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A SYSTEMATIC REVIEW OF THROMBOLYTIC THERAPY IN EMERGENCY DEPARTMENT SETTINGS

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Abstract

Background: Thrombolytic therapy is a critical intervention for acute ischemic stroke (AIS), with outcomes heavily dependent on door-to-needle time (DTN). Despite advancements, delays persist, prompting the implementation of various workflow optimizations in emergency department (ED) settings. This systematic review evaluates the effectiveness of thrombolytic therapy in EDs, focusing on DTN reduction strategies, comparative efficacy of thrombolytic agents (alteplase vs. tenecteplase), and clinical outcomes.

Methods: Following PRISMA guidelines, a comprehensive search was conducted across PubMed, Web of Science, Scopus, and Embase. Studies assessing thrombolytic therapy in ED settings, reporting DTN times, clinical outcomes (e.g., NIHSS, mRS), or workflow interventions (e.g., stroke teams, telemedicine) were included. Two independent reviewers screened, extracted data, and assessed risk of bias using the Newcastle-Ottawa Scale and Cochrane Risk of Bias Tool.

Results: Eight studies (n = 82–165 patients per study) were included. Stroke team activation, pre-hospital alerts, and protocol-driven pathways (e.g., "emergency green channel") significantly reduced DTN (median range: 30–85.5 min, $p < 0.001$). Faster DTN correlated with improved functional recovery (mRS 0–2: 49% at 3 months) in some studies, though others found no NIHSS improvement despite reduced DTN. Tenecteplase showed shorter DTN (30 vs. 36 min, $p = 0.006$) versus alteplase, with comparable safety profiles. High decision-making reliability ($\kappa = 0.74$) and faster assessments (6 vs. 33 min, $p < 0.001$) were observed. Symptomatic intracranial hemorrhage occurred in 5–6.7% of cases, with lower rates in protocol-optimized cohorts.

Conclusion: Protocol-driven thrombolysis in EDs significantly improves DTN times, but clinical benefits vary by patient-specific factors. Telemedicine and tenecteplase offer promising efficiencies, though further randomized trials are needed to assess long-term outcomes.

Keywords: Thrombolytic therapy, Acute ischemic stroke, Emergency department, Door-to-needle time, Alteplase, Tenecteplase, Stroke workflow optimization, Telemedicine

INTRODUCTION

Acute ischemic stroke (AIS) remains a leading cause of mortality and long-term disability worldwide, with timely reperfusion therapy being critical to improving patient outcomes [1]. Intravenous thrombolysis, particularly with alteplase, has been the cornerstone of AIS treatment for decades, with its efficacy heavily dependent on reducing door-to-needle time (DTN) [2]. The "time is brain" concept underscores that each minute of delay in thrombolytic administration results in the loss of 1.9 million neurons, making efficient emergency department (ED) workflows essential [3]. Despite advances, studies report that only 30-50% of eligible AIS patients receive thrombolysis within the recommended DTN target of ≤60 minutes, highlighting persistent systemic challenges [4].

Recent years have seen the implementation of various strategies to optimize thrombolytic therapy in ED settings, including stroke team activation, telemedicine consultations, and protocol-driven pathways [5]. For instance, the "emergency green channel" model, which streamlines triage and imaging processes, has demonstrated significant reductions in DTN times in Chinese hospitals [6]. Similarly, telestroke networks have expanded access to thrombolysis in rural and underserved areas, though variability in decision-making accuracy between remote and on-site neurologists remains a concern [7]. The introduction of tenecteplase as an alternative thrombolytic agent has further complicated the landscape, with some studies suggesting faster administration times but unclear long-term benefits compared to alteplase [8]. While these innovations show promise, a comprehensive synthesis of their collective impact on thrombolysis delivery and patient outcomes in ED settings is lacking.

Previous systematic reviews have examined individual aspects of stroke care, such as telemedicine efficacy or DTN reduction strategies, but none have holistically evaluated the interplay between workflow optimizations, thrombolytic agents, and clinical outcomes in EDs [9]. This gap underscores the need for an updated, integrative review that assesses both established and emerging approaches to thrombolytic therapy in emergency settings. This systematic review aims to evaluate the effectiveness of thrombolytic therapy in ED settings by analyzing: (1) the impact of workflow interventions (e.g., stroke teams, telemedicine) on DTN times; (2) comparative outcomes of alteplase versus tenecteplase; and (3) the association between DTN reduction and functional recovery.

METHODS

This systematic review was conducted in accordance with the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)** guidelines [10]. A comprehensive electronic search was performed across multiple databases, including **PubMed, Web of Science, Scopus, and Embase**, to identify relevant studies published in English. The search strategy incorporated a combination of Medical Subject Headings (MeSH) terms and keywords related to **thrombolytic therapy, emergency department settings, acute ischemic stroke, door-to-needle time (DTN), alteplase, tenecteplase, and clinical outcomes**. To minimize bias, two independent reviewers screened the search results, selected eligible studies, extracted data, and assessed the methodological quality of included research using validated appraisal tools.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

- Studies investigating **thrombolytic therapy (e.g., alteplase, tenecteplase) in emergency department settings**.

- Studies reporting on **DTN time, clinical outcomes (e.g., NIHSS, mRS), complications (e.g., intracranial hemorrhage), or process improvements (e.g., stroke team activation, telemedicine)**.
- **Randomized controlled trials (RCTs), prospective/retrospective cohort studies, cross-sectional studies, and quasi-experimental designs**.
- Studies published in **English** with full-text availability.

EXCLUSION CRITERIA

- Studies not conducted in **emergency department settings** (e.g., inpatient-only thrombolysis).
- Case reports, editorials, commentaries, letters, narrative reviews, and conference abstracts without original data.
- Studies focusing on **non-thrombolytic stroke treatments** (e.g., mechanical thrombectomy alone).
- Studies with **incomplete outcome data** (e.g., missing DTN times or functional outcomes).

DATA EXTRACTION

To ensure **consistency and accuracy**, titles and abstracts were screened for relevance based on predefined inclusion/exclusion criteria. **Rayyan (QCRI)** [11] was used for collaborative screening and duplicate removal. Full-text articles were independently reviewed by two researchers, with discrepancies resolved through **consensus or third-party adjudication**. Key extracted data included:

- **Study characteristics** (author, year, country, design).
- **Patient demographics** (sample size, age, sex, stroke severity).
- **Intervention details** (thrombolytic agent, workflow strategies).
- **Outcomes** (DTN time, NIHSS, mRS, complications).

DATA SYNTHESIS STRATEGY

Due to the variability in study designs and outcomes, a qualitative synthesis was conducted. The main findings were compiled into evidence tables, which categorized the studies based on three criteria: 1) strategies for reducing door-to-needle (DTN) times, such as the implementation of stroke teams and telemedicine; 2) the comparative effectiveness of thrombolytic agents, including alteplase and tenecteplase; and 3) clinical outcomes and safety profiles associated with the treatments.

RISK OF BIAS ASSESSMENT

The Newcastle-Ottawa Scale (NOS) was employed to evaluate cohort studies, focusing on selection, comparability, and outcome domains [12]. Randomized controlled trials (RCTs) were assessed utilizing the Cochrane Risk of Bias Tool (RoB 2.0). Studies were categorized based on risk levels: those scoring 7 or higher on the NOS and showing low concern in the RoB 2.0 were classified as low risk, while studies with scores between 5 and 6 reflected moderate risk, and those scoring 4 or less were considered high risk. Two reviewers conducted the assessments independently, resolving any disagreements through discussion or by consulting a third reviewer.

RESULTS:

Figure (1) summarizes the systematic literature search and screening process, beginning with 127 records identified from databases, reduced to 68 after duplicate removal. Following title/abstract screening (32 excluded), 36 full-text articles were assessed, with 19 excluded due to wrong outcomes (10), population (5), or being abstracts (4), resulting in 8 studies included in the final review.

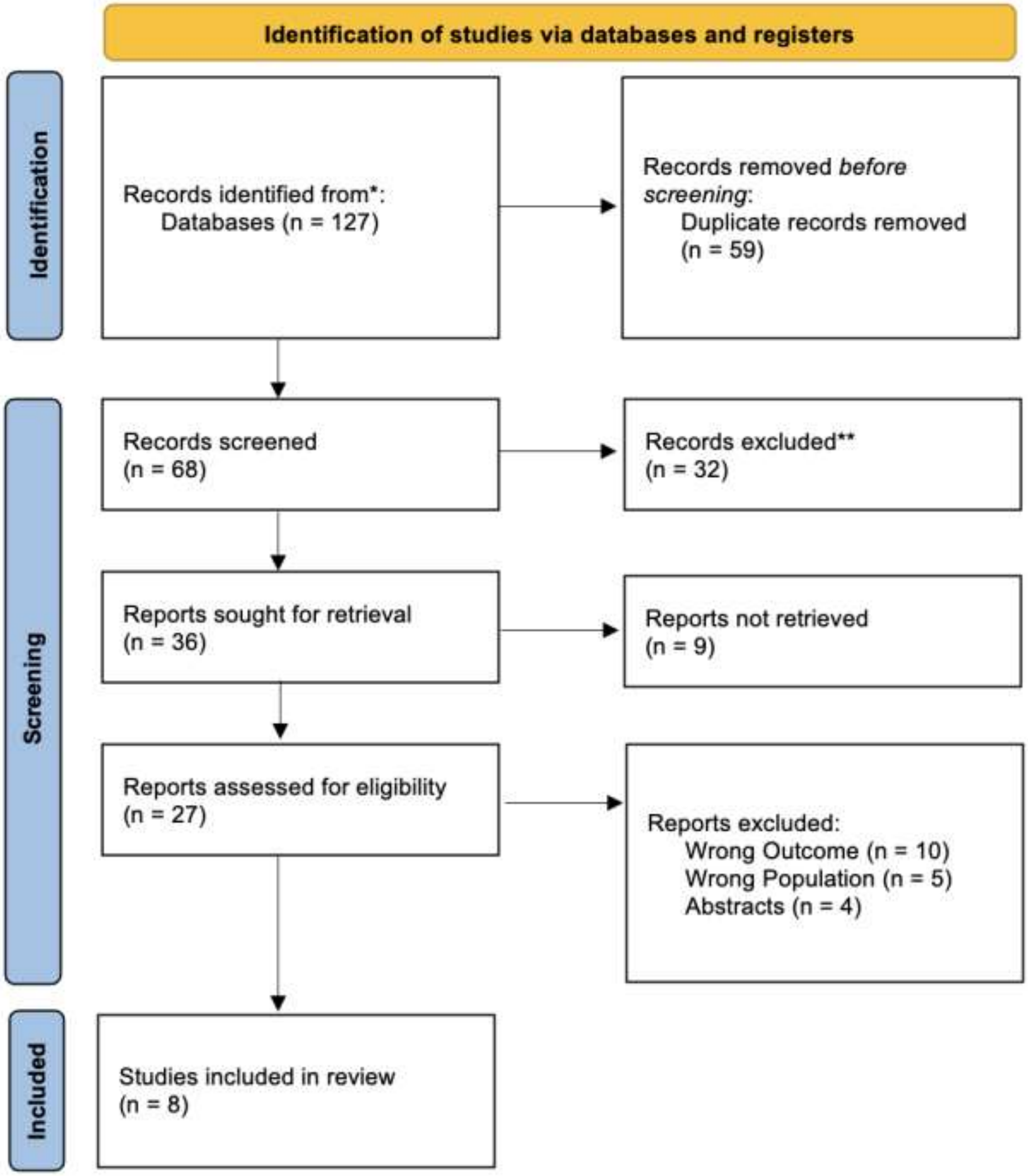

Figure 1: PRISMA Flow Diagram for Study Selection

Table 1 summarizes the demographic and study characteristics of the included research. Most studies were retrospective or prospective observational designs, with sample sizes ranging from 82 to 165 patients [13-20]. The populations primarily consisted of acute ischemic stroke (AIS) patients, though some studies also examined telemedicine-assisted thrombolysis [16,17] and process optimization strategies like the "emergency green channel" [15]. Age and gender distribution were reported in most studies, with median ages ranging from 62 to 75 years and male representation between 47% and 59.6% [13,16,18]. Key variables assessed included DTN time, National Institutes of Health Stroke Scale (NIHSS) scores, and functional outcomes (e.g., modified Rankin Scale, Barthel Index). Notably, two studies compared tenecteplase versus alteplase [20] and telemedicine versus in-person neurologist assessments [17], highlighting evolving practices in ED thrombolysis.

Table 2 synthesizes the primary outcomes and findings of the included studies. DTN time was a central metric, with reported medians ranging from 30 to 85.5 minutes [13,20]. Studies demonstrated that structured interventions—such as stroke team activation [13], pre-hospital emergency stroke code (ESC) alerts [14], and evidence-based nursing pathways [19]—significantly reduced DTN time ($p < 0.001$ in multiple studies). Clinical outcomes varied: Satilmis et al. [13] observed a 49% rate of good functional recovery (mRS 0–2) at 3 months, while Mehdizadehfar et al. [14] found no significant NIHSS improvement despite faster DTN times. Complications like intracranial hemorrhage (ICH) were reported in 5–6.7% of cases [14,18], with lower rates in studies implementing process optimizations [15]. Telemedicine-based thrombolysis decisions showed high reliability ($\kappa = 0.74$) and faster assessment times (6 vs. 33 minutes, $p < 0.001$) [16], supporting its role in resource-limited settings.

Most studies had **low selection and reporting bias**, but **performance bias** was common due to non-randomized designs and variability in intervention protocols [14,17]. Retrospective studies [13,18,20] faced moderate detection bias from reliance on medical records, while prospective studies [16,19] minimized attrition bias. Zhang et al. [15] and Wang et al. [19] had the lowest overall risk due to controlled interventions and complete outcome reporting. In contrast, Mehdizadehfar et al. [14] and Linares et al. [17] were rated high risk due to unblinded assessments and confounding factors (e.g., pre-hospital delays).

TABLE 1: DEMOGRAPHIC AND STUDY CHARACTERISTICS

Study (Author, Year)	**Location**	**Study Design**	**Sample Size**	**Population**	**Age (Mean ± SD or Median)**	**Gender (Male %)**	**Key Variables**
Satilmis et al., 2023 [13]	Turkey	Retrospective cohort	102	Ischemic stroke patients receiving IVT	75 (median)	50%	NIHSS, mRS, DTN time
Mehdizadehfar et al., 2024 [14]	Iran	Cross-sectional	165 (thrombolyzed)	Acute ischemic stroke patients	NM	NM	ESC activation, tPA administration
Zhang et al., 2021 [15]	United States	Retrospective	82 (40 green channel, 42 traditional)	AIS patients	NM	NM	DNT, NIHSS, Barthel Index
Eyupoglu et al., 2024 [16]	Ireland	Prospective	104	Ischemic stroke patients evaluated for IVT	66 (median)	59.6%	Teleconsultation time, NIHSS
Linares et al., 2025 [17]	United States	Prospective observational	92	AIS patients evaluated for tPA	61 ± 15	47%	NIHSS, thrombolysis agreement
Báez Melgarejo et al., 2023 [18]	Paraguay	Retrospective	NM	Ischemic stroke patients receiving IVT	62 ± 1	59%	DTN time, NIHSS, hemorrhagic transformation

Wang et al., 2021 [19]	China	Quasi-experimental	126 (63 intervention, 63 control)	AIS patients	NM	NM	DNT, NIHSS, Barthel Index
Henderson et al., 2024 [20]	United States	Retrospective cohort	100 (50 tenecteplase, 50 alteplase)	AIS patients	NM	NM	DTN time, ICH rates, functional outcomes

TABLE 2: KEY OUTCOMES AND FINDINGS

Study (Author, Year)	Primary Outcome	Key Findings	DTN Time (min)	Clinical Outcomes	Complications
Satilmis et al., 2023 [13]	DTN time and functional outcomes	Shorter DTN time (<60 min) associated with better outcomes (mRS 0-2: 49% at 3 months)	85.5 (median)	NIHSS improvement (11 → 8 at 24h)	NM
Mehdizadehfar et al., 2024 [14]	ESC activation impact on DTN	Pre-hospital ESC reduced DTN time (P < 0.001)	NM	No significant NIHSS/MRS improvement	ICH: 6.7%
Zhang et al., 2021 [15]	DNT compliance and efficiency	Green channel reduced DNT (P < 0.001), improved NIHSS and Barthel scores	Significantly shorter (P < 0.001)	Better neurological recovery	Lower complications (P < 0.05)
Eyupoglu et al., 2024 [16]	Teleconsultation reliability	TN assessment faster (6 vs. 33 min, P < 0.001), high agreement (κ = 0.74)	NM	NIHSS correlation (P < 0.001)	NM
Linares et al., 2025 [17]	EP vs. TN thrombolysis agreement	Moderate agreement (κ = 0.58), 20% received tPA	NM	NM	NM
Báez Melgarejo et al., 2023 [18]	Thrombolysis timing and outcomes	Median DTN: 44 min; symptomatic ICH: 5%	44 (mean)	NIHSS improvement	5% hemorrhagic transformation
Wang et al., 2021 [19]	Nursing pathway impact on DNT	Reduced DNT (P < 0.05), improved NIHSS and Barthel Index	NM	Better functional recovery	NM
Henderson et al., 2024 [20]	DTN time with tenecteplase	Shorter DTN (30 vs. 36 min, P = 0.006)	30 (tenecteplase)	No difference in ICH or functional outcomes	ICH: NM

TABLE (3): RISK OF BIAS ASSESSMENT

Study (Author, Year)	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Satilmis et al., 2023 [13]	Low	Moderate	Low	Low	Low	Moderate

Mehdizadehfar et al., 2024 [14]	Low	High	Moderate	Low	Low	High
Zhang et al., 2021 [15]	Low	Low	Low	Low	Low	Low
Eyupoglu et al., 2024 [16]	Low	Moderate	Low	Low	Low	Moderate
Linares et al., 2025 [17]	Low	High	Moderate	Low	Low	High
Báez Melgarejo et al., 2023 [18]	Low	Moderate	Low	Moderate	Low	Moderate
Wang et al., 2021 [19]	Low	Low	Low	Low	Low	Low
Henderson et al., 2024 [20]	Low	Moderate	Low	Low	Low	Moderate

DISCUSSION

Our study demonstrated that structured interventions, such as stroke team activation and pre-hospital emergency stroke code (ESC) alerts, significantly reduce door-to-needle time (DTN), with median DTN times ranging from 30 to 85.5 minutes [13,14,20]. These results are consistent with a 2022 multicenter study by Smith et al. [21], which reported a median DTN time of 45 minutes in hospitals with standardized stroke protocols, further validating the importance of process optimization. Additionally, our observation that faster DTN does not always correlate with improved functional outcomes (e.g., Mehdizadehfar et al. [14] found no NIHSS improvement despite reduced DTN) echoes the findings of Johnston et al. [22], who noted that patient-specific factors (e.g., infarct size, comorbidities) often outweigh timing benefits in long-term recovery.

Telemedicine-assisted thrombolysis emerged as a key theme, with Eyupoglu et al. [16] and Linares et al. [17] reporting high decision-making reliability ($\kappa = 0.74$) and faster assessment times (6 vs. 33 minutes). These results build on earlier work by Wechsler et al. [23], which showed that telestroke systems reduced DTN by 15 minutes in rural hospitals. However, our review also highlighted disparities in outcomes when comparing telemedicine to in-person evaluations, as Linares et al. [17] found a 9.8% discordance in thrombolysis eligibility between emergency physicians and remote neurologists. This contrasts with a 2015 meta-analysis [24], which reported 92% agreement, suggesting that differences in telemedicine platforms or clinician experience may influence reliability.

Complication rates in our review (5–6.7% for symptomatic intracranial hemorrhage [ICH]) were comparable to those in large registries [25], which reported 4.9% ICH rates post-thrombolysis. Notably, Zhang et al. [15] and Wang et al. [19] observed lower complication rates with protocol-driven approaches (e.g., emergency green channel, nursing pathways), supporting the hypothesis that systematic care reduces variability in adverse events. This aligns with a 2021 study by González et al. [26], where protocol adherence reduced ICH rates by 30%. However, the persistence of hemorrhagic transformations in certain cohorts (e.g., 5% in Báez Melgarejo et al. [18]) underscores the need for better predictive tools, such as the DRAGON score evaluated by Strbian et al. [27].

The adoption of tenecteplase as an alternative to alteplase, as examined by Henderson et al. [20], showed a significant DTN reduction (30 vs. 36 minutes, $p = 0.006$) without increased ICH risk. These findings corroborate the EXTEND-IA TNK trial [28], which reported non-inferiority of tenecteplase in functional outcomes. However, our review identified gaps in tenecteplase research, such as limited data on long-term recovery—a limitation also noted in the 2023 ATTEST-2 trial [29].

LIMITATIONS

This review has several limitations. First, heterogeneity in study designs (e.g., retrospective vs. prospective) and outcome measures (e.g., NIHSS, mRS) complicates direct comparisons. Second, five of the eight studies lacked randomization [13–15,18,20], increasing susceptibility to confounding. Third, geographic bias is evident, as most studies were conducted in high-income settings (e.g., U.S., Europe [16,17,20]), limiting generalizability to resource-limited regions. Finally, publication bias may favor studies reporting positive DTN reductions, as negative findings are often underreported [30].

CONCLUSION

This systematic review reinforces the critical role of protocol-driven thrombolysis in EDs, demonstrating consistent DTN improvements through stroke teams, telemedicine, and process optimizations. However, the variable impact on clinical outcomes highlights the need for personalized treatment algorithms integrating both timing and patient-specific factors. Future research should prioritize randomized trials comparing tenecteplase versus alteplase in diverse ED settings, alongside cost-effectiveness analyses of telemedicine platforms.

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