


## ORIGINAL ARTICLE

# Reasons and predictors of non-thrombolysis in patients with acute ischemic stroke admitted within 4.5 h

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**Objectives:** Thrombolytic treatment in acute ischemic stroke (AIS) reduces stroke-related disability. Nearly 40% of all patients with AIS (<4.5 h) receive thrombolysis, but there is a large variation in the use between hospitals. Little is known about reasons and predictors for not giving thrombolytic treatment. Therefore, we aimed to investigate reasons for non-thrombolysis in patients admitted within 4.5 h.

**Methods:** All patients with AIS (<4.5 h) admitted to Akershus University Hospital, Norway, between January 2015 and December 2017 were examined. Patient characteristics and reasons for not giving thrombolysis were registered. Descriptive statistics and logistic regression analyses were performed.

**Results:** Of 535 patients admitted with AIS (<4.5 h), 250 (47%) did not receive thrombolysis and of these only 26% had an absolute contraindication to treatment. Among the 74% with relative contraindications, the most common reasons given were mild and improving symptoms. Previous stroke (OR 3.32, 95%CI 1.99–5.52), arriving between 3 h and 4.5 h after onset (OR 7.76, 95%CI 3.73–16.11) or having mild symptoms (OR 2.33, 95%CI 1.56–3.49) were all significant predictors of not receiving thrombolytic treatment in the multivariable logistic regression model.

**Conclusion:** A large proportion of patients with AIS do not receive thrombolysis. This study highlights up-to-date findings that arriving late in the time window, mild symptoms, and previous stroke are strong predictors of non-treatment. It is uncertain whether there is an underuse of thrombolysis in AIS. Increasing the utility of thrombolysis in the 4.5 h time window must be weighed against possible harms.

## KEYWORDS

non-thrombolysis, predictors, reasons, Stroke

## 1 | INTRODUCTION

Intravenous thrombolysis with recombinant tissue plasminogen activator (tPA) improve neurological outcomes in selected patients with acute ischemic stroke (AIS).<sup>1–3</sup> Initially, tPA was considered effective

and safe administered within the first 3 h after symptom onset, but more recent studies have supported a time window of 4.5 h from the onset of stroke symptoms.<sup>1–3</sup> The use of tPA has increased during the past 2 decades, and in Scandinavia, 18–25% of patients with AIS receive the treatment.<sup>4–9</sup> However, there is a large variation in the

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use of the thrombolysis between hospitals and between different regions.<sup>4-9</sup> The causes for not giving thrombolysis are multifold. One prominent reason is arrival outside the time window for thrombolysis. However, according to studies, less than 40% of those who reach hospital within 4.5 h receive thrombolysis.<sup>4,10</sup> In addition, administration of thrombolytic treatment is limited by several relative and absolute exclusion criteria originally based on exclusions from the initial thrombolysis trials.<sup>11,12</sup> These criteria have consecutively been adjusted according to research updates and several are still under discussion.<sup>3</sup> Absolute contraindications to tPA were until recently treatment beyond >4.5 h from symptom onset, infarction involving more than one third of the middle cerebral artery territory, intracerebral hemorrhage (ICH), International Normalized Ratio (INR) >1.7, direct oral anticoagulation (DOAC) administered within the last 24 h and blood pressure >185/110 mmHg not responding to treatment. Several relative contraindications may in addition influence the use of thrombolysis in AIS. A few previous studies have investigated factors related to non-treatment, but these studies were conducted in the beginning of the tPA era, excluded patients with absolute contraindications and were limited to a narrower treatment time window than 4.5 h.<sup>6,13-15</sup> The time window and the significance of relative contraindications have changed over time, and more patients with high age, comorbidities, and mild symptoms are treated today compared to 10 years ago.<sup>8,16</sup> In this changing landscape, there is a lack of new knowledge about reasons for not treating patients with thrombolysis.

The aims of the present study were to estimate the reasons of non-thrombolysis in eligible patients with AIS and to identify patient-related factors associated with not receiving thrombolysis.

## 2 | METHODS

### 2.1 | Study design, setting, and population

The present study is a retrospective analysis of data from a local registry, the Akershus Study of Ischemic Stroke and Thrombolysis 1 (ASIST-1), which includes data on all consecutive patients admitted to the Stroke Unit at Akershus University Hospital (AUH), Norway, from January 2015 to December 2017. The data in ASIST-1 have been validated against the National Stroke Registry. AUH is the largest emergency care hospital in Norway and has a catchment area covering a population of 550,000, which is approximately 10% of Norway's population. The hospital has a stroke unit classified as a comprehensive stroke center according to European Stroke Organization (ESO) standards. The unit treats nearly 800 strokes (ischemic and hemorrhage) and 150 transient ischemic attacks (TIA) annually. In addition, around 300 stroke mimics are admitted each year. Acute stroke management follows current National and International guidelines.<sup>17</sup>

Since 2012, the hospital has operated a "stroke fast track" to administer thrombolysis as fast as possible. The emergency medical

services (EMS) contact the neurologist on call and give the hospital a prenotification that a possible candidate for intervention is on his/her way to hospital. All patients are evaluated with the National Institutes of Health Stroke Scale (NIHSS) by the neurologist on call, and an initial CT brain scan including CT angiography and CT perfusion are conducted before the decision of intervention is made.

All patients who presented from outside the hospital within 4.5 h from onset of acute ischemic stroke and who were discharged with an International Classification of Disorder 10 (ICD-10) diagnosis (I63) of cerebral infarction between January 2015 and December 2017 were included in the present study. Patients who were found to be outside the time window at arrival at hospital or not having acute ischemic stroke (transient ischemic attack (TIA), ICH, or stroke mimics) were excluded in the present study. [Figure 1](#) shows a flow-chart of the study.

### 2.2 | Data collection

Data collected were sex, age, living arrangements, admitted from nursing home, premorbid functional status measured by the Modified Rankin Scale (mRS), prior TIA and stroke, diabetes mellitus, atrial fibrillation, ongoing anticoagulation, antiplatelet therapy, antihypertensive treatment, the National Institutes of Health Stroke Scale (NIHSS) on admission, computed tomography (CT) at admission, treating physicians reasons for non-thrombolysis, onset to door time, and time from arrival to onset of tPA.

### 2.3 | Outcomes

Primary outcome was the proportion of patients not treated with thrombolysis when admitted within 4.5 h after onset of acute ischemic stroke.

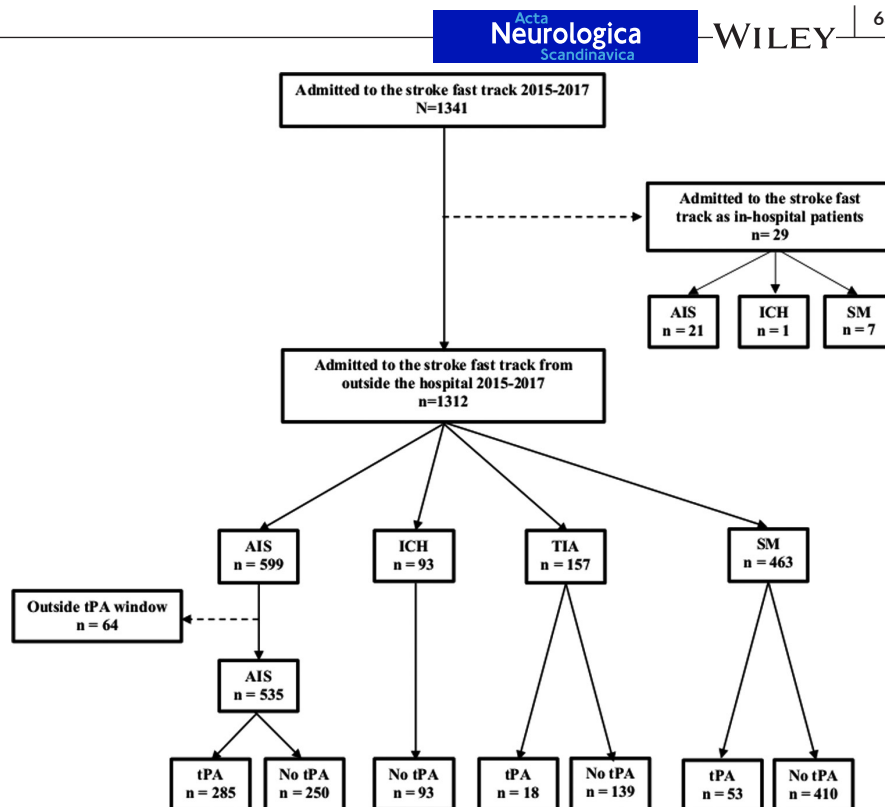
Patients not treated with thrombolysis were categorized according to reasons for exclusion from thrombolytic therapy and the main reason emphasized by the neurologist on call. Reasons for not administering intravenous thrombolysis within 4.5 h from symptom onset were divided into i) absolute contraindications (anticoagulation, severe uncontrolled hypertension, infarction >1/3 of middle cerebral artery) and ii) other relative contraindications (mild symptoms, symptom improvement, late arrival, advanced age, recent medical procedure, high bleeding risk, comorbidity, suspected stroke mimic, or other reasons).

Stroke severity was assessed by NIHSS and categorized into mild (NIHSS ≤5), moderate (NIHSS 6–14), and severe (NIHSS ≥15).

Premorbid functional status was measured by mRS and categorized into two groups 0–2 and 3–5.

Large vessel occlusion (LVO) was defined as a significant stenosis in one of the intracranial arteries (the internal carotid artery (ICA), the proximal segment or the insular part of the middle cerebral artery (M1 and M2), or the basilar artery (BA)), accompanied by corresponding symptoms.

**FIGURE 1** Flowchart of the Akershus Study of Ischemic Stroke and Thrombolysis-1 (ASIST-1). AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; TIA, transient ischemic attack; SM, stroke mimic; and tPA, tissue plasminogen activator



Time from symptom onset to admission was calculated based on information from the patient, their next of kin or other witnesses, Emergency Medical Service (EMS) report and the hospital record.

## 2.4 | Statistics

Descriptive data were presented as proportions, median, and interquartile range (IQR) for categorical variables and means and standard deviations (SDs) for continuous variables. Groups were compared using the t-test/Wilcoxon signed-rank test (continuous data) or the chi-square test (categorical data).

Logistic regression analyses for not receiving thrombolysis (yes or no, as the dependent variable) were calculated to estimate the influence of predefined characteristics. In the univariate logistic regression analyses age, sex (women vs. men), living alone (yes vs. no), admitted from nursing home (yes vs. no), mRS before admission (0–2 vs 3–5), diabetes mellitus (yes vs. no), antihypertensive treatment (yes vs. no), prior TIA (yes vs. no), prior stroke (yes vs. no), onset to admission between 3 h and 4.5 h (yes vs. no), large vessel occlusion (yes vs. no), and stroke severity (mild vs. moderate to severe based on NIHSS) were used as independent variables.

Independent variables with  $p < .25$  in the univariate analyses were subjected into the multivariable logistic regression analysis.

Subgroup analyses with the same logistic regression model excluding those with absolute contraindications (anticoagulation, hypertension (>185), or large visible infarction 1/3) were conducted. Based on the fact that the CT procedure and tPA administration takes some time, similar analyses were conducted for the subgroup arriving at the hospital within 4 h after onset.

Significance levels were set at  $p < .05$ , using two-sided test. Statistical analyses were performed using SPSS 27.00 (SPSS Inc.).

## 2.5 | Ethics

The Regional Committee for Medical Research Ethics South-East (REK 2018/498) and the Data Protection Officer at AUH approved the study. In accordance with the approval from the Regional Committee for Medical Research Ethics and the Norwegian law on medical research, the project did not require a written patient consent.

## 3 | RESULTS

Overall, 1341 patients with a suspected acute stroke (<4.5 h) were admitted to the stroke fast track at AUH between January 2015 and December 2017 (Figure 1). Of these, 535 had a confirmed AIS (176 in 2015, 177 in 2016, and 182 in 2017) and were included in the study. In all, 250 patients (47%) did not receive thrombolysis. The remaining 285 patients (53%) received thrombolysis within 4.5 h. Demographic and clinical characteristics are presented in Table 1.

The mean age was 74 years (range 17–98), and 219 (41%) were female. The median onset to door time was 83 (range 6–265). For those who received thrombolysis, the median door-to-needle time (DTN) was 38 min (range 9–208). Those receiving tPA were on average younger than those not receiving tPA (Students t-test,  $p = .039$ ). There were no significant differences between the two groups with respect to sex or place of living. The thrombolysis rates were the

TABLE 1 Patient characteristics in total and dichotomized by thrombolysis treatment

	Thrombolysis <i>n</i> = 285 (53.3%)	Not thrombolysis <i>n</i> = 250 (46.7%)	Total <i>n</i> = 535	<i>p</i> -value
<b>Demographics</b>				
Age, mean (SD), y	72.6 (13.7)	75.0 (13.0)	73.7 (13.4)	.039
Age ≥80 years, <i>n</i> (%)	100 (35.1)	97 (38.8)	197 (36.8)	.42
Female sex, <i>n</i> (%)	116 (40.7)	103 (41.2)	219 (40.9)	.93
Living alone, <i>n</i> (%)	73 (25.6)	64 (25.6)	137 (25.6)	1.00
Nursing home, <i>n</i> (%)	17 (6.0)	27 (10.8)	44 (8.2)	.057
<b>Medical history</b>				
mRS before admission, median, (IQR)	1 (0–2)	1 (0–2)	1 (0–2)	.022
Previous stroke, <i>n</i> (%)	31 (10.9)	69 (27.6)	100 (18.7)	<.001
Previous TIA, <i>n</i> (%)	26 (9.1)	34 (13.6)	60 (11.2)	.13
Diabetes mellitus I/II, <i>n</i> (%)	43 (15.1)	39 (15.6)	82 (15.3)	.91
Atrial fibrillation, <i>n</i> (%)	43 (15.1)	71 (28.4)	114 (21.3)	<.001
Anti-platelet therapy, <i>n</i> (%)	107 (37.5)	100 (40.0)	207 (38.7)	.59
Anticoagulation, <i>n</i> (%)	15 (5.3)	61 (24.4)	77 (14.4)	<.001
Anti-hypertensive treatment, <i>n</i> (%)	174 (61.1)	167 (66.8)	341 (63.7)	0.18
<b>Admissions</b>				
<b>Arrival</b>				
Weekdays (Mon-Fri), <i>n</i> (%)	207 (72.6)	184 (73.6)	391 (73.1)	
Weekend (Sat-Sun), <i>n</i> (%)	78 (27.4)	66 (26.4)	144 (26.9)	.85
<b>Arrival</b>				
Daytime 0800–1600, <i>n</i> (%)	145 (50.9)	124 (49.6)	269 (50.3)	
Afternoon/night 1600–0800, <i>n</i> (%)	140 (49.1)	126 (50.4)	266 (49.7)	.80
<b>Onset to admission</b>				
0–3 h, <i>n</i> (%)	275 (96.5)	201 (80.4)	476 (89.0)	
3–4.5 h, <i>n</i> (%)	10 (3.5)	49 (19.6)	59 (11.0)	<.001
<b>Stroke severity</b>				
Large vessel occlusion <sup>a</sup> , <i>n</i> (%)	79 (28.3)	54 (24.1)	133 (26.4)	.31
<b>NIHSS at admission</b>				
Median, (IQR)	6.0 (3–12)	4.0 (2–9)	5.0 (2–11)	.001
Mean (SD)	8.2 (6.8)	6.7 (7.1)	7.5 (7.0)	.019
<b>NIHSS score level</b>				
Mild, NIHSS 0–5	134 (47.0)	152 (60.8)	286 (53.5)	.002 <sup>b</sup>
Moderate, NIHSS 6–14	90 (31.6)	60 (24.0)	150 (28.0)	.054 <sup>c</sup>
Severe, NIHSS ≥15	61 (21.4)	38 (15.2)	99 (18.5)	.074 <sup>d</sup>

Note: Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; TIA, transitory ischemic attack.

<sup>a</sup>6% missing due to no CT angiography.

<sup>b</sup>Mild vs. moderate and severe.

<sup>c</sup>Moderate vs. mild and severe.

<sup>d</sup>Severe vs. mild and moderate.

Significance of Bold values indicates  $p < .05$

same for those admitted during daytime versus those admitted “out of hours” (4 pm–8 am) and those admitted during the weekdays (Monday–Friday) versus the weekend (Saturday–Sunday). The median NIHSS was higher for those receiving thrombolysis (median NIHSS 6) versus those who did not receive tPA (median NIHSS 4, Wilcoxon signed-rank test,  $p = .001$ ). Patients with mild stroke

symptoms defined as NIHSS ≤5 were less likely to receive thrombolysis than patients with more severe symptoms (47% vs. 63%,  $\chi^2$ -test,  $p = .001$ ).

Reasons for non-thrombolysis are shown in Table 2.

An absolute contraindication to IV tPA was documented in 26% ( $n = 65$ ) of those not treated. Among patients with absolute

TABLE 2 Main reasons for not administering intravenous thrombolysis within 4.5 h from symptom onset. *n* (%)

Reasons	<i>N</i> = 250
<b>Absolute contraindications</b>	<b><i>n</i> = 65 (26%)</b>
Anticoagulation	51 (21)
Severe uncontrolled hypertension (systolic blood pressure >185 mmHg or diastolic blood pressure >110 mm Hg)	7 (3)
>1/3 visible middle cerebral artery infarction on CT	7 (3)
<b>Other reasons</b>	<b><i>n</i> = 185 (74%)</b>
Mild symptoms	48 (19)
Symptom improvement	44 (18)
Late arrival	33 (13)
Advanced age	17 (7)
Recent medical procedures including percutaneous coronary intervention or surgery	5 (2)
High bleeding risk	17 (7)
Comorbidity incl. cancer	6 (2)
Suspected stroke mimic	10 (4)
Other reasons	4 (2)

contraindications, ongoing anticoagulation was the reason for non-thrombolysis in 51 patients (Table 2). Three quarters of the patients (*n* = 185) who did not receive tPA had no absolute contraindication. In this latter group, mild or improving clinical symptoms was listed as the reason in 92 patients. Advanced age was the main reason given for 17 patients and high bleeding risk in 17 patients. Ten patients who actually had AIS did not receive thrombolysis as they were considered to be stroke mimics at admission. Among those with relative contraindications, 39 out of 185 had more than one reason for not receiving thrombolysis.

Overall, arriving late in the time window was the main reason for the decision not to treat with thrombolysis for 33 patients. 476 patients arrived at the hospital within 3 h after onset, and among these, 275 (58%) received tPA. Fifty-nine patients arrived at the hospital more than 3 h after onset, and 10 (17%) received tPA. Five of the patients arriving and treated later than 3 h after onset had NIHSS ≤ 5.

Twenty-four patients arrived at the hospital more than 4 h after onset and among these, nine were not treated with thrombolysis due to arrival in the end of the time window.

Table 3 presents univariate and multivariable logistic regression analyses for predictors for not receiving thrombolysis.

Age, living at nursing home, previous stroke, early admission, and moderate/severe stroke severity were all significant predictors in unadjusted univariate analyses. However, in the multivariable logistic regression model previous stroke (OR 3.32, 95%CI 1.99–5.52, *p* < .001), arriving between 3 h and 4.5 h after onset (OR 7.76, 95%CI 3.73–16.11, *p* < .001) or having mild symptoms defined as NIHSS ≤ 5, at admission (OR 2.33, 95%CI 1.56–3.49, *p* < .001) all were significant predictors of not receiving thrombolytic treatment. Age, premorbid mRS > 2 or living at nursing home were not significant predictors of not receiving thrombolysis in the adjusted analyses.

In the subgroup analyses excluding those with absolute contraindications (*n* = 470 prior stroke (OR 3.14, 95%CI 1.79–5.48, *p* < .001),

arriving in the final third of the time window (OR 8.48, 95%CI 3.99–18.02, *p* < .001) and milder symptoms (OR 2.85, 95%CI 1.81–4.47, *p* < .001) all remained significantly predictors for not receiving thrombolysis in the multivariable logistic regression model.

Subgroup analyses (*n* = 510) of those arriving at the hospital within 4 h after onset did not differ significantly from the total population (data not shown).

## 4 | DISCUSSION

In this study of consecutive acute ischemic stroke patients admitted within 4.5 h of symptom onset, almost 47% did not receive thrombolysis. The majority of these patients (74%) had no absolute contraindications to treatment, but 21% of those with relative contraindications had more than one reason for not receiving thrombolysis highlighting the fact that treatment decisions are not always straight forward. Contrary to most other studies, this study included all patients up till the timeframe of 4.5 h which is in accordance with European and Norwegian guidelines.<sup>2,17</sup> A novel finding was that arriving in the last 1/3 of the treatment window resulted in an almost eightfold probability of not receiving thrombolysis. Excluding those with absolute contraindications strengthened this finding even further with an increased OR of 8.5 for no thrombolysis.

The use of thrombolytic in the 3 to 4.5 h time window is still under debate.<sup>3,18,19</sup>

The only study designed to specifically evaluate the efficacy of tPA within 3 and 4.5 h after symptom onset (ECASS-III) found benefit (mRS score 0–1 at 90 days) and safety (symptomatic ICH or death) independent to stroke severity.<sup>20</sup> However, only 128 patients with an NIHSS score of 0 to 5 were included in ECASS-III.<sup>21</sup> Thus, the US guidelines recommend that tPA may be reasonable, but treatment risks should be weighed against possible benefits for patients

TABLE 3 Univariate and multivariable logistic regression analyses

	N	Univariate			N	Multivariable		
		Odds ratio	95% CI	p-value		Odds ratio	95% CI	p-value
Age	535	1.01	1.00 to 1.03	.039	535	1.01	1.00 to 1.03	.087
Sex								
Women	219	1.00			219	1.00		
Men	316	0.98	0.69 to 1.38	.91	316	0.90	0.61 to 1.34	.61
Living alone								
No	398	1.00						
Yes	137	0.99	0.68 to 1.48	1.00				
Nursing home								
No	491	1.00			491	1.00		
Yes	44	1.91	1.01 to 3.59	.045	44	1.75	0.78 to 3.93	.17
mRS before admission								
0–2	422	1.00			422	1.00		
3–5	113	1.51	1.00 to 2.30	.052	113	1.34	0.74 to 2.43	.33
Diabetes mellitus								
No	453	1.00						
Yes	82	1.04	0.65 to 1.67	.87				
Anti-hypertensive treatment								
No	194	1.00			194	1.00		.58
Yes	341	1.28	0.90 to 1.83	.17	341	1.12	0.75 to 1.68	
Previous TIA								
No	475	1.00			475	1.00		
Yes	60	1.57	0.91 to 2.70	.10	60	0.84	0.45 to 1.56	.58
Previous stroke								
No	435	1.00			435	1.00		
Yes	100	3.12	1.96 to 4.97	<.001	100	3.32	1.99 to 5.52	<.001
Onset to admission >180 and <270 min								
No	476	1.00			476	1.00		
Yes	59	6.70	3.32 to 13.55	<.001	59	7.76	3.73 to 16.11	<.001
Large vessel occlusion								
No	370	1.00						
Yes	133	0.80	0.54 to 1.20	.29				
Stroke severity								
Moderate to severe	249	1.00			249	1.00		
Mild	286	1.75	1.24 to 2.47	.001	286	2.33	1.56 to 3.49	<.001

Predictors for not receiving thrombolysis among patients with acute ischemic stroke.

Significance of Bold values indicates  $p < .05$

within 3 and 4.5 h after symptom onset if NIHSS  $<6$ .<sup>3</sup> Recently, a reanalysis of ECASS-III does not support any significant benefits and support harms for the use of alteplase 3–4.5 h after stroke onset,<sup>22</sup> but a meta-analysis and registry-based studies support that tPA improves outcome and has the same safety profile between 0–3 and 3–4.5 h.<sup>23–26</sup>

In addition, we found that previous stroke or having milder stroke symptoms defined as NIHSS  $\leq 5$  were all predictors of not

receiving thrombolytic treatment. This is in accordance with previous findings.<sup>10,14,27</sup> In the meta-analysis of individual patient data from randomized trials of alteplase, there was an absolute difference of 10% in good outcome (mRS 0–1) in the subgroup of mild stroke (NIHSS 0–4) in favor of patients treated with thrombolysis.<sup>23</sup> The same meta-analysis, however, showed that among mild strokes with an otherwise good predicted outcome 0.9% suffered a fatal intracranial hemorrhage after thrombolysis.

Exclusion criteria in routine thrombolysis are based on exclusion criteria in the early thrombolysis trials, but are modified after the international stroke trials, subgroup analysis of earlier trials, and observational series.<sup>28,29</sup> In particular, it has been suggested that patients with advanced age, mild or rapid improving symptoms have a beneficial effect of thrombolysis.<sup>5</sup>

An almost doubling of treated patients with low NIHSS from 2003 to 2011 has been reported.<sup>16</sup> In Norway, 43% of those treated with tPA in 2018 had NIHSS < 5.<sup>4</sup> Data from the Swedish stroke registry showed that in 2020 nearly 40% of patients treated had a NIHSS 0–5.<sup>9</sup> The use of thrombolysis between regions differed from 8 to 25%. Most common reasons for not to treat were to late (admission > 4.5 h) or unknown debut of symptoms 58%, mild symptoms 20%, and other contraindications for thrombolysis 14%.<sup>9</sup>

Patients with mild stroke defined as NIHSS ≤ 5 and stroke with improving neurological symptoms were not included in the early trials on thrombolysis due to assumed good outcome and there is still an existing disagreement regarding benefit of IV tPA for these patients.<sup>28,30,31</sup> In line with the meta-analyses of data from randomized trials,<sup>23,32</sup> two recent meta-analyses of observational data show that patients with mild stroke may gain benefit from IV tPA without any significant increase in mortality.<sup>33,34</sup> On the contrary, the American PRISMS trial (2018) found no beneficial effect and an increased risk of symptomatic ICH in patients with non-disabling stroke with NIHSS 0–5 treated with i.v alteplase compared to aspirin (3 vs. 0%).<sup>35</sup> However, this study was terminated on an early stage precluding any definitive conclusions.

Advanced age was listed as the main reason for not giving thrombolysis in 14 patients and a significant predictor in the multivariable logistic regression model. Age is an independent risk factor for poor outcome in patients with ischemic stroke, regardless of whether tPA is given or not. This may reflect the numerous comorbidities of elderly patients and their decreased ability to regain function through rehabilitation. One study from 2010 included 3472 patients > 80 years that received thrombolysis and compared them to patients who had not received tPA.<sup>36</sup> The distribution of mRS scores at 3 months was better for those who had received thrombolysis both in the very elderly patients and in the younger patients. The meta-analysis of individual data from RCTs has also demonstrated no upper age limit for benefit of tPA.<sup>23</sup> There is reason to believe that increasing knowledge from trials and confidence in benefit to harm ratio will cause increased treatment of patients > 80 years.

Having a high pre-mRS or being admitted from a nursing home was not associated with no tPA in the adjusted analyses. This is also a trend seen over time with the very strict inclusion criteria from the original clinical trials not necessarily feasible in a real-world setting.

Any previous stroke was a predictor of not receiving thrombolysis in this study. For a long time, a history of stroke the previous 3 months was considered as an exclusion criterion to tPA.<sup>37</sup> A meta-analysis of six studies and 900 patients did not find any significant increase in symptomatic ICH (sICH) in patients with a recent history of AIS.<sup>38</sup> One study showed that patients with a very recent history

(< 14 days) of AIS had an increased risk of sICH.<sup>39</sup> The risk of bleeding is shown to be smaller when the volume of the previous stroke is small and no additional risk factors are identified.<sup>40</sup> However, it should be emphasized that treating patients with a recent stroke needs a careful approach.

Delay from onset of symptoms to arrival in hospital represents the overall most significant barrier to tPA. It is important to initiate all measures that can reduce the time-delay both pre- and intra-hospital.<sup>15,41,42</sup> This can be achieved by improving the public awareness of stroke, close cooperation between the EMS and the hospital and treatment of acute stroke patients according to continuously revised protocols and guidelines.

## 4.1 | Strengths and limitations

Certain potential limitations should be considered. The study was retrospective; however, we used prospectively collected data from original electronic medical reports so bias is unlikely. Even though it is a single-center study, it is a strength that the patients were admitted unselected, consecutively and the hospital serve more than 10% of the total Norwegian population. The population of our public hospital is reasonably representative for the total Norwegian population. The study covered three years so year-by-year variance is of minor importance. Management and treatment may change over time. Thus, we cannot rule out that the results may have been slightly different if we had included patients from 2018 and until the changes related to the pandemic.<sup>43</sup> Some cases may have been missed based on wrong ICD-10 code. To minimize this, all electronic medical reports were reviewed by one of the authors. In addition, the data have been linked to the Norwegian Stroke Registry.

## 5 | CONCLUSION

Although thrombolysis rates have increased over the past decade, this study shows that a large proportion of patients admitted within 4.5 h do not receive this treatment. Patient groups not treated are among those where the beneficial effects are probably modest and risks are uncertain. Data from stroke registries show that there are hospital and regional variations in the use of thrombolysis. More evidence is needed to explore these variations and whether there is an underuse of thrombolysis.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/ane.13622>.

## DATA AVAILABILITY STATEMENT

Data are available upon reasonable request from the corresponding author.

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