplase; ED, emergency department; LSN, last seen normal; tPA, alteplase.

administered within 45 minutes if they arrived during in-house stroke neurology coverage (63.4% versus 44.6%, $P < .001$). Baseline NIHSS were documented for a total of 320 patients. Overall, the median DTA time was 29 minutes (IQR 21.5-36) versus 64 minutes (IQR 55-80) in the DTA less than or equal to 45 minute arm and the DTA more than 45 minute arm, respectively. For the DTA less than or equal to 45 minute group, the NIHSS median was 6 (IQR 4-12) ($n = 168$) whereas for the DTA more than 45 minute group the median was 5 (IQR 3-9) ($n = 152$) ($P = .01$).

Overall, 210 patients achieved a favorable outcome (mRS 0-1) and 158 patients achieved a mRS 2-6. The primary outcome of a favorable outcome at 90-day (mRS 0-1) was achieved in 56% of patients in the less than or equal to 45 minutes group versus 58% in more than 45 minutes group ($P = .67$). Odds of achieving 90-day mRS 0-1 was not significantly impacted by DTA times (Table 2).

Individual DTA time intervals were examined for subgroup analyses. Patients who received doses less than or equal to 30 minutes compared to DTA more than 30 minutes did not have a significantly higher incidence of achieving good neurologic outcomes at 90 days; similarly, no differences were noted in the 60-minute group cohort.

In the multivariate regression analysis, patient characteristics associated with higher odds of good functional outcomes (mRS 0-1) were: younger age, male sex, not requiring mechanical ventilation in the ED,

and without prior history of hypertension, atrial fibrillation, or stroke (Table 3). Patients who had shorter last seen normal-to-alteplase times were not associated with better outcomes.

In total, there were 7 (1.9%) in-hospital deaths and 23 (6.25%) patients who developed ICH after alteplase administration during their hospital admission. The mortality rate in the less than or equal to 45 minutes group was 2.6% versus 1.1% in the more than 45 minutes group ($P = .3$). There was no significant difference in rates of ICH for patients less than or equal to 45 minutes versus more than 45 minutes (4.7% versus 7.9%, $P = .2$). Of the 23 patients with ICH, 7 (30.4%) had true symptomatic ICH—defined as occurring within 36 hours of alteplase administration, symptomatic with change in NIHSS by 4 or more points, and confirmed on radiographic imaging. Of these 7 patients, 3 patients had DTA less than or equal to 45 minutes, 1 had LSN-to-alteplase time less than or equal to 60 minutes, 2 had initial presenting NIHSS more than 20, and 6 were more than 65 years of age. None of the patients achieved a 90-day mRS of 0 or 1; 5 patients died, and the remaining 2 patients resulted with 90-day mRS scores 3-5. Overall, the composite rate of mortality or hospice (mRS 5 or 6) was 12.6% versus 7.3% ($P = .1$) (Table 4). Table 5 depicts the incidence of ICH based on DTA times further broken down by 15-minute intervals, showing no difference in ICH rates.

Table 1. Baseline characteristics of patients with DTA ≤ 45 minutes vs >45 minutes

Baseline characteristics	DTA ≤ 45 min (n = 191)	DTA > 45 min (n = 177)	P value
Median age [IQR] (y)	73 [60-82]	71 [57-83]	.53
Female (%)	50.3	57.6	.16
Race (%)			.45
White	75.4	71.2	
Black	17.8	23.7	
Asian	2.1	2.3	
Other/unknown	4.7	2.8	
ED location (%)			<.001
Comprehensive Stroke Center	91.6	70.1	
Primary Stroke Center	7.9	24.3	
Freestanding ED/nonstroke center	.5	5.7	
Required intubation in ED (%)	2.1	3.4	.45
Comorbidities (%)			
Hypertension	62.3	73.5	.02
Current or former smoker	53.4	48.6	.52
BMI ≥ 30	36.7	40.7	.07
Coronary artery disease	36.7	36.2	.92
Diabetes	30.4	33.9	.47
Previous TIA/stroke	23.0	28.3	.25
Valvular heart disease	22.0	22.6	.89
Atrial fibrillation/flutter	17.8	22.6	.25
Congestive heart failure	19.4	17.5	.65
History of cancer	12.6	11.9	.84
Arrived during in-house stroke neurology coverage (%)	63.4	44.6	<.001
Median baseline NIHSS (n = 320)	6 [4-12] (n = 168)	5 [3-9] (n = 152)	.01
Median DTA time [IQR] (min)	29 [21.5-36]	64 [55-80]	<.001
Door-to-alteplase-time distribution (%)			<.001
≤ 30 min	52.4	0	
31-45 min	47.6	0	
46-60 min	0	41.2	
61-120 min	0	58.8	
Time from last seen normal (LSN)-to-alteplase, median [IQR]	87 [66-135]	134 [109-179]	<.001
LSN-to-alteplase-time distribution (%)			<.001
≤ 60 min	13.1	2.3	
61-120 min	50.8	33.9	
121-180 min	21.5	40.1	
180-270 min	14.7	23.7	

Abbreviations: DTA, door-to-alteplase; ED, emergency department; LSN, last seen normal; NIHSS, National Institute of Health Stroke Scale; TIA, transient ischemic attack.

Discussion

This study analyzed 368 patients who received IV alteplase for AIS and did not find an association with earlier

DTA times and improved functional outcomes at 90 days. Faster administration times were also not associated with increased rates of symptomatic ICH nor increased in-hospital mortality, suggesting that targeting faster administration

Table 2. Primary outcome of achieving mRS 0-1 vs mRS 2-6 based on DTA time intervals

DTA time	mRS 0-1	mRS 2-6	Odds ratio	95% CI	P value
≤ 45 minutes (n = 191)	107 (56.0)	84 (44.0)	-	-	-
> 45 minutes (n = 177)	103 (58.2)	74 (41.8)	1.09	.72-1.65	.67
≤ 30 minutes (n = 100)	55 (55.0)	45 (45.0)	-	-	-
31-45 minutes (n = 91)	52 (57.1)	39 (42.9)	1.09	.62-1.93	.77
46-60 minutes (n = 73)	43 (58.9)	30 (41.1)	1.17	.64-2.16	.61
61-120 minutes (n = 104)	60 (57.7)	44 (42.3)	1.12	.64-1.94	.70

Abbreviations: DTA, door-to-alteplase; mRS, modified Rankin scale.

Table 3. OR for achieving mRS 0-1 using multivariate regression analysis

Variable	Odds ratio	95% CI	P value
Door-to-tPA (min)			
≤30	-	-	-
31-45	.93	.47-1.86	.84
46-60	.90	.42-1.93	.79
61-120	1.64	.79-3.41	.19
LSN to tPA (min)			
≤60	-	-	-
61-120	2.25	.84-6.02	.11
121-180	.88	.31-2.53	.82
>180	.96	.33-2.85	.95
Age (y)	.94	.92-.96	<.001
Female	.51	.30-.87	.01
Race			
White	-	-	-
Black	.60	.32-1.16	.13
Other	.82	.26-2.54	.73
During in-house stroke neurologist coverage	1.19	.70-2.02	.52
ED ventilator	.09	.01 – .81	.03
Comorbidities			
HTN	2.04	1.01-4.11	.05
CAD	1.55	.76-3.15	.23
DM	.71	.39-1.29	.26
AFIB	.44	.21-.90	.03
CHF	.58	.26-1.28	.18
TIA	.87	.42-1.78	.70
Stroke	.39	.18-.81	.01
Cancer	1.16	.55-2.44	.70
Renal failure	.50	.23-1.09	.08
COPD	1.08	.59-1.95	.81

Abbreviations: AFIB, atrial fibrillation; CAD, coronary artery disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ED, emergency department; HTN, hypertension; LSN, last seen normal; OR, odds ratio; TIA, transient ischemic attack; tPA, alteplase.

is a safe practice. Patients were more likely to receive alteplase within 45 minutes if arriving during in-house stroke neurology coverage and initially presenting to the Comprehensive Stroke Center campus. Factors contributing to poor functional outcomes included the need for intubation in the ED, female sex, and prior history of stroke. Odds for improved functional outcomes were not different across all

time intervals. Likewise, odds for developing ICH were not attributed DTA time interval. Patients who developed symptomatic ICH due to alteplase administration overall had poor outcomes—none achieved 90-day mRS 0 or 1 and had 71.4% mortality rate.

Despite increasing evidence on the benefits of timely administration of alteplase in addition to publication of

Table 4. Characteristics of individual patients with symptomatic ICH after alteplase administration

Age (y)	Change in NIHSS > 4 within 36 hours of tPA administration?	Baseline NIHSS	Confirmed on radiographic imaging?	DTA time (min)	LSN to tPA time (min)	90-day mRS score
67	Y	19	Y	36	67	Died inpatient
56	Y	7	Y	65	210	6
100	Y	7	Y	67	123	6
92	Y	23	Y	80	128	6
69	Y	27	Y	46	47	6
85	Y	17	Y	35	68	5
69	Y	16	Y	36	112	3

Abbreviations: DTA, door-to-alteplase; ICH, intracerebral hemorrhage; LSN, last seen normal; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; Y, yes.

Table 5. Incidence of ICH based on DTA times

DTA time	ICH	No ICH	P value
Category (n, %)			.18
≤30 min (n = 100)	2 (2.0)	98 (98.0)	
31-45 min (n = 91)	7 (7.7)	84 (92.3)	
46-60 min (n = 73)	7 (9.6)	66 (90.4)	
61-120 min (n = 104)	7 (6.7)	97 (93.3)	
Mean ± SD	51.0 ± 17.9	48.0 ± 24.5	.57
Median [IQR]	52 [36-67]	44 [28-63]	.21

Abbreviations: DTA, door-to-alteplase; ICH, intracerebral hemorrhage.

recent American Heart Association guidelines, there is a lack of data examining the effects of early alteplase administration under 60 minutes. Kamal et al analyzed characteristics of GWTG-Stroke registry patients and found that a delayed DTA time greater than 60 minutes was associated with higher odds of in-hospital mortality and reduced independent ambulation at discharge.

To adhere to guidelines and prescribed metrics, our institution relies on the collaborative practices between the stroke team and ED—including but not limited to emergency physicians, stroke neurologists, pharmacists, and nurses. Because of this collaboration, stroke patients were able to receive alteplase treatment at an average of 48 minutes across the 2.5-year study time frame. This study highlights the ability of our institution to achieve faster DTA times while examining the clinical outcomes of patients treated within 45 minutes of ED arrival.⁸

Prior studies were similarly conducted, but not using the 45 minute cutoff comparison. Strbian et al investigated whether time to tPA under 70 minutes was associated with improved outcomes. Out of the 878 patients included from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Registry, the authors found that median onset to treatment (OTT) was 115 minutes, 29% had OTT less than or equal to 90 minutes and 10% had OTT less than 70 minutes. Their results showed a higher proportion of patients achieving mRS 0-2 with OTT less than 70 minutes compared to OTT more than or equal to 70 minutes (67.8% versus 32.2%, $P = .016$); there was no difference in mRS with OTT less than or equal to 90 minutes compared to OTT more than 90 minutes. Patients with higher baseline NIHSS had highest likelihood of favorable outcomes if treated within 70 minutes. Overall rate of symptomatic ICH was 2.2%; of those patients, 15.7% had OTT less than 70 minutes. Mortality rates did not differ across all groups.⁹

Fonarow et al analyzed data from over 25,000 patients from the GWTG-Stroke database made available from 2003 to 2009. The mean DTA time was 79.3 ± 28.1 minutes and the median was 78 minutes. About 26.6% of patients

received doses less than or equal to 60 minutes. There was wide variability in tPA administration practices across institutions. Only 6.7% of hospitals achieved DTA times less than or equal to 60 minutes in at least 50% of patients. In general, larger institutions with higher annual volume of tPA-treated stroke patients were more likely to administer tPA within 60 minutes. The unadjusted in-hospital mortality was 8.6% in patients with door-to-needle less than or equal to 60 minutes versus 10.4% in patients with door-to-needle more than 60 minutes ($P < .0001$). Factors associated with faster door-to-needle times were younger age, male gender, no history of prior stroke, higher baseline NIHSS, and arrival during regular business hours via emergency medical service transport. Interestingly, patients with door-to-needle times less than or equal to 60 minutes were more likely to have longer times from symptom onset to hospital arrival. Complication rates due to tPA were lower in the less than or equal to 60 minutes group; rates of ICH were 4.7% versus 5.6% ($P = .002$). Odds ratio analysis showed that every 15-minute interval decrease in tPA administration time was associated with a 5% lower odds of mortality (adjusted OR .95 [95% CI .92-.98], $P = .0007$) and no significant association with odds of ICH.¹⁰

Several limitations are present in our study. First, this was a retrospective, single-center chart review encompassing patient data across a span of only 2.5 years. Out of the 600 patients originally identified for inclusion, 25% of patients were excluded solely due to lack of documented mRS scores at 90 days. Secondly, we used more stringent parameters for inclusion (eg, DTA less than 120 minutes) and to define favorable outcomes (eg, mRS 0-1 instead of 0-2). A 120-minute treatment time cutoff was used instead of 4 hours as the vast majority of our patients receive treatment within 120 minutes, and those receiving treatment after 120 minutes would be considered an outlier. It is encouraging to see that the majority of all patients (57%) were able to achieve mRS 0-1 with low rates of mortality and ICH. Third, due to the small numbers, confounders for ICH were not accounted for in the final analysis—variables such as prior anticoagulation

use and hemodynamic parameters. Further large-scale studies are needed to confirm our findings and potentially find a benefit in improved 90-day mRS scores.

Our results were not able to confirm that accelerated administration of tPA led to improved functional outcomes, as was suggested by Strbian et al and Fonarow et al. This study is one of the first to analyze outcomes associated with rapid alteplase administration within 45 minutes for AIS patients. Despite concerns that faster alteplase administration would potentially lead to errors and complications, there was no evidence of increased mortality or rates of ICH in our study. As mentioned previously, this data reflects a successful stroke program at one of the busiest stroke centers in the country and therefore, provides insight for other institutions seeking to implement a comprehensive stroke program.

Conclusion

Targeted DTA time less than or equal to 45 minutes was achieved in 52% of our ischemic stroke patients who presented to any of our EDs from 2015 to 2016. Although accelerated alteplase administration did not result in improved long-term functional outcomes or reduced mortality, there was no evidence of short-term or long-term adverse outcomes in those with more rapid DTA times. Our findings support the use of a multidisciplinary team for a structured response to AIS to facilitate rapid evaluation and faster treatment times without increasing risk to patients. Further studies should be performed to assess outcomes related to DTA times.

Declaration of Competing Interest

None of the authors have any conflicts of interest to declare.

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