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Impact of Door-to-Needle Time on Outcomes in Acute Ischemic Stroke Treated with Intravenous Thrombolysis at Thrombectomy-Capable Centers: A Systematic Review

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Abstract

Introduction: *Acute ischemic stroke (AIS) is a leading cause of disability and mortality worldwide, with intravenous thrombolysis (IVT) serving as the cornerstone of reperfusion therapy. Door-to-needle time (DTN) represents a key modifiable determinant of IVT effectiveness, yet its clinical impact in thrombectomy-capable settings remains incompletely defined* ***Objective:*** *To evaluate the association between DTN and clinical outcomes in AIS patients undergoing IVT in thrombectomy-capable centers.* ***Methods:*** *A systematic review was conducted following PRISMA 2020 guidelines, with searches performed across PubMed, Cochrane Library, and ScienceDirect. Adult AIS patients treated with IVT, with or without thrombectomy, were included. Outcomes of interest were functional independence, mortality, and symptomatic intracerebral hemorrhage* ***Results and Discussion:*** *Four studies were included. Shorter DTN, particularly under 60 minutes, was consistently associated with reduced mortality and superior neurological recovery in a dose-dependent manner. No significant association was identified between shorter DTN and increased hemorrhagic risk. The findings support the time-dependent effectiveness of intravenous thrombolysis, even in the era of endovascular thrombectomy. Early thrombolysis may enhance reperfusion and improve downstream outcomes. Despite heterogeneity across studies, the overall direction of evidence was consistent.* ***Conclusion:*** *Reducing door-to-needle time remains a critical priority in acute stroke management, including in thrombectomy-capable centers, and should be emphasized in workflow optimization strategies.*

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Introduction

Acute ischemic stroke (AIS) remains a major contributor to global morbidity and mortality, with ischemic stroke accounting for approximately 80–85% of all cases (Putri et al., 2024); (Agustiawan et al., 2024). Beyond its immediate neurological impact, AIS imposes long-term functional limitations that significantly affect quality of life, caregiver burden, and healthcare resource utilization, making optimization of acute management strategies a critical priority.

The pathophysiological cascade of AIS is initiated by abrupt occlusion of a cerebral artery, resulting in the formation of an irreversibly damaged infarct core surrounded by an ischemic penumbra—a region of hypoperfused yet potentially salvageable tissue. The fate of this penumbra is highly time-sensitive, as ongoing ischemia leads to progressive neuronal death and expansion of the infarcted area (Campbell et al., 2019; Ermine et al., 2021). The well-established concept that "time is brain" reflects this quantifiable relationship between treatment delay and neuronal loss, making reduction of treatment latency a central focus in modern stroke care (Ragoschke-Schumm et al., 2014)

Intravenous thrombolysis (IVT) with alteplase remains the first-line reperfusion therapy for eligible patients, with large-scale meta-analyses consistently demonstrating that earlier administration is associated with significantly higher likelihood of functional independence (Abdullah et al., 2024). International guidelines advocate for a door-to-needle time (DTN) of 60 minutes or less, with many centers now targeting 30–45 minutes as part of quality improvement initiatives (Powers et al., 2019). The emergence of endovascular thrombectomy (EVT) has further transformed AIS management, particularly for large vessel occlusion (LVO), with combined IVT and EVT—bridging therapy—now representing contemporary standard of care (Retnaningsih et al., 2025). In this context, early thrombolysis may facilitate partial clot dissolution, enhance microvascular perfusion, and improve technical success of subsequent thrombectomy, suggesting that DTN remains clinically relevant even in thrombectomy-capable centers (Sarraj et al., 2024).

Recent studies have explored the relationship between DTN and clinical outcomes in patients undergoing both IVT and EVT, with several reports indicating that shorter DTN is associated with improved functional outcomes and reduced mortality (Man et al., 2023; Sallustio et al., 2025). However, the existing literature is characterized by substantial heterogeneity in study design, DTN thresholds, and outcome definitions, limiting the ability to derive unified conclusions. Most available evidence is also derived from observational cohorts susceptible to confounding by indication and selection bias, necessitating a structured synthesis of the available data.

Therefore, this systematic review aims to evaluate the association between door-to-needle time and key clinical outcomes—including functional independence, mortality, and hemorrhagic complications—in patients with AIS undergoing intravenous thrombolysis in thrombectomy-capable centers, to clarify the role of DTN as a modifiable determinant of outcome and inform ongoing efforts to optimize acute stroke care pathways.

Methods

Study Design and Reporting Guideline

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The objective of this study was to evaluate the association between door-to-needle time (DTN) and clinical outcomes in patients with acute ischemic stroke undergoing intravenous thrombolysis in thrombectomy-capable centers.

Search Strategy and Data Sources

A comprehensive literature search was performed using three electronic databases, including PubMed, the Cochrane Library, and ScienceDirect. The search strategy was designed to specifically identify studies evaluating the impact of DTN in the context of intravenous thrombolysis with or without endovascular thrombectomy. The search strategy for PubMed was as follows: ("door-to-needle" OR DTN) AND (thrombolysis OR alteplase OR "intravenous thrombolysis") AND (thrombectomy OR "endovascular therapy" OR "large vessel occlusion") AND ("functional outcome" OR mortality OR "modified Rankin Scale" OR mRS OR hemorrhage) AND (stroke).

The search strategy for the Cochrane Library was as follows: ("door-to-needle" OR DTN) AND (intravenous thrombolysis OR alteplase) AND (thrombectomy OR endovascular therapy OR large vessel occlusion) AND (functional outcome OR mortality OR mRS OR hemorrhage) AND (stroke). The search strategy for ScienceDirect was as follows: (stroke) AND ("door-to-needle" OR DTN) AND (alteplase OR thrombolysis) AND (thrombectomy OR "large vessel occlusion") AND (outcome OR mortality). The search was conducted without restriction on publication year, and only studies published in English were included.

Eligibility Criteria

Studies were included if they met the following criteria: adult patients with acute ischemic stroke, particularly those with large vessel occlusion or managed in thrombectomy-capable centers; administration of intravenous thrombolysis with reported door-to-needle time; comparison between shorter and longer DTN or evaluation of DTN as a continuous variable; and reporting of at least one relevant clinical outcome, including functional independence (commonly defined as modified Rankin Scale score ≤ 2), mortality, or hemorrhagic outcomes such as symptomatic intracerebral hemorrhage. Both randomized controlled trials and observational studies were considered eligible. Studies were excluded if they were review articles, meta-analyses, case reports, conference abstracts without full-text availability, non-human studies, or studies that did not provide extractable data related to DTN and clinical outcomes.

Study Selection

All identified records were screened based on titles and abstracts, followed by full-text assessment of potentially eligible studies. Duplicate records were removed manually prior to screening. The selection process was conducted systematically, and discrepancies in study inclusion were resolved through discussion. The overall study selection process is presented in the PRISMA flow diagram.

Data Extraction

Data extraction was performed using a standardized data collection format. Extracted variables included first author, year of publication, country, study design, population characteristics, DTN thresholds, and clinical outcomes. Outcomes of interest included functional independence, mortality, and hemorrhagic complications, particularly symptomatic intracerebral hemorrhage. All extracted data were compiled into a single comprehensive table summarizing both study characteristics and results.

Risk of Bias Assessment

The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies. This tool evaluates three key domains: selection of study groups, comparability of cohorts, and assessment of outcomes. Each study was assigned a score based on the NOS criteria, with higher scores indicating better methodological quality. The risk of bias was interpreted conservatively and categorized as low to moderate, in line with the observational nature of the included studies. Particular attention was given to potential confounding factors, selection bias, and differences in baseline characteristics between groups.

Data Synthesis

A qualitative synthesis of the included studies was conducted to evaluate the association between door-to-needle time and clinical outcomes. Findings were summarized narratively, with emphasis on the direction and consistency of associations across studies. Variations in DTN thresholds, outcome definitions, and study populations were taken into account when interpreting the results.

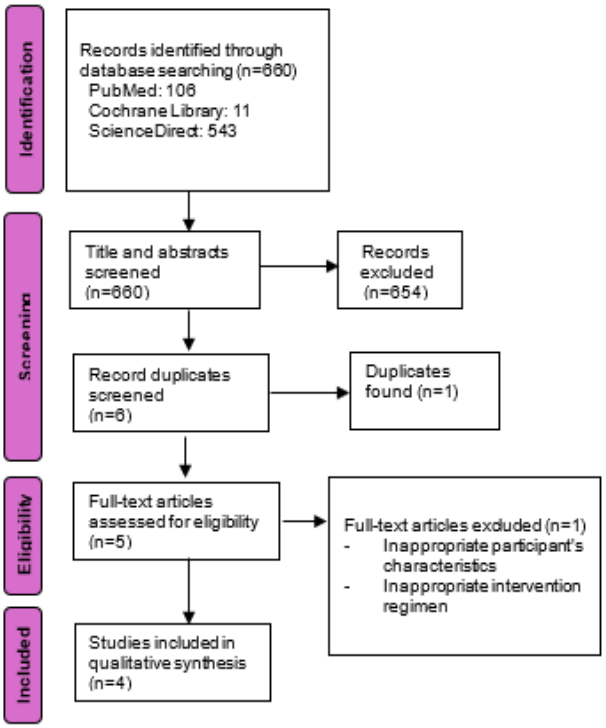

Figure 1. Diagram flow of literature search strategy for this systematic review

First Author (Year)	Country / Setting	Study Design	Population (LVO / suspected LVO, sample size, mean age)	Intervention (DTN ≤30–45 min)	Comparator (DTN >45–60 min)	Thrombectomy Use (%)	Outcomes Measured (mRS 0–2, mortality, sICH)	Summary of Findings	Risk of Bias
Wang et al. (2025)	Singapore, single comprehensive stroke center	Observational cohort	AIS patients receiving IVT (n = 1,146; mean age 68.6 years; ~49.9% large/medium vessel occlusion)	DTN ≤30 min	DTN >60 min (reference group)	EVT 3.66% overall	mRS 0–2 (3 months), in-hospital mortality, sICH	DTN ≤30 min associated with higher odds of functional independence (OR 2.35, 95% CI 1.26–4.39); no significant difference in mortality (OR 0.83) or sICH (OR 0.22); also reduced length of stay and hospitalization cost	Low
Man et al. (2023)	USA (GWTG-Stroke + Medicare linked database)	Retrospective cohort (large national registry)	Acute ischemic stroke patients ≥65 years; IVT only (n=38,913) and IVT+EVT (n=3,946)	DTN ≤30–45 min (also analyzed ≤60 min and continuous DTN per 15 min)	DTN >45–60 min (and continuous delay)	Mixed (IVT only + IVT+EVT subgroup)	Functional outcome (home time), mRS 0–2 (discharge), mortality (1-year), readmission	Each 15-min DTN delay increased odds of poor functional outcome and mortality (IVT+EVT: aOR 1.12 for zero home time; aHR 1.07 mortality); shorter DTN (≤30–60 min) associated with higher mRS 0–2 and more home time; benefit	Moderate

								attenuated when DTN >60 min	
Man et al. (2023)	USA (Get With The Guidelines–Stroke + Medicare linked database)	Retrospective cohort (national registry)	Acute ischemic stroke patients ≥65 years; IVT only (n=38,913) and IVT+EVT (n=3,946); EVT-only comparator (n=3,704)	Short DTN (≤30, ≤45, ≤60 min; also analyzed per 15-min increments)	Longer DTN (>45–60 min and continuous delay)	Mixed (separate IVT-only and IVT+EVT cohorts)	Functional outcome (home time at 90 days & 1 year), mRS 0–2 at discharge, all-cause mortality (1 year), readmission	In IVT+EVT patients, each 15-min DTN delay increased odds of poor functional outcome (aOR 1.12 for zero home time) and mortality (aHR 1.07). Shorter DTN (≤30–60 min) improved mRS 0–2 (25.0% vs 16.4%) and home time; benefit diminished when DTN >60 min. Similar but weaker trends in IVT-only cohort.	Moderate
Sallustio et al. (2025)	Italy (IRETAS registry, multicenter)	Prospective registry-based cohort (observational)	AIS due to anterior circulation LVO (MCA / ICA), n=1602, mean age 73.7±13.7 years	Short DTN (≤30, ≤45, ≤60 min)	Longer DTN (>30, >45, >60 min)	100% (all patients IVT + MT)	Effectiveness: 3-month functional independence (mRS≤2), excellent outcome (mRS≤1), successful reperfusion; Safety: any ICH, sICH, 3-month mortality	DTN≤60 min associated with higher functional independence (OR 1.36), higher reperfusion (OR up to 2.66), lower ICH (OR 0.61), and lower mortality (OR 0.24–0.58 depending on cut-off). No association with	Low

				sICH. Shorter DTN consistently improved outcomes.

Table 1. Characteristics and results of the included studies

Result and Discussion

1. Result

A total of 660 records were identified through database searching, including 106 from PubMed, 11 from the Cochrane Library, and 543 from ScienceDirect. After title and abstract screening, 654 records were excluded, leaving 6 records for further assessment. Following duplicate removal and full-text evaluation, 5 articles were assessed for eligibility, of which 1 was excluded due to inappropriate population characteristics and intervention regimen. Ultimately, 4 studies were included in the qualitative synthesis, as illustrated in Figure 1.

Study Characteristics

The four included studies comprised a combination of observational cohort analyses and secondary analyses of randomized trial datasets, encompassing a total of more than 3,000 patients with acute ischemic stroke. All studies evaluated the association between door-to-needle time (DTN) and clinical outcomes in patients receiving intravenous thrombolysis, with varying proportions of patients undergoing additional endovascular thrombectomy. Two studies specifically focused on patients with large vessel occlusion (LVO) undergoing combined IVT and mechanical thrombectomy, while the remaining studies included broader populations of thrombolysis-treated patients, with subgroup analyses relevant to LVO or thrombectomy-capable settings (Kaesmacher et al., 2024)

DTN thresholds varied across studies, most commonly categorized into ≤30, ≤45, and ≤60 minutes, with some studies additionally analyzing DTN as a continuous variable. Functional outcomes were consistently assessed using the modified Rankin Scale (mRS), typically at 3 months, while mortality and hemorrhagic complications, including symptomatic intracerebral hemorrhage (sICH), were also frequently reported. Detailed study characteristics and extracted outcomes are presented in Table 1.

The methodological quality of the included studies, assessed using the Newcastle-Ottawa Scale, was generally rated as low to moderate. Most studies demonstrated adequate selection of cohorts, with clearly defined patient populations and appropriate ascertainment of exposure. Comparability between groups was addressed in several studies through multivariable adjustment for key confounders, although residual confounding could not be entirely excluded due to the observational design. Outcome assessment was considered robust across studies, with standardized measures such as the modified Rankin Scale and mortality endpoints. Overall, no study was judged to have a high risk of bias, and the consistency of findings across studies further supports the reliability of the observed associations.

Functional Outcomes

All included studies demonstrated a consistent association between shorter DTN and improved functional outcomes. In large registry-based cohorts of patients undergoing combined IVT and thrombectomy, shorter DTN—particularly within 60 minutes—was significantly associated with higher rates of functional independence (mRS ≤2 at 3 months). For instance, patients treated within 60 minutes exhibited higher odds of achieving functional independence compared to those with longer treatment delays.

Similarly, analyses derived from randomized trial datasets in LVO populations showed that delays in DTN were associated with a progressive reduction in the likelihood of favorable functional outcomes. In these studies, each incremental delay in DTN corresponded to a measurable decline in the odds of achieving functional independence at 90 days. Consistent trends were also observed in large real-world datasets, where shorter DTN was associated with improved discharge functional status and increased time spent at home following stroke.

Mortality

Shorter DTN was consistently associated with reduced mortality across the included studies. In registry-based analyses of patients undergoing combined IVT and thrombectomy, DTN thresholds of ≤30, ≤45, and ≤60 minutes were all associated with significantly lower mortality rates at 3 months. The magnitude of this effect was most pronounced in patients treated within 30 minutes, with progressively attenuated benefits observed at longer DTN thresholds.

In large-scale observational datasets, increases in DTN were associated with a corresponding rise in mortality risk, with each incremental delay contributing to worse survival outcomes. These findings were consistent across both IVT-only and IVT-plus-thrombectomy populations, reinforcing the time-dependent nature of thrombolytic therapy effectiveness.

Hemorrhagic Outcomes

The relationship between DTN and hemorrhagic complications was less consistent compared to functional outcomes and mortality. While shorter DTN was associated with a reduction in overall intracranial hemorrhage rates in some studies, no significant association was observed between DTN and symptomatic intracerebral hemorrhage (sICH) across most analyses.

In particular, large registry-based studies demonstrated that earlier thrombolysis was associated with a lower incidence of any intracranial hemorrhage, suggesting a potential protective effect of rapid treatment initiation. However, this effect did not extend to sICH, which remained relatively stable across different DTN categories.

Additional Outcomes

Beyond functional outcomes and mortality, several studies reported secondary endpoints, including successful reperfusion and healthcare utilization metrics. Shorter DTN was associated with higher rates of successful reperfusion in patients undergoing thrombectomy, indicating a potential synergistic effect between early thrombolysis and mechanical clot retrieval.

Additionally, shorter DTN was linked to reduced hospital length of stay and lower overall healthcare costs in certain cohorts, further supporting the clinical and systemic benefits of rapid treatment initiation.

2. Discussion

Key Findings

This systematic review demonstrates a consistent and clinically meaningful association between shorter door-to-needle time (DTN) and improved outcomes in

patients with acute ischemic stroke undergoing intravenous thrombolysis in thrombectomy-capable centers. Across all included studies, shorter DTN, particularly within 60 minutes, was associated with higher rates of functional independence, reduced mortality, and, in some cases, lower rates of intracranial hemorrhage. Notably, these findings were observed not only in patients receiving intravenous thrombolysis alone but also in those undergoing combined intravenous thrombolysis and endovascular thrombectomy, underscoring the continued relevance of rapid thrombolytic administration in the modern era of stroke care (Sallustio et al., 2025); (Man et al., 2023); (Sedghi & Siepmann, 2024); (Kaesmacher et al., 2024)

The magnitude and consistency of these associations suggest that DTN remains a critical determinant of outcome, even in settings where highly effective mechanical reperfusion strategies are available. Importantly, the benefit of shorter DTN appeared to follow a dose–response relationship, with progressively worse outcomes observed as treatment delays increased (Kaesmacher et al., 2024)

Biological and Clinical Mechanisms

The observed relationship between shorter DTN and improved clinical outcomes can be explained by the underlying pathophysiology of cerebral ischemia. Rapid restoration of cerebral blood flow limits infarct core expansion and preserves the ischemic penumbra, thereby increasing the likelihood of favorable neurological recovery.(Campbell et al., 2019; Ermine et al., 2021) Delays in treatment, even within the accepted therapeutic window, result in continued neuronal loss and irreversible tissue damage, reinforcing the time-sensitive nature of reperfusion therapy (Ragoschke-Schumm et al., 2014)

In the context of large vessel occlusion, intravenous thrombolysis may provide additional benefits beyond direct clot dissolution. Early administration of alteplase can soften thrombi, enhance distal microvascular reperfusion, and facilitate subsequent mechanical thrombectomy (Campbell et al., 2015). Furthermore, in a subset of patients, thrombolysis alone may achieve early recanalization prior to endovascular intervention, thereby reducing procedural complexity and improving outcomes. These mechanisms support the hypothesis that minimizing DTN is essential even in thrombectomy-capable centers.

Comparison with Previous Studies

The findings of this review are consistent with prior evidence demonstrating the time-dependent effectiveness of intravenous thrombolysis. Large meta-analyses of randomized controlled trials have shown that earlier treatment is associated with improved functional outcomes and reduced disability.(Emberson et al., 2014)[18] Similarly, pooled analyses of endovascular thrombectomy trials have highlighted the importance of timely reperfusion in determining clinical outcomes (Goyal et al., 2016)

More recent studies focusing on DTN in the era of thrombectomy further support these observations. Analyses from large registry datasets have demonstrated that shorter DTN is independently associated with improved functional outcomes and reduced mortality, even after adjusting for confounding variables (Man et al., 2023); (Sallustio et al., 2025) These findings align with the results of the present review, which synthesizes evidence across different study designs and populations.

In addition, prior investigations have suggested that delays in in-hospital processes, including imaging and treatment initiation, are modifiable factors that significantly influence stroke outcomes (Fonarow et al., 2011); (Saver et al., 2013) Quality improvement initiatives targeting reductions in DTN have been associated with measurable improvements in clinical outcomes, highlighting the importance of system-level interventions in optimizing stroke care delivery (Meretoja et al., 2012)

Clinical Implications

The results of this systematic review have important implications for clinical practice and healthcare systems. First, they reinforce the concept that achieving rapid DTN should remain a priority in all stroke centers, including those equipped with endovascular capabilities. The availability of thrombectomy should not lead to delays in intravenous thrombolysis, as both modalities appear to have complementary roles in improving patient outcomes

Second, these findings support ongoing efforts to streamline in-hospital workflows, including rapid triage, early imaging, and parallel processing of diagnostic and treatment steps. Achieving DTN targets of ≤60 minutes, and ideally ≤30–45 minutes, may significantly improve functional outcomes and survival in patients with AIS.

Finally, the consistent association between shorter DTN and improved outcomes highlights the need for continuous performance monitoring and quality improvement initiatives within stroke systems of care. Benchmarking DTN performance and implementing standardized protocols may help reduce variability and improve overall treatment efficiency.

Limitations

Several limitations must be considered when interpreting the conclusions of this review. First, the included evidence relies primarily on observational cohort data, which introduces potential risks for residual confounding and selection bias. For example, patients who receive ultra-rapid treatment may inherently have more favorable pre-hospital logistics or milder initial presentation compared to those who experience treatment delays.

Second, there was notable variation in how DTN thresholds were defined across the studies, with authors using different categorical cut-offs such as 30, 45, or 60 minutes. This variation limits direct cross-study comparisons and prevents a formal quantitative meta-analysis. Additionally, variations in follow-up intervals—such as measuring mRS scores at hospital discharge versus at 3 months—introduced further heterogeneity. Finally, some registries combined data from patients receiving IVT alone with those undergoing bridging therapy, which may obscure the specific treatment effects within these distinct sub-populations.

Third, some studies included mixed populations of patients receiving intravenous thrombolysis alone and those undergoing combined therapy with thrombectomy. Although subgroup analyses were often performed, the potential influence of treatment heterogeneity cannot be fully excluded.

Conclusion

In conclusion, shorter door-to-needle times are reliably associated with improved long-term functional recovery and decreased mortality rates among acute ischemic stroke patients treated at thrombectomy-capable centers. This clear clinical benefit is achieved without causing any corresponding increase in the risk of symptomatic intracerebral hemorrhage. These findings confirm that rapid thrombolytic administration remains highly effective in the endovascular era, demonstrating that DTN is a vital, modifiable target for quality improvement in acute stroke care.

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