

Reperfusion Decision-Making and In-Hospital Workflow Performance in Wake-Up, Unknown-Onset, and Known Beyond-Window Acute Ischemic Stroke: A Three-Year Single-Center Real-World Retrospective Study

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Abstract

Objective: To characterize reperfusion decision-making, in-hospital workflow efficiency, and the principal reasons for withholding intravenous thrombolysis in an extended-window acute ischemic stroke (AIS) pathway including wake-up stroke, unknown-onset stroke, and known beyond-window presentations. **Methods:** We retrospectively screened 349 consecutive emergency stroke-pathway records from January 2023 to December 2025. Four records with a final diagnosis other than AIS were excluded, leaving 345 AIS cases. The historical binary 4.5-h field was treated as a registry-recorded operational variable because a uniform last-known-well or symptom-discovery anchor could not be verified across years. Missing covariates were not randomly imputed for the final analysis. Because of the limited number of thrombolysis events, multivariable associations were assessed using Firth penalized logistic regression with profile-likelihood 95% confidence intervals (CIs). **Results:** Twenty-seven of 345 patients (7.8%) received intravenous thrombolysis: 26/186 (14.0%) with wake-up stroke, 0/3 (0%) with unknown onset, and 1/156 (0.6%) with known beyond-window presentation. Median age was 71 (61, 80) years and 217 (62.9%) were men. Baseline NIHSS was available in 201 patients and was 4 (2, 7) overall; treated patients had higher scores than untreated patients [8 (5, 14) vs. 3 (1, 6), $P < 0.001$]. Registry-recorded 4.5-h status was available in 269 patients and was positive in 24/27 treated versus 90/242 untreated patients (88.9% vs. 37.2%, $P < 0.001$). Median door-to-needle time among 25 patients with valid values was 66 (54, 83) min; 44.0% achieved ≤ 60 min. The leading reasons for non-thrombolysis were time-window/unknown-onset

limitation (160/318, 50.3%), patient/family refusal or transfer (52/318, 16.4%), and imaging ineligibility/no treatment indication (39/318, 12.3%). In the complete-case Firth model ($n = 176$; 26 thrombolysis events), registry-recorded 4.5-h status (adjusted OR 18.49, 95% CI 5.76 - 80.28; $P < 0.001$) and baseline NIHSS (adjusted OR 1.17 per point, 95% CI 1.06 - 1.29; $P < 0.001$) remained associated with thrombolysis, whereas the calendar-year trend was attenuated (adjusted OR 1.85, 95% CI 0.90 - 4.10; $P = 0.096$). Conclusion: In this county-level extended-window stroke pathway, thrombolysis increased descriptively after 2023, but Firth regression indicated that documented time-window status and neurological severity were the more robust treatment correlates. Workflow improvement should prioritize standardized onset-time documentation, rapid treatment decision-making, structured risk communication, and prospective capture of source-verifiable imaging and outcome data.

Keywords

Wake-Up Stroke, Unknown-Onset Stroke, Known Beyond-Window Stroke, Acute Ischemic Stroke, Intravenous Thrombolysis, Reperfusion Therapy, Door-to-Needle Time, Workflow Performance, Firth Regression, Real-World Study

1. Introduction

Acute ischemic stroke (AIS) is a leading cause of death and long-term disability in adults. Outcomes depend strongly on early recognition, rapid imaging, and timely reperfusion. Intravenous thrombolysis and endovascular therapy are highly time dependent; earlier treatment increases the likelihood of salvaging ischemic penumbra and improves long-term functional outcomes. Intravenous alteplase within 4.5 h is supported by robust evidence and guideline recommendations [1]-[3]. However, a substantial proportion of patients develop symptoms during sleep or cannot reliably identify the time of onset. These patients with wake-up stroke or stroke of unknown onset have historically been excluded from thrombolysis solely because onset time was uncertain, potentially denying treatment to patients who might benefit.

With the development of MRI diffusion-weighted imaging/fluid-attenuated inversion recovery (DWI-FLAIR) mismatch, computed tomography perfusion (CTP) core-perfusion mismatch, and CT angiography (CTA), the paradigm of reperfusion selection has expanded from a purely clock-based window to a tissue-based window. WAKE-UP showed improved 90-day functional outcomes with alteplase in patients with unknown onset selected by a DWI-positive/FLAIR-negative pattern [4]. EXTEND used perfusion imaging to extend thrombolysis to selected patients 4.5 - 9 h after onset or with wake-up stroke [5]. An individual-patient meta-analysis likewise demonstrated an overall net clinical benefit of alteplase in unknown-onset stroke selected by DWI-FLAIR or perfusion mismatch [6]. Current interna-

tional and Chinese guidelines therefore recommend individualized decisions integrating advanced imaging, stroke severity, vascular occlusion, and bleeding risk [1]-[3].

In real-world practice, a guideline-supported option is not necessarily operationally deliverable. Patients with wake-up stroke, unknown onset, or a known presentation beyond the conventional thrombolysis window may enter the same extended-window assessment pathway, but they differ in the relationship among last-known-well time, symptom discovery, and hospital arrival. These patients require rapid noncontrast CT and, when indicated, CTA, CTP, or MRI; clinicians must integrate deficit disability, tissue viability, large-vessel occlusion (LVO), contraindications, and patient preferences. Risk-benefit communication is also more complex than in straightforward conventional-window treatment. For county-level advanced stroke centers, consistent execution of imaging selection, consultation, communication, and treatment decisions is therefore crucial.

Most previous studies have focused on treatment efficacy or imaging-selection criteria. Evidence describing consecutive real-world decision-making, workflow delay, and reasons for non-thrombolysis in county hospitals is more limited, particularly when wake-up, unknown-onset, and known beyond-window presentations are managed within one pathway. We therefore analyzed quality-control data from 2023-2025 to describe baseline characteristics, in-hospital workflow, advanced stroke imaging, reperfusion treatment, reasons for non-thrombolysis, and factors associated with intravenous thrombolysis.

2. Methods

2.1. Study Design and Setting

This was a single-center retrospective real-world cohort study. Consecutive records were identified from the emergency stroke pathway and stroke quality-control database between January 1, 2023 and December 31, 2025. A total of 349 pathway records were screened: 106 from 2023, 101 from 2024, and 142 from 2025. Four records with a final diagnosis other than AIS were excluded (2023, $n = 2$; 2024, $n = 0$; 2025, $n = 2$), leaving 345 AIS cases for descriptive analyses. Data were de-identified before analysis. The study focused on reperfusion decisions and in-hospital workflow rather than long-term treatment efficacy.

The hospital serves as a regional stroke center. Its emergency pathway comprises triage recognition, rapid neurologic assessment, glucose and basic laboratory testing, noncontrast head CT to exclude hemorrhage, and CTA, CTP, or MRI-DWI/FLAIR when indicated. Intravenous thrombolysis or mechanical thrombectomy is selected according to time window, tissue window, deficit severity, contraindications, and patient/family preference. Key timestamps are prospectively recorded for continuous quality improvement.

2.2. Eligibility Criteria

Inclusion criteria were: age ≥ 18 years; emergency stroke-pathway assessment

during the study period; final diagnosis of AIS; and presentation within the center's extended-window evaluation pathway as wake-up stroke, unknown-onset stroke, or known presentation beyond the conventional 4.5-h window. Missing individual covariates did not by themselves trigger exclusion; variable-specific analyses used available observations.

Exclusion criteria were a final diagnosis other than AIS or a stroke mimic, or an encounter for which the local emergency-pathway decision process was not evaluable. In the supplied screened dataset, the only exclusions were the four non-AIS records noted above; no record was excluded solely because of missing NIHSS or registry-recorded 4.5-h status. The Firth multivariable analysis used complete cases for its prespecified predictors.

2.3. Data Collection and Definitions

Collected variables included year, age, sex, onset category, registry-recorded 4.5-h status, baseline NIHSS score, door-to-blood, door-to-sample, door-to-complete blood count (CBC) report, door-to-coagulation report, door-to-biochemistry report, door-to-CT dispatch, door-to-CT completion, DNT, intravenous thrombolysis, mechanical thrombectomy, and the principal reason for non-thrombolysis. Source-tagged CTA, CTP, MRI-DWI/FLAIR, LVO, and tissue-mismatch fields were also audited. However, a substantial proportion of these imaging variables in the preprocessing extract had been reconstructed or imputed for database-building purposes rather than being uniformly source-verifiable. They were therefore excluded from final quantitative utilization rates and inferential regression analyses.

Wake-up stroke was defined as a new focal neurological deficit identified on awakening after an asymptomatic sleep period. Unknown onset indicated that last-known-well or symptom-onset time could not be established accurately. Known beyond-window presentation indicated a documented presentation beyond the conventional 4.5-h treatment window. The binary 4.5-h field was inherited from annual quality-control datasets. Because the historical extract did not consistently preserve timestamp provenance sufficient to identify a single uniform anchor (last-known-well, symptom discovery, or another operational timestamp) across all onset categories and all three years, we refer to it as registry-recorded 4.5-h status. It was analyzed as an operational process variable and was not equated with guideline-defined conventional clock-window eligibility in wake-up or unknown-onset stroke.

Where source documentation was available, MRI DWI-FLAIR mismatch referred to an acute DWI lesion without corresponding unequivocal FLAIR hyperintensity in the same region, and CTP mismatch referred to a documented core-hypoperfusion mismatch with salvageable tissue. No blinded central imaging re-read was performed. The historical database did not uniformly preserve CTP vendor/software, ischemic-core volume thresholds, hypoperfusion thresholds (for example, Tmax), or mismatch-ratio cutoffs. Because source verification was incom-

plete and the preprocessing file contained reconstructed/imputed imaging fields, no quantitative imaging-utilization rate or mismatch coefficient was retained in the final inferential analysis. No trial-specific imaging threshold was retrospectively imposed.

DNT was the interval from emergency-department arrival to initiation of thrombolytic administration. Targets were ≤ 60 , ≤ 45 , and ≤ 30 min; patients without a valid DNT were excluded from those denominators. Reasons for non-thrombolysis were standardized as time-window/unknown-onset limitation; patient/family refusal or transfer; imaging ineligibility/no indication; direct thrombectomy; contraindication/high bleeding risk; large infarct/large core; mild, low-NIHSS, non-disabling, or improving symptoms; imaging-assessment failure; and other/unclear documentation. The cleaned database used a rule-based standardization of the free-text final-decision remark. One principal reason was retained per patient; when no single terminal factor was explicit or competing factors could not be resolved from the available remark, the case was classified as other/unclear. Independent duplicate adjudication and an inter-rater reliability statistic were not available.

The three annual datasets were merged and harmonized before analysis. Field names and time formats were standardized, implausible time intervals were checked, and misaligned fields in selected 2023 rows were corrected. The string sentinel value '66' used in non-age fields was treated as missing. No random imputation was used in the final statistical analysis. Source-unverified imaging fields that had been reconstructed/imputed during preprocessing were not used for quantitative imaging rates or regression modeling.

2.4. Statistical Analysis

Continuous variables were assessed for distribution and are reported as mean $\pm$ standard deviation when normally distributed or median (25th, 75th percentile) when skewed. Most continuous variables were skewed and are therefore presented as M (P25, P75). Categorical variables are reported as n (%).

Continuous variables were compared using the Mann-Whitney U test between treatment groups and the Kruskal-Wallis test across years; categorical variables were compared using the chi-square test or Fisher exact test when appropriate. Variable-specific denominators are reported when data were missing. Because only 27 thrombolysis events occurred and baseline NIHSS/registry-recorded 4.5-h status were incompletely captured, the primary multivariable analysis used Firth penalized logistic regression on complete cases. Prespecified predictors were calendar-year trend (coded 0, 1, and 2 for 2023, 2024, and 2025), age per 10 years, registry-recorded 4.5-h status, and baseline NIHSS score. The complete-case model included 176 patients and 26 thrombolysis events. Results are reported as odds ratios (ORs) or adjusted ORs (aORs) with profile-likelihood 95% CIs; P values were obtained from penalized likelihood-ratio tests. Two-sided $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline Characteristics

Among 349 screened pathway records, 4 non-AIS records were excluded (2023: 2/106; 2024: 0/101; 2025: 2/142), yielding 345 AIS cases: 104 (30.1%) in 2023, 101 (29.3%) in 2024, and 140 (40.6%) in 2025. No case was excluded solely for missing covariates. Registry-recorded 4.5-h status was missing in 76 AIS cases (2023, $n = 63$; 2024, $n = 10$; 2025, $n = 3$), and baseline NIHSS was missing in 144 (2023, $n = 53$; 2024, $n = 39$; 2025, $n = 52$). Median age was 71 (61, 80) years and 217 (62.9%) were men. Among 201 patients with available NIHSS, the median score was 4 (2, 7). There were 186 (53.9%) wake-up strokes, 3 (0.9%) strokes of unknown onset, and 156 (45.2%) known beyond-window presentations. Intravenous thrombolysis was administered to 26/186 patients with wake-up stroke (14.0%), 0/3 with unknown onset (0%), and 1/156 with known beyond-window presentation (0.6%).

Among patients with an available registry-recorded 4.5-h field, treated patients more often had a positive status than untreated patients (24/27 [88.9%] vs. 90/242 [37.2%], $P < 0.001$). Baseline NIHSS was also higher in treated patients with available scores [8 (5, 14), $n = 26$] than in untreated patients [3 (1, 6), $n = 175$; $P < 0.001$]. Wake-up stroke accounted for 96.3% of treated patients versus 50.3% of untreated patients (overall onset-category comparison, $P < 0.001$). Age and sex did not differ significantly (Table 1).

Table 1. Baseline characteristics of patients with AIS presenting with wake-up, unknown-onset, or known beyond-window stroke.

Variable	Overall (N = 345)	IV thrombolysis (n = 27)	No IV thrombolysis (n = 318)	P value
Year, n (%)				0.027
2023	104 (30.1)	2 (7.4)	102 (32.1)	
2024	101 (29.3)	11 (40.7)	90 (28.3)	
2025	140 (40.6)	14 (51.9)	126 (39.6)	
Age, years, M (P25, P75)	71 (61, 80)	75 (64.5, 78)	71 (61, 80)	0.556
Male, n (%)	217 (62.9)	19 (70.4)	198 (62.3)	0.403
Onset category, n (%)				<0.001
Wake-up stroke	186 (53.9)	26 (96.3)	160 (50.3)	
Unknown onset	3 (0.9)	0 (0.0)	3 (0.9)	
Known beyond-window presentation	156 (45.2)	1 (3.7)	155 (48.7)	
Registry-recorded ≤ 4.5 h, n/N (%)	114/269 (42.4)	24/27 (88.9)	90/242 (37.2)	<0.001
Baseline NIHSS, M (P25, P75)	4 (2, 7) [n = 201]	8 (5, 14) [n = 26]	3 (1, 6) [n = 175]	<0.001
Mechanical thrombectomy, n (%)	11 (3.2)	0 (0.0)	11 (3.5)	1.000

Note: Continuous variables are presented as M (P25, P75) and compared using the Mann-Whitney U test; categorical variables are n (%) unless an n/N denominator is shown. Registry-recorded 4.5-h status is an operational historical quality-control field and is not assumed to equal uniform guideline-defined last-known-well eligibility across onset categories. NIHSS and 4.5-h status are reported with available-case denominators.

3.2. Workflow Trends from 2023 to 2025

Among records with an available registry-recorded 4.5-h field, the corresponding proportions were 43.9% (18/41), 47.3% (43/91), and 38.7% (53/137) in 2023, 2024, and 2025, respectively ($P = 0.430$). Door-to-CT dispatch and completion remained stable; overall door-to-CT completion was 15 (12, 19) min among 299 patients with valid timestamps and was 14 (11, 19), 14 (12, 19), and 15 (13, 18) min by year ($P = 0.503$). Door-to-sample and door-to-biochemistry-report times differed by year, but these differences should be interpreted in light of changing documentation practices and year-specific missingness.

Intravenous thrombolysis increased from 1.9% in 2023 to 10.9% in 2024 and 10.0% in 2025 ($P = 0.027$). Any reperfusion therapy increased from 6.7% to 12.9% and 12.9%, although the annual difference was not statistically significant ($P = 0.248$). Among 25 thrombolysis patients with valid DNT, median DNT was 66 (54, 83) min; 11/25 (44.0%) achieved ≤ 60 min, 2/25 (8.0%) achieved ≤ 45 min, and none achieved ≤ 30 min (**Table 2**). Because the post-review source audit identified non-verifiable reconstructed/imputed imaging fields, annual advanced-imaging utilization rates were not retained in the final quantitative analysis. **Figure 1** therefore displays the two source-verifiable reperfusion-treatment trends.

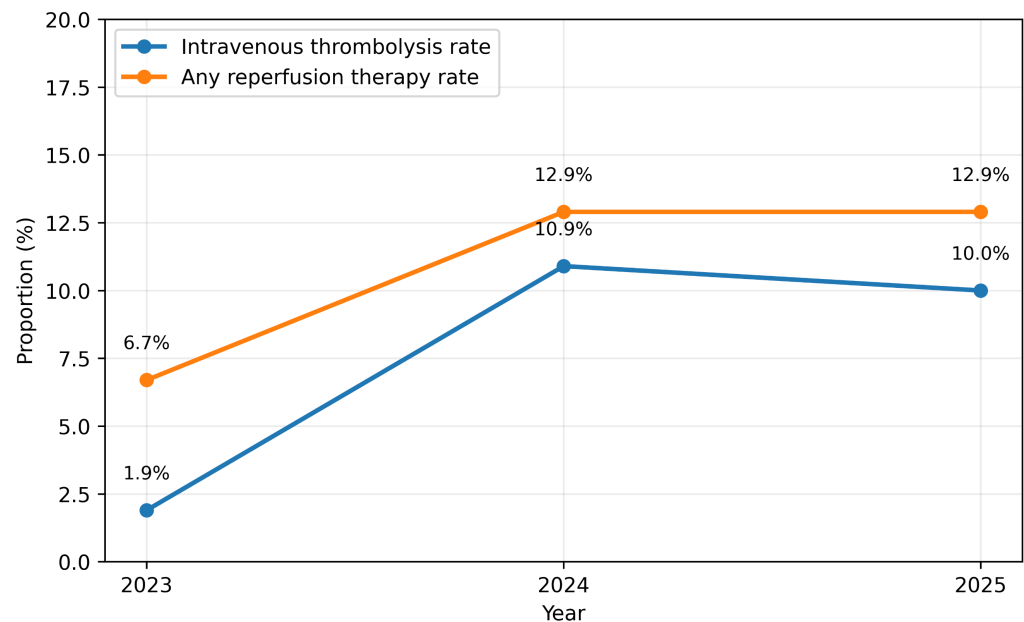
Table 2. Workflow and treatment trends from 2023 to 2025.

Variable	Overall (N = 345)	2023 (n = 104)	2024 (n = 101)	2025 (n = 140)	P value
Study population, n	345	104	101	140	-
Registry-recorded ≤ 4.5 h, n/N (%)	114/269 (42.4)	18/41 (43.9)	43/91 (47.3)	53/137 (38.7)	0.430
Baseline NIHSS, M (P25, P75)	4 (2, 7) [n = 201]	3 (1, 6.5) [n = 51]	4 (2.25, 7.75) [n = 62]	3.5 (1, 7.25) [n = 88]	0.259
Door-to-blood, min, M (P25, P75)	1 (1, 3) [n = 322]	2 (1, 3) [n = 97]	1 (1, 3) [n = 97]	1 (1, 2) [n = 128]	0.224
Door-to-sample, min, M (P25, P75)	6 (3, 8) [n = 324]	2 (1, 3) [n = 97]	7 (6, 9) [n = 98]	8 (6, 9) [n = 129]	<0.001
Door-to-CBC report, min, M (P25, P75)	17 (14, 21) [n = 221]	-	16 (13, 21) [n = 94]	17 (14.5, 20) [n = 127]	0.449
Door-to-coag report, min, M (P25, P75)	33 (31, 37) [n = 217]	-	33 (31, 37) [n = 93]	33 (31, 36) [n = 124]	0.668
Door-to-biochem report, min, M (P25, P75)	42 (11, 47) [n = 272]	7.5 (5, 11) [n = 74]	46 (42, 53.5) [n = 80]	44 (38, 48) [n = 118]	<0.001
Door-to-CT send, min, M (P25, P75)	7 (5, 9) [n = 318]	6 (5, 9) [n = 96]	7 (6, 10) [n = 96]	7 (5, 9) [n = 126]	0.137
Door-to-CT complete, min, M (P25, P75)	15 (12, 19) [n = 299]	14 (11, 19) [n = 93]	14 (12, 19) [n = 81]	15 (13, 18) [n = 125]	0.503
Intravenous thrombolysis, n (%)	27 (7.8)	2 (1.9)	11 (10.9)	14 (10.0)	0.027

Continued

DNT, min, M (P25, P75)	66 (54, 83) [n = 25]	75.5 (70.8, 80.2) [n = 2]	57 (54, 76) [n = 9]	68.5 (53.2, 83) [n = 14]	0.560
DNT ≤ 30 min, n/N (%)	0/25 (0.0)	0/2 (0.0)	0/9 (0.0)	0/14 (0.0)	-
DNT ≤ 45 min, n/N (%)	2/25 (8.0)	0/2 (0.0)	2/9 (22.2)	0/14 (0.0)	0.145
DNT ≤ 60 min, n/N (%)	11/25 (44.0)	0/2 (0.0)	5/9 (55.6)	6/14 (42.9)	0.356
Mechanical thrombectomy, n (%)	11 (3.2)	5 (4.8)	2 (2.0)	4 (2.9)	0.494
Any reperfusion therapy, n (%)	38 (11.0)	7 (6.7)	13 (12.9)	18 (12.9)	0.248

Note: Continuous variables are presented as M (P25, P75) with valid n shown where data were incomplete. Annual continuous-variable comparisons used the Kruskal-Wallis test, except CBC and coagulation-report times, which were available only in 2024-2025 and were compared between those two years. Categorical variables were compared using the chi-square or Fisher exact test as appropriate. DNT metrics include only thrombolysis patients with valid DNT (overall n = 25; 2023 n = 2; 2024 n = 9; 2025 n = 14).



Note: Annual AIS cases were used as denominators. Any reperfusion therapy was defined as intravenous thrombolysis and/or mechanical thrombectomy.

Figure 1. Trends in intravenous thrombolysis and any reperfusion therapy from 2023 to 2025.

3.3. Workflow Measures by Thrombolysis Status

Door-to-blood, door-to-sample, laboratory-report, CT-dispatch, and CT-completion times did not differ significantly by thrombolysis status among patients with valid timestamps. In treated patients, median DNT was 66 (54, 83) min (valid n = 25); 44.0%, 8.0%, and 0% met the ≤60-, ≤45-, and ≤30-min targets, respectively. These data suggest that initial CT access was generally rapid, whereas integrated decision-making and treatment preparation remained targets for improvement (Table 3).

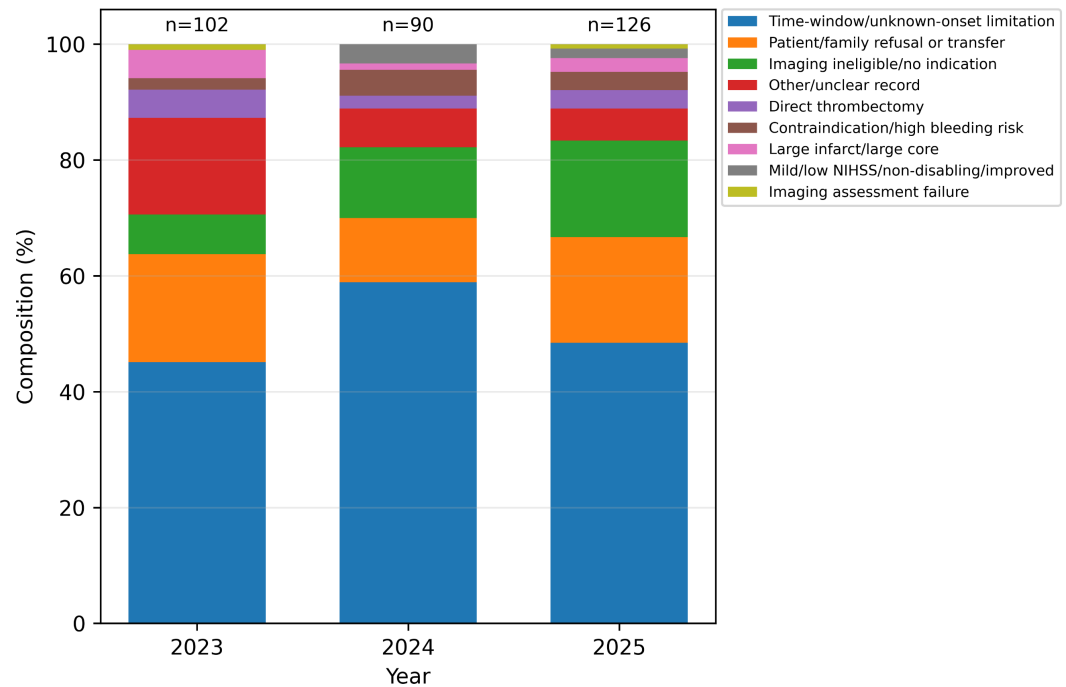
Table 3. Clinical characteristics and workflow measures by intravenous-thrombolysis status.

Variable	Overall (N = 345)	IV thrombolysis (n = 27)	No IV thrombolysis (n = 318)	P value
Year, n (%)				0.027
2023	104 (30.1)	2 (7.4)	102 (32.1)	
2024	101 (29.3)	11 (40.7)	90 (28.3)	
2025	140 (40.6)	14 (51.9)	126 (39.6)	
Age, years, M (P25, P75)	71 (61, 80)	75 (64.5, 78)	71 (61, 80)	0.556
Male, n (%)	217 (62.9)	19 (70.4)	198 (62.3)	0.403
Onset category, n (%)				<0.001
Wake-up stroke	186 (53.9)	26 (96.3)	160 (50.3)	
Unknown onset	3 (0.9)	0 (0.0)	3 (0.9)	
Known beyond-window presentation	156 (45.2)	1 (3.7)	155 (48.7)	
Registry-recorded ≤ 4.5 h, n/N (%)	114/269 (42.4)	24/27 (88.9)	90/242 (37.2)	<0.001
Baseline NIHSS, M (P25, P75)	4 (2, 7) [n = 201]	8 (5, 14) [n = 26]	3 (1, 6) [n = 175]	<0.001
Door-to-blood, min, M (P25, P75)	1 (1, 3) [n = 322]	1 (1, 1.8) [n = 26]	1 (1, 3) [n = 296]	0.154
Door-to-sample, min, M (P25, P75)	6 (3, 8) [n = 324]	6.5 (5.2, 8) [n = 26]	6 (3, 8) [n = 298]	0.396
Door-to-CBC report, min, M (P25, P75)	17 (14, 21) [n = 221]	18.5 (14.8, 28.8) [n = 24]	16 (14, 21) [n = 197]	0.084
Door-to-coag report, min, M (P25, P75)	33 (31, 37) [n = 217]	34 (30, 37.5) [n = 23]	33 (31, 36) [n = 194]	0.535
Door-to-biochem report, min, M (P25, P75)	42 (11, 47) [n = 272]	43 (25, 47) [n = 23]	42 (11, 47) [n = 249]	0.597
Door-to-CT send, min, M (P25, P75)	7 (5, 9) [n = 318]	7 (6, 9) [n = 25]	7 (5, 9) [n = 293]	0.627
Door-to-CT complete, min, M (P25, P75)	15 (12, 19) [n = 299]	16 (12, 20) [n = 21]	15 (12, 19) [n = 278]	0.488
Mechanical thrombectomy, n (%)	11 (3.2)	0 (0.0)	11 (3.5)	1.000
DNT, min, M (P25, P75)	66 (54, 83) [n = 25]	66 (54, 83) [n = 25]	-	-
DNT ≤ 30 min, n/N (%)	0/25 (0.0)	0/25 (0.0)	-	-
DNT ≤ 45 min, n/N (%)	2/25 (8.0)	2/25 (8.0)	-	-
DNT ≤ 60 min, n/N (%)	11/25 (44.0)	11/25 (44.0)	-	-

Note: Variable-specific denominators are shown for incomplete workflow fields. DNT applies only to patients receiving intravenous thrombolysis; valid DNT n = 25. Registry-recorded 4.5-h status is an operational historical field as defined in Methods.

3.4. Reasons for Non-Thrombolysis

Among 318 untreated patients, the most frequent principal reason was a time-window/unknown-onset limitation (160, 50.3%), followed by patient/family refusal or transfer (52, 16.4%), imaging ineligibility or no treatment indication (39, 12.3%), and other/unclear documentation (30, 9.4%). The overall distribution of principal reasons did not differ significantly across years ($P = 0.059$), although the other/unclear category decreased over time ($P = 0.010$) (Figure 2 and Table 4).



Note: Percentages are calculated among patients not receiving intravenous thrombolysis in each year. One principal reason was retained per patient from the rule-standardized final-decision remark; ambiguous or competing factors without a clearly documented terminal reason were classified as other/unclear.

Figure 2. Annual composition of principal reasons for non-thrombolysis, 2023-2025.

Table 4. Principal reasons for non-thrombolysis by year.

Variable	Overall (N = 318)	2023 (n = 102)	2024 (n = 90)	2025 (n = 126)	P value
Time-window/unknown-onset limitation	160(50.3)	46(45.1)	53(58.9)	61(48.4)	0.139
Patient/family refusal or transfer	52(16.4)	19(18.6)	10(11.1)	23(18.3)	0.283
Imaging ineligible/no indication	39(12.3)	7(6.9)	11(12.2)	21(16.7)	0.081
Other/unclear record	30(9.4)	17(16.7)	6(6.7)	7(5.6)	0.010
Direct thrombectomy/thrombectomy	11(3.5)	5(4.9)	2(2.2)	4(3.2)	0.583
Contraindication/high bleeding risk	10(3.1)	2(2.0)	4(4.4)	4(3.2)	0.616
Large infarct/large core	9(2.8)	5(4.9)	1(1.1)	3(2.4)	0.266
Mild/low NIHSS/non-disabling/improved	5(1.6)	0(0.0)	3(3.3)	2(1.6)	0.180
Imaging assessment failure	2(0.6)	1(1.0)	0(0.0)	1(0.8)	0.662

Note: Only AIS patients who did not receive intravenous thrombolysis are included. Values are n (%). One principal reason was retained per patient from the standardized final-decision remark; interacting secondary factors could coexist. Overall annual difference in reason distribution, $P = 0.059$.

3.5. Firth Penalized Logistic Regression Analysis

In univariable Firth analyses, calendar-year trend (OR 1.74, 95% profile CI 1.06 - 3.02; $P = 0.027$), registry-recorded 4.5-h status (OR 11.80, 95% CI 4.21 - 44.96; $P < 0.001$), and baseline NIHSS score (OR 1.15 per point, 95% CI 1.08 - 1.24; $P < 0.001$) were associated with thrombolysis, whereas age was not.

The multivariable Firth model included 176 complete cases and 26 thrombolysis events. Registry-recorded 4.5-h status (aOR 18.49, 95% profile CI 5.76 - 80.28; $P < 0.001$) and baseline NIHSS score (aOR 1.17 per point, 95% CI 1.06 - 1.29; $P < 0.001$) remained associated with thrombolysis. The calendar-year trend was attenuated and no longer statistically significant (aOR 1.85, 95% CI 0.90 - 4.10; $P = 0.096$), and age was not associated (aOR 0.74 per 10 years, 95% CI 0.46 - 1.18; $P = 0.205$) (**Table 5**). Thus, the penalized analysis preserved the main conclusions for registry-recorded time status and NIHSS but weakened the evidence for an independent calendar-year effect.

Table 5. Firth penalized logistic regression analysis of factors associated with intravenous thrombolysis.

Variable	Univariable Firth OR (95% CI)	P value	Multivariable Firth aOR (95% CI)	P value
Calendar-year trend (per year)	1.74 (1.06 - 3.02)	0.027	1.85 (0.90 - 4.10)	0.096
Age (per 10 years)	1.10 (0.81 - 1.53)	0.542	0.74 (0.46 - 1.18)	0.205
Registry-recorded ≤ 4.5 h	11.80 (4.21 - 44.96)	<0.001	18.49 (5.76 - 80.28)	<0.001
Baseline NIHSS (per point)	1.15 (1.08 - 1.24)	<0.001	1.17 (1.06 - 1.29)	<0.001

Note: Univariable denominators vary because registry-recorded 4.5-h status and baseline NIHSS were incomplete. The multivariable Firth model used complete cases ($n = 176$; thrombolysis events $n = 26$) and included calendar-year trend, age per 10 years, registry-recorded 4.5-h status, and baseline NIHSS. CIs are profile-likelihood 95% CIs and P values are penalized likelihood-ratio tests. Source-unverified imaging/mismatch fields were excluded from the final inferential model after data-provenance audit.

4. Discussion

4.1. Principal Findings and Clinical Implications

This three-year real-world analysis included 345 patients with AIS in an extended-window county stroke pathway. Twenty-seven (7.8%) received intravenous thrombolysis, 11 (3.2%) underwent mechanical thrombectomy, and 38 (11.0%) received any reperfusion therapy. Thrombolysis increased descriptively from 1.9% in 2023 to approximately 10% in 2024-2025. The cohort was broader than wake-up or unknown-onset stroke alone and included 156 known beyond-window presentations; thrombolysis was most frequent in wake-up stroke (14.0%). Importantly, Firth penalized regression confirmed strong associations of thrombolysis with registry-recorded 4.5-h status and higher NIHSS, whereas the calendar-year association was attenuated and was no longer statistically significant after penalization and complete-case adjustment.

The value of this study is its process-of-care perspective: it describes who entered the extended-window pathway, how quickly core emergency workflow steps were completed, who ultimately received reperfusion, and why thrombolysis was withheld. The post-review data audit also illustrates an important quality-improvement lesson: variables that cannot be traced reliably to source documentation should not be converted into apparently precise imaging-performance metrics. This is relevant because ischemic stroke continues to impose a major health and economic burden in China and globally [7]-[9].

4.2. From Clock Time to Tissue Viability: Clinical Context and Data-Provenance Limits

Although 4.5 h remains the conventional intravenous-thrombolysis window [1]-[3], advanced imaging can assess tissue viability when true onset is unknown or when patients present beyond the standard window. DWI-FLAIR mismatch, CTP core-perfusion mismatch, and CTA-defined occlusion support individualized selection [10] [11], and WAKE-UP, EXTEND, and pooled individual-patient evidence established benefit from imaging-guided alteplase in appropriately selected patients [4]-[6].

The present retrospective dataset could not support a defensible quantitative analysis of annual advanced-imaging utilization or mismatch because the source-tagged preprocessing extract contained a substantial proportion of reconstructed/imputed imaging fields and did not preserve uniform quantitative CTP thresholds. We therefore removed those variables from final regression and utilization-rate claims rather than treating non-verifiable values as observed data. This limits imaging-specific conclusions but strengthens the validity of the remaining workflow and treatment analyses. Future registries should prospectively store the actual imaging modality, vendor/software version, core volume, hypoperfusion volume and threshold, mismatch ratio, image-reader role, and final treatment decision. Automated mismatch tools may then be evaluated reliably [12]-[15].

4.3. Evolving Evidence for Late-Window Thrombolysis

Recent trials have refined late-window selection. TIMELESS did not show overall superiority of tenecteplase over placebo in perfusion-selected LVO at 4.5 - 24 h, whereas TRACE-III demonstrated more disability-free outcomes with tenecteplase among selected patients unable to undergo thrombectomy, at the cost of more symptomatic intracranial hemorrhage [16] [17]. HOPE likewise found improved functional independence with alteplase in perfusion-selected patients 4.5 - 24 h after onset who were not planned for immediate thrombectomy [18]. Meta-analytic evidence supports possible benefit beyond 4.5 h in imaging-selected patients while underscoring the need to balance benefit and bleeding risk [19].

Thus, the pertinent question is no longer simply whether late-window thrombolysis is possible, but in whom, by which imaging criteria, and in which care setting it is appropriate. The low overall treatment rate in this county-level cohort may reflect appropriate caution as well as workflow constraints. Further expansion should be paired with rigorous image interpretation, standardized benefit-risk communication, and post-treatment safety surveillance.

4.4. Registry-Recorded Time Status and NIHSS as Decision Correlates

Registry-recorded 4.5-h status remained strongly associated with thrombolysis in the Firth model (aOR 18.49). However, because the historical binary field did not preserve a uniform auditable time anchor across wake-up, unknown-onset, and

known beyond-window categories, this association should not be interpreted as the causal effect of guideline-defined last-known-well eligibility. Rather, it is an operational correlate that may capture temporal proximity, pathway categorization, clinician recommendation, and family acceptance.

Baseline NIHSS was also independently associated with treatment (aOR 1.17 per point). Median NIHSS was 8 in treated patients and 3 in untreated patients among those with available scores, suggesting lower treatment propensity in minor stroke. Current guidelines support thrombolysis for mild but disabling deficits but recommend caution for mild non-disabling symptoms [1] [3] [10]. Low NIHSS does not necessarily imply low risk, particularly with aphasia, hemianopia, dominant-hand dysfunction, severe ataxia, or LVO [20] [21]. Quality-control forms should therefore distinguish disabling from non-disabling minor stroke rather than relying on the total score alone.

4.5. Workflow Quality: Rapid CT but Persistent DNT Delays

Median door-to-CT completion was 15 min among 299 patients with valid timestamps and remained stable across years, indicating a generally rapid initial pathway. By contrast, median DNT among 25 treated patients with valid values was 66 min; only 44.0% achieved ≤ 60 min, 8.0% achieved ≤ 45 min, and none achieved ≤ 30 min. Target: Stroke and related studies demonstrate that team activation, emergency medical services prenotification, rapid image interpretation, ready-to-use thrombolytic medication, and continuous feedback shorten DNT and improve outcomes [22]-[26]. Canadian best-practice metrics similarly track thrombolysis, DNT, and endovascular times [27].

For an extended-window pathway, DNT may include additional vascular/tissue imaging, interpretation, parallel thrombectomy discussion, and more complex communication. Future monitoring should therefore decompose delay into door-to-imaging, imaging-to-decision, decision-to-needle, and door-to-puncture intervals, while separately reporting conventional clock-window and tissue-selected treatment. Prospective capture is particularly important because the present historical dataset had incomplete values for several workflow fields.

4.6. Non-Thrombolysis: Three Actionable Domains

Time-window/unknown-onset limitations accounted for 50.3% of non-thrombolysis. This combined category should not be equated entirely with prehospital delay because it also captures uncertainty in onset-time documentation and extended-window eligibility; nevertheless, prehospital delay remains an important population-level barrier [28]. Patient/family refusal or transfer accounted for 16.4%. Refusal may reflect fear of hemorrhage, uncertainty about benefit, limited trust, or preference for transfer [29], and may be amplified when tissue-window concepts must be explained. Standardized visual decision aids could communicate tissue viability, expected benefit, bleeding risk, and the time cost of transfer.

Imaging ineligibility or absence of an indication accounted for 12.3% of non-

thrombolysis decisions in the standardized reason field. This should not automatically be interpreted as poor performance: appropriate exclusion because of established infarction, unfavorable tissue profile, excessive bleeding risk, or thrombectomy-priority anatomy can itself represent correct decision-making. However, because the final analytic dataset did not contain uniformly source-verifiable quantitative imaging parameters, the specific imaging mechanisms underlying these exclusions cannot be analyzed reliably here.

4.7. Tenecteplase in County Stroke Pathways

Evidence supporting tenecteplase has expanded. AcT, ORIGINAL, and ATTEST-2 support noninferiority to alteplase in eligible AIS populations [30]-[32], and the European Stroke Organisation notes potential practical and early-recanalization advantages, particularly before thrombectomy [33]. A single-bolus regimen may simplify preparation and interhospital transfer. Our dataset did not distinguish thrombolytic agents, so future quality registries should record drug, dose, administration time, bridging thrombectomy, hemorrhagic transformation, and 90-day modified Rankin Scale outcomes.

4.8. LVO and Mechanical Thrombectomy as a Parallel Decision

Eleven patients (3.2%) underwent mechanical thrombectomy. Reperfusion pathways for unknown-onset and beyond-window stroke must evaluate thrombolysis and thrombectomy in parallel. Guidelines support thrombectomy for appropriately selected anterior-circulation LVO, including late-window presentations [34] [35], and SELECT2, ANGEL-ASPECT, and RESCUE-Japan LIMIT expanded evidence to selected large-core infarction [36]-[38], with subsequent practice guidance. In the present database, source-verifiable LVO/CTA fields were insufficiently complete for reliable quantitative LVO-rate analysis; future county-center registries should prospectively record CTA findings, occlusion site, transfer destination, puncture time, reperfusion grade, and 90-day outcome.

4.9. A Reproducible Pathway for County-Level Advanced Stroke Centers

County centers may face limitations in overnight MRI/CTP access, interventional staffing, stroke coordination, health literacy, and data completeness; however, stable referral catchments and short communication chains can enable rapid CT and initial decisions. Our 15-min median door-to-CT completion demonstrates this potential.

Improvement should be system based: create an extended-window triage label; use a tiered imaging strategy of noncontrast CT, rapid CTA, and conditional CTP/MRI; establish rapid LVO and transfer protocols; review non-thrombolysis reasons monthly; follow up refusals; prospectively record last-known-well, symptom discovery, arrival, imaging, decision, consent, and treatment timestamps; and monitor segmented workflow intervals. These priorities align with national rec-

ommendations for regional coordination and quality improvement [9].

4.10. Strengths, Limitations, and Future Directions

Strengths include three consecutive years of real-world county-center data, explicit inclusion of wake-up, unknown-onset, and known beyond-window presentations, analysis of both treatment and non-treatment decisions, and detailed emergency workflow timestamps. The revision also applied a source-provenance audit and Firth penalized regression rather than retaining unsupported imaging metrics or sparse-event conventional estimates.

Limitations include the single-center retrospective design, only 27 thrombolysis events, and substantial missingness in two key historical fields: registry-recorded 4.5-h status (76/345 missing) and baseline NIHSS (144/345 missing). Consequently, the Firth multivariable model was a complete-case analysis of 176 patients with 26 events and may still be affected by selection bias. The 4.5-h field lacked a uniform auditable time anchor. Several imaging fields in the preprocessing extract had been reconstructed/imputed rather than uniformly source-verified, so they were excluded from final quantitative imaging and regression analyses. The non-thrombolysis reason variable was rule-standardized from free-text remarks without independent duplicate adjudication. Systematic 90-day modified Rankin Scale, discharge outcomes, 24-h NIHSS improvement, hemorrhagic transformation, symptomatic intracranial hemorrhage, thrombolytic agent, recanalization, and complete transfer thrombectomy data were unavailable.

Future studies should establish a prospective multicenter database with a complete screening log; standardized last-known-well, symptom-discovery, arrival, imaging, decision, consent, and treatment timestamps; explicit CTP software and quantitative thresholds; source-verifiable imaging and LVO fields; structured adjudication of non-treatment reasons; and functional and safety outcomes. Pre-specified sparse-event modeling, including Firth regression, should be incorporated when event counts are limited. Structured late-window decision tools, automated mismatch/LVO alerts, and comparisons of imaging resources and transfer models across county centers remain important directions [14] [15] [18] [19].

5. Conclusion

From 2023 to 2025, intravenous thrombolysis increased descriptively among patients managed in an extended-window county stroke pathway that included wake-up, unknown-onset, and known beyond-window AIS. Thrombolysis was most frequent in wake-up stroke. In Firth penalized regression, registry-recorded 4.5-h status and higher baseline NIHSS remained robust treatment correlates, whereas the calendar-year trend was attenuated. Maintaining rapid CT access while improving standardized onset-time documentation, decision-to-needle workflow, risk communication, and prospective source-verifiable imaging/outcome capture may improve the timeliness and interpretability of reperfusion care.

Ethics Statement

This retrospective study used de-identified clinical quality-control data and was approved by the Ethics Committee of Zhuji People's Hospital (Approval No. [2026] Kelun (0831)). The requirement for informed consent was waived by the Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki, the committee-approved protocol, and applicable institutional requirements for retrospective research.

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Author Contributions

Conceptualization, Y.J.C. and Y.P.H.; methodology, Y.J.C. and F.F.; data curation, Y.J.C., F.F., and Y.C.; formal analysis, Y.J.C.; investigation, all authors; writing-original draft preparation, Y.J.C.; writing-review and editing, all authors; supervision, Y.P.H. All authors have read and agreed to the submitted version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

- [1] Chinese Society of Neurology and Chinese Stroke Society. (2024) Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2023. *Chinese Journal of Neurology*, **57**, 523-559.
- [2] Prabhakaran, S., Gonzalez, N.R., Zachrison, K.S., Adeoye, O., Alexandrov, A.W., Ansari, S.A., *et al.* (2026) 2026 Guideline for the Early Management of Patients with Acute Ischemic Stroke: A Guideline from the American Heart Association/American Stroke Association. *Stroke*, **57**, e316-e436.
<https://doi.org/10.1161/str.0000000000000513>
- [3] Berge, E., Whiteley, W., Audebert, H., De Marchis, G., Fonseca, A.C., Padiglioni, C., *et al.* (2021) European Stroke Organisation (ESO) Guidelines on Intravenous Thrombolysis for Acute Ischaemic Stroke. *European Stroke Journal*, **6**, I-LXII.
<https://doi.org/10.1177/2396987321989865>
- [4] Thomalla, G., Simonsen, C.Z., Boutitie, F., Andersen, G., Berthezene, Y., Cheng, B., *et al.* (2018) MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. *New England Journal of Medicine*, **379**, 611-622.
<https://doi.org/10.1056/nejmoa1804355>

- [5] Ma, H., Campbell, B.C.V., Parsons, M.W., Churilov, L., Levi, C.R., Hsu, C., *et al.* (2019) Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke. *New England Journal of Medicine*, **380**, 1795-1803. <https://doi.org/10.1056/nejmoa1813046>
- [6] Thomalla, G., Boutitie, F., Ma, H., Koga, M., Ringleb, P., Schwamm, L.H., *et al.* (2020) Intravenous Alteplase for Stroke with Unknown Time of Onset Guided by Advanced Imaging: Systematic Review and Meta-Analysis of Individual Patient Data. *The Lancet*, **396**, 1574-1584. [https://doi.org/10.1016/s0140-6736\(20\)32163-2](https://doi.org/10.1016/s0140-6736(20)32163-2)
- [7] Tu, W., Wang, L., Yan, F., Peng, B., Hua, Y., Liu, M., *et al.* (2023) China Stroke Surveillance Report 2021. *Military Medical Research*, **10**, Article No. 33. <https://doi.org/10.1186/s40779-023-00463-x>
- [8] Feigin, V.L., Abate, M.D., Abate, Y.H., Abd ElHafeez, S., Abd-Allah, F., Abdelalim, A., *et al.* (2024) Global, Regional, and National Burden of Stroke and Its Risk Factors, 1990-2021: A Systematic Analysis for the Global Burden of Disease Study 2021. *The Lancet Neurology*, **23**, 973-1003. [https://doi.org/10.1016/s1474-4422\(24\)00369-7](https://doi.org/10.1016/s1474-4422(24)00369-7)
- [9] National Program for Stroke Prevention and Million Disability Reduction Initiative Expert Committee (2025) China Stroke Prevention and Control Report 2024: An Executive Summary. *Brain Circulation*, **11**, 251-260. https://doi.org/10.4103/bc.bc_198_25
- [10] Liu, L., Li, Z., Zhou, H., Duan, W., Huo, X., Xu, W., *et al.* (2023) Chinese Stroke Association Guidelines for Clinical Management of Ischaemic Cerebrovascular Diseases: Executive Summary and 2023 Update. *Stroke and Vascular Neurology*, **8**, e3-e3. <https://doi.org/10.1136/svn-2023-002998>
- [11] Xiong, Y., Li, S., Wang, C., Sun, D., Li, Z., Gu, H., *et al.* (2025) Chinese Stroke Association Guidelines on Reperfusion Therapy for Acute Ischaemic Stroke 2024. *Stroke and Vascular Neurology*, **10**, 527-541. <https://doi.org/10.1136/svn-2024-003977>
- [12] Ahmed, H.K., Mathisen, S.M., Kurz, K., Dalen, I., Logallo, N., Thomassen, L., *et al.* (2024) Thrombolysis in Wake-Up Stroke Based on MRI Mismatch. *Journal of the Neurological Sciences*, **466**, Article ID: 123265. <https://doi.org/10.1016/j.jns.2024.123265>
- [13] Zhang, J., Ta, N., Fu, M., Tian, F.H., Wang, J., Zhang, T., *et al.* (2022) Use of DWI-FLAIR Mismatch to Estimate the Onset Time in Wake-Up Strokes. *Neuropsychiatric Disease and Treatment*, **18**, 355-361. <https://doi.org/10.2147/ndt.s351943>
- [14] Tavakkol, E., Kihira, S., McArthur, M., Polson, J., Zhang, H., Arnold, C.W., *et al.* (2024) Automated Assessment of the DWI-FLAIR Mismatch in Patients with Acute Ischemic Stroke: Added Value to Routine Clinical Practice. *American Journal of Neuroradiology*, **45**, 562-567. <https://doi.org/10.3174/ajnr.a8170>
- [15] Namgung, E., Kim, Y.S., Lee, E., Chang, D., Cho, H.J., Lee, J., *et al.* (2025) Deep Learning to Identify Stroke within 4.5 H Using DWI and FLAIR in a Prospective Multicenter Study. *Scientific Reports*, **15**, Article No. 26262. <https://doi.org/10.1038/s41598-025-10804-6>
- [16] Albers, G.W., Jumaa, M., Purdon, B., Zaidi, S.F., Streib, C., Shuaib, A., *et al.* (2024) Tenecteplase for Stroke at 4.5 to 24 Hours with Perfusion-Imaging Selection. *New England Journal of Medicine*, **390**, 701-711. <https://doi.org/10.1056/nejmoa2310392>
- [17] Xiong, Y., Campbell, B.C.V., Schwamm, L.H., Meng, X., Jin, A., Parsons, M.W., *et al.* (2024) Tenecteplase for Ischemic Stroke at 4.5 to 24 Hours without Thrombectomy. *New England Journal of Medicine*, **391**, 203-212. <https://doi.org/10.1056/nejmoa2402980>

- [18] Zhou, Y., He, Y., Campbell, B.C.V., Liebeskind, D.S., Yuan, C., Chen, H., *et al.* (2025) Alteplase for Acute Ischemic Stroke at 4.5 to 24 Hours: The HOPE Randomized Clinical Trial. *JAMA*, **334**, 788-797. <https://doi.org/10.1001/jama.2025.12063>
- [19] Günkân, A., Ferreira, M.Y., Vilardo, M., Scarcia, L., Bocanegra-Becerra, J.E., Cardoso, L.J.C., *et al.* (2025) Thrombolysis for Ischemic Stroke beyond the 4.5-Hour Window: A Meta-Analysis of Randomized Clinical Trials. *Stroke*, **56**, 580-590. <https://doi.org/10.1161/strokeaha.124.048536>
- [20] Slawski, D. and Heit, J.J. (2021) Treatment Challenges in Acute Minor Ischemic Stroke. *Frontiers in Neurology*, **12**, Article 723637. <https://doi.org/10.3389/fneur.2021.723637>
- [21] Chen, T., Zhi, W., Hao, N., Li, Z., Cao, X., Chen, Q., *et al.* (2025) Low NIHSS Score in Large Vessel Occlusion Stroke: Optimal Treatment and Clinical Controversies. *Frontiers in Neurology*, **16**, Article 1681311. <https://doi.org/10.3389/fneur.2025.1681311>
- [22] American Heart Association/American Stroke Association (2026) Target: Stroke Phase III. <https://www.heart.org/en/professional/quality-improvement/target-stroke/introducing-target-stroke-phase-iii>
- [23] Fonarow, G.C., Smith, E.E., Saver, J.L., Reeves, M.J., Hernandez, A.F., Peterson, E.D., *et al.* (2011) Improving Door-to-Needle Times in Acute Ischemic Stroke. *Stroke*, **42**, 2983-2989. <https://doi.org/10.1161/strokeaha.111.621342>
- [24] Xian, Y., Xu, H., Smith, E.E., Saver, J.L., Reeves, M.J., Bhatt, D.L., *et al.* (2022) Achieving More Rapid Door-to-Needle Times and Improved Outcomes in Acute Ischemic Stroke in a Nationwide Quality Improvement Intervention. *Stroke*, **53**, 1328-1338. <https://doi.org/10.1161/strokeaha.121.035853>
- [25] Man, S., Solomon, N., Mac Grory, B., Alhanti, B., Uchino, K., Saver, J.L., *et al.* (2023) Shorter Door-to-Needle Times Are Associated with Better Outcomes after Intravenous Thrombolytic Therapy and Endovascular Thrombectomy for Acute Ischemic Stroke. *Circulation*, **148**, 20-34. <https://doi.org/10.1161/circulationaha.123.064053>
- [26] Wang, J.D.J., Dong, Y., Yeo, J.Y.P., Teo, K.S.H., Ng, S., Jing, M., *et al.* (2025) Improved Functional Outcomes and Cost Benefits of Door-to-Needle Time under 30 Min in Acute Ischemic Stroke: An Observational Study. *Frontiers in Stroke*, **4**, Article 1583875. <https://doi.org/10.3389/fstro.2025.1583875>
- [27] Heart and Stroke Foundation of Canada (2025) Canadian Stroke Best Practice Recommendations: Acute Stroke Management-Acute Ischemic Stroke Treatment. <https://www.strokebestpractices.ca/recommendations/acute-stroke-management/acute-ischemic-stroke-treatment>
- [28] Su, Y., Qi, W., Yu, Y., Zhu, J., Shi, X., Wu, X., *et al.* (2025) Analysis of Prehospital Delay in Acute Ischaemic Stroke and Its Influencing Factors: A Multicentre Prospective Case Registry Study in China. *Stroke and Vascular Neurology*, **10**, 637-647. <https://doi.org/10.1136/svn-2024-003535>
- [29] von Kleist, T., Meyer, D., Rapp, K., Meyer, B.C. and Modir, R. (2020) Characteristics and Outcomes of Patients Who Refuse Intravenous Thrombolysis for Acute Ischemic Stroke—The San Diego Experience. *Journal of Stroke and Cerebrovascular Diseases*, **29**, Article ID: 105137. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105137>
- [30] Menon, B.K., Buck, B.H., Singh, N., Deschaintre, Y., Almekhlafi, M.A., Coutts, S.B., *et al.* (2022) Intravenous Tenecteplase Compared with Alteplase for Acute Ischaemic Stroke in Canada (Act): A Pragmatic, Multicentre, Open-Label, Registry-Linked, Randomised, Controlled, Non-Inferiority Trial. *The Lancet*, **400**, 161-169.

- [https://doi.org/10.1016/s0140-6736\(22\)01054-6](https://doi.org/10.1016/s0140-6736(22)01054-6)
- [31] Meng, X., Li, S., Dai, H., Lu, G., Wang, W., Che, F., *et al.* (2024) Tenecteplase vs Alteplase for Patients with Acute Ischemic Stroke: The ORIGINAL Randomized Clinical Trial. *JAMA*, **332**, 1437-1445. <https://doi.org/10.1001/jama.2024.14721>
 - [32] Muir, K.W., Ford, G.A., Ford, I., Wardlaw, J.M., McConnachie, A., Greenlaw, N., *et al.* (2024) Tenecteplase versus Alteplase for Acute Stroke within 4.5 H of Onset (AT-TEST-2): A Randomised, Parallel Group, Open-Label Trial. *The Lancet Neurology*, **23**, 1087-1096. [https://doi.org/10.1016/s1474-4422\(24\)00377-6](https://doi.org/10.1016/s1474-4422(24)00377-6)
 - [33] Alamowitch, S., Turc, G., Palaodimou, L., Bivard, A., Cameron, A., De Marchis, G.M., *et al.* (2023) European Stroke Organisation (ESO) Expedited Recommendation on Tenecteplase for Acute Ischaemic Stroke. *European Stroke Journal*, **8**, 8-54. <https://doi.org/10.1177/23969873221150022>
 - [34] Turc, G., Bhogal, P., Fischer, U., Khatri, P., Lobotesis, K., Mazighi, M., *et al.* (2019) European Stroke Organisation (ESO)—European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischaemic Stroke endorsed by Stroke Alliance for Europe (Safe). *European Stroke Journal*, **4**, 6-12. <https://doi.org/10.1177/2396987319832140>
 - [35] Nguyen, T.N., Castonguay, A.C., Siegler, J.E., Nagel, S., Lansberg, M.G., de Havenon, A., *et al.* (2023) Mechanical Thrombectomy in the Late Presentation of Anterior Circulation Large Vessel Occlusion Stroke: A Guideline from the Society of Vascular and Interventional Neurology Guidelines and Practice Standards Committee. *Stroke: Vascular and Interventional Neurology*, **3**, e000512. <https://doi.org/10.1161/svin.122.000512>
 - [36] Sarraj, A., Hassan, A.E., Abraham, M.G., Ortega-Gutierrez, S., Kasner, S.E., Hussain, M.S., *et al.* (2023) Trial of Endovascular Thrombectomy for Large Ischemic Strokes. *New England Journal of Medicine*, **388**, 1259-1271. <https://doi.org/10.1056/nejmoa2214403>
 - [37] Huo, X., Ma, G., Tong, X., Zhang, X., Pan, Y., Nguyen, T.N., *et al.* (2023) Trial of Endovascular Therapy for Acute Ischemic Stroke with Large Infarct. *New England Journal of Medicine*, **388**, 1272-1283. <https://doi.org/10.1056/nejmoa2213379>
 - [38] Yoshimura, S., Sakai, N., Yamagami, H., Uchida, K., Beppu, M., Toyoda, K., *et al.* (2022) Endovascular Therapy for Acute Stroke with a Large Ischemic Region. *New England Journal of Medicine*, **386**, 1303-1313. <https://doi.org/10.1056/nejmoa2118191>